Martindale

The Complete Drug Reference

Thirty-eighth Edition

Edited by
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BPharm, MRPharmS

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Martindale is published by the Pharmaceutical Press, the publishing division of the Royal Pharmaceutical Society. Content is created and updated by the Martindale Editorial Team, a group of pharmacists and life science graduates with relevant expertise who are given formal training in literature evaluation and searching techniques, as well as on-the-job training in internal procedures. The Editorial Team is supported by a number of external contributors.

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Preface

Drug information is constantly developing as the use of existing drugs grows, new drugs emerge, new preparations are launched, and old preparations are abandoned, reformulated, or redefined. The needs of those practising pharmacy and medicine are also changing, and during its long history Martindale has evolved to meet those needs by becoming much more than a simple encyclopaedia of medicines. It aims to provide healthcare professionals with evaluated, unbiased information on drugs and medicines used throughout the world. Our content is also carefully structured to enable readers to find this information easily and quickly, whether it is to answer specific questions about drugs or to give a broad overview of pharmaceutical topics.

Our readers should note that Martindale is not a book of standards: the inclusion of a substance or a preparation is not to be considered as a recommendation for use, nor does it confer any status on the substance or preparation and readers are reminded that knowledge and best practice in this field are constantly changing. While considerable efforts have been made to check the material in Martindale, neither the publisher nor the authors accept any responsibility for errors and omissions. The publisher and authors make no representation, expressed or implied, that doses are correct for particular purposes and readers should check up to date product information, codes of conduct, and safety regulations. The reader is also assumed to possess the necessary knowledge to interpret the information that Martindale provides. It is the responsibility of practitioners to determine dosages and treatments for individual patients, taking into account up to date therapeutic standards, and to take all appropriate safety precautions.

Further details on the basic editorial philosophy behind content creation, as well as guidance on how the data is set out, are provided in the guide to Martindale section on the next page.

Major changes for the 38TH Edition

There have been several changes to this new edition of Martindale, but the most striking is its new format. The cover design has been refreshed and, to overcome a common problem, the page layout has been totally re-designed with a new and larger font. This ensures that the page is easier to read as well as making it quicker to find the information the reader is looking for on the page. Alongside this, and in response to user feedback, the layout of the monographs has been restructured and readers will now find a monograph's uses at the start of a monograph; knowing how a drug acts and is used may help to contextualise any subsequent adverse effects and precautions related to that drug. In addition, a drug's nomenclature information is highlighted within its own shaded text box. To allow for these changes, the chemical structure graphics are no longer reproduced in the print editions of Martindale; however, they remain available on our digital platform, MedicinesComplete.

Alongside much of the revalidation work that is undertaken with every edition of Martindale, other changes for this edition include:

- over 200 new monographs including:
  - the sodium-glucose co-transporter 2 inhibitors, canagliflozin and dapagliflozin, have been added as a new drug group to the chapter on antidiabetic drugs
  - the antivirals, daclatasvir and sofosbuvir, for use in the management of hepatitis C
- restructuring of the section on diabetes mellitus management in the antidiabetic drugs chapter, to improve its readability
- updated reviews on the treatment of acute lymphoblastic leukaemia and non-small cell lung cancer, which prototype a new approach to our treatment reviews
- revised paracetamol nomograms for the treatment of paracetamol poisoning
- extensive revision of the porphyria abstracts
- expansion of the coverage of proprietary preparations to cover 43 countries and regions, including China

The Martindale editorial team have been assisted by many individuals in the production of this edition, and it is their valuable contribution that help to ensure Martindale's validity. Thanks are due to Lina Bladh, Alessandro Gabbi, Judy van Engeldorp Gastelaars, Špela Godec, Jan Horn, Montserrat Jané, Andrius Kairys, Maria Kouimtzi, Carla Oliveira, Kamila Ramešová, Elsa Simon, Gyöngyver Soós, Carina Tukukino, Robert Wasilewski, Larry Callahan, and Frank Switzer.

The team have also been able to call on the advice and expertise of other members of the Royal Pharmaceutical Society's Pharmaceutical Press division. In particular, the Editor would like to thank Rachel Ryan and the staff of the British National Formulary, Claire Preston and the staff of Stockley's Drug Interactions, and Sam Driver and the Science team. Thanks are also due to Tamsin Cousins and Linda Paulus, for their patience and guidance in handling the various aspects of producing a print publication, and to David Granger, Mesfin Mebrate, Karl Parsons, and Ian White, for their technical expertise in producing digital and print datasets. We are also grateful for the support of Karen Baxter, Frank Gibson, and Alina Lourie.

The Editor would also like to thank Sean Sweetman, Paul Blake, Gail Neathercoat, Anne Parsons, Susan Handy, Fauziah Hashmi, Joanna Humm, Kelli Kalb, Priya Patel, Gerda Viedge, Elizabeth King, and Christine Iskandar. Their input over the years and to this edition has been greatly valued and is not forgotten.

Our digital version of Martindale, which is updated quarterly, is available on MedicinesComplete (www.medicinescomplete.com). It maintains the familiar layout of the print publication but, as it is not limited in its size, extra content such as the archive chapter of deleted monographs and graphical representations of the chemical structures of many of the drugs are also available. For more information about the digital product, please visit our website.

We continue to value our readers' feedback and anyone wishing to contact us may do so at our email address: PhpEditorial@rpharms.com

London, February 2014

A guide to Martindale

Martindale contains information on drugs in clinical use worldwide, as well as selected investigational and veterinary drugs, herbal and complementary medicines, pharmaceutical excipients, vitamins and nutritional agents, vaccines, radiopharmaceuticals, contrast media and diagnostic agents, medicinal gases, drugs of abuse and recreational drugs, toxic substances, disinfectants, and pesticides.

The information on over 6000 drugs and other substances is arranged into monographs that contain details on nomenclature, properties, and actions. These text sections summarise the relevant information, notably for licensed uses, followed, if appropriate, by referenced abstracts or reviews that expand upon the details given in the text or add additional information. Multicentre studies, meta-analyses, and systematic reviews play an important role in the study of drug treatment, and their findings and conclusions are considered in much of our content. However, there is also a place for the anecdotal report and the small study, and information from such sources is included where appropriate. In compiling the text of a Martindale monograph, use is made of the drug's licensed product information as published in various countries and approved by the relevant regulatory authorities. Acknowledgement is also given to information referenced from a number of authoritative sources including the *British National Formulary*, the *British National Formulary for Children*, the *British Pharmacopoeia*, the *European Pharmacopoeia*, the *United States National Formulary*, and the *United States Pharmacopeia*.

In addition, disease treatment reviews offer overviews of nearly 700 diseases and the drugs used in their treatment, along with key references and guidelines. Cross-references are provided between these treatment reviews and relevant drug monographs.

Preparations summaries of more than 180,000 proprietary products from 43 countries or regions are included. Information is provided on proprietary name, manufacturer or distributor, country/region of origin, active ingredients, and a summary of the indications as given by the manufacturer. Page numbers link ingredients to an appropriate drug monograph where possible.

Philosophy and methodology

Martindale's uses are as varied as its users. However, the primary aims are:

- to summarise clinically useful information on all drugs and medicines around the world
- to provide accurate, unbiased, and reasonably comprehensive information in a concise format
- to provide a lead-in to the published evidence base from which we derive our information

To achieve the above aims, working practices have to be safe and efficient, while making optimum use of available information. This section describes some of these working practices.

Data collection

The team proactively monitor the published literature for potential content updates. This involves regularly searching selected major medical journals and websites of regulatory authorities such as EMA, FDA, Health Canada, and MHRA; other sources of high-quality systematic reviews and guidelines, including the Cochrane library and NICE, are also monitored, as are pharmacopoeial, governmental, and WHO publications, for information relating to drugs and drug therapy.

The list of sources used has been developed over many years by analysis of previous citations, and is reviewed and updated regularly.

Licensed product information for 43 countries and regions is evaluated, to maintain the widest possible coverage of drugs in use internationally. Preparation names, manufacturers, ingredients, and licensed uses are included in the internal Martindale database for review during the revision process.

Editorial processes

Write, review, and approve. To maintain the quality and currency of our content, it is constantly revised and updated. Our revision processes cover both scheduled revision of the content, and revision of particular points in reaction to new information as it arrives.

The revision procedure involves the editorial writer re-evaluating standing information, assessing newly-collected references for quality and relevance, and searching bibliographic databases and the Internet to identify further candidate information.

Once the material for new content has been re-evaluated and updated, it is rigorously reviewed by a second editorial writer to ensure not only that all changes are valid and appropriate, but also that important points have not been missed.

The material is then passed to the editor, who performs a final, high-level check and approval of the data. This process is designed to ensure consistency of approach and style, as well as offering an opportunity to pick up any errors that may have been missed. Changes and questions are fed back to the writer.

Keying, proof-reading, and dose-checking. Once approved by the editor, content changes can be made in the database, which has remained untouched until this stage as a security measure. These changes are then proofread for errors, corrected if necessary, and any corrections checked. Extensive electronic testing for spelling, style, and format is also carried out at all stages.

The amended content then undergoes an independent review of the dose information against its recorded sources. This review is performed by a writer not involved in the original content generation process, and is an additional safeguard against the inadvertent introduction of potentially dangerous dose errors.

Release. Once past all these stages, the data are cleared for release and can be published in the next update of the Martindale digital products; changes to the print version will appear in the next edition.

Additional checks for publication. Some additional checks are made before publishing a print edition of Martindale. A second independent dose review of all chapters is made by external experts.

How the information is arranged

Martindale is divided into 2 volumes:

Volume A covers:

- **Monographs on drugs and ancillary substances.** This section contains over 6000 monographs arranged in 49 chapters. These chapters generally bring together monographs on drugs and groups of drugs that have similar uses or actions. The disease treatment reviews, which provide descriptions of diseases together with reviews of the choice of treatments, are usually located in the chapter introduction. The chapter titled Miscellaneous Drugs and Other Substances contains monographs on drugs not easily classified, herbals, and drugs no longer used clinically but still of interest. There are also monographs on toxic substances, the effects of which may require drug therapy.

Volume B includes:

- **Preparations.** This section contains over 180,000 proprietary preparations from a range of countries and regions. The information provided includes the proprietary name, the manufacturer or distributor, the active ingredients with cross-references to the drug monographs, and a summary of the indications as given by the manufacturer.
- **Directory of manufacturers.** In Martindale the names of manufacturers and distributors are abbreviated. Their full names are given in this directory together with contact details if available. Manufacturers' records are listed alphabetically. This directory contains over 20,000 entries.
- **Pharmaceutical terms in various languages.** This index lists nearly 5600 of the commoner pharmaceutical forms and routes in 13 major European languages. It is provided as an aid to the non-native speaker in interpreting packaging, product information, or prescriptions written in another language.
- **General index.** To make the fullest use of the contents of Martindale the general index should always be consulted. The exhaustive index, prepared from over 175,000 entries, including entries for drugs

(approved names, synonyms, and chemical names), preparations, pharmacological and therapeutic groups, and clinical uses (disease treatment reviews). As in previous editions, the index is arranged alphabetically 'word-by-word' rather than 'letter-by-letter'. The index indicates the column in which the relevant entry appears as well as the page and in which volume the entry may be found. To improve clarity and the ease of location of index entries, long chemical names have been omitted from the index.

- **Cyrillic index.** Both non-proprietary and proprietary names may be found in Cyrillic alphabetical order in this section.

The monographs

Chapters within Martindale are composed of an introduction of varying length, and a set of monographs describing individual drugs. Each monograph begins with its title, synonyms in English and other languages, identificatory codes, and chemical and pharmaceutical information about the compound, including any pharmacopoeial standards. This is followed by one or more sections describing pharmacological and therapeutic information about the drug or substance. A typical monograph includes:

- Nomenclature
- Uses and Administration
- Adverse Effects
- Treatment of Adverse Effects
- Precautions
- Interactions
- Pharmacokinetics

Sections begin with unreferenced summary text, based on licensed product information and other high-quality validated sources. This may optionally be followed by abstracts or referenced text expanding on particular points, and providing a lead-in to the published literature from which we derive our information.

Lists of single and multi-ingredient proprietary and non-proprietary preparations are given at the end of each monograph.

Nomenclature

The nomenclature section of each monograph may include the following information:

Titles and synonyms. The title of each monograph is in English, with preference usually being given to International Nonproprietary Names (INN), British Approved Names (BAN), and United States Adopted Names (USAN). These 3 authorities are shown where appropriate. A European Directive (92/27/EEC) requires the use of Recommended International Nonproprietary Names (rINNs) in the labelling of medicinal products throughout member states of the European Union and where the BAN and INN differed in the past the BAN has been changed to accord with the rINN. The major exception to this convention is the retention of the names adrenaline and noradrenaline, these being the terms used as the titles of the monographs in the European Pharmacopoeia and therefore the official names in the member states. In some approved names it is general policy to use 'f' for 'ph' in sulpha, 't' for 'th', and 'i' for 'y'; for this reason entries in alphabetical lists should be sought in alternative spellings if the expected spellings are not found. Inevitably there may be some inconsistencies of style with older approved names but wherever possible the names used for drugs or radicals in Martindale have been altered in accordance with the guidelines on the use of INNs for pharmaceutical substances. For a table of contracted names for ions and groups used in approved names and titles see p. xii.

This section also includes names given as synonyms such as commonly used abbreviated names; Latin versions of the titles in the European Pharmacopoeia; English, American, Spanish, and Latin synonyms; names used in other languages when these may not be readily identifiable; manufacturers' code numbers; and chemical names. BAN names for substance combinations and United States Pharmacy Equivalent Names (PEN) for dosage forms containing two or more active ingredients are given in the text of the relevant monographs; these names start with the prefix 'Co-'.

Official titles and synonyms used in the British, European, and US Pharmacopoeias are given in the section on pharmacopoeias where the relevant pharmacopoeial substance is described.

Street Names. Street terms and other slang names for drugs of abuse are included for guidance only and should be used with caution. Because of the very nature of their origin they cannot be relied upon for definitive identification of a substance. The use of such terms changes rapidly, and can vary between different geographical locations, and any given name may potentially be applied to more than one substance or even to a mixture of substances. Furthermore, established or well recognised generic drug names or herbal names have sometimes been misused as street terms for completely unrelated substances. In order to enable the reader to distinguish them from the better validated synonyms in the index, such names are included in italics and in quotation marks.

CAS Registry numbers. Chemical Abstracts Service (CAS) registry numbers are provided, where available, for each monograph substance to help readers refer to other information systems. Numbers for various forms of the monograph substance are listed with the variation in form given in parentheses.

ATC codes. Codes from the Anatomical Therapeutic Chemical (ATC) classification system (see http://www.whocc.no) have been provided, where available, for each monograph substance to help readers refer to other information systems. The codes assigned in the equivalent classification system for veterinary medicines (ATC Vet–see http://www.whocc.no/atcvet) and herbal medicines have been included where possible.

UNII codes. The unique ingredient identifiers, which are generated by the joint FDA/USP Substance Registration System have been provided, where available. Numbers for various forms of the monograph or related substances are listed with the variation in form given in parentheses.

Atomic and molecular weights. Atomic weights are based on the table of Atomic Weights as revised in 2011 by the Commission on Isotopic Abundances and Atomic Weights, International Union of Pure and Applied Chemistry (IUPAC) and based on the ^{12}C scale (see p. xiv). Molecular weights are given corrected to one place of decimals or to four significant figures for relative weights of less than 100.

Pharmacopoeias

The selected pharmacopoeias in which each substance appears are listed. A description of the substance and a summary of the pharmaceutical information that appears in the British, European, or US Pharmacopoeias is also included. Current copies of the pharmacopoeias and their addenda should be consulted for confirmation and for details of standards.

The pharmacopoeias covered include *British, British Veterinary, Chinese, European, French, German, International, Italian, Japanese, Polish, Spanish, Swiss, United States* (including the *National Formulary*), and *Vietnamese*. The abbreviations for these pharmacopoeias are included in the list of abbreviations used in Martindale (see p. ix), which also includes details of the edition and/or supplement(s) consulted.

Several countries are parties to the Convention on the Elaboration of a European Pharmacopoeia. This means that they must adopt the standards of the European Pharmacopoeia. These countries are currently Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Montenegro, the Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Turkey, Ukraine, the United Kingdom, the Former Yugoslav Republic of Macedonia, and the European Union. Hence the European Pharmacopoeia is cited in the drug monograph lists of pharmacopoeias rather than these individual national pharmacopoeias.

Official preparations, mainly from the current British, European, and US Pharmacopoeias, are listed at the end of drug monographs.

Pharmaceutical information

Information on the chemical and physical properties of each substance is given when it is likely to be of use or interest, but only when it is certain that it applies to the form of substance being described in the monograph.

Percentage strengths. Unless otherwise stated, solutions of solids in liquids are expressed as percentage w/v, of liquids in liquids as percentage v/v, and of gases in liquids as percentage w/w.

Solubility. The figures given for solubility in each monograph have generally been obtained from the major pharmacopoeias in which the substance is described, but should not be considered absolute. Unless otherwise indicated in the text, the figures are for solubility at temperatures between 15 degrees and 25 degrees. The information

usually relates to w/v solubilities but in some cases is v/v if the monograph substance itself is a liquid. Where solubilities are given in words, the following terms describe the indicated solubility ranges:

- very soluble: 1 in less than 1
- freely soluble: 1 in 1 to 1 in 10
- soluble: 1 in 10 to 1 in 30
- sparingly soluble: 1 in 30 to 1 in 100
- slightly soluble: 1 in 100 to 1 in 1000
- very slightly soluble: 1 in 1000 to 1 in 10,000
- practically insoluble: 1 in more than 10,000

Storage. Substances and preparations should be stored under conditions that prevent contamination and diminish deterioration, and the conditions of storage given in the text indicate the precautions recommended in specific cases. The term 'a cool place' is generally used to describe a place in which the temperature is between 8 degrees and 15 degrees. In general, the storage conditions apply to the monograph substance and not its solutions or preparations.

Temperature. Temperatures are expressed in degrees Celsius (centigrade) unless otherwise indicated.

Drugs in Sport

Wherever possible we have attempted to indicate those drugs and substances that may be subject to restriction in some or all sports, either in their own right, or because they are a derivative of a restricted substance or a member of a prohibited group. Proprietary preparations containing such compounds are also marked in the preparation section. The guide used for identifying restricted drugs is the Prohibited List issued by the World Anti-Doping Agency (WADA–see www.wada-ama.org). These regulations, which are issued annually, are subject to interpretation and therapeutic exemption, and may vary from sport to sport; particular sporting authorities may also issue additional restrictions, and competitors should always check with the appropriate body. The rules are constantly evolving and the absence of any indication of restriction in Martindale should not be taken as absolute confirmation that the substance may legitimately be taken by a competitor.

Pharmacological and therapeutic information

Information on uses and administration, adverse effects, treatment of adverse effects, precautions (including contra-indications), interactions, and pharmacokinetics of each substance is provided by concise statements and these may be elaborated and expanded by referenced reviews and abstracts from papers and other publications. This edition contains nearly 14,000 such abstracts or reviews based on information in an ever widening range of publications.

An increasing amount of information is published digitally and this material is available on the Internet as web pages. Because of the nature of the Internet, there is no way to guarantee that the material referred to by a URL will remain at that location, as many sites are subject to periodic reorganisation; additionally, the content of Internet documents may change without warning. The accession date given in the citation represents the last date on which the content of the document referred to was revalidated.

Much information has been found in sources such as WHO publications, government reports and legislation, and other official and standard publications. Licensed product information and manufacturers' literature have been considered in the light of other available information.

The risks of administering drugs in pregnancy are well known and the general principle is to give a drug only when the benefit to the individual mother outweighs the risk to the fetus. Where there is a clear risk it is noted under the Precautions or Adverse Effects heading but safety should not be inferred from the absence of a statement for any drug.

Some drugs given to the mother are distributed into breast milk and therefore may pose a risk to a breast-fed infant. Whenever possible, information has been included to help determine the safety of continuing to breast feed while the mother is receiving a particular drug. Safety during breast feeding should not be inferred from the absence of a statement for any drug.

Doses. Doses are described under the Uses and Administration headings with as much detail as is necessary and available. Unless otherwise stated the doses represent the average range of quantities that are generally regarded as suitable for adults when given orally. More information on doses and drug administration may be given in the abstracts or reviews. Unless otherwise specified, glucose injection is 5% w/v and sodium chloride injection is 0.9% w/v.

When doses for children are expressed as a range of quantities within specified age limits, the lower dose applies at the lower age and the higher dose at the higher age.

The Preparations

This part of Martindale contains brief details of proprietary preparations available in a number of countries or regions and includes those supplied on prescription as well as those sold directly to the public. They are provided to help the reader identify preparations and to suggest their uses. Inclusion is not an endorsement of the activity of any ingredient, nor of the preparation's indications.

For this edition we have covered Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, China, the Czech Republic, Denmark, Finland, France, Germany, Greece, Hong Kong, Hungary, India, Indonesia, Ireland, Israel, Italy, Japan, Malaysia, Mexico, the Netherlands, New Zealand, Norway, Philippines, Poland, Portugal, Russia, Singapore, South Africa, Spain, Sweden, Switzerland, Thailand, Turkey, Ukraine, the United Arab Emirates, UK, USA, and Venezuela. Generally, each entry consists of the proprietary name, the manufacturer or distributor and country, the active ingredients and a summary of the indications as given by the manufacturer. Where possible, entries from different countries but with the same name and active ingredients have been amalgamated for clarity. Instances where a preparation name has been used for preparations with significantly different ingredients have been highlighted. Such names may be for actively marketed preparations or for preparations that have been withdrawn from the market.

An entry may cover a range of dosage forms and strengths. Dosage forms are only specified when different forms have the same proprietary name but different active ingredients. Furthermore, this section is not intended as a guide to prescribing; where a preparation is to be supplied the dose should be appropriate for that preparation and that particular patient, and authoritative local sources should be consulted.

With the exception of homoeopathic preparations the names of the ingredients have been translated into English. Almost all the ingredients listed are described in the monographs in Drugs and Ancillary Substances, and readers are directed to an appropriate monograph by the page numbers provided after the ingredient.

Preparations that have been withdrawn from the market in the last few years or are no longer being actively marketed may be identified by the symbol †. These preparations are retained in Martindale since they may still be in circulation or their names may still be referred to in the literature and in practice. Readers should be aware that since this section was prepared other preparations are likely to have been withdrawn or introduced; also ingredients may change, as may indications.

The manufacturer's full name and contact details can be found in the Directory of Manufacturers.

Each preparation title is listed in the General Index. Where thought helpful, preparation titles have been listed at the end of the relevant monograph. However, it should be noted that the absence of such a list at the end of a monograph is no indication as to the availability of a substance as many drugs are marketed as generic or unbranded preparations.

Abbreviations

For abbreviations of the names of manufacturers or their distributors, see Directory of Manufacturers, in Volume B.

ACE—angiotensin-converting enzyme.
ADHD—attention deficit hyperactivity disorder.
agg.—aggregate (in botanical names), including 2 or more species which resemble each other closely.
AIDS—acquired immunodeficiency syndrome.
a.m.—*ante meridiem*, 'before noon'.
ARC—AIDS-related complex.
Arg.—Argentina.
ATC—Anatomical Therapeutic Chemical classification.
AUC—area under the concentration-time curve.
Austral.—Australia.
AV—atrioventricular.
BAN—British Approved Name.
BANM—British Approved Name Modified.
Belg.—Belgium.
BMA—British Medical Association.
BMI—body mass index.
BNF—British National Formulary.
BNFC—British National Formulary for Children.
b.p.—boiling point.
BP—British Pharmacopoeia. Unless otherwise specified, BP references are to the 2014 edition.
BP(Vet)—British Pharmacopoeia (Veterinary) 2014.
BPC—British Pharmaceutical Codex.
Br.—British.
Braz.—Brazil.
Bulg.—Bulgaria.
BUN—Blood-urea-nitrogen.
°C—degrees Celsius (centigrade). Unless otherwise indicated in the text, temperatures are expressed in this thermometric scale.
Canad.—Canada.
CAPD—continuous ambulatory peritoneal dialysis.
CAS—Chemical Abstracts Service.
CCPD—continuous cycle peritoneal dialysis.
CDC—Centers for Disease Control and Prevention (USA) (formerly Centers for Disease Control).
Chin. P.—Chinese Pharmacopoeia 2005.
CHM—Commission on Human Medicines (UK).
CI—Colour Index.
CMV—cytomegalovirus.
CNS—central nervous system.
cP—centipoise(s).
CPMP—Committee on Proprietary Medicinal Products of the European Union.
cs—Czech.
CSF—cerebrospinal fluid.
CSM—Committee on Safety of Medicines (UK) (now subsumed within the Commission on Human Medicines).
cSt—centistokes.
Cz.—Czech Republic.
D & C—designation applied in USA to dyes permitted for use in drugs and cosmetics.
de—German.
d.c.—direct current.
DEFRA—Department for Environment, Food, and Rural Affairs (UK).
Denm.—Denmark.
DHSS—the former Department of Health and Social Security (UK).
dL—decilitre(s).
DNA—deoxyribonucleic acid.
DoH—Department of Health (UK).
DTF—Drug Tariff Formulary.
ECG—electrocardiogram.
ECT—electroconvulsive therapy.
Ecuad.—Ecuador.
ed.—editor(s) *or* edited by *or* edition.
EEC—European Economic Community, now the European Union.
EEG—electro-encephalogram.
e.g.—*exempli gratia* 'for example'.
el—Greek.
EMA/EMEA—European Medicines Agency.
ENL—erythema nodosum leprosum.
es—Spanish.
ESRD—end-stage renal disease.
et al.—*et alii*, 'and others': for three or more co-authors or co-workers.
et seq.—and what follows.
EU—European Union.
Eur. P.—see Ph. Eur.
Ext. D & C—designation applied in USA to dyes permitted for use in external drug and cosmetic preparations.
°F—degrees Fahrenheit.
FAC—Food Additives and Contaminants Committee of the former Ministry of Agriculture, Fisheries and Food (UK).
FAO—Food and Agriculture Organization of the United Nations.
FAO/WHO—Food and Agriculture Organization of the United Nations *and the* World Health Organization.
FDA—Food and Drug Administration of USA.
FdAC—Food Advisory Committee of the former Ministry of Agriculture, Fisheries and Food (UK).
FD & C—designation applied in USA to dyes permitted for use in foods, drugs, and cosmetics.
FEV_1—forced expiratory volume in 1 second.
Fin.—Finland.
FIP—Fédération Internationale Pharmaceutique.
f.p.—freezing point.
FPA—Family Planning Association (UK).
fr—French.
Fr.—France.
Fr. P.—French Pharmacopoeia 1982 (Pharmacopée Francaise, X^e Edition) and updates up to 2003.
g—gram(s).
Ger.—Germany.
Ger. P.— German Pharmacopoeia (Deutsches Arzneibuch, 2007).
GFR—glomerular filtration rate.
G6PD—glucose-6-phosphate dehydrogenase.
Gr.—Greece.
HAART—highly active antiretroviral therapy.

Hb—haemoglobin.
Hib—*Haemophilus influenzae* type b.
HIV—human immunodeficiency virus.
HLA—human lymphocyte antigens.
HLB—hydrophilic-lipophilic balance.
HRT—hormone replacement therapy.
HSE—Health and Safety Executive (UK).
hu—Hungarian.
Hung.—Hungary.
IARC—International Agency for Research on Cancer.
ibid.—*ibidem*, 'in the same place (journal or book)'.
idem—'the same': used for the same authors and titles.
i.e.—*id est*, 'that is'.
Ig—immunoglobulin.
Indon.—Indonesia.
INN—International Nonproprietary Name.
INNM—International Nonproprietary Name Modified.
Int. P.—International Pharmacopoeia 4th ed., 2006, and Supplement 1, 2008.
IPCS—International Programme on Chemical Safety.
IQ—intelligence quotient.
Irl.—Ireland.
ISH—International Society of Hypertension.
it—Italian.
It. P.—Italian Pharmacopoeia 11th ed., 2002 (Farmacopea Ufficiale della Repubblica Italiana, XI Edizione, 2002).
Ital.—Italy.
IUD—intra-uterine device.
IUPAC—International Union of Pure and Applied Chemistry.
IVF—*in-vitro* fertilisation.
J—joule(s).
Jpn—Japan.
Jpn P.—The Pharmacopoeia of Japan, 15th ed., 2006 and Supplement 1.
K—kelvin.
kcal—kilocalorie(s).
kg—kilogram(s).
kJ—kilojoule(s).
lb—pound(s) avoirdupois.
LD50—a dose lethal to 50% of the specified animals or micro-organisms.
Lf—limes flocculation.
lt—Lithuanian.
m—metre(s).
m^2—square metre(s).
m^3—cubic metre(s).
M—molar.
MAFF—the former Ministry of Agriculture, Fisheries and Food (UK), now Department of Environment, Food, and Rural Affairs (DEFRA).
MAOI—monoamine oxidase inhibitor.
max.—maximum.
MBC—minimum bactericidal concentration.
MCA—Medicines Control Agency, now MHRA (UK).
mEq—milliequivalent(s).
Mex.—Mexico.
mg—milligram(s).
MHRA—Medicines and Healthcare products Regulatory Agency (UK).
MIC—minimum inhibitory concentration.
min—minute.
min.—minimum.
MJ—megajoule(s).
mL—millilitre(s).
mm—millimetre(s).
mm^2—square millimetre(s).
mm^3—cubic millimetre(s).
mmHg—millimetre(s) of mercury.
mmol—millimole.
mol—mole.
mol. wt—molecular weight.
Mon.—Monaco.
mosmol—milliosmole.
m.p.—melting point.
MRC—Medical Research Council (UK).
MRSA—meticillin-resistant *Staphylococcus aureus*.
µg—microgram(s).
µm—micrometre(s).
N—normal.
n.b.—*nota bene*, note carefully.
Neth.—The Netherlands.
NICE—National Institute for Health and Clinical Excellence (formerly the National Institute for Clinical Excellence) (UK).
NIH—National Institutes of Health (USA).
nl—Dutch.
nm—nanometre(s).
NMDA—*N*-methyl-D-aspartate.
NNRTI—non-nucleoside reverse transcriptase inhibitor.
Norw.—Norway.
NRTI—nucleoside reverse transcriptase inhibitor.
NSAID—nonsteroidal anti-inflammatory drug.
NYHA—New York Heart Association.
NZ—New Zealand.
OP—over proof.
o/w—oil-in-water.
P—probability.
Pa—pascal(s).
Pak.—Pakistan.
pCO_2—plasma partial pressure (concentration) of carbon dioxide.
p_aCO_2—arterial plasma partial pressure (concentration) of carbon dioxide.
PEN—Pharmacy Equivalent Name, see page vi.
pg—picogram(s).
pH—the negative logarithm of the hydrogen ion concentration.
Ph. Eur.—European Pharmacopoeia, 8th ed., 2014.
Pharm. Soc. Lab. Rep.—Royal Pharmaceutical Society's Laboratory Report.
Philipp.—Philippines.
PHLS—Public Health Laboratory Service (UK).
pINN—Proposed International Nonproprietary Name.
pINNM—Proposed International Nonproprietary Name Modified.
pK_a—the negative logarithm of the dissociation constant.
pl—Polish.
p.m.—*post meridiem*, 'afternoon'.
pO_2—plasma partial pressure (concentration) of oxygen.
p_aO_2—arterial plasma partial pressure (concentration) of oxygen.
Pol.—Poland.
Pol. P.—Polish Pharmacopoeia 6th ed., 2002 (Farmakopea Polska VI, 2002) and Supplement 2005.
Port.—Portugal.
ppm—parts per million.
PSGB—The Pharmaceutical Society of Great Britain. Now the Royal Pharmaceutical Society.

pt—Portuguese.
PUVA—psoralen with UVA light irradiation.
PVC—polyvinyl chloride.
RCGP—Royal College of General Practitioners (UK).
RIMA—reversible inhibitor of monoamine oxidase type A.
rINN—Recommended International Nonproprietary Name.
rINNM—Recommended International Nonproprietary Name Modified.
RNA—ribonucleic acid.
RPSGB—The Royal Pharmaceutical Society of Great Britain. Now the Royal Pharmaceutical Society
RSV—respiratory syncytial virus.
Rus.—Russia.
S. Afr.—South Africa.
SGOT—serum glutamic oxaloacetic transaminase (serum aspartate aminotransferase *now preferred*).
SGPT—serum glutamic pyruvic transaminase (serum alanine aminotransferase *now preferred*).
SI—Statutory Instrument *or* Système International d'Unités (International System of Units).
sic—written exactly as it appears in the original.
SLE—systemic lupus erythematosus.
sp.—species (plural spp.).
sp. gr.—specific gravity.
Span.—Spanish.
Span. P.—Spanish Pharmacopoeia 2nd ed., 2002 (Real Farmacopoea Española, Segunda Edición, 2002) and Supplement 2.1.
SSRI—selective serotonin reuptake inhibitor.
St—stokes.
subsp.—subspecies.
suppl—supplement(s).
sv—Swedish.
Swed.—Sweden.
Swiss P.—Swiss Pharmacopoeia 2006 (Pharmacopoea Helvetica, 10 Ausgabe, Deutsche Ausgabe).
Switz.—Switzerland.
Thai.—Thailand.
TNF—tumour necrosis factor.
THM—traditional herbal medicine.
THMP—traditional herbal medicinal product.
TPN—total parenteral nutrition.
Turk.—Turkey.
UAE—United Arab Emirates.
UK—United Kingdom.
Ukr.—Ukraine.
UNICEF—United Nations Children's Fund.
UP—under proof.
Urug.—Uruguay.
US and ***USA***—United States of America.
USAN—United States Adopted Name.
USNF—The United States 'National Formulary 31', 2013.
USP—The United States Pharmacopeia 36, 2013.
UV—ultraviolet.
var.—variety.
Venez.—Venezuela.
Viet.—Vietnamese.
Viet. P.—Vietnamese Pharmacopoeia 2002 (Pharmacopoeia Vietnamica, Editio III).
vol.—volume(s).
v/v—volume in volume.
v/w—volume in weight.
WHO—World Health Organization.
w/o—water-in-oil.
wt—weight.
wt per mL—weight per millilitre.
w/v—weight in volume.
w/w—weight in weight.

Contracted Names for Ions and Groups

Contracted Name	Chemical Name
acefurate	acetate (ester) and furan-2-carboxylate (ester)
aceglumate	*rac*-hydrogen *N*-acetylglutmate
aceponate	acetate (ester) and propionate (ester)
acetonide	isopropylidenedioxy or propane-2,2-diylbis(oxy)
aceturate	*N*-acetylglycinate
acibutate	acetate (ester) and 2-methylpropanoate (ester)
acistrate	acetate (ester) and stearate (salt)
acoxil	acetoxymethyl or (acetyloxy)methyl
alfoscerate	(2*R*)-2,3-dihydroxypropyl hydrogen phosphate
alideximer	poly([oxy(2-hydroxyethane-1,1-diyl)]{oxy{1-(hydroxymethyl)ethane-1,2-diyl}}) partly *O*-etherified with carboxymethyl groups with some carboxy groups amide linked to the tetrapeptide residue (glyglyglycyl-L-phenylalanylglycyl)
amsonate	4,4′-diaminostilbene-2,2′-disulfonate or 2,2′-ethene-1,2-diylbis(5-aminobenzene-1-sulfonate)
anisatil	2-(4-methoxyphenyl)-2-oxoethyl or *p*-methoxyphenacyl
arbamel	2-(dimethylamino)-2-oxoethyl or ester with *N*,*N*-dimethylglycolamide
argine	30^{B}α-L-argine-30^{B}β-L-argine
aritox	ricin A chain-MAB immunotoxine
aspart	28^{B}-L-aspartic acid-
axetil	(*RS*)-1-acetoxyethyl or *rac*-1-(acetyloxy)ethyl
beloxil	benzyloxy
benetonide	*N*-benzoyl-2-methyl-β-alanine (ester) and acetonide
besilate (besylate)	benzenesulfonate
betadex	β-cyclodextrin
bezomil	(benzoyloxy)methyl
buciclate	*trans*-4-butylcyclohexanecarboxylate
bunapsilate	3,7-di-*tert*-butylnaphthalene-1,5-disulfonate
buteprate	butyrate (ester) and propionate (ester)
camsilate (camsylate)	camphor-10-sulfonate or (7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methanesulfonate
caproate	hexanoate
carbesilate	4-sulfobenzoate
ciclotate (cyclotate)	4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylate
cilexetil	(*RS*)-1-{[(cyclohexyloxy)carbonyl]oxy}ethyl or *rac*-1-{[(cyclohexyloxy)carbonyl]oxy}ethyl
cipionate (cypionate)	cyclopentanepropionate or 3-cyclopentylpropanoate
cituxetan	*rac*-*N*-(4-{2-[bis(carboxymethyl)amino]-3-({2-[bis(carboxymethyl)amino]ethyl}(carboxymethyl)amino)propyl}phenyl)thiocarbamoyl
clofibrol	2-(4-chlorophenoxy)-2-methylpropyl
closilate (closylate)	4-chlorobenzene-1-sulfonate
crobefate	*rac*-{3-[(3*E*)-4-methoxybenzylidene]-2-(4-methoxyphenyl)chroman-6-yl phosphate(2-)}
cromacate	2-[(6-hydroxy-4-methyl-2-oxo-2*H*-chromen-7-yl)oxy]acetate
cromesilate	6,7-dihydroxycoumarin-4-methanesulfonate or (6,7-dihydroxy-2-oxo-2*H*-chromen-4-yl)methanesulfonate

Contracted Name	Chemical Name
crosfumaril	(2*E*)-but-2-enedioyl
cyclamate	cyclohexylsulfamate
daloxate	L-alaninate (ester) and (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl
daropate (dapropate)	*N*,*N*-dimethyl-β-alaninate or 3-(dimethylamino)propanoate
deanil	2-(dimethylamino)ethyl
decil	decyl
defalan	des-1^{B}-L-phenylalanine-insulin
detemir	tetradecanoyl
dibudinate	2,6-di-*tert*-butylnaphthalene-1,5-disulfonate
dibunate	2,6-di-*tert*-butylnaphthalene-1-sulfonate
dicibate	dicyclohexylmethyl carbonate
diftitox	*N*-L-methionyl-387-L-histidine-388-L-alanine-1-388-toxin (*Corynebacterium diphtheriae* strain C7) (388→2′)-protein
digolil	2-(2-hydroxyethoxy)ethyl
diolamine	2,2′-azanediyldiethanol or diethanolamine
docosil	docosyl
dofosfate	octadecyl hydrogen phosphate
ecamate	*N*-ethylcarbamate
edamine	ethane-1,2-diamine or ethylenediamine
edetate	ethylenediamine-*NNN′N′*-tetra-acetate
edisilate (edisylate)	ethane-1,2-disulfonate
embonate	4,4′-methylenebis(3-hydroxynaphthalene-2-carboxylate) or 4,4′-methylenebis(3-hydroxy-2-naphthoate) (=pamoate)
emtansine	4-({3-[(3-{[(1*S*)-2-{[(1*S*,2*R*,3*S*,5*S*,6*S*,16*E*,18*E*,-20*R*,21*S*)-11-chloro-21-hydroxy-12,20-dimethoxy-2,5,9,16-tetramethyl-8,23-dioxo-4,24-dioxa-9,22-diazatetracyclo[19.3.1.$1^{10,14}$.$0^{3,5}$]hexacosa-10,12,14(26),16,18-pentaen-6-yl]oxy}-1-methyl-2-oxoethyl]methylamino}-3-oxopropyl)sulfanyl]-2,5-dioxopyrrolidin-1-yl}methyl)cyclohexylcarbonyle
enantate (enanthate)	heptanoate
enbutate	acetate (ester) and butanoate (ester)
epolamine	1-pyrrolidineethanol or 2-(pyrrolidin-1-yl)ethanol
erbumine	*tert*-butylamine or 2-methylpropan-2-amine
esilate (esylate)	ethanesulfonate
estolate	propanoate (ester) and dodecyl sulfate (salt) or propionate dodecyl sulfate
etabonate	(ethoxycarbonyl)oxy (=ethyl carbonate)
etilsulfate	ethyl sulfate
farnesil	(2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl
fendizoate	2-(6-hydroxybiphenyl-3-carbonyl)benzoate
fostedate	tetradecyl hydrogen phosphate
furetonide	1-benzofurane-2-carboxylate (ester) and propane-2,2-diylbis(oxy)
gamolenate	(6*Z*,9*Z*,12*Z*)-octadeca-6,9,12-trienoate
glargine	21^{A}-glycine-30^{B}α-L-arginine-30^{B}β-L-arginine
gluceptate	D-*glycero*-D-*gulo*-heptanoate or D-*glycero*-D-*gulo*-heptonate
glulisine	[3^{B}-L-lysine,29^{B}-L-glutamic acid]

Contracted Name	Chemical Name
glutamer	glutaraldehyde polymer
guacil	2-methoxyphenyl
hemisuccinate	hydrogen butanedioate
hexacetonide	3,3-dimethylbutanoate (ester) and propan-2,2-diylbis(oxy) or 3,3-dimethylbutyrate (ester) and acetonide
hibenzate (hybenzate)	2-(4-hydroxybenzoyl)benzoate
hyclate	monohydrochloride hemi-ethanolate hemihydrate
hydroxynaphtoate	3-hydroxynapthalene-2-carboxylate
isetionate (isethionate)	2-hydroxyethane-1-sulfonate
laurate	dodecanoate
lauril	dodecyl
laurilsulfate (lauryl sulphate)	dodecyl sulfate
lisetil	L-lysinate (ester) and diethyl (ester)
lisicoi	{*N*-[(5*S*)-5-carboxy-5-(3α,7α,12α-trihydroxy-5β-cholan-24-amido)pentyl]carbamothioyl}amino
lispro	28^{B}-L-lysine-29^{B}-L-proline
mafenatox	enterotoxin A (227-alanine) (*Staphylococcus aureus*)
medoxomil	(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl
megallate	3,4,5-trimethoxybenzoate
meglumine	*N*-methylglucamine
merpentan	4,5-bis(2-mercaptoacetamido) valeric acid or {*N*,*N*′-[1-(3-oxopropyl)ethane-1,2-diyl]bis(2-sulfanylacetamidato)}(4-)
mertansine	tetrakis{(4*RS*)-4[(3-{[(1*S*)-2-{[(1*S*,2*R*,3*S*,5*S*,6*S*,16*E*,18*E*,20*R*,21*S*)-11-chloro-21-hydroxy-12,20-dimethoxy-2,5,9,16-tetramethyl-8,23-dioxo-4,24-dioxa-9,22-diazatetracyclo[19.3.1.$1^{10,14}$.$0^{3,5}$]hexacosa-10,12,14(26),16,18-pentaen-6-yl]oxy}-1-methyl-oxoethyl]methylamino}-3-oxopropyl)disulfanyl]pentanoyl}
mesilate (mesylate)	methanesulfonate
metembonate	4,4′-methylenebis(3-methoxynaphthalene-2-carboxylate)
methonitrate	*N*-methyl, nitrate (salt)
metilsulfate	methyl sulfate
metiodide	*N*-methyl, iodide (salt)
methylbromide	*N*-methyl, bromide (salt)
mofetil	2-(morpholino)ethyl or 2-(morpholin-4-yl)ethyl
napadisilate	naphthalene-1,5-disulfonate
napsilate (napsylate)	naphthalene-2-sulfonate
nicotinate	pyridine-3-carboxylate
octil	octyl
olamine	2-aminoethanol or ethanolamine
oleate	(9*Z*)-octadec-9-enoate
oxoglurate	hydrogen 2-oxopentanedioate
palmitate	hexadecanoate
pamoate	4,4′-methylenebis(3-hydroxy-2-naphthoate) (=embonate)
pegol	α-(2-carboxyethyl)-ω-methoxypoly(oxyethane-1,2-diyl)
pendetide	N^{6}-{*N*-[2-({2-[bis(carboxymethyl)amino]-ethyl}(carboxymethyl)amino)ethyl]-*N*-(carboxymethyl)glycyl}-N^{2}-(*N*-glycyl-L-tyrosyl)-L-lysine
pentexil	(*RS*)-1-[(2,2-dimethylpropanoyl)oxy]ethyl
phenpropionate	3-phenylpropionate
pivalate	2,2-dimethylpropanoate (ester) or trimethylacetate
pivoxetil	*rac*-1-[(2-methoxy-2-methylpropanoyl)oxy]ethyl or 1-(2-methoxy-2-methylpropionyloxy)ethyl
pivoxil	(2,2-dimethyl-1-oxopropoxy)methyl or [(2,2-dimethylpropanoyl)oxy]methyl or (pivaloyloxy)methyl
poliglurnex	[poly(L-glutamic acid)$_z$—(L-glutamate-γ-ester)—poly(L-glutamic acid)$_y$]$_n$
probutate	17-(1-oxobutoxy) (ester) and 21-(1-oxopropoxy) (ester) or propionate (ester) and butyrate (ester)
proxetil	1-[(isopropoxycarbonyl)oxy]ethyl or *rac*-1-{[(propan-2-yloxy)carbonyl]oxy}ethyl
raffimer	(2*S*,4*R*,6*R*,8*S*,11*S*,13*S*)-2,4,8,13-tetrakis(hydroxymethyl)-4,6,11-tris(ylomethyl)-3,5,7,10,12-pentaoxatetradecane-1,14-diyl
salicylate	2-hydroxybenzoate
sesquioleate	(9*Z*)-octadec-9-enoate(1.5)
soproxil	{[(propan-2-yloxy)carbonyl]oxy}methyl
steaglate	2-(octadecanoyloxy)acetate (ester)
stearate	octadecanoate
stinoprate	*N*-acetylcysteinate (salt) and propanoate (ester)
succinil	3-carboxypropanoyl
sudotox	248-L-histidine-249-L-methionine-250-L-alanine-251-L-glutamic acid-248-613-endotoxin A (*Pseudomonas aeruginosa* reduced)
suleptanate	monosodium 8-[methyl(2-sulfoethyl)amino]-8-oxooctanoate or monosodium 7-[methyl(2-sulfonatomethyl)carbamoyl]heptanoyl
sulfoxylate	sulfinomethyl, monosodium salt
tafenatox	enterotoxin A (*Staphylococcus aureus*)
tartrate	(2*R*,3*R*)-2,3-dihydroxybutanedioate
tebutate	*tert*-butylacetate or 3,3-dimethylbutyrate
tenoate	thiophene-2-carboxylate
teoclate	8-chloro-1,3-dimethyl-2,6-dioxo-3,6-dihydro-1*H*-purin-7-(2*H*)-ide or 8-chlorotheophyllinate
teprosilate	3-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purin-7-yl)propane-1-sulfonate
tidoxil	*rac*-2-(decyloxy)-3-(dodecylsulfanyl)propyl
tiuxetan	*N*-(4-{(2*S*)-2-[bis(carboxymethyl)amino]-3-[(2*RS*)-{2-[bis(carboxymethyl)amino]propyl}(carboxymethyl)amino]propyl}phenyl)thiocarbamoyl
tocoferil	*rac*-(2*R*)-2,5,7,8-tetramethyl-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]chroman-6-yl
tofesilate	3-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purin-7-yl)ethane-1-sulfonate
tosilate (tosylate)	4-methylbenzene-1-sulfonate or toluene-4-sulfonate
triclofenate	2,4,5-trichlorophenolate
triflutate	trifluoroacetate
trioleate	(9*Z*)-octadec-9-enoate(3) or tris[(9*Z*)-octadec-9-enoate]
tristearate	octadecanoate(3) or tris(octadecanoate)
trolamine	2,2′,2″-nitrilotriethanol or triethanolamine
troxundate	[2-(2-ethoxyethoxy)ethoxy]acetate or 3,6,9-trioxaundecanoate
undecylate	undecanoate
undecylenate	undec-10-enoate
valerate	pentanoate
xinafoate	1-hydroxynaphthalene-2-carboxylate or 1-hydroxy-2-naphthoate

Atomic Weights of the Elements—$^{12}C=12$

Atomic Number	Name	Symbol	Atomic Weight
89	Actinium[1]	Ac	
13	Aluminium	Al	26.9815386
95	Americium[1]	Am	
51	Antimony	Sb	121.760
18	Argon	Ar	39.948
33	Arsenic	As	74.92160
85	Astatine[1]	At	
56	Barium	Ba	137.327
97	Berkelium[1]	Bk	
4	Beryllium	Be	9.012182
83	Bismuth[2]	Bi	208.98040
107	Bohrium[1]	Bh	
5	Boron[3]	B	10.81
35	Bromine[3]	Br	79.904
48	Cadmium	Cd	112.411
55	Caesium	Cs	132.9054519
20	Calcium	Ca	40.078
98	Californium[1]	Cf	
6	Carbon[3]	C	12.011
58	Cerium	Ce	140.116
17	Chlorine[3]	Cl	35.45
24	Chromium	Cr	51.9961
27	Cobalt	Co	58.933195
112	Copernicium[1]	Cn	
29	Copper	Cu	63.546
96	Curium[1]	Cm	
110	Darmstadtium[1]	Ds	
105	Dubnium[1]	Db	
66	Dysprosium	Dy	162.500
99	Einsteinium[1]	Es	
68	Erbium	Er	167.259
63	Europium	Eu	151.964
100	Fermium[1]	Fm	
114	Flerovium[1]	Fl	
9	Fluorine	F	18.9984032
87	Francium[1]	Fr	
64	Gadolinium	Gd	157.25
31	Gallium	Ga	69.723
32	Germanium	Ge	72.630
79	Gold	Au	196.966569
72	Hafnium	Hf	178.49
108	Hassium[1]	Hs	
2	Helium	He	4.002602
67	Holmium	Ho	164.93032
1	Hydrogen[3]	H	1.008
49	Indium	In	114.818
53	Iodine	I	126.90447
77	Iridium	Ir	192.217
26	Iron	Fe	55.845
36	Krypton	Kr	83.798
57	Lanthanum	La	138.90547
103	Lawrencium[1]	Lr	
82	Lead	Pb	207.2
3	Lithium[3]	Li	6.94
116	Livermorium[1]	Lv	
71	Lutetium	Lu	174.9668
12	Magnesium[3]	Mg	24.305
25	Manganese	Mn	54.938045
109	Meitnerium[1]	Mt	
101	Mendelevium[1]	Md	
80	Mercury	Hg	200.592
42	Molybdenum	Mo	95.96
60	Neodymium	Nd	144.242
10	Neon	Ne	20.1797
93	Neptunium[1]	Np	
28	Nickel	Ni	58.6934
41	Niobium	Nb	92.90638
7	Nitrogen[3]	N	14.007
102	Nobelium[1]	No	
76	Osmium	Os	190.23
8	Oxygen[3]	O	15.999
46	Palladium	Pd	106.42
15	Phosphorus	P	30.973762
78	Platinum	Pt	195.084
94	Plutonium[1]	Pu	
84	Polonium[1]	Po	
19	Potassium	K	39.0983
59	Praseodymium	Pr	140.90765
61	Promethium[1]	Pm	
91	Protactinium[2]	Pa	231.03588
88	Radium[1]	Ra	
86	Radon[1]	Rn	
75	Rhenium	Re	186.207
45	Rhodium	Rh	102.90550
111	Roentgenium[1]	Rg	
37	Rubidium	Rb	85.4678
44	Ruthenium	Ru	101.07
104	Rutherfordium[1]	Rf	
62	Samarium	Sm	150.36
21	Scandium	Sc	44.955912
106	Seaborgium[1]	Sg	
34	Selenium	Se	78.96
14	Silicon[3]	Si	28.085
47	Silver	Ag	107.8682
11	Sodium	Na	22.98976928
38	Strontium	Sr	87.62
16	Sulfur[3]	S	32.06
73	Tantalum	Ta	180.94788
43	Technetium[1]	Tc	
52	Tellurium	Te	127.60
65	Terbium	Tb	158.92535
81	Thallium[3]	Tl	204.38
90	Thorium[2]	Th	232.03806
69	Thulium	Tm	168.93421
50	Tin	Sn	118.710
22	Titanium	Ti	47.867
74	Tungsten	W	183.84
118	Ununoctium[1]	Uuo	
115	Ununpentium[1]	Uup	
117	Ununseptium[1]	Uus	
113	Ununtrium[1]	Uut	
92	Uranium[2]	U	238.02891
23	Vanadium	V	50.9415
54	Xenon	Xe	131.293
70	Ytterbium	Yb	173.054
39	Yttrium	Y	88.90585
30	Zinc	Zn	65.38
40	Zirconium	Zr	91.224

1. Elements with no stable isotopes. IUPAC states "There is no general agreement on which of the isotopes of radioactive elements is, or is likely to be judged, 'important'. Various criteria, such as 'longest half-life', 'production in quantity', and 'used commercially', have been applied in the past."

2. Radioactive elements with a characteristic terrestrial isotopic composition for which atomic weights are given.

3. Conventional atomic-weight value. These have been provided as representative values for elements that have a variation in atomic weight related to two or more stable isotopes in natural terrestrial occurrences.

IUPAC Commission on Isotopic Abundances and Atomic Weights. Atomic Weights of the Elements 2011. Available at http://www.chem.qmul.ac.uk/iupac/AtWt/

Volume A

Monographs on Drugs and Ancillary Substances

Analgesics Anti-inflammatory Drugs and Antipyretics

The drugs described in this chapter are used mainly in the relief of pain, inflammation and, in some cases, fever. They can be grouped broadly into one of the categories briefly described below.

Drug Groups

Aspirin and other salicylates

Aspirin and other salicylates have analgesic, anti-inflammatory, and antipyretic properties. Like other NSAIDs (see below) they are inhibitors of the enzyme cyclo-oxygenase; however, aspirin (though not the non-acetylated salicylates) irreversibly acetylates the enzyme whereas other NSAIDs compete with arachidonic acid for the active site. Salicylates are used for the relief of mild to moderate pain, minor febrile conditions, and for acute and chronic inflammatory disorders such as osteoarthritis, rheumatoid arthritis, juvenile idiopathic arthritis, and ankylosing spondylitis. Some salicylates are applied topically in rubefacient preparations for the relief of muscular and rheumatic pain. Aspirin also inhibits platelet aggregation and is used in cardiovascular disorders. Non-acetylated salicylates do not have antiplatelet activity.

For further discussion of the actions and uses of salicylates, see Aspirin, p. 22.2.

Described in this chapter are

Aloxiprin, p. 20.3
Aluminium Aspirin, p. 20.3
Ammonium Salicylate, p. 21.1
Amyl Salicylate, p. 21.2
Aspirin, p. 22.2
Bornyl Salicylate, p. 30.1
Carbasalate Calcium, p. 36.2
Choline Magnesium Trisalicylate, p. 39.2
Choline Salicylate, p. 39.2
Diethylamine Salicylate, p. 51.3
Diflunisal, p. 51.3
Ethenzamide, p. 56.2
Ethyl Salicylate, p. 56.3
Glycol Salicylate, p. 66.2
Imidazole Salicylate, p. 71.2
Lysine Aspirin, p. 84.3
Magnesium Salicylate, p. 85.2
Methyl Butetisalicylate, p. 91.3
Methyl Salicylate, p. 92.1
Morpholine Salicylate, p. 97.1
Salamidacetic Acid, p. 129.2
Salicylamide, p. 129.2
Salix, p. 129.2
Salol, p. 129.3
Salsalate, p. 130.1
Sodium Salicylate, p. 132.2
Thurfyl Salicylate, p. 137.1
Trolamine Salicylate, p. 141.2

Disease-modifying antirheumatic drugs

Disease-modifying antirheumatic drugs (DMARDs) have anti-inflammatory properties thought to be mediated, in some cases, by the inhibition of the release or activity of cytokines. They are used in the treatment of rheumatoid arthritis and juvenile idiopathic arthritis; some are also of benefit in ankylosing spondylitis and psoriatic arthritis. Many DMARDs also possess other therapeutic properties and are used in non-rheumatic conditions. The DMARD gold is referred to below; other DMARDs include sulfasalazine (p. 1893.1), penicillamine (p. 1567.1), the antimalarials chloroquine (p. 650.1) and hydroxychloroquine (p. 655.2), the monoclonal antibody rituximab (p. 852.1), and the immunosuppressants azathioprine (p. 1944.3), ciclosporin (p. 1949.2), cyclophosphamide (p. 771.1), and methotrexate (p. 822.2).

Described in this chapter are

Abatacept, p. 15.2
Actarit, p. 17.1
Adalimumab, p. 17.2
Anakinra, p. 21.2
Certolizumab, p. 39.1
Etanercept, p. 55.1
Golimumab, p. 66.3
Infliximab, p. 74.2
Leflunomide, p. 81.3
Tocilizumab, p. 77.3
Tofacitinib, p. 138.1

Gold compounds

Gold compounds are used mainly for their anti-inflammatory effect in active progressive rheumatoid arthritis and progressive juvenile idiopathic arthritis; they may also be beneficial in psoriatic arthritis. The mechanism of action of gold compounds in rheumatic disorders is as yet unknown.

For further discussion of the actions and uses of gold compounds, see Sodium Aurothiomalate, p. 130.2.

Described in this chapter are

Auranofin, p. 27.3
Aurothioglucose, p. 28.2
Aurotioprol, p. 28.2
Gold Keratinate, p. 66.3
Sodium Aurothiomalate, p. 130.2
Sodium Aurotiosulfate, p. 132.1

Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a group of structurally unrelated organic acids that have analgesic, anti-inflammatory, and antipyretic properties (see p. 102.3). NSAIDs are inhibitors of the enzyme cyclo-oxygenase, and so directly inhibit the biosynthesis of prostaglandins and thromboxanes from arachidonic acid (see p. 2598.1). There are 2 forms of cyclo-oxygenase (COX), COX-1, which is the constitutive form of the enzyme, and COX-2, which is the form induced in the presence of inflammation. Inhibition of COX-2 is therefore thought to be responsible for at least some of the analgesic, anti-inflammatory, and antipyretic properties of NSAIDs whereas inhibition of COX-1 is thought to produce some of their toxic effects, particularly those on the gastrointestinal tract. Most NSAIDs available for clinical use inhibit both COX-1 and COX-2, although some selective COX-2 inhibitors such as celecoxib are also marketed.

NSAIDs are used for the relief of mild to moderate pain, minor febrile conditions, and for acute and chronic inflammatory disorders such as osteoarthritis, rheumatoid arthritis, juvenile idiopathic arthritis, and ankylosing spondylitis. Indometacin and some other NSAIDs are used to close patent ductus arteriosus in premature neonates. Some NSAIDs are applied topically for the relief of muscular and rheumatic pain, and some are used in ophthalmic preparations for ocular inflammatory disorders. Aspirin (see above) is considered to be an NSAID, although it also has other properties.

Described in this chapter are

Aceclofenac, p. 16.2
Acemetacin, p. 16.3
Alminoprofen, p. 20.2
Aminophenazone, p. 21.1
Ampiroxicam, p. 21.1
Amtolmetin Guacil, p. 21.1
Azapropazone, p. 28.3
Bendazac, p. 29.1
Benzydamine, p. 29.2
Beta-aminopropionitrile, p. 30.1
Bromfenac, p. 30.1
Bufexamac, p. 30.2
Bumadizone, p. 30.2
Carprofen, p. 36.3
Celecoxib, p. 36.3
Clofexamide, p. 40.1
Clofezone, p. 40.1
Clonixin, p. 40.1
Dexibuprofen, p. 43.1
Dexketoprofen, p. 79.1
Diclofenac, p. 48.3
Dipyrone, p. 53.3
Eltenac, p. 54.2
Epirizole, p. 54.3
Etodolac, p. 57.1
Etofenamate, p. 57.2
Etoricoxib, p. 57.3
Felbinac, p. 58.3
Fenbufen, p. 59.1
Fenoprofen, p. 59.2
Fentiazac, p. 64.2
Fepradinol, p. 64.2
Feprazone, p. 64.3
Firocoxib, p. 64.3
Floctafenine, p. 64.3
Flufenamic Acid, p. 65.1
Flunixin, p. 65.1
Flurbiprofen, p. 65.2
Glucametacin, p. 66.2
Ibuprofen, p. 68.2
Indometacin, p. 71.2
Isonixin, p. 78.3
Kebuzone, p. 78.3
Ketoprofen, p. 79.1
Ketorolac, p. 80.2
Licofelone, p. 83.2
Lornoxicam, p. 83.2
Loxoprofen, p. 83.3
Lumiracoxib, p. 84.1
Meclofenamic acid, p. 85.2
Mefenamic Acid, p. 85.3
Meloxicam, p. 86.3
Mofezolac, p. 92.2
Morniflumate, p. 92.2
Nabumetone, p. 97.1
Naproxen, p. 98.2
Nepafenac, p. 101.1
Niflumic Acid, p. 101.2
Nimesulide, p. 101.3
Oxaprozin, p. 112.3
Oxyphenbutazone, p. 114.3
Parecoxib, p. 119.3
Phenazone, p. 124.1
Phenylbutazone, p. 125.1
Piketoprofen, p. 125.3
Piroxicam, p. 125.3
Pranoprofen, p. 127.1
Proglumetacin, p. 127.1
Propyphenazone, p. 127.3
Proquazone, p. 128.1
Rofecoxib, p. 128.3
Sulindac, p. 134.2
Suprofen, p. 135.3
Suxibuzone, p. 136.1
Tenoxicam, p. 136.2
Tepoxalin, p. 137.1
Tetridamine, p. 137.1
Tiaprofenic Acid, p. 137.1
Tiaramide, p. 137.3
Tinoridine, p. 138.1
Tolfenamic Acid, p. 138.3
Tolmetin, p. 139.1
Valdecoxib, p. 141.3
Vedaprofen, p. 142.1
Zaltoprofen, p. 142.2

Opioid analgesics

Opioid analgesics include the opium alkaloids morphine and codeine and their derivatives as well as synthetic substances with agonist, partial agonist, or mixed agonist and antagonist activity at opioid receptors (see p. 108.1). The term opiate analgesics refers only to those opioids derived from opium, or their semisynthetic congeners. The term narcotic analgesics has legal connotations and is no longer used pharmacologically or clinically.

Most opioids are used as analgesics, and morphine is the standard against which all other opioid analgesics are compared. Opioids such as codeine are used in the treatment of less severe pain, and are often combined with non-opioid analgesics such as aspirin, other NSAIDs, or paracetamol. More potent opioids such as morphine are used in severe acute and chronic pain, including cancer pain. Some opioids such as codeine, morphine, and diamorphine are also used as antitussives, although the latter two are usually reserved for use in terminal lung disease. Some opioid analgesics such as fentanyl and its congeners are used mainly as adjuncts to anaesthesia; some of these may also be used in higher doses as the sole anaesthetic drug.

Some opioids are rarely if ever used as analgesics and are described elsewhere; they include the antitussives dextromethorphan (p. 1660.1) and pholcodine (p. 1675.1), and the antidiarrhoeals diphenoxylate (p. 1838.3) and loperamide (p. 1857.2).

Opioids can produce physical dependence and withdrawal symptoms if suddenly stopped. They are also subject to abuse.

Described in this chapter are

Alfentanil, p. 18.2
Anileridine, p. 22.2
Buprenorphine, p. 30.2
Butorphanol, p. 33.2
Carfentanil, p. 36.2
Codeine, p. 40.2
Dextromoramide, p. 43.2
Dextropropoxyphene, p. 43.2
Dezocine, p. 45.2
Diamorphine, p. 46.1
Dihydrocodeine, p. 52.2
Dipipanone, p. 53.2
Embutramide, p. 54.2
Ethoheptazine, p. 56.2
Ethylmorphine, p. 56.3
Etorphine, p. 58.3
Fentanyl, p. 60.1
Hydrochlorides of Mixed Opium Alkaloids, p. 112.2
Hydrocodone, p. 67.2
Hydromorphone, p. 67.3
Ketobemidone, p. 78.3
Levacetylmethadol, p. 83.1
Levomethadone, p. 83.1
Levorphanol, p. 83.2
Meptazinol, p. 87.3
Methadone, p. 88.3
Morphine, p. 92.3
Nalbuphine, p. 97.3
Nicomorphine, p. 101.1

Paracetamol and other para-aminophenols

Paracetamol is the principal para-aminophenol derivative in use. Acetanilide and phenacetin have generally been replaced by safer analgesics. Propacetamol is hydrolysed to paracetamol in the plasma.

Paracetamol has analgesic and antipyretic properties and weak anti-inflammatory activity. The mechanism of analgesic action remains to be fully elucidated, but may be due to inhibition of prostaglandin synthesis both centrally and peripherally. Paracetamol is used for the relief of mild to moderate pain and minor febrile conditions.

Described in this chapter are

Analgesia and Pain

Pain is defined by the International Association for the Study of Pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.'

Under normal circumstances pain is the result of stimulation of peripheral receptors that transmit impulses through pain pathways to the brain. Pain receptors or nociceptors are of two basic types:

- *mechanoheat receptors* have a high stimulation threshold and respond to intense or potentially damaging noxious stimuli. These receptors are associated with rapidly conducting, thinly myelinated A δ fibres, and their stimulation produces rapid sharp localised pain that serves to activate withdrawal reflexes
- *polymodal nociceptors* respond to mechanical, thermal, or chemical insults. These receptors are also activated by cellular components that are released after tissue damage. Their impulses are transmitted slowly along unmyelinated C type fibres and produce dull, aching, and poorly localised pain with a slower onset

Nerve fibres from nociceptors terminate in the dorsal root of the spinal cord before transmission by ascending pathways to the brain. There have been many theories on the processing of pain signals at the spinal level but the 'gate theory' proposed by Melzack and Wall is one of the best known. This theory postulates that the transmission of impulses to the brain is modulated by a gate mechanism in the substantia gelatinosa. Stimulation of small fibres opens the gate and facilitates transmission whereas stimulation of large fibres, which normally carry non-painful sensory input, can close the gate and inhibit transmission. Transmission also appears to be modulated by several other mechanisms which can influence the sensitivity of the gate.

Inflammatory mediators such as bradykinin, histamine, serotonin, and prostaglandins produced in response to tissue damage can produce peripheral sensitisation so that receptors respond to low intensity or innocuous stimuli; central sensitisation also occurs. Pain associated with tissue damage hence results in increased sensitivity of the sensory system so that the pain can occur in the absence of a clear stimulus. Pain that occurs due to a stimulus that does not usually provoke pain is termed *allodynia*; this applies to conditions such as sunburn, inflammation, and trauma that may result in sensitisation of the skin. *Hyperalgesia* is defined as an increased response to a stimulus that is usually painful. *Hyperaesthesia* is an increased sensitivity to stimulation, excluding the special senses and includes allodynia and hyperalgesia. *Hyperpathia* is characterised by an abnormally painful reaction to a stimulus, particularly a repetitive stimulus, and may occur with allodynia, hyperalgesia, or hyperaesthesia.

Pain is often classified as being acute or chronic in nature.

- **Acute pain** is associated with trauma or disease and usually has a well-defined location, character, and timing. It is accompanied by symptoms of autonomic hyperactivity such as tachycardia, hypertension, sweating, and mydriasis.
- **Chronic pain** is usually regarded as pain lasting more than a few months. It may not be clearly associated with trauma or disease or may persist after the initial injury has healed; its localisation, character, and timing are more vague than with acute pain. Furthermore, as the autonomic nervous system adapts, the signs of autonomic hyperactivity associated with acute pain disappear. Some forms of pain regarded as being chronic may consist of intermittent attacks of pain followed by relatively long pain-free periods. Patients with chronic pain have physical, psychological, social, and functional deterioration which contributes towards exacerbation of the pain.

Physiologically, pain may be divided into nociceptive pain and neuropathic pain.

- **Nociceptive pain** follows activation of nociceptors by noxious stimuli as described above but is not associated with injury to peripheral nerves or the CNS. It may be somatic or visceral, depending on which receptors or nerves are involved. *Somatic pain* is usually well localised and may be described as deeply located, sharp or dull, nagging, stabbing, throbbing, or pressure-like. *Visceral pain* is generally less localised and more diffuse than somatic pain and may be referred to remote areas of the body. Depending on the structure involved it is variously described as deeply located, aching, nagging, cramping, or pressing and may be accompanied by nausea and vomiting. Nociceptive pain usually responds to treatment with conventional analgesics.
- Pain resulting from damage or dysfunction of peripheral nerves/receptors or of the CNS is known as **neuropathic pain** (or neurogenic pain). The term covers *sympathetically maintained pain* including causalgia and reflex sympathetic dystrophy, and painful conditions such as postherpetic and trigeminal neuralgia, and diabetic neuropathy. Neuropathic pain associated with central nervous tissue, such as in central post-stroke pain (the thalamic syndrome) is referred to as *central pain*. The clinical signs of neuropathic pain can vary greatly. Some of the more common features include heightened pain sensitivity and sensations of superficial burning or stabbing (lancinating) pain. The pain may be associated with areas of sensory deficit or some form of autonomic instability. Neuropathic pain responds poorly to conventional analgesics and can be difficult to treat.

Early **treatment** of pain is important as unrelieved pain can have profound psychological effects on the patient, and acute pain that is poorly managed initially can degenerate into chronic pain, which may prove to be much more difficult to treat. It is important to assess and treat the mental and emotional aspects of the pain as well as its physical aspects. Although drug therapy is a mainstay of pain treatment (see Choice of Analgesic, below), physical methods such as physiotherapy (including massage and the application of heat and cold), surgery, and nervous system stimulation techniques such as acupuncture, spinal cord stimulation, and transcutaneous electrical nerve stimulation (TENS) are also used.

General references to pain and its management.

1. Melzack R, Wall PD. Pain mechanisms: a new theory. *Science* 1965; **150**: 971–9.
2. International Association for the Study of Pain. Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms. *Pain* 1986; (suppl 3): S1–S225.
3. Lewis KS, *et al.* Effect of analgesic treatment on the physiological consequences of acute pain. *Am J Hosp Pharm* 1994; **51**: 1539–54.
4. Loeser JD, Melzack R. Pain: an overview. *Lancet* 1999; **353**: 1607–9.
5. Ashburn MA, Staats PS. Management of chronic pain. *Lancet* 1999; **353**: 1865–9.
6. Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. *Lancet* 1999; **353**: 1959–64.
7. Carr DB, Goudas LC. Acute pain. *Lancet* 1999; **353**: 2051–8.
8. Cervero F, Laird JM. Visceral pain. *Lancet* 1999; **353**: 2145–8.
9. American Society of Anesthesiologists Task Force on Acute Pain Management. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. *Anesthesiology* 2004; **100**: 1573–81. Also available at: http://www.asahq.org/publicationsAndServices/pain.pdf (accessed 23/06/08)
10. Gordon DB, *et al.* American Pain Society recommendations for improving the quality of acute and cancer pain management: American Pain Society Quality of Care Task Force. *Arch Intern Med* 2005; **165**: 1574–80. Also available at: http://archinte.ama-assn.org/cgi/reprint/165/14/1574 (accessed 23/06/08)
11. Spacek A. Modern concepts of acute and chronic pain management. *Biomed Pharmacother* 2006; **60**: 329–35.
12. Markman JD, Philip A. Interventional approaches to pain management. *Anesthesiol Clin* 2007; **25**: 883–898.
13. European Association of Urology. Guidelines on pain management (issued March 2007). Available at: http://www.uroweb.org/fileadmin/user_upload/Guidelines/21_Pain_Management_2007.pdf (accessed 23/06/08)
14. Brennan F, *et al.* Pain management: a fundamental human right. *Anesth Analg* 2007; **105**: 205–21.
15. Knape JT, *et al.* Board of Anaesthesiology of the European Union of Medical Specialists. Guidelines for sedation and/or analgesia by non-anaesthesiology doctors. *Eur J Anaesthesiol* 2007; **24**: 563–7.
16. Manchikanti L, *et al.* Evidence-based interventional pain management: principles, problems, potential and applications. *Pain Physician* 2007; **10**: 329–56.
17. Cawley D, Bennett MI. Management of pain. *Br J Hosp Med* 2009; **70**: 197–201.

Choice of analgesic

Paracetamol and **NSAIDs** are the first choice analgesics for treating mild to moderate pain and are also used in moderate to severe pain to potentiate the effects of opioids. They are suitable for use in acute or chronic pain. Effective relief of acute pain can be achieved with oral NSAIDs and with paracetamol (particularly in combination with an opioid—see below). Dependence and tolerance are not a problem with non-opioid analgesics but they have a rather flat dose-response curve: as the dose is increased, the increase in pain relief may be quite small. Aspirin and other non-selective NSAIDs inhibit blood platelet function, adversely affect the gastrointestinal tract, and can precipitate hypersensitivity reactions including asthma. The risk of severe upper gastrointestinal adverse effects may be less with selective inhibitors of cyclo-oxygenase-2 (COX-2) such as the coxibs, but their use has been greatly restricted by concerns about serious cardiovascular effects. Paracetamol does not have the haematological or gastrointestinal adverse effects of aspirin but large doses can produce severe or sometimes fatal hepatotoxicity. Giving paracetamol with an NSAID improves analgesia.

For the treatment of moderate or moderate to severe opioid-sensitive pain **codeine** is the traditional choice; alternatives include **dihydrocodeine** and **tramadol**. The are often given with non-opioid analgesics. Combinations of codeine with paracetamol at full doses produce a small but significant increase in analgesia compared with paracetamol alone and are one of the most effective options for acute pain, but the incidence of adverse effects increases with repeated use. Combinations of **dextropropoxyphene** with paracetamol or aspirin are no more effective in acute pain than the non-opioid alone; efficacy in chronic pain is unclear and adverse effects may become troublesome. The EMEA and the FDA have recommended that all dextropropoxyphene-containing preparations be no longer available in the EU and USA, respectively, because of the risk of toxicity in overdosage and of cardiotoxicity; such preparations remain on the market in other countries.

More potent opioids such as **morphine** are mainly used in the treatment of severe acute non-malignant pain and cancer pain (see p. 7.1). Their use in chronic non-malignant pain is somewhat controversial because of fears of psychological dependence and respiratory depression. However, in practice such problems rarely occur and those fears should not prevent patients being given effective analgesic therapy. Opioids may also be of value in neuropathic pain in some patients.

Morphine is the opioid of choice in severe pain. It is absorbed when given orally and has a short half-life so that the use of immediate-release oral preparations offers a flexible means of dosage titration in, for example, palliative care. Once initial pain relief has been achieved, use of a modified-release preparation every 12 or 24 hours is more convenient for maintenance of analgesia in severe chronic pain. It may also be given parenterally (e.g. for control of acute severe pain in emergency departments or in patient-controlled analgesia—see also p. 5.3), or rectally or transdermally, where there would be problems with the oral route.

Occasionally **other opioids** may be useful. Switching to an alternative opioid may be effective in patients who have inadequate pain control or intolerable adverse effects with morphine. Methadone (which also acts as an NMDA antagonist) or oxycodone have a longer duration of action than morphine, but it should be noted that methadone, which has a long half-life, should not be given more than twice daily when used long term because of the risk of progressive CNS depression and overdosage. A rapid onset of action is provided by alfentanil and fentanyl but use of pethidine is no longer recommended. Diamorphine or hydromorphone may be preferred to morphine when the parenteral route has to be used because they are more soluble and can be given in a smaller volume. Tramadol, which may impair respiratory and gastrointestinal function less than other opioids at equianalgesic doses, is also of benefit in neuropathic pain.

Adverse effects of opioids include sedation, nausea, vomiting, constipation, and, most seriously, respiratory depression. Tolerance generally develops to all of these effects except constipation, which may be prevented by regular use of laxatives.

Some other groups of drugs have significant roles in pain management either alone or as **analgesic adjuvants**.

Subantidepressant doses of tricyclic **antidepressants** (usually amitriptyline) are considered to be useful in refractory chronic pain, including neuropathic pain of the burning, dysaesthetic type such as postherpetic neuralgia and diabetic neuropathy; shooting pain has also been reported to respond. They may be used in addition to conventional analgesics, notably in the treatment of cancer pain of mixed aetiology. There is little evidence for benefit in acute pain although musculoskeletal pain has sometimes responded. Amitriptyline has also been found to be useful for tension-type headache and for the prophylaxis of migraine. The role of other antidepressants in the treatment of neuropathic pain is less clear although venlafaxine may be useful.

Antiepileptics (often carbamazepine and, more recently, gabapentin and pregabalin) have been found useful in the relief of neuropathic pain, especially when there is a stabbing (lancinating) element, as in trigeminal neuralgia; there have also been reports of efficacy in the treatment of diabetic neuropathy and for migraine prophylaxis.

Benzodiazepines and **other muscle relaxants** such as baclofen or dantrolene are useful for relieving painful muscle spasm in acute or chronic conditions.

Bone modulating drugs such as calcitonin and bisphosphonates may be useful in cancer pain arising from bone metastases (see p. 7.1) but have a slow onset of action and are second choice to NSAIDs. Bisphosphonates may cause an initial transient increase in bone pain.

Caffeine has been used with the aim of enhancing the effects of non-opioid and opioid analgesics but is of debatable benefit. There are similar doubts about whether caffeine enhances the effect of ergotamine in the treatment of migraine (see Pharmacokinetics, p. 675.3); it may also add to gastrointestinal adverse effects and in large doses can itself cause headache.

Corticosteroids have produced improvement, often substantial, in neuropathic pain. They can also relieve headache caused by raised intracranial pressure and refractory pain caused by bone metastases, and have the added benefits of increasing well-being and appetite.

Some **inhalational anaesthetics** are used in subanaesthetic doses as inhalation analgesics for acute pain. In particular, nitrous oxide is given with oxygen for pain relief in obstetrics and during dental and other procedures, and in emergency management. Isoflurane, enflurane, and in some countries methoxyflurane or trichloroethylene have been used similarly.

Miscellaneous drugs. After the discovery that epidural or intrathecal injection of opioids can produce effective analgesia many other drugs have been tried by these routes, either alone or with opioids or local anaesthetics, but their role, if any, in the management of pain is unclear. Some, such as clonidine and ketamine, also appear to have analgesic properties when given by other routes, and ketamine may be useful in reducing opioid requirements. Some antiarrhythmics (including systemic lidocaine) may be effective in chronic neuropathic pain, but must be used with extreme caution. The use of antipsychotics, such as the phenothiazines, as adjuvant analgesics is controversial; levomepromazine is sometimes used as an adjunct in palliative care.

See below for discussions of the use of patient-controlled analgesia (below), and rubefacients and topical analgesics (p. 6.3). Nerve blocks are discussed under Pain, on p. 1981.1.

References.

1. Sawynok J. Pharmacological rationale for the clinical use of caffeine. *Drugs* 1995; 49: 37–50.
2. Watson CP. The treatment of neuropathic pain: antidepressants and opioids. *Clin J Pain* 2000; 16 (suppl): S49–S55.
3. Curatolo M, Sveticic G. Drug combinations in pain treatment: a review of the published evidence and a method for finding the optimal combination. *Best Pract Res Clin Anaesthesiol* 2002; 16: 507–19.
4. McQuay HJ. Neuropathic pain: evidence matters. *Eur J Pain* 2002; 6 (suppl A): 11–18.
5. Anonymous. Acute pain (Bandolier Extra, issued February 2003). Available at: http://www.jr2.ox.ac.uk/bandolier/Extraforbando/APain.pdf (accessed 23/06/08)
6. Ballantyne JC, Mao J. Opioid therapy for chronic pain. *N Engl J Med* 2003; 349: 1943–53.
7. Backonja M. Anticonvulsants for the treatment of neuropathic pain syndromes. *Curr Pain Headache Rep* 2003; 7: 39–42.
8. McQuay H. Pain and its control (issued 1st January, 2004). Available at: http://www.medicine.ox.ac.uk/bandolier/booth/painpag/wisdom/C13.html (accessed 26/11/09)
9. The College of Emergency Medicine. Clinical Effectiveness Committee guideline for the management of pain in adults (2004). Available at: http://www.collemergencymed.ac.uk/asp/document.asp?ID=4193 (accessed 26/11/09)
10. Attal N, *et al.* Systemic lidocaine in pain due to peripheral nerve injury and predictors of response. *Neurology* 2004; 62: 218–25.
11. Quigley C. Opioid switching to improve pain relief and drug tolerability. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 23/06/08).
12. Rathmell JP, *et al.* The role of intrathecal drugs in the treatment of acute pain. *Anesth Analg* 2005; 101 (suppl): S30–S43.
13. Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine. Acute pain management: scientific evidence, 2nd ed, 2005. Available at: http://www.anzca.edu.au/resources/books-and-publications/acutepain.pdf (accessed 23/06/08)
14. Eisenberg E, *et al.* Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin: systematic review and meta-analysis of randomized controlled trials. *JAMA* 2005; 293: 3043–52.
15. Davis MP, *et al.* Controversies in pharmacotherapy of pain management. *Lancet Oncol* 2005; 6: 696–704.
16. Nicholas MK, *et al.* Using opioids with persisting noncancer pain: a biopsychosocial perspective. *Clin J Pain* 2006; 22: 137–46.
17. McQuay HJ, Moore RA. Dose-response in direct comparisons of different doses of aspirin, ibuprofen and paracetamol (acetaminophen) in analgesic studies. *Br J Clin Pharmacol* 2007; 63: 271–8.
18. Knotkova H, Pappagallo M. Adjuvant analgesics. *Anesthesiol Clin* 2007; 25: 775–86.
19. Tamchès E, *et al.* Acute pain in adults admitted to the emergency room: development and implementation of abbreviated guidelines. *Swiss Med Wkly* 2007; 137: 223–7.
20. Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine. Acute pain management: scientific evidence. Update to 2nd ed, December 2007. Available at: http://www.anzca.edu.au/resources/books-and-publications/acutepain_update.pdf (accessed 23/06/08)
21. Guindon J, *et al.* Recent advances in the pharmacological management of pain. *Drugs* 2007; 67: 2121–33.
22. Ghaloor VL, *et al.* Intrathecal drug therapy for long-term pain management. *Am J Health-Syst Pharm* 2007; 64: 2447–61.
23. Seidel S, *et al.* Antipsychotics for acute and chronic pain in adults. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 26/11/09).
24. Verdu B, *et al.* Antidepressants for the treatment of chronic pain. *Drugs* 2008; 68: 2611–32.
25. British Pain Society. Intrathecal drug delivery for the management of pain and spasticity in adults: recommendations for best clinical practice (issued August 2008). Available at: http://www.britishpainsociety.org/book_ittd_main.pdf (accessed 26/11/09)
26. Barber JB, Gibson SJ. Treatment of chronic non-malignant pain in the elderly: safety considerations. *Drug Safety* 2009; 32: 457–74.
27. British Pain Society. Opioids for persistent pain: good practice (issued January 2010). Available at: http://www.britishpainsociety.org/book_opioid_main.pdf (accessed 15/04/10)

Choice of analgesics in children

Pain has often been undertreated in infants and children because of fears of respiratory depression, cardiovascular collapse, depressed levels of consciousness, and addiction with potent opioid analgesics. Assessment of pain is also a problem in children of all ages[1-3] and it is not that long since it was widely believed that neonates were incapable of feeling pain.

Non-opioid analgesics are used in *infants and children*, either alone for minor pain or as an adjunct to opioid analgesics in severe pain,[4-6] (they can reduce opioid requirements,[1,7] perhaps by up to 40%[4]). Paracetamol is frequently used but it lacks any anti-inflammatory effect. NSAIDs such as ibuprofen are useful for minor pain,[4,6,8] especially when associated with inflammation or trauma. The use of aspirin is greatly restricted by its association with Reye's syndrome.

The **opioids** are still the mainstay of analgesia for moderate to severe pain in paediatric patients, and morphine is the standard against which the others are compared. It is given intravenously for rapid relief of severe pain (for example after burns, fractures or other injuries), and is titrated to achieve a suitable analgesic dose.[4-6,8,9] Where intravenous access is not readily achievable, oral morphine may be given but its onset is slower and less predictable; some favour intranasal diamorphine as an alternative to intravenous morphine.[6] Continuous intravenous morphine infusion with or without initial loading doses has become popular for postoperative pain relief,[7,9] but titration of the infusion rate is necessary to achieve a balance between analgesia and respiratory depression (particular care is needed in neonates, see below). Subcutaneous infusions of morphine have also been used,[4] mostly for the relief of terminal cancer pain in children. Intramuscular injections are painful[8-11] and therefore probably only suitable for short-term use. Fentanyl has also been widely used for short-term analgesia in surgical procedures,[7-9,11,12] and other opioids such as buprenorphine, hydromorphone, oxycodone, and tramadol have been given.[4] The use of codeine in children is restricted by its significantly increased risk of serious and life-threatening adverse effects in ultrarapid metabolisers.

Patient-controlled analgesia using morphine (see below) has been tried in children. Morphine has also been given to children by the epidural route;[9] experience with the intrathecal route is more limited. Other methods of opioid drug delivery of possible value in paediatric analgesia include transmucosal,[7,12] nasal,[6,8] and transdermal[7,10] dosage.

Cancer pain in children may be treated using the analgesic ladder scheme described under Cancer Pain (see p. 7.1).

Inhaled **nitrous oxide** and oxygen mixtures may be useful for preliminary pain relief and short, painful procedures.[6,8,9,11]

Local anaesthetics are especially suitable for the management of acute pain in day-care situations. Single injections given by the epidural route are often used to provide analgesia during and after surgery. Continuous epidural infusions of local anaesthetics have also been used. However, simpler techniques such as wound infiltration or peripheral nerve blocks can also provide effective analgesia for some procedures and are free of the problems of lower limb weakness or urinary retention associated with caudal blocks.[4,8,9,11] Application of eutectic creams (see Surface Anaesthesia, p. 1993.3) containing lidocaine with prilocaine to intact skin, to produce surface anaesthesia, may be sufficient for some minor painful procedures in children.[5,7,10,12]

Ketamine is used in outpatients for brief, painful procedures such as fracture reduction and to provide immobility for repair of facial lacerations in young children.[5,12,13] The emergence reactions that limit its use in adults are less common in children,[12] and can be ameliorated by benzodiazepines.[8,11]

Most *neonates* requiring analgesia and receiving respiratory support can be managed with an infusion of morphine but in neonates who are breathing spontaneously there is a substantial risk of respiratory depression. Morphine has been used in such neonates[9] but should be limited to those under intensive care, as for example after major surgery (see also Intensive Care, p. 1033.1). Fentanyl citrate[1] has also been used in neonates. **Sucrose** and other sweet tasting solutions have been shown to reduce physiologic and behavioural indicators of stress and pain in neonates undergoing painful procedures[10] although there had been some doubt expressed over whether this indicates effective analgesia.[14] The American Academy of Pediatrics has suggested that oral sucrose together with other non-pharmacological methods such as swaddling should be used for minor routine procedures; topical local anaesthetics may be used for more painful procedures such as venepuncture if time permits. Opioids should be the basis of postoperative analgesia after major surgery in the absence of regional anaesthesia; a rapidly acting opioid such as fentanyl is advocated, together with infiltration of the site with a local anaesthetic where time permits, for insertion of a chest drain.[15] Similar recommendations for painful procedures in neonates have been made by an international consensus group.[16]

The use of **analgesic adjuvants** (see Choice of Analgesic, p. 4.2) has also been advocated in some children.[17]

1. American Academy of Pediatrics and Canadian Paediatric Society. Prevention and management of pain and stress in the neonate. *Pediatrics* 2000; 105: 454–61. Also available at: http://aappolicy.aappublications.org/cgi/reprint/pediatrics;105/2/454.pdf (accessed 23/06/08)
2. American Academy of Pediatrics Committee on Psychosocial Aspects of Child and Family Health, American Pain Society Task Force on Pain in Infants, Children, and Adolescents. The assessment and management of acute pain in infants, children, and adolescents. *Pediatrics* 2001; 108: 793–7. Also available at: http://pediatrics.aappublications.org/cgi/reprint/108/3/793.pdf (accessed 23/06/08)
3. Maurice SC, *et al.* Emergency analgesia in the paediatric population (part I): current practice and perspectives. *Emerg Med J* 2002; 19: 4–7.
4. Morton NS. Management of postoperative pain in children. *Arch Dis Child Educ Pract Ed* 2007; 92: ep14–ep19.
5. Atkinson P, *et al.* Pain management and sedation for children in the emergency department. *BMJ* 2009; 339: 1074–9.
6. The College of Emergency Medicine. Best practice guideline: management of pain in children (issued July 2013). Available at: http://secure.collemergencymed.ac.uk/asp/document.asp?ID=4682 (accessed 11/12/13)
7. Berde CB, Sethna NF. Analgesics for the treatment of pain in children. *N Engl J Med* 2002; 347: 1094–1103.
8. Maurice SC, *et al.* Emergency analgesia in the paediatric population (part II): pharmacological methods of pain relief. *Emerg Med J* 2002; 19: 101–5.
9. Alder Hey Royal Liverpool Children's NHS Trust. Guidelines on the management of pain in children. 1st ed, 1998. Available at: http://painsourcebook.ca/pdfs/pps55.pdf (accessed 23/06/08)
10. Zempsky WT, *et al.* Relief of pain and anxiety in pediatric patients in emergency medical systems. *Pediatrics* 2004; 114: 1348–56.
11. Harvey AJ, Morton NS. Management of procedural pain in children. *Arch Dis Child Educ Pract Ed* 2007; 92: ep20–ep26.
12. Krauss B, Green SM. Sedation and analgesia for procedures in children. *N Engl J Med* 2000; 342: 938–45.
13. Howes MC. Ketamine for paediatric sedation/analgesia in the emergency department. *Emerg Med J* 2004; 21: 275–80.
14. Stevens B, *et al.* Sucrose for analgesia in newborn infants undergoing painful procedures. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 23/06/08).
15. American Academy of Pediatrics Committee on Fetus and Newborn and Section on Surgery, Canadian Paediatric Society Fetus and Newborn Committee. Prevention and management of pain in the neonate: an update. *Pediatrics* 2006; 118: 2231–41. Correction. *Ibid.* 2007; 119: 425. Also available at: http://pediatrics.aappublications.org/cgi/reprint/118/5/2231.pdf (accessed 23/06/08)
16. Anand KJ; International Evidence-Based Group for Neonatal Pain. Consensus statement for the prevention and management of pain in the newborn. *Arch Pediatr Adolesc Med* 2001; 155: 173–80. Also available at: http://archpedi.ama-assn.org/cgi/reprint/155/2/173.pdf (accessed 23/06/08)
17. Chambliss CR, *et al.* The assessment and management of chronic pain in children. *Paediatr Drugs* 2002; 4: 737–46.

Nerve blocks

For a discussion of the use of nerve blocks in the management of pain, see under Pain, p. 1981.1.

Patient-controlled analgesia

Patient-controlled analgesia (PCA) involves the use of automated delivery systems that enable patients to receive doses of an analgesic on demand. The technique is now widely favoured in the management of acute pain,[1-3] and appears to produce slightly better analgesia, and greater patient acceptance, than conventional analgesic methods.[4,5] It has been used successfully in children as young as 4 years, and in elderly patients.[6] Most experience relates to systems using intravenous opioids.

Initial analgesia must be established by giving the patient bolus doses of the analgesic, to achieve effective blood concentrations.[2,3] In the simplest type of PCA the patient is then able to self-administer a small fixed dose on demand; further doses are not permitted until a pre-programmed lockout interval has expired. The demand dose should be large enough to produce an appreciable analgesic effect, but not large enough to lead readily to toxic concentrations; the lockout period should also be long enough for the maximum analgesic effect to be felt before another dose is permitted, and should therefore relate to the speed of onset of action of the drug.[2] Some devices allow the dose to be given as a short infusion[2] to reduce adverse effects associated with high peak concentrations of opioids. In another commonly used method, sometimes described as patient-augmented analgesia, the patient is given a continuous background infusion which is supplemented by self-administered bolus doses.[2,3,6] However, with this method patients may receive more opioids without any improvement in analgesia;[6,7] there is also a greater risk of adverse effects, including respiratory depression.[2,3,7] It remains to be seen if there is any advantage with the more sophisticated devices that can be programmed to adjust the background infusion according to the frequency of the bolus demands.[6,7]

Most of the common opioids have been used successfully for PCA.[2] Morphine remains the gold standard, and fentanyl, hydromorphone, or tramadol are widely used alternatives.[2,3] Use of pethidine is no longer advised because of the risk of accumulation of its toxic metabolite, norpethidine.[2] Drugs with very short (remifentanil) or very long (methadone) half-lives may be less suitable for use.

Although generally perceived as safer than conventional opioid analgesia, occasional serious adverse effects and fatalities have resulted from errors in programming, or incorrect or inappropriate use (including operation by persons other than the patient). These risks can be minimised by safety features built into the PCA device itself, and by the development of standard protocols for the use of the technique.[2,3]

Most experience relates to the use of the intravenous route. However, epidural PCA is also used. It appears to be as effective, or more effective, than intravenous PCA,[2,3] although it may not be suitable in all cases, and carries additional risks to do with the placement of the epidural catheter.[3] Epidural PCA generally produces analgesia with a combination of a lipid-soluble opioid such as fentanyl or sufentanil plus a long-acting local anaesthetic such as bupivacaine or ropivacaine; the optimum combination has yet to be defined.[2,3] In addition, unlike intravenous PCA, the use of a background infusion is recommended.

Other routes have been investigated, including intranasal[7] and, in particular, transdermal[2,8] PCA. An iontophoretic patient-controlled delivery system for transdermal fentanyl that allowed PCA to be given in a non-invasive manner was available;[8,9] however, this was withdrawn from the market because of a defective delivery system.

Although it is not always considered in terms of PCA, inhaled nitrous oxide in oxygen also has a long history of effective use as a patient-controlled analgesic during childbirth; opioid PCA may not be suitable for such pain although local anaesthetics have been used with satisfactory results.[10]

1. Walder B, *et al.* Efficacy and safety of patient-controlled opioid analgesia for acute postoperative pain: a quantitative systematic review. *Acta Anaesthesiol Scand* 2001; 45: 795–804.
2. Grass JA. Patient-controlled analgesia. *Anesth Analg* 2005; 101 (suppl): S44–S61.
3. Momeni M, *et al.* Patient-controlled analgesia in the management of postoperative pain. *Drugs* 2006; 66: 2321–37.
4. Hudcova J, *et al.* Patient controlled opioid analgesia versus conventional opioid analgesia for postoperative pain. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 23/06/08).
5. Bainbridge D, *et al.* Patient-controlled versus nurse-controlled analgesia after cardiac surgery—a meta-analysis. *Can J Anaesth* 2006; 53: 492–9.
6. Macintyre PE. Safety and efficacy of patient-controlled analgesia. *Br J Anaesth* 2001; 87: 36–46.
7. Lehmann KA. Recent developments in patient-controlled analgesia. *J Pain Symptom Manage* 2005; 29 (suppl): S72–S89.
8. Sinatra R. The fentanyl HCl patient-controlled transdermal system (PCTS): an alternative to intravenous patient-controlled analgesia in the postoperative setting. *Clin Pharmacokinet* 2005; 44 (suppl 1): 1–6.
9. Eberhart L. The safety and tolerability of the fentanyl HCl iontophoretic transdermal system: an alternative to currently available analgesic modalities. *J Opioid Manag* 2007; 3: 249–56.
10. van der Vyver M, *et al.* Patient-controlled epidural analgesia versus continuous infusion for labour analgesia: a meta-analysis. *Br J Anaesth* 2002; 89: 459–65.

Postoperative analgesia

Pain relief after surgery has often been inadequate and it is now recognised that pain control should be adjusted for each patient and each situation.[1–3] Multimodal regimens, using several classes of analgesic, and ideally more than one route, are now generally favoured.[3–5] Pre-operative evaluation of the patient,[2,4] and frequent assessment of pain intensity after surgery (both to allow appropriate analgesia, and to detect possible complications)[3] are fundamental. Evidence-based procedure-specific guidelines have been issued.[6,7] Giving pain control on a preventative basis (pre-emptive analgesia) has been recommended, and may be more effective than conventional management, at least for some regimens, although results have varied.[8,9]

Patients undergoing minor surgery can be adequately managed with oral analgesics, such as paracetamol, NSAIDs, tramadol, and oxycodone. Those undergoing more extensive surgery usually require parenteral opioids or local analgesic techniques such as regional block, sometimes in combination.[3]

- **Opioid analgesics**, in particular morphine, are the mainstay of treatment for moderate to severe postoperative pain.[3] Opioid dose should be individually titrated; they may be given by several routes, but intravenous doses give more predictable results than intramuscular or subcutaneous doses and are widely favoured.[2,3,10] Intravenous *patient-controlled analgesia* (see p. 5.3) is now a standard method of management for postoperative pain.[3,4] Where it is unavailable, intramuscular or subcutaneous dosage every 2 hours as needed for 24 to 72 hours, followed by conversion to an oral analgesic regimen, may be an alternative.[3] Careful monitoring for potential adverse effects, in particular respiratory depression, is needed.[3]

  Opioids injected centrally via the epidural and intrathecal routes provide effective regional analgesia[2,4,10] (and may be more effective than intravenous opioids,[11] although whether this improves the ultimate outcome is unclear[3]). Morphine is the opioid most commonly given centrally, but others such as fentanyl, which is more lipid soluble, may be preferable in the case of epidural injection. The epidural and intrathecal routes have also been used for patient-controlled analgesia.

  Oral opioids may not be suitable in the immediate postoperative period, but oral regimens are generally preferred if the patient can swallow and gastrointestinal function has recovered.[1,3] Tramadol is useful in patients undergoing minor or intermediate surgery.[3]

  Management of postoperative pain in patients who have been receiving long-term opioids before surgery may be particularly difficult.[3,12] Baseline requirements should be calculated for each patient, but may go up or down after surgery; typically, at least 50% of the baseline dose will be needed postoperatively, with additional opioids titrated according to pain requirements. Such patients may thus require larger than normal doses of opioids to be given, and a balanced multimodal approach to analgesia is particularly important.[12]

- **NSAIDs** and **paracetamol** are useful analgesic adjuncts that can improve pain relief,[3] but are not suitable alone after major surgery.[2] After minor or intermediate surgery an oral regimen of paracetamol plus an NSAID such as naproxen may be adequate, with oxycodone or tramadol being given for breakthrough pain.[3] NSAIDs can be used effectively with other drugs, and use of an NSAID with an opioid after major surgery enables the dose of the opioid to be reduced without loss of analgesic effect.[1–5,10] However, the risk of gastric ulceration, impaired coagulation, and reduced renal function may limit the use of NSAIDs in some patients,[3,10] and the potential cardiovascular effects of the selective inhibitors of cyclo-oxygenase-2 (COX-2) have also been a cause of great concern.[3]

  Diclofenac, flurbiprofen, ketoprofen, ketorolac, lornoxicam, and naproxen are among the NSAIDs used for postoperative pain; the COX-2 inhibitors including parecoxib have also been used. Diclofenac, ketoprofen, ketorolac, and parecoxib may be given by injection, and a parenteral formulation of paracetamol is available in some countries.

- Infiltration of **local anaesthetics** at the site of operation is a simple method of preventing postoperative wound pain.[1,4] Central nerve blocks obtained with epidural or intrathecal local anaesthetics produce excellent analgesia,[1,2,4] although again, whether this improves outcome is unclear.[2,3] Insertion of a catheter during the operation allows subsequent infusion or bolus injection.[10] However, there may be complications related to both the procedure and the drugs used (see also Adverse Effects of Central Block, p. 1982.1). Local anaesthetics are rarely used alone, as a mixture of an opioid and a local anaesthetic produces effective analgesia using relatively smaller doses of each drug.[10] Such combinations are also used in patient-controlled epidural analgesia (see p. 5.3).

- There is growing interest in the use of **analgesic adjuvants**, including antiepileptics such as gabapentin or pregabalin,[13] or the NMDA antagonist ketamine,[14,15] to modulate opioid dosage and efficacy for postoperative pain. (For further discussion of analgesic adjuvants see Choice of Analgesic, p. 4.2.)

1. Shang AB, Gan TJ. Optimising postoperative pain management in the ambulatory patient. *Drugs* 2003; 63: 855–67.
2. Rosenquist RW, Rosenberg J. United States Veterans Administration. Postoperative pain guidelines. *Reg Anesth Pain Med* 2003; 28: 279–88. Also available at: http://www.oqp.med.va.gov/cpg/PAIN/PAIN_base.htm (accessed 23/06/08)
3. Myles PS, Power I. Clinical update: postoperative analgesia. *Lancet* 2007; 369: 810–12.
4. American Society of Anesthesiologists Task Force on Acute Pain Management. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. *Anesthesiology* 2004; 100: 1573–81. Also available at: http://www.asahq.org/publicationsAndServices/pain.pdf (accessed 23/06/08)
5. Elia N, *et al.* Does multimodal analgesia with acetaminophen, nonsteroidal antiinflammatory drugs, or selective cyclooxygenase-2 inhibitors and patient-controlled analgesia morphine offer advantages over morphine alone? Meta-analyses of randomized trials. *Anesthesiology* 2005; 103: 1296–1304.
6. The PROSPECT Working Group. PROSPECT: procedure specific postoperative pain management. Available at: http://www.postoppain.org (accessed 26/11/09)
7. Association of Paediatric Anaesthetists. Good practice in postoperative and procedural pain (issued 2008). Available at: http://www.britishpainsociety.org/book_apa_part1.pdf (accessed 15/04/10)
8. Ong CK-S, *et al.* The efficacy of preemptive analgesia for acute postoperative pain management: a meta-analysis. *Anesth Analg* 2005; 100: 757–73.
9. Grape S, Tramèr MR. Do we need preemptive analgesia for the treatment of postoperative pain? *Best Pract Res Clin Anaesthesiol* 2007; 21: 51–63.
10. Brown AK, *et al.* Strategies for postoperative pain management. *Best Pract Res Clin Anaesthesiol* 2004; 18: 703–17.
11. Block BM, *et al.* Efficacy of postoperative epidural analgesia: a meta-analysis. *JAMA* 2003; 290: 2455–63.
12. James C, Williams JE. How should postoperative pain in patients on long-term opioids be managed? *Br J Hosp Med* 2006; 67: 500.
13. Dahl JB, *et al.* Protective premedication': an option with gabapentin and related drugs? A review of gabapentin and pregabalin in the treatment of post-operative pain. *Acta Anaesthesiol Scand* 2004; 48: 1130–6.
14. Subramaniam K, *et al.* Ketamine as adjuvant analgesic to opioids: a quantitative and qualitative systematic review. *Anesth Analg* 2004; 99: 482–95.
15. Bell RF, *et al.* Perioperative ketamine for acute postoperative pain. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 23/06/08).

Rubefacients and topical analgesia

Substances applied topically can relieve local pain through several different mechanisms.[1] Rubefacients or counter-irritants can relieve superficial or deep-seated local pain probably by producing counter stimulation, which according to the 'gate theory' of pain (see Analgesia and Pain, p. 4.1) helps to inhibit the transmission of pain signals. Their topical application produces hyperaemia or irritation of the skin and they are used alone or as an adjunct to massage in the management of a variety of painful musculoskeletal conditions.[2] Some are also traditionally used in preparations for the symptomatic relief of minor peripheral vascular disorders such as chilblains. Substances commonly used in **rubefacient** preparations include nicotinate and salicylate compounds, essential oils, capsicum, solutions of ammonia, camphor, and nonivamide. However, a systematic review[3] concluded that the evidence did not support the use of rubefacient preparations containing salicylate compounds for acute musculoskeletal pain, and suggested that their efficacy compared poorly with topical NSAIDs for chronic musculoskeletal pain; no evidence was found to support the use of rubefacient preparations containing other substances. **Capsaicin**, which is one of the active ingredients of capsicum, is used alone as a topical analgesic in a range of painful conditions, including neuropathic pain and rheumatic disorders; its benefits are modest though it may be useful in some patients.[4] It does not rely on vasodilatation in the skin and it is therefore not considered to be a traditional counter-irritant.

Some **NSAIDs** have been used topically in the treatment of soft-tissue injuries and inflammatory musculoskeletal conditions, although this route does not necessarily avoid the adverse effects of systemic treatment. There is evidence[5,6] to suggest that topical NSAIDs are more effective than placebo.

Other agents used as topical analgesics include compounds such as ethyl chloride and the halogenated hydrocarbon propellants; their evaporation produces an intense cold that numbs the tissues. Transdermal clonidine has been used in the treatment of chronic pain. Ketamine also appears to have some local analgesic effect when applied topically.[1]

Local anaesthetics are sometimes included in topical preparations used for the relief of painful skin and musculoskeletal disorders.

Application of heat to the skin can also help to relieve pain and melted hard paraffin has been used in wax baths as an adjunct to physiotherapy for painful joints and sprains. Warm kaolin poultices have also been used as a means of applying heat for pain relief.

1. Argoff CE. Topical agents for the treatment of chronic pain. *Curr Pain Headache Rep* 2006; 10: 11–19.
2. Sawynok J. Topical and peripherally acting analgesics. *Pharmacol Rev* 2003; 55: 1–20.
3. Matthews P, *et al.* Topical rubefacients for acute and chronic pain in adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2009 (accessed 26/11/09).
4. Mason L, *et al.* Systematic review of topical capsaicin for the treatment of chronic pain. *BMJ* 2004; 328: 991–4.
5. Mason L, *et al.* Topical NSAIDs for chronic musculoskeletal pain: systematic review and meta-analysis. *BMC Musculoskelet Disord* 2004; 5 28. Available at: http://www.biomedcentral.com/1471-2474/5/28 (accessed 23/06/08)
6. Massey T, *et al.* Topical NSAIDs for acute pain in adults. Available in The Cochrane Database of Systematic Reviews: Issue 6. Chichester: John Wiley; 2010 (accessed 20/08/10).

Specific pain states

Biliary and renal colic. Gallstones (see Ursodeoxycholic Acid, p. 2639.1) or other biliary disorders that result in obstruction of the bile ducts may produce **biliary colic**. Morphine may relieve the accompanying pain, but as it can also produce spasm of the sphincter of Oddi it can raise intrabiliary pressure and exacerbate the pain. It is therefore usually recommended that morphine and its derivatives should either be avoided in patients with biliary disorders or that they should be given with an antispasmodic. Historically, pethidine has been regarded as a more suitable choice because it was thought to have less smooth muscle activity than morphine; however, this has been questioned. Prostaglandins have also been implicated in the aetiology of biliary colic and NSAIDs such as diclo-

fenac or ketorolac have been successfully used to relieve the pain.[1-3] Antimuscarinic antispasmodics have been tried for their action on biliary smooth muscle and the sphincter of Oddi.

Ureteral obstruction, such as in the formation and passage of renal calculi (see p. 2350.3), produces painful **renal or ureteral colic.**[4-6] The acute pain of renal or ureteral colic has been traditionally relieved using opioid analgesics such as pethidine that were thought to have a minimal effect on smooth muscle, although morphine has also been used.[4,6] However, opioids, and especially pethidine, are particularly associated with nausea and vomiting,[5,7] and NSAIDs are increasingly used in their place; they appear to be at least comparable with the opioids in terms of efficacy.[4-7] They can be given intramuscularly, intravenously, orally, and rectally, although the best route is unclear.[5,8] Diclofenac sodium given intramuscularly is recommended as first-line treatment by some authors.[4] Parenteral ketorolac also seems to be effective.[5] The use of intranasal desmopressin has also been studied.[4,5]

1. Akriviadis EA, *et al.* Treatment of biliary colic with diclofenac: a randomized, double-blind, placebo-controlled study. *Gastroenterology* 1997; 113: 225–31.
2. Dula DJ, *et al.* A prospective study comparing im ketorolac with im meperidine in the treatment of acute biliary colic. *J Emerg Med* 2001; 20: 121–4.
3. Henderson SO, *et al.* Comparison of intravenous ketorolac and meperidine in the treatment of biliary colic. *J Emerg Med* 2002; 23: 237–41.
4. Shokeir AA. Renal colic: new concepts related to pathophysiology, diagnosis and treatment. *Curr Opin Urol* 2002; 12: 263–9.
5. Heid F, Jage J. The treatment of pain in urology. *BJU Int* 2002; 90: 481–8.
6. Wright PJ, *et al.* Managing acute renal colic across the primary-secondary care interface: a pathway of care based on evidence and consensus. *BMJ* 2002; 325: 1408–12.
7. Holdgate A, Pollock T. Non-steroidal anti-inflammatory drugs (NSAIDS) versus opioids in the treatment of acute renal colic. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 23/06/08).
8. Lee C, *et al.* Rectal or intravenous non-steroidal anti-inflammatory drugs in acute renal colic. *Emerg Med J* 2005; 22: 653–4.

Cancer pain. The pain cancer patients have may be acute, chronic, or intermittent. It may result from tumour involvement of the viscera and extension into soft tissues, tumour-induced nerve compression and injury, raised intracranial pressure, or bone metastases. Pain may also arise as a result of adverse effects of treatment, or from a concurrent disease, and may be exacerbated by emotional or mental changes. Many patients will have more than one type of pain. There may also be exacerbations due to movement (incident pain) or worsening of cancer: pain occurs in about a quarter of patients with newly diagnosed malignancies, but in up to three-quarters of those with advanced disease.

Pain relief involves the treatment of the cause of the pain as well as treatment of the pain itself, together with explanation, reassurance, and supportive care to improve any mental and social complicating factors. The mainstay of cancer pain management is drug treatment with non-opioid or opioid analgesics, or both together, plus adjuvant analgesics if necessary. A small proportion of patients (about 10 to 20%) may have pain that responds poorly or not at all to opioid analgesics given at tolerable doses, e.g. neuropathic pain resulting from nerve destruction or compression, incident bone pain, pancreatic pain, and muscle spasm.

In the management of cancer pain the aim is to achieve adequate continuous pain relief with the minimum of adverse effects and this calls for appropriate assessment of the intensity and quality of pain, and regular monitoring of the treatment. Guidelines for the relief of cancer pain, published by WHO in 1986[1] and revised in 1996,[2] are widely endorsed by specialists in pain relief and the care of the terminally ill[3-7] despite some questions about the robustness of supporting studies.[7] Subsequent guidelines issued by the Scottish Intercollegiate Guidelines Network[8] in 2008 and the British Pain Society[9] in 2010, and the annually updated guidelines of the US National Comprehensive Cancer Network (NCCN)[10] are also available. Specific guidelines for the relief of cancer pain in children have also been published.[11]

Treatment should be given regularly, orally if possible, and should follow the accepted three-step **'analgesic ladder'.**[1,2] This approach is often described as treatment 'by mouth, by the clock, and by the ladder'. Regular dosage rather than treatment as required aims to prevent pain re-emerging and to minimise the expectation of pain. The analgesic ladder consists of 3 stages, treatment beginning at step 1 and progressing to step 3 if pain is uncontrolled or increases. The stages are as follows:

1. a non-opioid analgesic such as aspirin, other NSAIDs, or paracetamol; an adjuvant (see below) may also be given if necessary to tackle specific pain or associated symptoms
2. an opioid analgesic such as codeine, dihydrocodeine, or tramadol plus a non-opioid analgesic; an adjuvant may also be given
3. a potent opioid analgesic such as oral morphine; a non-opioid analgesic may also be given, as may an adjuvant.

Combining analgesics with different pharmacological actions can produce additive or synergistic increases in analgesia but only one analgesic from each of the 3 groups (non-opioid, less potent opioid, potent opioid) should be used at the same time.

Evidence to support the **choice of analgesic** is often scanty. A systematic review[12] found some evidence of benefit from the use of NSAIDs to treat cancer pain, and supported their use in mild pain (WHO step 1), but there was little to support the choice of one NSAID over another, and little evidence for the addition of an opioid to an NSAID in moderate pain (WHO step 2).

In moderate to severe pain (WHO step 3), morphine is generally held to be the opioid of choice;[5] alternatives include fentanyl, hydrocodone, and oxycodone.[5,8,10] Mixed opioid agonist-antagonists may precipitate withdrawal symptoms in opioid-dependent patients; opioids with long half-lives (such as methadone or levorphanol) are also less suitable for treatment than pure opioid agonists with less prolonged actions.[10] In patients who do not achieve effective analgesia at an acceptable level of adverse effects with one opioid, **opioid rotation,** switching to an alternative opioid at an equivalent dose, may enable pain control.[8,10,13]

The optimal **route** for use is oral dosage. For best effect, both conventional (for dose titration) and modified-release (for maintenance) dosage forms are required. The European Association for Palliative Care (EAPC) suggests[5] that the simplest method of dose titration is with conventional morphine dosage every 4 hours, and the same dose for breakthrough pain. This 'rescue' dose may be given as often as required, up to hourly. The total daily dose of morphine should be reviewed each day and the regular dose adjusted to take account of the amount needed for breakthrough pain. If pain returns consistently before the next dose is due the regular dose should be increased. Conventional formulations do not generally need to be given more often than every 4 hours, and modified-release products should be given according to the intended duration of the preparation (usually every 12 or 24 hours). Patients stabilised on regular oral morphine require continued access to a rescue dose for breakthrough pain. For patients taking conventional morphine preparations every 4 hours, a double dose at bedtime is effective to prevent pain disturbing sleep.

Similar recommendations are given by the NCCN.[10] They advise that the oral rescue dose for breakthrough pain should be calculated as 10 to 20% of the total 24-hour requirement; this may then be increased by 50 to 100% in patients who still have increased pain, with hourly reassessment of efficacy and adverse effects. If inadequate response is still seen after 2 or 3 cycles, a change of route (e.g. intravenous titration) may be considered.

If patients are unable to take morphine orally the EAPC considers the preferred alternative route to be subcutaneous,[5] and the NCCN suggests either continuous parenteral infusion, intravenous, or subcutaneous dosage.[10] There is no indication for intramuscular morphine for cancer pain since subcutaneous dosage is simpler and less painful.[5] In the UK diamorphine hydrochloride is often preferred to morphine sulfate for parenteral use because it is more soluble and allows a smaller dose volume. Hydromorphone hydrochloride is an alternative to diamorphine.

Epidural or intrathecal opioids, either by injection or infusion, have been used when conventional routes have failed.[10,14] Some advocate the use of these routes because smaller doses may produce analgesia equivalent to that of larger doses given orally or parenterally, although there has been little conclusive evidence for a lower incidence of adverse effects or a better quality of analgesia.

The buccal, sublingual, and nebulised routes have been investigated, but these are not recommended for morphine because there is no current evidence of clinical advantage over conventional routes.[5] However, buprenorphine is given sublingually and may be a useful alternative in patients with dysphagia, although experience of long-term use in cancer pain is limited. Transdermal opioids are an alternative to oral morphine in patients whose pain and opioid requirements are stable.[5,8,10] Buprenorphine or fentanyl can be given via a transdermal system that provides continuous and controlled delivery for up to 72 hours. Calculating an appropriate conversion regimen for transfer of patients from oral or parenteral therapy to transdermal can be difficult,[15] but the NCCN suggests that the total daily requirement of oral morphine is equivalent to about 2000 times the hourly dose of transdermal fentanyl.[10] Oral transmucosal dosage forms[10,16] and an intranasal spray of fentanyl are also available for the management of breakthrough cancer pain.

Automated delivery systems for self-administration of parenteral analgesics (patient-controlled analgesia) have been used to administer opioid analgesics (see p. 5.3).

Adjuvant drugs that may be necessary at any stage include antidepressants, antiepileptics, and class I antiarrhythmics for neuropathic pain, corticosteroids for nerve compression and headache resulting from raised intracranial pressure, and muscle relaxants for muscle spasm. Radiotherapy and radioisotopes such as strontium-89 may be of use when the bone pain of metastases is unresponsive to analgesics.[17] Bone modulating drugs such as calcitonin and bisphosphonates may be of additional benefit but have a slow onset of action and bisphosphonates may cause an initial transient increase in pain. Corticosteroids have been used as an alternative to NSAIDs in refractory bone pain but long-term use should be avoided. Nerve blocks with local anaesthetics or neurolytic solutions may benefit a few patients, in particular those with sympathetically maintained pain or specific localised pain (see under Pain, p. 1981.1). Topical local anaesthetics or NSAIDs may also be of use in some patients.[10] Physiotherapy and relaxation techniques may be useful for painful muscle spasm. The addition of an NMDA antagonist such as dextromethorphan or ketamine to conventional analgesic regimens has been tried with some success in patients with refractory pain.[13] Adjuvant therapy should be fully explored before moving on to the next 'rung' of the treatment ladder or increasing the dosage of an opioid analgesic.[18] For further details of analgesic adjuvants, see Choice of Analgesic, p. 4.2. Nabiximols (a mixture of cannabis extracts containing dronabinol and cannabidiol) has been used as adjunctive analgesic treatment in adult patients with advanced cancer who have persistent moderate to severe background pain despite maximal opioid therapy.

Management of cancer pain also requires monitoring to prevent and reduce **adverse effects** of therapy, particularly of opioids. Appropriate bowel regimes to manage constipation should be started at the same time as opioid therapy, as should antiemetic therapy; sedation and nausea usually become less marked as treatment progresses,[5] and warrant reassessment if they persist for longer than a week.[10] Concerns about respiratory depression and dependence should not be allowed to interfere with appropriate treatment: patients whose pain ameliorates can generally reduce and stop opioid treatment without difficulty.[5]

1. WHO. *Cancer pain relief*. Geneva: WHO, 1986.
2. WHO. *Cancer pain relief*. 2nd ed. Geneva: WHO, 1996.
3. American Society of Anesthesiologists Task Force on Pain Management, Cancer Pain Section. Practice guidelines for cancer pain management. *Anesthesiology* 1996; 84: 1243–57. Also available at: http://www.asahq.org/publicationsAndServices/cancer.html (accessed 23/06/08)
4. Portenoy RK, Lesage P. Management of cancer pain. *Lancet* 1999; 353: 1695–1700.
5. Hanks GW, *et al.* Expert Working Group of the Research Network of the European Association for Palliative Care. Morphine and alternative opioids in cancer pain: the EAPC recommendations. *Br J Cancer* 2001; 84: 587–93. Also available at: http://www.eapcnet.org/download/forPublications/BJC_English.pdf (accessed 23/06/08)
6. European Society for Medical Oncology Guidelines Task Force. ESMO Minimum Clinical Recommendations for the management of cancer pain. *Ann Oncol* 2005; 16 (suppl 1): i83–i85. Also available at: http://annonc.oxfordjournals.org/cgi/reprint/16/suppl_1/i83.pdf (accessed 23/06/08)
7. Mercadante S, Fulfaro F. World Health Organization guidelines for cancer pain: a reappraisal. *Ann Oncol* 2005; 16 (suppl 4): iv132–iv135.
8. Scottish Intercollegiate Guidelines Network. Control of pain in adults with cancer: a national clinical guideline (issued November 2008). Available at: http://www.sign.ac.uk/pdf/SIGN106.pdf (accessed 26/11/09)
9. British Pain Society. Cancer pain management (issued January 2010). Available at: http://www.britishpainsociety.org/book_cancer_pain.pdf (accessed 20/04/10)
10. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: adult cancer pain (version 1.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/pain.pdf (accessed 16/08/10)
11. WHO. *Cancer pain relief and palliative care in children*. Geneva: WHO, 1998.
12. McNicol E, *et al.* NSAIDS or paracetamol, alone or combined with opioids, for cancer pain. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 23/06/08).
13. Vielhaber A, *et al.* Advances in cancer pain management. *Hematol Oncol Clin North Am* 2002; 16: 527–41.
14. Ballantyne JC, Carwood CM. Comparative efficacy of epidural, subarachnoid, and intracerebroventricular opioids in patients with pain due to cancer. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 23/06/08).
15. Skaer TL. Practice guidelines for transdermal opioids in malignant pain. *Drugs* 2004; 64: 2629–38.
16. Zeppetella G, Ribeiro MDC. Opioids for the management of breakthrough (episodic) pain in cancer patients. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 27/11/09).
17. Paes FM, Serafini AN. Systemic metabolic radiopharmaceutical therapy in the treatment of metastatic bone pain. *Semin Nucl Med* 2010; 40: 89–104.
18. Lussier D, *et al.* Adjuvant analgesics in cancer pain management. *Oncologist* 2004; 9: 571–91.

Central post-stroke pain. Central pain is a neuropathic pain arising from lesions of the CNS.[1-6] Pain following a cerebrovascular accident has been referred to as thalamic syndrome but is now commonly known as central post-stroke pain and may arise not only from classical stroke but also from surgery or trauma to the head. The pain,

which has been described as burning, stabbing, and aching, may be mild to intolerable and occurs spontaneously or in response to a mild stimulus.

As in other types of neuropathic pain, whether opioid analgesics can be of benefit is controversial: it has been suggested that the value of conventional opioids such as high-dose morphine is modest, but that NMDA receptor antagonists such as methadone may be of more benefit.[2] Ketamine, another NMDA antagonist, may also be of value. Conventional management of central post-stroke pain involves the use of antidepressants such as amitriptyline and antiepileptics including lamotrigine or gabapentin. Early peripheral sympathetic blockade may produce temporary relief in some cases. Mexiletine may be of use in patients with refractory pain; it has often been given with amitriptyline. Oral or intrathecal baclofen may be tried. Transcutaneous electrical nerve stimulation (TENS) may occasionally be of help but some advocate brain or spinal cord stimulation. Surgical treatment generally gives disappointing results.

1. Bowsher D. The management of central post-stroke pain. *Postgrad Med J* 1995; 71: 598–604.
2. Bowsher D. Central post-stroke ('thalamic syndrome') and other central pains. *Am J Hosp Palliat Care* 1999; 16: 593–7.
3. Frese A, *et al.* Pharmacologic treatment of central post-stroke pain. *Clin J Pain* 2006; 22: 252–60.
4. Canavero S, Bonicalzi V. Central pain syndrome: elucidation of genesis and treatment. *Expert Rev Neurother* 2007; 7: 1485–97.
5. Kumar B, *et al.* Central poststroke pain: a review of pathophysiology and treatment. *Anesth Analg* 2009; 108: 1644–57.
6. Klit H, *et al.* Central post-stroke pain: clinical characteristics, pathophysiology, and management. *Lancet Neurol* 2009; 8: 857–68.

Complex regional pain syndrome. Complex regional pain syndrome (CRPS) is a regional, post-traumatic neuropathic pain that generally affects the limbs. CRPS has also been referred to as reflex sympathetic dystrophy, post-traumatic dystrophy, causalgia, Sudeck's atrophy, and shoulder-hand syndrome. Causalgia has also been used to describe the burning pain that follows a penetrating injury. Historically, it was considered that the pain was maintained by the sympathetic nervous system and the term 'reflex sympathetic dystrophy' was commonly used to describe the syndrome (although recent studies have shown that the sympathetic nervous system is not always involved). However, the terms given above are now considered to be inappropriate and CRPS is now broadly classified as:

- Type I: (previously reflex sympathetic dystrophy) which develops after tissue trauma, such as that accompanying myocardial infarction, stroke, burns, frostbite, fractures, and shoulder or limb injury, but where there is no identifiable nerve lesion
- Type II: (previously causalgia) which develops after trauma to a major peripheral nerve

Clinically the two subsets are identical and typical symptoms include pain, allodynia, and hyperalgesia; as the syndrome becomes chronic, trophic changes to the bone, muscles, and skin may occur. Sympathetic dysfunction may also be present. If the pain is relieved by a sympathetic block (see below), this pain is regarded as 'sympathetically-maintained', if not it is known as 'sympathetically-independent' pain.

The treatment of CRPS is difficult especially in chronic disorders and is usually aimed at pain control and restoring limb function. The cornerstone of treatment is physiotherapy, with pain relief provided in order to allow physical exercise. Patients with mild disease may not require pain management; those with moderate pain should be tried with a tricyclic antidepressant, an antiepileptic such as gabapentin, or a less potent opioid. Oral or intravenous bisphosphonates have also produced some promising results. A sympathetic nerve block with bretylium or perhaps a local anaesthetic may be useful in carefully selected patients with sympathetically-maintained pain; those who do not respond to a sympathetic nerve block may be given an epidural block. Other methods that have been tried in refractory pain include spinal cord stimulation and intrathecal baclofen or opioids. There are small studies or anecdotal reports of the use of a variety of other drugs and interventions.

References.

1. Kingery WS. A critical review of controlled clinical trials for peripheral neuropathic pain and complex regional pain syndromes. *Pain* 1997; 73: 123–39.
2. Baron R, Wasner G. Complex regional pain syndromes. *Curr Pain Headache Rep* 2001; 5: 114–23.
3. Schott GD. Reflex sympathetic dystrophy. *J Neurol Neurosurg Psychiatry* 2001; 71: 291–5.
4. Rho RE, *et al.* Complex regional pain syndrome. *Mayo Clin Proc* 2002; 77: 174–80.
5. Wasner G, *et al.* Complex regional pain syndrome—diagnostic, mechanisms, CNS involvement and therapy. *Spinal Cord* 2003; 41: 61–75.
6. Hord ED, Oaklander AL. Complex regional pain syndrome: a review of evidence-supported treatment options. *Curr Pain Headache Rep* 2003; 7: 188–96.
7. Ghai B, Dureja GP. Complex regional pain syndrome: a review. *J Postgrad Med* 2004; 50: 300–7.
8. Harden RN. Pharmacotherapy of complex regional pain syndrome. *Am J Phys Med Rehabil* 2005; 84 (suppl): S17–S28.
9. Quisel A, *et al.* Complex regional pain syndrome: which treatments show promise? *J Fam Pract* 2005; 54: 599–603.
10. Cepeda MS, *et al.* Local anesthetic sympathetic blockade for complex regional pain syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 23/06/08).
11. Sharma A, *et al.* Advances in treatment of complex regional pain syndrome: recent insights on a perplexing disease. *Curr Opin Anaesthesiol* 2006; 19: 566–72.
12. Rowbotham MC. Pharmacologic management of complex regional pain syndrome. *Clin J Pain* 2006; 22: 425–9.
13. Nelson DV, Stacey BR. Interventional therapies in the management of complex regional pain syndrome. *Clin J Pain* 2006; 22: 438–42.
14. Albazaz R, *et al.* Complex regional pain syndrome: a review. *Ann Vasc Surg* 2008; 22: 297–306.
15. Hsu ES. Practical management of complex regional pain syndrome. *Am J Ther* 2009; 16: 147–54.

Diabetic neuropathy. Sensory polyneuropathy, a complication of diabetes mellitus, is the commonest of the neuropathies producing neuropathic pain. The pain mainly manifests as a burning sensation, sometimes accompanied by shooting, or aching pain. Painful neuropathy may benefit from optimal diabetic control (see p. 467.2). Non-opioid analgesics such as aspirin or other NSAIDs, or paracetamol may be tried, although neuropathic pain is often resistant to conventional analgesics, and the treatment of painful diabetic neuropathy is generally as for postherpetic neuralgia (see p. 10.3). Relief may be obtained using tricyclic antidepressants and the *BNF* considers amitriptyline and nortriptyline to be the drugs of choice. SSRIs have been tried but studies suggest that they are ineffective or less effective than tricyclic antidepressants. Duloxetine, a serotonin and noradrenaline reuptake inhibitor, is licensed for use in diabetic neuropathy. Antiepileptics such as carbamazepine, gabapentin, phenytoin, and pregabalin can be used to control any shooting or stabbing components of the pain; lamotrigine and topiramate are also under investigation. Antiarrhythmics such as lidocaine given intravenously or mexiletine given orally have been shown to be effective against some components of the pain, although it has been suggested that in the absence of strong efficacy data the latter should be confined to patients with extreme refractory pain and no cardiac risk. Topical application of capsaicin or lidocaine may have some effect; use of capsaicin may be limited by the burning sensation it can cause. Neuropathic pain may respond partially to some opioid analgesics, such as methadone, oxycodone, and tramadol, and they may be of use when other treatments are ineffective. Transcutaneous electrical nerve stimulation (TENS) may also be tried.

References.

1. Jensen PG, Larson JR. Management of painful diabetic neuropathy. *Drugs Aging* 2001; 18: 737–49.
2. Boulton AJ. Treatments for diabetic neuropathy. *Curr Diab Rep* 2001; 1: 127–32.
3. Barbano R, *et al.* Pharmacotherapy of painful diabetic neuropathy. *Curr Pain Headache Rep* 2003; 7: 169–77.
4. Llewelyn JG. The diabetic neuropathies: types, diagnosis and management. *J Neurol Neurosurg Psychiatry* 2003; 74 (suppl II): ii15–ii19.
5. Duby JJ, *et al.* Diabetic neuropathy: an intensive review. *Am J Health-Syst Pharm* 2004; 61: 160–73.
6. Vinik A. Use of antiepileptic drugs in the treatment of chronic painful diabetic neuropathy. *J Clin Endocrinol Metab* 2005; 90: 4936–45.
7. Argoff CE, *et al.* Consensus guidelines: treatment planning and options. Diabetic peripheral neuropathic pain. *Mayo Clin Proc* 2006; 81 (suppl 4): S12–S25.
8. Wong M-C, *et al.* Effects of treatments for symptoms of painful diabetic neuropathy: systematic review. Abridged version: *BMJ* 2007; 335: 87–90. Full version: http://www.bmj.com/cgi/reprint/335/7610/87 (accessed 23/06/08)
9. Chong MS, Hester J. Diabetic painful neuropathy: current and future treatment options. *Drugs* 2007; 67: 569–85. Correction. *ibid.*: 1702.
10. Ziegler D. Painful diabetic neuropathy: treatment and future aspects. *Diabetes Metab Res Rev* 2008; 24 (suppl 1): S52–S57.
11. Tavakoli M, *et al.* Pathophysiology and treatment of painful diabetic neuropathy. *Curr Pain Headache Rep* 2008; 12: 192–7.
12. National Collaborating Centre for Chronic Conditions/NICE. Type 2 diabetes: the management of type 2 diabetes (issued May 2009). Available at: http://www.nice.org.uk/nicemedia/pdf/CG87NICEGuideline.pdf (accessed 11/08/11)
13. Dubinsky RM, Miyasaki J. Assessment: efficacy of transcutaneous electric nerve stimulation in the treatment of pain in neurologic disorders (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2010; 74: 173–6. Also available at: http://www.neurology.org/cgi/reprint/74/2/173 (accessed 07/09/10)
14. American Diabetes Association. Standards of medical care in diabetes—2011. *Diabetes Care* 2011; 34 (suppl 1): S11–S61. Also available at: http://care.diabetesjournals.org/content/34/Supplement_1/S11.full.pdf+html (accessed 11/08/11)

Dysmenorrhoea. Dysmenorrhoea is painful menstruation. The primary form arises from uterine contractions produced by release of prostaglandins from the endometrium in the luteal phase of the menstrual cycle. For this reason, drugs that inhibit ovulation or prostaglandin production are often effective treatments.[1] NSAIDs inhibit cyclo-oxygenase (prostaglandin synthetase) and are usually the drugs of first choice.[1–6] They are taken at the onset of discomfort and continued for a few days while symptoms persist. Those most commonly used have included aspirin, diflunisal, flurbiprofen, ibuprofen, indometacin, ketoprofen, mefenamic acid, naproxen, and piroxicam. Theoretically, mefenamic acid has the advantage of inhibiting both the synthesis and the peripheral action of prostaglandins, but clinical studies have not consistently shown fenamates to be more effective than other cyclo-oxygenase inhibitors. Paracetamol has also been given for pain relief. A systematic review[2] comparing several of these drugs concluded that ibuprofen appeared to have the best risk-benefit ratio in dysmenorrhoea and was the preferred analgesic; naproxen, mefenamic acid, and aspirin were also effective, but the limited data on paracetamol did not show such clear benefits. Another such review considered that there was insufficient evidence to determine which NSAID should be preferred.[3]

Patients who fail to respond to analgesics may benefit from the use of progestogens either alone for part of the cycle or more usually with oestrogens in the form of combined oral contraceptive preparations.[1,4–6] A systematic review[7] found limited evidence of pain improvement with the use of such preparations for primary dysmenorrhoea; however, the authors noted a paucity of studies, and that the included studies were of variable quality and had methodological flaws.

Antispasmodic drugs such as hyoscine butylbromide are included in some preparations promoted for the relief of spasm associated with dysmenorrhoea but the *BNF* considers that they do not generally provide significant relief. There is limited evidence[8] that vitamin B_1 may be effective and some consider[1] that it may be worth trying; evidence of benefit from other therapies such as magnesium or vitamin E is considered to be weaker.[1,8,9]

Secondary dysmenorrhoea is associated with various other disorders such as endometriosis, and treatment is mainly aimed at the underlying cause.

1. Lefebvre G, *et al.* Society of Obstetricians and Gynaecologists of Canada. SOGC clinical practice guideline: no. 169, December 2005. Primary dysmenorrhea consensus guideline. *J Obstet Gynaecol Can* 2005; 27: 1117–30. Also available at: http://www.sogc.org/guidelines/public/169E-CPG-December2005.pdf (accessed 23/06/08)
2. Zhang WY, Li Wan Po A. Efficacy of minor analgesics in primary dysmenorrhoea: a systematic review. *Br J Obstet Gynaecol* 1998; 105: 780–9.
3. Marjoribanks J, *et al.* Nonsteroidal anti-inflammatory drugs for primary dysmenorrhoea. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 23/06/08).
4. French L. Dysmenorrhea in adolescents: diagnosis and treatment. *Pediatr Drugs* 2008; 10: 1–7.
5. Harel Z. Dysmenorrhea in adolescents. *Ann N Y Acad Sci* 2008; 1135: 185–95.
6. Morrow C, Naumburg EH. Dysmenorrhea. *Prim Care* 2009; 36: 19–32.
7. Wong CL, *et al.* Oral contraceptive pill for primary dysmenorrhoea. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 27/11/09).
8. Proctor ML, Murphy PA. Herbal and dietary therapies for primary and secondary dysmenorrhoea. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2001 (accessed 23/06/08).
9. Proctor M, Farquhar C. Diagnosis and management of dysmenorrhoea. *BMJ* 2006; 332: 1134–8.

Headache. Aspirin and other NSAIDs, or paracetamol are often tried first for the symptomatic treatment of various types of headache including migraine (p. 670.3) and tension-type headache (p. 671.3). NSAIDs may also be effective for the prophylaxis of migraine, although they are not considered first-line options.

Opioid analgesics such as codeine are sometimes included in oral compound analgesic preparations used in the initial treatment of migraine or tension-type headache, but are best avoided, especially in patients who have frequent attacks.

Labour pain. It is important to assess the adverse effects, on both the mother and the fetus, when selecting any method for the management of labour pain. Non-pharmacological methods of pain relief may include relaxation techniques, transcutaneous electrical nerve stimulation (TENS) (which is popular with patients, although there is no robust evidence of benefit[1]), and various other complementary therapies: of the latter, there is some evidence of benefit with the use of acupuncture and hypnosis.[2] Water immersion (use of a birthing pool) during the first stage of labour has been shown to reduce reported maternal pain.[3] Subcutaneous or intradermal injection of sterile water into the back has also been used for the relief of low back pain during labour.[4,5]

However, at some point during labour many women will request some sort of pharmacological analgesia.

The inhalational anaesthetic **nitrous oxide**, given with oxygen, is suitable for self-administration and is commonly used to relieve labour pain. It is relatively safe and can produce substantial analgesia in most patients.[6] Other inhalational analgesics such as isoflurane or sevoflurane are also sometimes used[7] (see Choice of Analgesic, p. 4.2).

Opioid analgesics have been given systemically in the management of labour pain for many years, although they do not appear to provide adequate analgesia in most patients at a tolerable dosage.[8,9] There is no clear evidence to favour one opioid over another.[10] Morphine is considered unsuitable,[7] and the widest experience has been with pethidine.[7,10] However, its efficacy has been queried,[7,10] and its use has declined in many countries.[7] Fentanyl and its derivatives sufentanil and alfentanil have been used, particularly when given as intravenous patient-controlled analgesia (PCA),[7] but it is not clear that they have any great

advantages, and as with other opioids they may cross the placenta and produce respiratory depression and other adverse effects in the newborn. The use of the very short-acting opioid remifentanil for PCA during labour has been investigated, with some benefit,[11] but although it is less likely to produce effects on neonatal respiration it is not clear that the degree of supervision required to guard against unacceptable respiratory depression in the mother can be widely achieved on busy labour wards.[7] Nalbuphine has been used in some countries because of its mixed agonist/antagonist action,[7] although there does not seem to be clear evidence that it conveys any substantial benefit.

Epidural analgesia with a *local anaesthetic* is now considered the gold standard for treatment and provides the most effective pain relief during labour.[9,12-14] Medical indications may include a history of malignant hyperthermia, certain cardiovascular or respiratory disorders, or pre-eclampsia, but the primary indication is the patient's desire for pain relief.[9,13] Bupivacaine is one of the local anaesthetics most often used in epidural analgesia; others include ropivacaine and lidocaine.[14]

Epidural block has few contra-indications and serious adverse events are rare. Nonetheless, it has been associated with an increased risk of prolonged second-stage labour, forceps delivery, and caesarean section[9,13,14] (although meta-analysis[8] and a systematic review[14] refute the latter), and it may not improve maternal experience of childbirth. Many centres stop epidural analgesia for the second stage of labour to reduce the incidence of forceps delivery but substantive evidence for this is lacking.[13] Central blocks may also produce adverse effects including shivering, post-puncture headache, and hypotension (for further details of the adverse effects of and precautions for epidural block, see p. 1982.1 and p. 1983.2, respectively). Occasionally epidural local anaesthetic does not produce adequate analgesia due to patchy or incomplete block.

Some of the adverse effects associated with epidural analgesia are associated with the motor block and profound analgesia resulting from traditional techniques using relatively high concentrations of local anaesthetic. There has therefore been an increasing trend to the use of lower-dose techniques. Although *opioid analgesics* are not particularly effective for labour analgesia when given systemically (see above), addition of a small amount of an opioid to epidural solutions enables effective analgesia to be achieved with lower concentrations of local anaesthetic, and with less motor block;[9,12,16,17] however, the incidence of pruritus (a known effect of opioids) is greater than with a local anaesthetic alone.[18] There is no standard combination of local anaesthetic and opioid, although one large study used bupivacaine 0.1% with fentanyl 2 micrograms/mL.[16] Sufentanil is also widely used with either bupivacaine[18] or ropivacaine. The epidural use of other adjuvants such as clonidine and neostigmine is also being studied.[19] Low-dose techniques are the basis of so-called 'ambulatory' or 'walking' epidural management, although it is unclear to what extent this mobility improves outcomes or patient satisfaction.[20]

Once an initial block is established, additional analgesia can be provided through a catheter by intermittent 'top-up' doses or by a continuous epidural infusion; a combination of the two methods forms the basis of some types of patient-controlled epidural analgesia.

Another method of reducing the adverse effects of traditional epidural techniques is to combine a spinal block, which is quick acting but not long lasting enough to be used alone for analgesia in labour, with epidural delivery. Although studies have reported superior pain relief[17] with such **combined spinal-epidural analgesia**, a systematic review[18] considered that there was no overall benefit with the technique when compared with low-dose epidural techniques, although onset of analgesia was faster.

The use of **spinal blocks** in obstetrics has been more commonly associated with anaesthesia and management of postoperative pain in caesarean section.[12] Spinal blocks with local anaesthetics have a greater tendency to produce hypotension and headache than epidural blocks (for further details of the adverse effects of and precautions for spinal block, see p. 1982.1 and p. 1983.2, respectively).

Pudendal nerve blocks with lidocaine followed by a local anaesthetic given into the perineum provide pain relief during labour.[12] However, the technique of paracervical local anaesthetic block is now largely of historic interest in labour analgesia[21] because of reports of fetal arrhythmias, acidosis, and asphyxia and isolated reports of fetal death.

Local anaesthetics have been applied topically for **perineal pain** caused by tearing or episiotomy in women who have given birth. However, a systematic review[22] considered that the evidence of efficacy was not compelling.

1. Carroll D, *et al.* Transcutaneous electrical nerve stimulation in labour pain: a systematic review. *Br J Obstet Gynaecol* 1997; 104: 169–75.
2. Smith CA, *et al.* Complementary and alternative therapies for pain management in labour. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 23/06/08).
3. Cluett ER, *et al.* Immersion in water in pregnancy, labour and birth. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2002 (accessed 23/06/08).
4. Mårtensson L, Wallin G. Labour pain treated with cutaneous injections of sterile water: a randomised controlled trial. *Br J Obstet Gynaecol* 1999; 106: 633–7.
5. Bahasadri S, *et al.* Subcutaneous sterile water injection for labour pain: a randomised controlled trial. *Aust N Z J Obstet Gynaecol* 2006; 46: 102–6.
6. Rosen MA. Nitrous oxide for relief of labor pain: a systematic review. *Am J Obstet Gynecol* 2002; 186 (suppl 1): S110–S126.
7. Bruyère M, Mercier FJ. Alternatives à l'analgésie péridurale au cours du travail. *Ann Fr Anesth Reanim* 2005; 24: 1375–82.
8. Halpern SH, *et al.* Effect of epidural vs parenteral opioid analgesia in the progress of labor. *JAMA* 1998; 280: 2105–10.
9. Goetzl LM, *et al.* American College of Obstetricians and Gynecologists. ACOG Practice Bulletin. Clinical management guidelines for obstetrician-gynecologists number 36, July 2002: obstetric analgesia and anesthesia. *Obstet Gynecol* 2002; 100: 177–91.
10. Bricker L, Lavender T. Parenteral opioids for labor pain relief: a systematic review. *Am J Obstet Gynecol* 2002; 186 (suppl 1): S94–S109.
11. Evron S, *et al.* Remifentanil: a novel systemic analgesic for labor pain. *Anesth Analg* 2005; 100: 233–8.
12. Findley I, Chamberlain G. ABC of labour care. Relief of pain. *BMJ* 1999; 318: 927–30.
13. Eltzschig HK, *et al.* Regional anesthesia and analgesia for labor and delivery. *N Engl J Med* 2003; 348: 319–32.
14. Anim-Somuah M, *et al.* Epidural versus non-epidural or no analgesia in labour. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 23/06/08).
15. Torvaldsen S, *et al.* Discontinuation of epidural analgesia late in labour for reducing the adverse delivery outcomes associated with epidural analgesia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 23/06/08).
16. Comparative Obstetric Mobile Epidural Trial (COMET) Study Group UK. Effect of low-dose mobile versus traditional epidural techniques on mode of delivery: a randomised controlled trial. *Lancet* 2001; 358: 19–23.
17. Comparative Obstetric Mobile Epidural Trial (COMET) Study Group UK. Randomized controlled trial comparing traditional with two "mobile" epidural techniques: anesthetic and analgesic efficacy. *Anesthesiology* 2002; 97: 1567–75.
18. Simmons SW, *et al.* Combined spinal-epidural versus epidural analgesia in labour. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 23/06/08).
19. Roelants F, *et al.* Epidural administration of neostigmine and clonidine to induce labor analgesia: evaluation of efficacy and local anesthetic-sparing effect. *Anesthesiology* 2005; 102: 1205–10.
20. Roberts CL, *et al.* Impact of first-stage ambulation on mode of delivery among women with epidural analgesia. *Aust N Z J Obstet Gynaecol* 2004; 44: 489–94.
21. Rosen MA. Paracervical block for labor analgesia: a brief historic review. *Am J Obstet Gynecol* 2002; 186 (suppl 1): S127–S130.
22. Hedayati H, *et al.* Topically applied anaesthetics for treating perineal pain after childbirth. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 23/06/08).

Low back pain. Low back pain (sometimes referred to as lumbago), is a common complaint but only a small percentage of patients suffer from a recognised organic disease, most frequently disc disease. In patients with a lumbar disc prolapse or herniation, the rupture of one of the fibrocartilagenous intervertebral discs can exert pressure on spinal nerve roots and produce a condition characterised by severe and often acute pain radiating from the back along the distribution of the nerves affected (radiculopathy). The sciatic nerve may be involved and patients have pain (sciatica), usually in one leg along the typical distribution of the nerve. Non-specific back pain (back pain of unknown origin) is usually self-limiting with a good prognosis, although recurrence is common.[1-3] Back pain is considered to be acute if it lasts for less than 6 weeks, subacute if it lasts for 6 to 12 weeks, or chronic if it persists for more than 12 weeks.[4]

Treatment for **acute back pain** should be given early to prevent the condition becoming chronic. For simple back pain (in the absence of nerve root symptoms or signs of serious spinal pathology) paracetamol should be tried first. NSAIDs are probably more effective,[2,5] but are associated with a higher frequency of adverse effects and should be reserved for those in whom paracetamol is ineffective.[2,4-8] If these treatments fail, muscle relaxants, including baclofen or tizanidine, may be added to therapy, although adverse effects may limit their usefulness;[1-6,9,10] benzodiazepines such as diazepam (which should only be given for a short period because of the risk of dependence)[2] are among the most effective muscle relaxants, but there is little comparative evidence, and some suggest that they act mainly as sedatives.[6] Opioids have moderate benefits in severe or disabling pain not relieved by paracetamol or NSAIDs,[2,5,6,8] but again should only be used in the short term.[3,8] There is strong evidence that remaining active speeds recovery and reduces the risk of chronicity, even if pain or discomfort is caused: bed rest delays recovery and is not recommended.[1,3,4,9,11,12] Other non-pharmacological approaches that have evidence of a benefit include topical heat wraps and spinal manipulation.[1,2,4,8,13,14] There is little or no clinical evidence that acupuncture, transcutaneous electrical nerve stimulation (TENS), massage, traction, specific back exercises, or lumbar support are beneficial.[1,2,4,11,14] However, in the UK, NICE[8] recommends offering acupuncture, manual therapy, or a structured exercise programme as part of the treatment regimen for persistent or recurrent non-specific acute or chronic lower back pain. Moreover, patient expectations of benefit from different therapies may influence outcomes, and this should be taken into consideration.[2]

Sciatica usually resolves with conservative management including analgesics and continued activity; however, if sciatic pain persists for longer than 6 to 8 weeks, surgery may be indicated.[15] Dissolution of the disc by injection of enzymes (chemonucleolysis) such as chymopapain or collagenase has been used as an effective alternative to surgery, but concerns about its safety have led to a decline in use, and discectomy is often preferred.[16]

Epidural injections of corticosteroids, using either the caudal or lumbar route, have been given to patients with sciatica; any relief is temporary only, the evidence of a benefit is conflicting, and their use is no longer recommended.[15,17] There is no evidence of benefit in patients with non-specific acute or chronic back pain;[1,4,8,18,19] however, it cannot be ruled out that some types of injection therapy may be effective in some subgroups of patients.[19]

About 2 to 7% of patients with acute lower back pain go on to develop **chronic pain**,[4] and in the majority of cases, the source of the pain cannot be identified. Chronic pain is not necessarily the same as prolonged acute back pain and treatment is difficult. Conservative treatment is as for acute pain (see above);[1,2,5,18,20] tricyclic antidepressants may also be tried[1-3,5,8,18,20] although a systematic review found the evidence of benefit to be lacking.[21] Topical application of capsaicin may be considered for short-term relief.[18] Surgery may be indicated for disc disease (see above) or spondylosis,[22] although it is not recommended for non-specific chronic back pain until conservative treatments have been tried for at least 2 years.[18] Epidural corticosteroids, intra-articular corticosteroid injections, local facet nerve blocks, trigger point injections, and spinal cord stimulation also lack evidence of efficacy.[18] Other methods that may be tried for intractable chronic back pain include multidisciplinary physical and psychological approaches;[1-3,8,14,18] evidence for TENS, massage, acupuncture, laser therapy, and traction is either equivocal or scant, however.[1,18,20,23,24]

1. Koes BW, *et al.* Diagnosis and treatment of low back pain. *BMJ* 2006; 332: 1430–4.
2. Chou R, *et al.* Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. *Ann Intern Med* 2007; 147: 478–91. Correction. *ibid.* 2008; 148: 247–8. Available at: http://www.annals.org/cgi/reprint/147/7/478.pdf (accessed 23/06/08)
3. Wilson JF. American College of Physicians. In the clinic: low back pain. *Ann Intern Med* 2008; 148: ITC5–1–ITC5–16. Also available at: http://www.annals.org/cgi/reprint/148/9/ITC5-1.pdf (accessed 15/08/08)
4. van Tulder M, *et al.* COST B13 Working Group on Guidelines for the Management of Acute Low Back Pain in Primary Care. Chapter 3. European guidelines for the management of acute nonspecific low back pain in primary care. *Eur Spine J* 2006; 15 (suppl 2): S169–S191. Also available at: http://www.backpaineurope.org/web/files/WG1_Guidelines.pdf (accessed 23/06/08)
5. Chou R, Huffman LH. Medications for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. *Ann Intern Med* 2007; 147: 505–14.
6. Mens JMA. The use of medication in low back pain. *Best Pract Res Clin Rheumatol* 2005; 19: 609–21.
7. Roelofs PDDM, *et al.* Non-steroidal anti-inflammatory drugs for low back pain. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 21/07/08).
8. National Collaborating Centre for Primary Care/NICE. Low back pain: early management of persistent non-specific low back pain—full guideline (issued May 2009). Available at: http://www.nice.org.uk/nicemedia/pdf/CG88fullguideline.pdf (accessed 27/11/09)
9. Deyo RA, Weinstein JN. Low back pain. *N Engl J Med* 2001; 344: 363–70.
10. van Tulder MW, *et al.* Muscle relaxants for non-specific low-back pain. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 23/06/08).
11. Ehrlich GE. Low back pain. *Bull WHO* 2003; 81: 671–6.
12. Hagen KB, *et al.* Bed rest for acute low-back pain and sciatica. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 23/06/08).
13. French SD, *et al.* Superficial heat or cold for low back pain. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 23/06/08).
14. Chou R, Huffman LH. Nonpharmacologic therapies for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. *Ann Intern Med* 2007; 147: 492–504. Also available at: http://www.annals.org/cgi/reprint/147/7/492.pdf (accessed 24/06/08)
15. Koes BW, *et al.* Diagnosis and treatment of sciatica. *BMJ* 2007; 334: 1313–17.
16. Gibson JN, Waddell G. Surgical interventions for lumbar disc prolapse. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 23/06/08).
17. Armon C, *et al.* Assessment: use of epidural steroid injections to treat radicular lumbosacral pain: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2007; 68: 723–9. Also available at: http://www.neurology.org/cgi/reprint/68/10/723.pdf (accessed 24/06/08)
18. Airaksinen O, *et al.* COST B13 Working Group on Guidelines for Chronic Low Back Pain. Chapter 4. European guidelines for the management of chronic nonspecific low back pain. *Eur Spine J* 2006; 15 (suppl 2): S192–S300. Also available at: http://www.backpaineurope.org/web/files/WG2_Guidelines.pdf (accessed 23/06/08)
19. Staal JB, *et al.* Injection therapy for subacute and chronic low-back pain. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 27/11/09).
20. Priest TD, Hoggart B. Chronic pain: mechanisms and treatment. *Curr Opin Pharmacol* 2002; 2: 310–15.
21. Urquhart D, *et al.* Antidepressants for non-specific low back pain. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 23/06/08).
22. Gibson JN, Waddell G. Surgery for degenerative lumbar spondylosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 23/06/08).

23. Khadilkar A, *et al.* Transcutaneous electrical nerve stimulation (TENS) for chronic low-back pain. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 23/06/08).
24. Dubinsky RM, Miyasaki J. Assessment: efficacy of transcutaneous electric nerve stimulation in the treatment of pain in neurologic disorders (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2010; **74**: 173–6. Also available at: http://www.neurology.org/cgi/reprint/74/2/173 (accessed 07/09/10)

Myocardial infarction pain. The severe pain of acute myocardial infarction is located in the retrosternal area with radiation to the arms, neck, jaw, and epigastrium. Pain relief is of benefit not only in its own right but also because pain may cause adverse haemodynamic effects such as increases in blood pressure, heart rate, and stroke volume. Although early treatment of the myocardial infarction (p. 1257.1) may relieve pain dramatically, opioid analgesics are the first-line treatment for pain and should be given intravenously as soon as possible, that is before hospital admission, to patients with suspected infarction.[1-4] Opioids can also help to reduce anxiety. An inhaled mixture of nitrous oxide and oxygen has sometimes been used to provide pain relief before arrival in hospital; sublingual glyceryl trinitrate or an alternative fast-acting nitrate may also be given.

Diamorphine or morphine given by slow intravenous injection have generally been the opioids of choice, partly because of a better haemodynamic profile, but pethidine has also been used. An intravenous antiemetic such as metoclopramide or, if left ventricular function is not compromised, cyclizine, should also be given. The intramuscular route should only be used if venous access is unobtainable since it is relatively ineffective in shocked patients, complicates the enzymatic assessment of the infarction, and may result in large haematomas when patients are given thrombolytics. Alternative analgesics include nalbuphine or buprenorphine, although the latter may not produce pain relief as quickly as diamorphine. The cardiovascular effects of pentazocine make it unsuitable for use during or after myocardial infarction. Selective cyclo-oxygenase-2 (COX-2) inhibitors and non-selective NSAIDs (other than aspirin) should not be used in patients with acute myocardial infarction because of their known cardiovascular risks[5] (see Thrombotic Events under Adverse Effects of NSAIDs, p. 105.1).

1. Gershlick AH. The acute management of myocardial infarction. *Br Med Bull* 2001; **59**: 89–112.
2. Antman EM, *et al.* ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). Executive summary: *Circulation* 2004; **110**: 588–636. Correction. *ibid.* 2005; **111**: 2013. Full guidelines available at: http://circ.ahajournals.org/cgi/reprint/110/9/e82.pdf (accessed 23/06/08)
3. Anderson JL, *et al.* ACC/AHA 2007 guidelines for the management of patients with unstable angina/non–ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction). *Circulation* 2007; **116**: e148–e304. Full guidelines available at: http://circ.ahajournals.org/cgi/reprint/116/7/e148.pdf (accessed 23/06/08)
4. Van de Werf F, *et al.* The Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation. *Eur Heart J* 2008; **29**: 2909–45. Also available at: http://eurheartj.oxfordjournals.org/content/29/23/2909.full.pdf+html (accessed 20/04/10)
5. Antman EM, *et al.* 2007 focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2008; **117**: 296–329. Also available at: http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.107.188209.pdf (accessed 23/06/08)

Neuropathic pain syndromes. The definition and characteristics of neuropathic pain are described under Analgesia and Pain, p. 4.1. Treatment can be difficult and is best undertaken in specialist pain clinics, since neuropathic pain often responds poorly to conventional analgesics.[1-8] The painful disorders characterised by neuropathic pain (either as the predominant form of pain or as one component of the overall pain) discussed in this section are:

- Central Post-stroke Pain (p. 7.3)
- Complex Regional Pain Syndromes (p. 8.1)
- Diabetic Neuropathy (p. 8.2)
- Phantom Limb Pain (below)
- Postherpetic Neuralgia (below)
- Trigeminal Neuralgia (p. 11.2)

1. Vadalouca A, *et al.* Therapeutic management of chronic neuropathic pain: an examination of pharmacologic treatment. *Ann N Y Acad Sci* 2006; **1088**: 164–86.
2. Jackson KC. Pharmacotherapy for neuropathic pain. *Pain Pract* 2006; **6**: 27–33.
3. Cruccu G. Treatment of painful neuropathy. *Curr Opin Neurol* 2007; **20**: 531–5.
4. Dworkin RH, *et al.* Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain* 2007; **132**: 237–51.
5. Moulin DE, *et al.* Pharmacological management of chronic neuropathic pain–consensus statement and guidelines from the Canadian Pain Society. *Pain Res Manag* 2007; **12**: 13–21.
6. NICE. Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin: Technology Appraisal Guidance 159 (issued October 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA159Guidance.pdf (accessed 25/11/09)
7. Besson M, *et al.* New approaches to the pharmacotherapy of neuropathic pain. *Expert Rev Clin Pharmacol* 2008; **1**: 683–93.
8. Freynhagen R, Bennett MI. Diagnosis and management of neuropathic pain. Abridged version: *BMJ* 2009; **339**: 391–5. Full version: http://www.bmj.com/cgi/content/full/339/aug12_1/b3002?view=long&pmid=19675082 (accessed 26/11/09)

Orofacial pain. Orofacial pain may arise from many disorders so its effective management depends very much on the correct identification and treatment of any underlying cause, which may include:

- dental disease
- cluster headache (p. 670.1)
- migraine (p. 670.3)
- trigeminal neuralgia (see p. 11.2)
- sinusitis (p. 208.2)
- ear disease such as otitis media (p. 197.2)
- giant cell arteritis (p. 1604.2)
- aneurysms
- neoplasms

In the treatment of dental pain, analgesics are used judiciously as a temporary measure until the underlying cause has been effectively managed. Paracetamol or aspirin or other NSAIDs are adequate for most purposes. Opioid analgesics are relatively ineffective and are rarely needed.

Burning mouth syndrome (stomatodynia; glossodynia) is characterised by a burning sensation or other dysaesthesias of the oral mucosa in the absence of specific oral lesions. It is often accompanied by xerostomia and altered taste. Those treatments for which there is the best evidence of efficacy include topical therapy with clonazepam, systemic treatment with thioctic acid, SSRIs, or amisulpride, and cognitive therapy. Other treatments that may produce some benefit include capsaicin used topically or systemically, topical lidocaine, or systemic therapy with other antidepressants.

In addition, a large number of patients have a type of facial pain of unknown cause which is typically exacerbated by stress and can develop into a chronic debilitating disorder. Many patients with such idiopathic facial pain respond to non-opioid analgesics, explanation, and reassurance. Antidepressants such as the tricyclics are often of value. Antiepileptics, including carbamazepine and sodium valproate, and the oral lidocaine analogue mexiletine have been used as adjuncts to the tricyclics. Topical treatment with capsaicin has also been tried. Treatment needs to be continued for several months to avoid pain recurrence on withdrawal. Psychological treatments can also be helpful. Botulinum A toxin has been tried for the relief of facial pain associated with some disorders of the orofacial muscles.

References.
1. Vickers ER, Cousins MJ. Neuropathic orofacial pain part 2—diagnostic procedures, treatment guidelines and case reports. *Aust Endod J* 2000; **26**: 53–63.
2. List T, *et al.* Pharmacologic interventions in the treatment of temporomandibular disorders, atypical facial pain, and burning mouth syndrome: a qualitative systematic review. *J Orofac Pain* 2003; **17**: 301–10.
3. Lewis MA, *et al.* Management of neuropathic orofacial pain. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; **103** (suppl 1): S32.e1–S32.e24.
4. Patton LL, *et al.* Management of burning mouth syndrome: systematic review and management recommendations. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; **103** (suppl 1): S39.e1–S39.e13.
5. Mínguez Serra MP, *et al.* Pharmacological treatment of burning mouth syndrome: a review and update. *Med Oral Patol Oral Cir Bucal* 2007; **12**: E299–E304.
6. Sardella A. An up-to-date view on burning mouth syndrome. *Minerva Stomatol* 2007; **56**: 327–35.
7. Marino R, *et al.* Different therapeutic strategies for burning mouth syndrome: preliminary data. *J Oral Pathol Med* 2010; **39**: 611–16.

Pancreatic pain. Pain in pancreatitis (p. 2580.2) can be severe and may require opioid analgesics. Concerns over the long-term use of opioids in non-malignant pain should not prevent the patient being given effective analgesia which may be achieved by following the general principles recommended by the WHO for treatment of cancer pain (see p. 7.1); this involves giving non-opioid analgesics such as NSAIDs for mild attacks, with or without antispasmodics such as antimuscarinics, and progressing to 'weak' opioids such as codeine, and 'strong' opioids including morphine, according to the severity of pain.

There has been some controversy about the appropriate choice of opioid: traditionally, morphine and its derivatives have been avoided in favour of pethidine, in the belief that they are more likely to cause spasm of the sphincter of Oddi. However, the evidence supporting this has been questioned. Some suggest that κ-receptor agonists such as oxycodone may be of value. In addition, there is some evidence that pancreatic pain may have a neuropathic element, and the use of an antiepileptic such as gabapentin, or an SSRI such as paroxetine, may be considered for pain syndromes associated with chronic pancreatitis.

Analgesics are given before meals to help to alleviate the postprandial exacerbation of pain. They should be given on a regular basis and doses titrated for each patient. Pancreatic extracts may ease the pain but are otherwise reserved for those with symptomatic malabsorption. Coeliac plexus block has been used for the relief of severe intractable pain in some patients with chronic pancreatitis; it has also been used similarly in patients with cancer of the pancreas. However, the benefits of such a block are unclear.

References.
1. Thompson DR. Narcotic analgesic effects on the sphincter of Oddi: a review of the data and therapeutic implications in treating pancreatitis. *Am J Gastroenterol* 2001; **96**: 1266–72.
2. Khalid A, Whitcomb DC. Conservative treatment of chronic pancreatitis. *Eur J Gastroenterol Hepatol* 2002; **14**: 943–9.
3. El Kamar FG, *et al.* Metastatic pancreatic cancer: emerging strategies in chemotherapy and palliative care. *Oncologist* 2003; **8**: 18–34.
4. Mitchell RMS, *et al.* Pancreatitis. *Lancet* 2003; **361**: 1447–55.
5. Ståhl C, *et al.* Managing pain in chronic pancreatitis: therapeutic value of opioid treatment. *J Pain Palliat Care Pharmacother* 2007; **21**: 63–5.
6. Ceyhan GO, *et al.* Pancreatic pain. *Best Pract Res Clin Gastroenterol* 2008; **22**: 31–44.
7. Gachago C, Draganov PV. Pain management in chronic pancreatitis. *World J Gastroenterol* 2008; **14**: 3137–48.
8. Cruciani RA, Jain S. Pancreatic pain: a mini review. *Pancreatology* 2008; **8**: 230–5.

Phantom limb pain. Phantom limb pain is associated with an amputated limb and is more common when there has been severe pre-amputation pain. It is frequently a mixture of neuropathic and other types of pain. Management may be difficult[1-9] but in a survey of war veteran amputees, for those who took any form of treatment for phantom limb pain, conventional analgesics such as NSAIDs or paracetamol with or without opioid analgesics were reported as being satisfactory.[1] The use of the WHO analgesic ladder, as in cancer pain (see p. 7.1) may guide the choice of analgesic[9] although the use of opioids has been questioned in what is essentially a neuropathic pain syndrome, many consider them of potential value in phantom limb pain.[3,6] Transcutaneous electrical nerve stimulation (TENS) was another method used by some and considered to be at least as effective as other therapies.[1] Tricyclic antidepressants and antiepileptics may be of help for the neuropathic components of the pain[2-4] and some relief may be obtained with sympathetic blocks. Intravenous ketamine may also be of use.[2-4] From a review[7] of studies investigating the effect of regional anaesthesia in preventing phantom limb pain in patients undergoing lower-limb amputation it appeared that epidural blockade started before and continuing for the duration of surgery or for several days after amputation conferred more protection from long-term pain than blockade begun late intra-operatively or postoperatively. However, a randomised, double-blind, controlled study[8] failed to show any benefit of pre-emptive analgesia using epidural blockade in such patients. A subsequent review[3] that included this study concluded that the pre-emptive use of epidural block was of limited success.

1. Wartan SW, *et al.* Phantom pain and sensation among British veteran amputees. *Br J Anaesth* 1997; **78**: 652–9.
2. Nikolajsen L, Jensen TS. Phantom limb pain. *Br J Anaesth* 2001; **87**: 107–16.
3. Halbert J, *et al.* Evidence for the optimal management of acute and chronic phantom pain: a systematic review. *Clin J Pain* 2002; **18**: 84–92.
4. Flor H. Phantom-limb pain: characteristics, causes, and treatment. *Lancet Neurol* 2002; **1**: 182–9.
5. Manchikanti L, Singh V. Managing phantom pain. *Pain Physician* 2004; **7**: 365–75.
6. Wilfen P, *et al.* Diagnostic and treatment issues in postamputation pain after landmine injury. *Pain Med* 2006; **7** (suppl 2): S209–S212.
7. Katz J. Prevention of phantom limb pain by regional anaesthesia. *Lancet* 1997; **349**: 519–20.
8. Nikolajsen L, *et al.* Randomised trial of epidural bupivacaine and morphine in prevention of stump and phantom pain in lower-limb amputation. *Lancet* 1997; **350**: 1353–7.

Postherpetic neuralgia. About 10% of patients who have had acute herpes zoster still have neuropathic pain resulting from peripheral nerve injury one month or more after the rash has healed. The elderly are the most susceptible. The affected area (commonly head, neck, and limbs) is extremely sensitive to any stimuli; even the pressure of clothing can produce unbearable pain. Spontaneous remission occurs in many patients within a few months. However, in a small percentage of patients the pain can last for several years.

Attempts have been made to **prevent** the development of postherpetic neuralgia. An early meta-analysis[1] concluded that, if started within 72 hours of the onset of rash, aciclovir might reduce the incidence of residual pain at 6 months in some patients. A more recent systematic review[2] found that oral aciclovir or famciclovir did not have a significant effect on the incidence of postherpetic neuralgia 4 or 6 months after the onset of rash when compared with placebo. It is, however, generally agreed that antiviral treatment does reduce the duration of postherpetic neuralgia.[3-5] Epidural injection of methylprednisolone with bupivacaine has been shown to reduce short-term pain from herpes zoster, but was ineffective in preventing postherpetic neuralgia in the longer term,[6] and evidence of the preventive value of corticosteroids is generally lacking.[7]

Various **treatments** have been tried once neuralgia develops.[3-5,8-15] The value of conventional analgesics is limited because of the neuropathic character of the pain although opioid analgesics have been used in refractory

cases (see below). Low-dose tricyclics such as amitriptyline, or in particular nortriptyline, have been widely used for treatment, and appear to be of benefit in about half of all cases;[5] however, the antiepileptics gabapentin and pregabalin may now be preferred, and gabapentin is licensed for this indication in some countries. A comparative study has suggested that gabapentin is as effective as nortriptyline and better tolerated.[16] Topical lidocaine has also been licensed for treatment of postherpetic neuralgia, but the evidence for such use has been questioned.[17] However, it is likely to be better tolerated than the other main topical alternative, capsaicin.[5] Opioids, including methadone, morphine, and oxycodone, are usually reserved for patients who fail to respond to tricyclics or gabapentin.[10] Nerve blocks and surgical techniques may provide temporary pain relief, but results have generally been disappointing. Transcutaneous electrical nerve stimulation (TENS) has also been tried. Topical preparations of aspirin or indometacin, have shown some promise.

1. Jackson JL, *et al.* The effect of treating herpes zoster with oral acyclovir in preventing postherpetic neuralgia: a meta-analysis. *Arch Intern Med* 1997; **157**: 909–12.
2. Li Q, *et al.* Antiviral treatment for preventing postherpetic neuralgia. Available in The Cochrane Database of Systematic Reviews: Issue 2. Chichester: John Wiley; 2009 (accessed 27/11/09).
3. Alper BS, Lewis PR. Does treatment of acute herpes zoster prevent or shorten postherpetic neuralgia? *J Fam Pract* 2000; **49**: 255–64.
4. Panlilio LM, *et al.* Current management of postherpetic neuralgia. *Neurolog* 2002; **8**: 339–50.
5. Tyring SK. Management of herpes zoster and postherpetic neuralgia. *J Am Acad Dermatol* 2007; **57** (suppl): S136–S142.
6. van Wijck AJM, *et al.* The PINE study of epidural steroids and local anaesthetics to prevent postherpetic neuralgia: a randomised controlled trial. *Lancet* 2006; **367**: 219–24.
7. He L, *et al.* Corticosteroids for preventing postherpetic neuralgia. Available in The Cochrane Database of Systematic Reviews: Issue 1. Chichester: John Wiley; 2008 (accessed 23/06/08).
8. Collins SL, *et al.* Antidepressants and anticonvulsants for diabetic neuropathy and postherpetic neuralgia: a quantitative systematic review. *J Pain Symptom Manage* 2000; **20**: 449–58.
9. Johnson R, Patrick D, eds. Recommendations from the International Herpes Management Forum management strategies workshop: improving the management of varicella, herpes zoster and zoster-associated pain (issued November 2002). Available at: http://www.ihmf.org/Library/monograph/m_11.pdf (accessed 23/06/08)
10. Johnson RW, Dworkin RH. Treatment of herpes zoster and postherpetic neuralgia. *BMJ* 2003; **326**: 748–50.
11. Dworkin RH, Schmader KE. Treatment and prevention of postherpetic neuralgia. *Clin Infect Dis* 2003; **36**: 877–82.
12. Dubinsky RM, *et al.* Practice parameter: treatment of postherpetic neuralgia—an evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2004; **63**: 959–65. Also available at: http://www.neurology.org/cgi/reprint/63/6/959 (accessed 29/08/08)
13. Douglas MW, *et al.* Tolerability of treatments for postherpetic neuralgia. *Drug Safety* 2004; **27**: 1217–33.
14. Dainty P. Prevention and medical management of postherpetic neuralgia. *Br J Hosp Med* 2008; **69**: 275–8.
15. Sampathkumar P, *et al.* Herpes zoster (shingles) and postherpetic neuralgia. *Mayo Clin Proc* 2009; **84**: 274–80.
16. Chandra K, *et al.* Gabapentin versus nortriptyline in post-herpetic neuralgia patients: a randomized, double-blind clinical trial—the GONIP Trial. *Int J Clin Pharmacol Ther* 2006; **44**: 358–63.
17. Khaliq W, *et al.* Topical lidocaine for the treatment of postherpetic neuralgia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 23/06/08).

Sickle-cell crisis. The management of pain of sickle-cell crisis that can occur in sickle-cell disease (p. 1123.2) is similar to that of other forms of acute pain. The pain of mild crises may be controlled using oral analgesics such as paracetamol, an NSAID, codeine, or dihydrocodeine. Partial agonist and antagonist opioids such as buprenorphine are not recommended to treat acute pain before transfer to hospital.[1] Crises severe enough to need hospital admission usually require the use of more potent parenteral opioid analgesics but NSAIDs may be useful as an adjunct for bone pain. In most centres, morphine is the opioid of choice for moderate to severe pain. Some patients appear to prefer pethidine but many clinicians[2-8] avoid its use if possible as control of pain may be inadequate and doses of pethidine needed to manage crises can lead to accumulation of its neuroexcitatory metabolite norpethidine and precipitate seizures (see also Effects on the Nervous System, p. 122.3). UK guidelines[8,9] recommend that pethidine should only be used in exceptional circumstances such as in patients hypersensitive to other opioids. Diamorphine, fentanyl, hydromorphone, and methadone have been used as alternatives to morphine. Nalbuphine may also be suitable.[10] As the dose of opioid required to control the pain can vary considerably, not only during each episode but also from one episode to another and between individual patients, patient-controlled analgesia (see p. 5.3) may be of help to manage the pain once initial pain relief has been obtained with loading doses of parenteral opioids;[4,11,12] opioids used have included morphine and fentanyl. The use of continuous epidural analgesia with local anaesthetics alone or with opioids has been tried. However, a randomised study[13] of morphine for the management of severe painful sickle-cell crises in children showed that oral modified-release morphine was a safe and effective alternative to continuous intravenous morphine. Inhalation of a mixture of nitrous oxide and oxygen may be a useful analgesic during transfer to hospital.[1,9]

1. Report of a working party of the Standing Medical Advisory Committee on sickle cell, thalassaemia and other haemoglobinopathies. London: HMSO, 1993.
2. Pryle BJ, *et al.* Toxicity of norpethidine in sickle cell crisis. *BMJ* 1992; **304**: 1478–9.
3. Davies SC, Oni L. Management of patients with sickle cell disease. *BMJ* 1997; **315**: 656–60.
4. Vijay V, *et al.* The anaesthetist's role in acute sickle cell crisis. *Br J Anaesth* 1998; **80**: 820–8.
5. Yaster M, *et al.* The management of pain in sickle cell disease. *Pediatr Clin North Am* 2000; **47**: 699–710.
6. Marlowe KF, Chicella MF. Treatment of sickle cell pain. *Pharmacotherapy* 2002; **22**: 484–91.
7. Stinson J, Naser B. Pain management in children with sickle cell disease. *Paediatr Drugs* 2003; **5**: 229–41.
8. Sickle Cell Society. Standards for the clinical care of adults with sickle cell disease in the UK (issued 2008). Available at: http://www.sicklecellsociety.org/pdf/CareBook.pdf (accessed 14/12/09)
9. Rees DC, *et al.* British Committee for Standards in Haematology. Guidelines for the management of the acute painful crisis in sickle cell disease. *Br J Haematol* 2003; **120**: 744–52. Also available at: http://www.bcshguidelines.com/pdf/sicklecelldisease_0503.pdf (accessed 23/06/08)
10. Buchanan ID, *et al.* Opioid selection during sickle cell pain crisis and its impact on the development of acute chest syndrome. *Pediatr Blood Cancer* 2005; **45**: 716–24.
11. Grundy R, *et al.* Practical management of pain in sickling disorders. *Arch Dis Child* 1993; **69**: 256–9.
12. van Beers EJ, *et al.* Patient-controlled analgesia versus continuous infusion of morphine during vaso-occlusive crisis in sickle cell disease, a randomized controlled trial. *Am J Hematol* 2007; **82**: 955–60.
13. Jacobson SJ, *et al.* Randomised trial of oral morphine for painful episodes of sickle-cell disease in children. *Lancet* 1997; **350**: 1358–61.

Trigeminal neuralgia. Trigeminal neuralgia (tic douloureux) is a neuropathic pain characterised by sudden, brief, sharp, agonising, episodic pain in the distribution of one or more branches of the fifth cranial nerve. There may be several episodes (lasting several seconds or minutes) a day over a number of weeks, followed by a pain-free interval that may last for weeks or years. Trigeminal neuralgia generally has a 'trigger zone' in which even a very light stimulus such as a draught of air produces pain. In some cases firm pressure applied around but not to the zone itself may help to relieve pain. Trigeminal neuralgia may be idiopathic or may be secondary to nerve compression (such as that caused by a tumour), facial injury, or multiple sclerosis.

The management of trigeminal neuralgia is distinct from other forms of neuropathic pain. Carbamazepine is the drug of choice and initially may produce satisfactory pain relief in 70% or more of patients, although increasingly large doses may be required.[1-8] If pain relief is inadequate phenytoin or baclofen may be added to carbamazepine therapy; these drugs may also be used alone in patients intolerant of carbamazepine.[4] Other antiepileptics such as gabapentin, lamotrigine, oxcarbazepine, valproate, and clonazepam have also been used in patients intolerant of, or resistant to, carbamazepine.[1-4,8] Evidence for the value of non-antiepileptic drugs in trigeminal neuralgia is mostly poor.[9]

In some patients drug therapy eventually fails to control the pain or produces unacceptable adverse effects and invasive procedures become necessary. These may include the selective destruction of pain bearing nerve fibres with radiofrequency thermocoagulation, instillation of glycerol (although the efficacy and safety of the procedure is debatable), gamma knife radiation, and microvascular decompression of the trigeminal nerve root.[2,3,6-8]

1. Zakrzewska JM. Trigeminal neuralgia. *Prim Dent Care* 1997; **4**: 17–19.
2. Jolfroy A, *et al.* Trigeminal neuralgia: pathophysiology and treatment. *Acta Neurol Belg* 2001; **101**: 20–5.
3. Nurmikko TJ, Eldridge PR. Trigeminal neuralgia—pathophysiology, diagnosis and current treatments. *Br J Anaesth* 2001; **87**: 117–32.
4. Rozen TD. Antiepileptic drugs in the management of cluster headache and trigeminal neuralgia. *Headache* 2001; **41** (suppl 1): S25–S32.
5. Sindrup SH, Jensen TS. Pharmacotherapy of trigeminal neuralgia. *Clin J Pain* 2002; **18**: 22–7.
6. Scrivani SJ, *et al.* Trigeminal neuralgia. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005; **100**: 527–38.
7. Bennetto L, *et al.* Trigeminal neuralgia and its management. Abridged version: *BMJ* 2007; **334**: 201–5. Full version: http://www.bmj.com/cgi/reprint/334/7586/201.pdf (accessed 23/06/08)
8. Gronseth G, *et al.* Practice parameter: the diagnostic evaluation and treatment of trigeminal neuralgia (an evidence-based review)—report of the Quality Standards Subcommittee of the American Academy of Neurology and the European Federation of Neurological Societies. *Neurology* 2008; **71**: 1183–90.
9. He L, *et al.* Non-antiepileptic drugs for trigeminal neuralgia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 23/06/08).

Increased Body Temperature

The hypothalamus is the centre of the thermoregulatory system and is responsible for maintaining the body temperature at a set point (known as the set-point temperature) which is normally 37 degrees. Mechanisms that produce or conserve body heat include passive heat absorption from the environment, peripheral vasoconstriction, and thermogenic processes such as metabolic reactions and shivering. Heat loss is achieved mainly through sweating and peripheral vasodilatation. Various states may lead to an abnormal increase in body temperature.

Fever and hyperthermia

As mentioned above, body temperature is normally regulated by the hypothalamus. *Fever* (pyrexia) is a controlled increase in body temperature due to an elevated hypothalamic set-point temperature. Common reasons for this include infections, inflammatory disorders, neoplastic disease, and some drug treatment. *Hyperthermia* (hyperpyrexia) implies a disturbance of thermoregulatory control. It is caused by external factors such as injury to the hypothalamus, heat stroke following defective heat loss (as occurs in dehydration or excessive heat production following strenuous activities), excessive dosage of some drugs, or a reaction to certain drugs such as anaesthetics (malignant hyperthermia, p. 2024.1) or antipsychotics (neuroleptic malignant syndrome, p. 1050.2). Underlying thermoregulatory defects may be a particular problem in sedentary elderly subjects.

Whenever possible the underlying cause of fever should be identified and treated.[1] Body temperatures up to 41 degrees are relatively harmless[2] and it is not clear if there is any value in treating fever at lower temperatures,[1] but some groups may be more vulnerable, such as young children, pregnant women, or patients who are already dehydrated or malnourished or those with cardiac, respiratory, or neurological diseases.

Both physical means and antipyretics may be used to reduce body temperature in fever. Maintaining an adequate fluid intake is important. Fanning, removal of clothing, and tepid sponging are often used,[1-3] but they do not reduce the set-point of the hypothalamus, and lead to shivering (rigor) or other adverse effects as the body tries to meet the raised set-point, and their value is therefore questionable;[1,4,5] similarly, cold baths should not be used as they may actually increase body temperature by inducing vasoconstriction, and the risks of a cold-induced pressor response should be borne in mind. Antipyretics appear mostly to help return the set-point temperature to normal by inhibiting central synthesis and release of prostaglandin E_2, which mediates the effect of endogenous pyrogens in the hypothalamus.[6] This mechanism cannot lower the body temperature below normal, and antipyretics are ineffective against raised body temperature not associated with fever.

Choice of antipyretic in children has been widely debated. The drugs most commonly used are paracetamol and ibuprofen; salicylates (including aspirin) are generally contra-indicated because of the possible link between their use and the development of Reye's syndrome. A systematic review[7] found inconsistent evidence to support the use of paracetamol to reduce fever in children, since the number of reliable studies was too low to be sure that it was effective. Although studies have found that ibuprofen was superior to paracetamol in terms of both efficacy and duration of action, some of the doses of paracetamol were below those recommended in the UK and NICE did not consider that either drug had a significant advantage over the other.[1] Alternation of the two may be more effective than either alone[8,9] but again this is controversial.[1,4,5,9-12]

Antipyretics should not be given to all children with fever, but only to those in obvious discomfort or distress because of the fever or associated symptoms such as headache or myalgia.[1,4,5,13] It has been suggested that the use of antipyretics might prolong infection,[2] and that in severe infection the use of antipyretics might increase mortality:[14] WHO has[14] recommended that in developing countries antipyretics should not be given routinely to children with fever but should be reserved for those with severe discomfort or high fever. In the UK, the Joint Committee on Vaccination and Immunisation recommends antipyretic therapy to treat post-immunisation fever developing after some vaccines. However, if the fever persists after the second dose of antipyretic medical advice should be sought.

Antipyretics have also been given as *prophylaxis* against febrile convulsions, especially in those with a history of such seizures or in those with epilepsy. However, antipyretic therapy does not appear to prevent recurrence of febrile convulsions (p. 511.2).[1,15,16] There is also little to support the use of antipyretics for prophylaxis of post-immunisation fever. Furthermore, there is preliminary evidence that, although effective in preventing fever, prophylactic paracetamol can reduce antibody response to the vaccine.[17] Routine use may not be justified although some have suggested offering it to infants at higher risk of seizures receiving diphtheria-tetanus-pertussis or polio immunisation.[18]

Recommendations for management of fever in adults are similar to those for children,[2-6] although salicylates such as aspirin may also be used.

Hyperthermia may produce body temperatures greater than 41 degrees. These high temperatures are life-threatening and need to be lowered immediately. Antipyretics are ineffective since the high temperatures are a result of thermoregulatory failure. One of the most rapid and effective means of cooling is to immerse the patient in very

cold water but core temperature should be monitored to avoid inducing hypothermia.[19] Evaporative cooling methods may be more efficient.[20] Intravenous or intraperitoneal administration of cool fluids, gastric lavage or enemas with ice water have also been used.[19,21]

When hyperthermia is associated with muscle rigidity and fulminant hypermetabolism of skeletal muscle, as in the neuroleptic malignant syndrome and malignant hyperthermia, temperature reductions may be obtained using the muscle relaxant dantrolene. There is also anecdotal evidence that dantrolene may produce beneficial effects for the treatment of similar symptoms resulting from poisoning with various agents. However, dantrolene is not an effective treatment for all types of hyperthermia and rigidity accompanying poisoning. Although dantrolene has been tried in patients with heat stroke, there is no evidence that it affects outcome.[22] In severe cases of hyperthermia when neuromuscular hyperactivity may also impair ventilation, a neuromuscular blocker has been used, although suxamethonium is best avoided as it can itself precipitate malignant hyperthermia.

1. National Collaborating Centre for Women's and Children's Health/NICE. Feverish illness in children: assessment and initial management in children younger than 5 years (issued May 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/CG47Guidance.pdf (accessed 23/06/08)
2. Plaisance KI, Mackowiak PA. Antipyretic therapy: physiologic rationale, diagnostic implications, and clinical consequences. *Arch Intern Med* 2000; 160: 449–56.
3. Meremikwu M, Oyo-Ita A. Physical methods for treating fever in children. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 23/06/08).
4. Anonymous. When the child has a fever. *Drug Ther Bull* 2008; 46: 17–20.
5. El-Radhi ASM. Why is the evidence not affecting the practice of fever management? *Arch Dis Child* 2008; 93: 918–20.
6. Aronoff DM, Nielson EG. Antipyretics: mechanism of action and clinical use in fever suppression. *Am J Med* 2001; 111: 304–15.
7. Meremikwu M, Oyo-Ita A. Paracetamol for treating fever in children. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2002 (accessed 23/06/08).
8. Sarrell EM, *et al.* Antipyretic treatment in young children with fever: acetaminophen, ibuprofen, or both alternating in a randomized, double-blind study. *Arch Pediatr Adolesc Med* 2006; 160: 197–202.
9. Hay AD, *et al.* Paracetamol plus ibuprofen for the treatment of fever in children (PITCH): randomised controlled trial. Abridged version: *BMJ* 2008; 337: 729–33. Full version: http://www.bmj.com/cgi/reprint/337/sep02_2/a1302 (accessed 14/12/09) Correction. *ibid.* 2009; 339: 510.
10. Hay AD, *et al.* Antipyretic drugs for children. *BMJ* 2006; 333: 4–5.
11. Wright AD, Liebelt EL. Alternating antipyretics for fever reduction in children: an unfounded practice passed down to parents from pediatricians. *Clin Pediatr (Phila)* 2007; 46: 146–50.
12. Nabulsi M. Is combining or alternating antipyretic therapy more beneficial than monotherapy for febrile children? *BMJ* 2010; 340: 92–4.
13. Russell FM, *et al.* Evidence on the use of paracetamol in febrile children. *Bull WHO* 2003; 81: 367–72.
14. Shann F. Antipyretics in severe sepsis. *Lancet* 1995; 345: 338.
15. Joint Working Group of the Research Unit of the Royal College of Physicians and the British Paediatric Association. Guidelines for the management of convulsions with fever. *BMJ* 1991; 303: 634–6. Also available at: http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1671156&blobtype=pdf (accessed 24/06/08)
16. Uhari M, *et al.* Effect of acetaminophen and of low intermittent doses of diazepam on prevention of recurrences of febrile seizures. *J Pediatr* 1995; 126: 991–5.
17. Prymula R, *et al.* Effect of prophylactic paracetamol administration at time of vaccination on febrile reactions and antibody responses in children: two open-label, randomised controlled trials. *Lancet* 2009; 374: 1339–50.
18. Anonymous. Prophylactic paracetamol with childhood immunisation? *Drug Ther Bull* 1990; 28: 73–4.
19. Simon HB. Hyperthermia. *N Engl J Med* 1993; 329: 483–7.
20. Slovis CM. Hyperthermia. *N Engl J Med* 1994; 330: 218–19.
21. Duthie DJR. Heat-related illness. *Lancet* 1998; 352: 1329–30.
22. Bouchama A, Knochel JP. Heat stroke. *N Engl J Med* 2002; 346: 1978–88.

Musculoskeletal and Joint Disorders

The **rheumatic disorders** are painful disorders affecting mainly the joints and related structures of the musculoskeletal system, but there may also be widespread involvement of other systems. The term arthritis is used when the disease is largely confined to the joints. Some of the most common forms of arthritis are discussed in this section and these include rheumatoid arthritis (p. 13.2), osteoarthritis (below), juvenile idiopathic arthritis (below), and the spondyloarthropathies (p. 14.3) such as ankylosing spondylitis. Other conditions that are associated with arthritis and which are discussed elsewhere include gout (p. 600.1) and SLE (p. 1613.3).

The names **soft-tissue rheumatism** (see p. 14.2) and **non-articular rheumatism** have been used to describe some painful conditions associated with disease of the structures that surround a joint. For a discussion of the management of **low back pain**, see p. 9.2.

Juvenile idiopathic arthritis

Juvenile idiopathic arthritis (juvenile chronic arthritis) is a term used to describe a clinically heterogeneous group of idiopathic arthritides occurring in children under 16 years of age; subtypes include systemic arthritis, oligoarthritis and extended oligoarthritis (particularly of leg joints), polyarthritis, either positive or negative for rheumatoid factor, and enthesitis-related arthritis (commonly affects the joints of the leg and spine).[1-3]

Treatment involves many of the same drugs used for rheumatoid arthritis in adults (see p. 13.2), although there may be limited evidence for their use in children.[1-11] Appropriate management will depend on the subtype of disease, but there is no definitive consensus on the drugs of choice.

- The **NSAIDs** have been a mainstay of treatment for many years, and continue to be important.[1,2] Most children begin therapy with an NSAID,[1] and they may be particularly useful in oligoarthritis.[2] Naproxen, ibuprofen, or indometacin are among the most often used.[1] Aspirin is now rarely prescribed,[9] although in many juvenile idiopathic arthritis remains one of its few licensed indications in children.
- Intra-articular injections of a **corticosteroid** (often triamcinolone hexacetonide) are rapidly effective, and well tolerated, and are often used in oligoarthritis with, or instead of, NSAIDs;[1-3,6,10] they may reduce the development of deformity secondary to contracture.[1] They also have a role in the management of disease flare in patients already taking second-line drugs, although it is unclear whether multiple intra-articular injections would be preferable to systemic corticosteroids in patients with polyarthritis.[6]
  Moderate or high-dose systemic corticosteroids are more generally reserved for patients with systemic arthritis whose disease is not controlled by NSAIDs. In other subtypes, the adverse effects of systemic therapy are likely to outweigh the benefits. A course of low-dose prednisone might be considered for reduction of pain and stiffness in patients with severe polyarthritis who are unresponsive to other drugs, or awaiting response to slow-acting second-line treatments.[1]
- The second-line treatment of choice in children with persistent active arthritis is **methotrexate**.[1-3,7,9,10] Like several other second-line drugs it is of less benefit in systemic arthritis than in polyarthritis or refractory oligoarthritis.[9] Improvement may take up to 12 weeks to be seen.[1]
- The so-called **biological therapies** have become increasingly important in managing more severe or refractory forms of juvenile idiopathic arthritis.[1-3,7,9,11] The TNF inhibitor etanercept, which is licensed for paediatric use in many countries, produces excellent responses in many patients with polyarthritis, particularly those who are rheumatoid-factor positive.[9] Like methotrexate, it may be less effective in those with systemic juvenile idiopathic arthritis.[2,11] Infliximab, although unlicensed, also seems to be of benefit,[1-3,9,11] and may be more effective than etanercept in the treatment of associated uveitis.[2] Other drugs that have been tried with some evidence of benefit include abatacept, adalimumab, tocilizumab, anakinra, and canakinumab;[1,2,9,11,12] there is some evidence that the interleukin-1 receptor antagonist, anakinra, may be more effective than the TNF inhibitors in treating patients with systemic arthritis.[2] Abatacept, adalimumab, canakinumab, and tocilizumab are now licensed in some countries for paediatric use in active disease.
- Many **other drugs** have been tried in juvenile idiopathic arthritis, often on the basis of efficacy in adults. Sulfasalazine may be of benefit in late-onset oligoarthritis[4] but adverse effects are often troublesome.[9,10] Concern about adverse effects may also have limited the use of cytotoxic and immunosuppressant drugs other than methotrexate, and there are few controlled studies,[9] although benefit has been reported with leflunomide in polyarticular disease.[1,9,10] Thalidomide has been suggested for treatment-resistant systemic arthritis.[1] In very severe unremitting disease, autologous bone marrow transplantation has been tried.[1,3,8-10]

Drug treatment aimed at the complications of disease, rather than the disease process itself, may be needed. There is some evidence that bisphosphonates may be useful in controlling low bone mineral density and fragility fractures associated with juvenile idiopathic arthritis.[1,13] Growth hormone has also been widely used to moderate the severe growth retardation that is often seen.[1] Topical treatment with glucocorticoids and mydriatics may be needed for eye disease.[1]

Physiotherapy and occupational therapy are also important components of disease management, and surgery may be needed in selected cases.[1]

1. Ravelli A, Martini A. Juvenile idiopathic arthritis. *Lancet* 2007; 369: 767–78
2. Haines KA. Juvenile idiopathic arthritis: therapies in the 21st century. *Bull NYU Hosp Jt Dis* 2007; 65: 205–11.
3. Southwood TR, Szer IS. Juvenile idiopathic arthritis. In: Adebajo A, ed. *ABC of Rheumatology*. 4th ed. Chichester: Wiley-Blackwell, 2010. 85–97.
4. Cron RQ. Current treatment for chronic arthritis in childhood. *Curr Opin Pediatr* 2002; 14: 684–7.
5. Wilkinson N, *et al.* Biologic therapies for juvenile arthritis. *Arch Dis Child* 2003; 88: 186–91.
6. Cleary AG, *et al.* Intra-articular corticosteroid injections in juvenile idiopathic arthritis. *Arch Dis Child* 2003; 88: 192–6.
7. Ramanan AV, *et al.* Use of methotrexate in juvenile idiopathic arthritis. *Arch Dis Child* 2003; 88: 197–200.
8. Wedderburn LR, *et al.* Autologous haematopoietic stem cell transplantation in juvenile idiopathic arthritis. *Arch Dis Child* 2003; 88: 201–5.
9. Hashkes PJ, Laxer RM. Medical treatment of juvenile idiopathic arthritis. *JAMA* 2005; 294: 1671–84.
10. Beresford MW, Baildam EM. New advances in the management of juvenile idiopathic arthritis—1: non-biological therapy. *Arch Dis Child Educ Pract Ed* 2009; 94: 144–50.
11. Beresford MW, Baildam EM. New advances in the management of juvenile idiopathic arthritis—2: the era of biologicals. *Arch Dis Child Educ Pract Ed* 2009; 94: 151–6.
12. Horneff G. Update on biologicals for treatment of juvenile idiopathic arthritis. *Expert Opin Biol Ther* 2013; 13: 361–76.
13. Thornton J, *et al.* Systematic review of effectiveness of bisphosphonates in treatment of low bone mineral density and fragility fractures in juvenile idiopathic arthritis. *Arch Dis Child* 2006; 91: 753–61.

Osteoarthritis

Osteoarthritis is the clinical and pathological outcome of a range of disorders that cause structural and functional failure of synovial joints. It is characterised by involvement of the entire joint, with loss and erosion of articular cartilage, subchondral bone changes, meniscal degeneration, mild to moderate synovial inflammation, and outgrowth of bone and cartilage at the joint margins (osteophytes). These changes result in pain, stiffness (especially after inactivity) and reduced mobility, although patients with changes characteristic of osteoarthritis are often asymptomatic. Increased loading of the joint, and mechanical factors such as misalignment and muscle weakness, contribute to joint damage and loss of function. The joints most often affected are hands, hips, and knees.

Current treatment for osteoarthritis is not curative, and management is largely concerned with relief of pain and maintenance of joint function.[1-6]

Physical methods of treatment may be preferred initially, and include physiotherapy, heat and cold therapy, exercises, splinting, correction of misalignment, and weight reduction in the obese.[1-8] Acupuncture may also be tried, and appears to be of benefit in improving pain and functionality in knee osteoarthritis.[9] Transcutaneous electrical nerve stimulation (TENS) may also be of benefit; however, a systematic review[10] was found to be inconclusive due to the inclusion of small and poor studies.

For the management of pain, paracetamol is recommended as the drug of first choice.[1,4,5] Despite its benefits paracetamol has been shown to be less effective than an NSAID in patients with osteoarthritis,[11] and the latter may therefore be considered as an alternative first-line treatment.[2,4] However, the possibility of cardiovascular, gastrointestinal, or renal toxicity with NSAID treatment should be considered as its use is in a largely elderly group of patients; it is generally advised that a low-dose NSAID should only be added or substituted in patients with an inadequate response to paracetamol alone,[2,4-6] and the long-term use needed for osteoarthritis management may be problematic.[12]

In order to reduce the risk of gastrointestinal toxicity with NSAIDs, use of a gastroprotective drug such as a proton pump inhibitor or misoprostol has been recommended.[1-6,8] Cardiovascular safety is a particular concern with NSAIDs such as celecoxib that are selective inhibitors of cyclo-oxygenase-2 (COX-2); their use is limited to those patients considered to be at high risk of developing serious gastrointestinal problems if given a non-selective NSAID and who do not have pre-existing cardiovascular risk factors (see Effects on the Gastrointestinal Tract, p. 105.3). The use of topical NSAIDs has also been advocated,[4-6,8] although a meta-analysis[13] in 2004 found little evidence of long-term benefit.

In patients in whom paracetamol and/or NSAIDs are ineffective or not tolerated, addition of an opioid analgesic may be appropriate;[2,3,5,6,8,14] codeine or dihydrocodeine are often used as combinations with paracetamol, and there is evidence of benefit with tramadol, but more potent opioids such as hydrocodone, oxycodone, transdermal fentanyl, or morphine, may have a role in a selected subgroup of patients.[14]

The anthraquinone derivative diacerein has been widely used in some countries, and appears to produce a small but consistent benefit in the treatment of osteoarthritis.[15] Topical capsaicin also produces some relief of pain.[1,4-6,8] There are some interesting data[16] to suggest that doxycycline may have a favourable effect on the progression of osteoarthritis, which might open the way for the development of disease-modifying drugs. Experimental therapies include anakinra[17] and the combined cyclo-oxygenase/lipoxygenase inhibitor licofelone.[18]

Systemic corticosteroids have no place in the management of osteoarthritis. Intra-articular injection of a corticosteroid produces short-term relief of pain and inflammation,[2-4,6,8,19,20] and may be useful for acute exacerbations. Triamcinolone hexacetonide appears to be more effective than betamethasone.[20] There may also be some benefit from intra-articular injection of hyaluronic acid, to improve the viscosity and elasticity of the synovial

fluid;[21,22] improvement may be longer lasting than with intra-articular corticosteroids.[20]

Alternative and complementary therapies have been widely used in osteoarthritis.[2] Powdered rose hip has been reported to be of benefit,[23] as has a mixture of unsaponifiable fractions from avocado and soya oils (avocado-soybean unsaponifiables; ASU).[24] Particular attention has focused on the use of oral glucosamine and chondroitin. Results, however, have been ambiguous;[25-28] overall it is not clear to what extent these therapies have a benefit over placebo, but there is some evidence that combined treatment may be useful in the subset of patients with moderate to severe knee pain.[25] Evidence for chondroitin seems particularly weak.[28] An evidence-based report[29] by the Arthritis Research Campaign in the UK of 27 alternative and complementary medicines used for osteoarthritis, including ASU, capsaicin, chondroitin, glucosamine, and rose hip, found topical capsaicin to be the most effective and that ademetionine, the active derivative of methionine, may also be effective; evidence for the efficacy of glucosamine was inconclusive. However, a systematic review[30] of ademetionine therapy for osteoarthritis of the knee or hip was found to be inconclusive and routine use was not recommended.

Surgery, including joint replacement, is of great benefit to patients with severe osteoarthritis that cannot be effectively managed by physical or medical therapy.[2-6,8]

1. Felson DT. Osteoarthritis of the knee. *N Engl J Med* 2006; **354**: 841–8. Correction. *ibid.*; 2520.
2. Hunter DJ, Felson DT. Osteoarthritis. *BMJ* 2006; **332**: 639–42.
3. Lane NE. Clinical practice. Osteoarthritis of the hip. *N Engl J Med* 2007; **357**: 1413–21.
4. Hunter DJ. American College of Physicians. In the clinic: osteoarthritis. *Ann Intern Med* 2007; **147**: ITC8–1–ITC8–16. Also available at: http://www.annals.org/cgi/reprint/147/3/ITC8-1.pdf (accessed 24/06/08)
5. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. *Arthritis Rheum* 2000; **43**: 1905–15. Also available at: http://www.rheumatology.org/publications/guidelines/oa-mgmt/oa-mgmt.asp (accessed 23/06/08)
6. Byers Kraus V, Doherty M. Osteoarthritis. In: Adebajo A, ed. *ABC of Rheumatology* 4th ed. Chichester: Wiley-Blackwell, 2010: 51–8.
7. Brosseau L, *et al.* Thermotherapy for treatment of osteoarthritis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 23/06/08).
8. National Collaborating Centre for Chronic Conditions/NICE. Osteoarthritis: national clinical guideline for care and management in adults (issued February 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/CG059FullGuideline.pdf (accessed 22/07/08)
9. Scharf H-P, *et al.* Acupuncture and knee osteoarthritis: a three-armed randomized trial. *Ann Intern Med* 2006; **145**: 12–20.
10. Rutjer AWS, *et al.* Transcutaneous electrostimulation for osteoarthritis of the knee. Available in The Cochrane Database of Systematic Reviews: Issue 4. Chichester: John Wiley; 2009 (accessed 14/12/09).
11. Towheed TE, *et al.* Acetaminophen for osteoarthritis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 23/06/08).
12. Bjordal JM, *et al.* Non-steroidal anti-inflammatory drugs, including cyclo-oxygenase-2 inhibitors, in osteoarthritic knee pain: meta-analysis of randomised placebo controlled trials. *BMJ* 2004; **329**: 1317–20.
13. Lin J, *et al.* Efficacy of topical non-steroidal anti-inflammatory drugs in the treatment of osteoarthritis: meta-analysis of randomised controlled trials. *BMJ* 2004; **329**: 324–6.
14. Goodwin JL, *et al.* The use of opioids in the treatment of osteoarthritis: when, why, and how? *Curr Pain Headache Rep* 2005; **9**: 390–8.
15. Fidelix TSA, *et al.* Diacerein for osteoarthritis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 23/06/08).
16. Brandt KD, *et al.* Effects of doxycycline on progression of osteoarthritis: results of a randomized, placebo-controlled, double-blind trial. *Arthritis Rheum* 2005; **52**: 2015–25.
17. Iqbal I, Fleischmann R. Treatment of osteoarthritis with anakinra. *Curr Rheumatol Rep* 2007; **9**: 31–5.
18. Cicero AF, Laghi L. Activity and potential role of licofelone in the management of osteoarthritis. *Clin Interv Aging* 2007; **2**: 73–9.
19. Arroll B, Goodyear-Smith F. Corticosteroid injections for osteoarthritis of the knee: meta-analysis. *BMJ* 2004; **328**: 869–70.
20. Bellamy N, *et al.* Intraarticular corticosteroid for treatment of osteoarthritis of the knee. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 23/06/08).
21. Lo GH, *et al.* Intra-articular hyaluronic acid in treatment of knee osteoarthritis: a meta-analysis. *JAMA* 2003; **290**: 3115–21.
22. Bellamy N, *et al.* Viscosupplementation for the treatment of osteoarthritis of the knee. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 23/06/08).
23. Rossnagel K, *et al.* Klinische Wirksamkeit von Hagebuttenpulver bei Patienten mit Arthrose: eine systematische Übersicht. *MMW Fortschr Med* 2007; **149**: 51–6.
24. Christensen R, *et al.* Symptomatic efficacy of avocado-soybean unsaponifiables (ASU) in osteoarthritis (OA) patients: a meta-analysis of randomized controlled trials. *Osteoarthritis Cartilage* 2008; **16**: 399–408.
25. Clegg DO, *et al.* Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. *N Engl J Med* 2006; **354**: 795–808.
26. Towheed TE, *et al.* Glucosamine therapy for treating osteoarthritis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 23/06/08).
27. Towheed TE, Anastassiades T. Glucosamine therapy for osteoarthritis: an update. *J Rheumatol* 2007; **34**: 1787–90.
28. Reichenbach S, *et al.* Meta-analysis: chondroitin for osteoarthritis of the knee or hip. *Ann Intern Med* 2007; **146**: 580–90.
29. Arthritis Research Campaign. Complementary and alternative medicines for the treatment of rheumatoid arthritis, osteoarthritis and fibromyalgia (issued February 2009). Available at: http://www.arthritisresearchuk.org/Files/Complementary%20and%20alternative%20medicines_1101201015433l.pdf (accessed 08/04/10)
30. Rutjes AWS, *et al.* S-Adenosylmethionine for osteoarthritis of the knee or hip. Available in The Cochrane Database of Systematic Reviews: Issue 4. Chichester: John Wiley; 2009 (accessed 15/12/09).

Rheumatoid arthritis

Rheumatoid arthritis is a common chronic systemic inflammatory disease that results in progressive disability and increased mortality. Early disease is characterised mainly by inflammation of the synovium (the inner membrane of the capsule of synovial joints); as the disease progresses the patient suffers destruction of cartilage and bone. Extra-articular features commonly include general malaise, fatigue, weight loss, fever, and anaemia. More severe disease may be associated with vasculitis, pericarditis, pleurisy, pleural effusion, pulmonary interstitial fibrosis, peripheral neuropathies, subcutaneous and pulmonary nodules, scleritis, and Sjögren's syndrome. Palindromic rheumatism is characterised by repeated episodes of arthritis and periarthritis without fever; the joints appear normal between attacks.

The severity and course of rheumatoid arthritis varies greatly between patients. Some have brief attacks with little or no disease progression, but the majority will have slowly progressive joint destruction and deformity despite intermittent relapses and remissions; a few patients may have very severe and rapidly progressive disease. Because irreversible joint damage occurs early in the course of disease, rapid diagnosis and institution of treatment aimed at preventing progression is crucial.[1-4] Although there is no cure, remission or substantial slowing of the disease process is increasingly seen as an achievable goal in the majority of patients.[4-6]

The choice of **drugs for relief of pain** depends upon the severity of symptoms. NICE[7] recommends using analgesics such as paracetamol, codeine, or combination preparations in patients with inadequate pain control, to potentially reduce their need for long-term treatment with NSAIDs. Nevertheless, most patients prefer an NSAID; although these are thought to have an advantage because of their anti-inflammatory effects, the clinical evidence for this has been questioned.[8] There is little apparent difference between the various NSAIDs in terms of anti-inflammatory activity, but patient responses vary widely. When starting an NSAID the dose is gradually increased to the recommended maximum over 1 to 2 weeks; if the response is inadequate after a total of about 4 weeks, or if adverse effects are intolerable, other NSAIDs are tried. In the light of concerns about cardiovascular safety, treatment with selective inhibitors of cyclo-oxygenase-2 (COX-2) inhibitors such as celecoxib is limited to those patients considered to be at high risk of developing serious gastrointestinal problems if given a non-selective NSAID and who do not have pre-existing cardiovascular risk factors[9] (see Effects on the Gastrointestinal Tract, p. 105.3). Topical analgesics such as NSAIDs or capsaicin, or rubefacients may provide slight relief of pain but their role, if any, is unclear.

Once the diagnosis is confirmed and severity and progression of the disease have been assessed, introduction of a **disease-modifying antirheumatic drug** (DMARD) should take place as early as possible.[1-3,5] Although opinions vary, there is an increasing trend to aggressive management in early disease, with tight control of the disease process.[4-7,10]

Available DMARDs include antimalarials (hydroxychloroquine), sulfasalazine, gold compounds (auranofin, sodium aurothiomalate), penicillamine, conventional immunosuppressants (methotrexate, azathioprine, ciclosporin, cyclophosphamide, and leflunomide), and Janus tyrosine kinase inhibitors (tofacitinib). So-called biological therapies include the TNF-α inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab), co-stimulation blockers (abatacept), interleukin-1 receptor antagonists (anakinra), and B-cell-targeted monoclonal antibodies (rituximab). It is thought that most DMARDs inhibit the release or activity of cytokines involved in maintaining the inflammatory process, although other actions may also contribute. Since any therapeutic effect may not be apparent for 4 to 6 months, treatment should continue for at least 6 months before considered ineffective.

There is evidence of disease-modifying effect for methotrexate, sulfasalazine, leflunomide, and intramuscular gold, with less compelling data for hydroxychloroquine, penicillamine, oral gold, ciclosporin, and azathioprine.[10-16] Concerns about toxicity or efficacy mean that gold compounds and penicillamine seem now to be less widely used. There is good evidence of the efficacy of the TNF-α inhibitors,[5,6,10,16-20] and some in favour of anakinra,[17,19] but good evidence of an effect of other biological therapies on disease progression is currently scanty, although clinical benefit has been found with, for example, abatacept and rituximab.[6,17,19,21]

The choice of DMARD to begin treatment is based on the risk/benefit ratio, with the antimalarial hydroxychloroquine an option in mild disease, and sulfasalazine or methotrexate preferred in those with moderate to severe disease, or judged likely to progress.[10] Methotrexate has become the DMARD of first choice in the majority of patients.[1,2,4,10] Subcutaneous or intramuscular methotrexate may be an option in patients who cannot be satisfactorily managed with weekly oral dosage.[1,10] Addition of sulfasalazine, hydroxychloroquine, or both may be a suitable option in patients refractory to optimal methotrexate therapy,[1,10] and addition of corticosteroids or leflunomide are also options, although evidence for combining methotrexate with ciclosporin is not entirely convincing.[10] At what stage biological therapies are to be recommended remains a matter of debate. In the UK, official recommendations are still that TNF-α inhibitors should be reserved for patients who have failed treatment with two conventional (non-biological) DMARDs,[18,20,22] but others permit earlier introduction, for example after failure of the first conventional DMARD.[17,23,24] Other classes of biological therapy are likely to be reserved for patients in whom TNF-α inhibitors are ineffective or contra-indicated, as is currently the case with abatacept[4,24] and rituximab.[4,21,24,25] In the UK, rituximab is recommended in patients who have an inadequate response to TNF-α inhibitors; abatacept or an alternative TNF-α inhibitor may be tried in those who cannot be given, or have an inadequate response to, rituximab.[21]

There is also some evidence in favour of beginning therapy with a combination of DMARDs, and subsequently 'stepping down' once control is achieved.[1,5,6,10,26,27] Indeed, NICE[7] in the UK recommends using a combination of DMARDs (including methotrexate and at least one other conventional DMARD, plus short-term corticosteroids) as first-line treatment, ideally within 3 months of the onset of persistent symptoms. The large, multicentre BeSt study found that although initial combination therapy (methotrexate and infliximab, or methotrexate, sulfasalazine, and tapered high-dose prednisone) produced earlier clinical improvement and less progression of joint damage, the ultimate clinical improvement was similar in patients assigned to sequential monotherapy or 'step-up' therapy.[28] There is a concern that combination therapy may expose patients to an increased risk of toxicity,[26] although the BeSt study did not find this to be the case.[28] Combinations of TNF-α inhibitors with other biological therapies such as anakinra or abatacept are not advisable, because of an increased risk of serious infection.[6,17]

Since rheumatoid arthritis is a chronic disease, treatment may need to be very prolonged, but evidence of the long-term tolerability and efficacy of DMARDs is patchy. Studies have suggested that many DMARDs are stopped after a few years, usually because of a decline in efficacy rather than adverse events.[29]

Addition of **corticosteroids** to DMARD therapy may be useful in early disease to control synovitis, or as bridging therapy when starting or increasing DMARDs, since they produce rapid symptomatic control.[10] Although they produce bone loss, this may be outweighed (at least short-term) by their beneficial effects on the disease process: there is good evidence that adding a corticosteroid to treatment reduces the progression of joint erosion.[30] Short- and moderate-term intermittent use of relatively low doses has therefore been suggested (not exceeding the equivalent of 15 mg of prednisolone daily).[31,32] However, prolonged therapy is associated with significant adverse effects and long-term use is not usually considered justified,[10] except in a select group of patients with established disease where all other treatment options (including biological DMARDs) have been tried.[7] Intra-articular injection is recommended for acute flares, and may be particularly effective when combined with aggressive DMARD therapy.[10]

There is little good evidence to support most **other drugs** tried in rheumatoid arthritis. Meta-analysis[33] has confirmed that tetracyclines, and in particular minocycline, can produce some reduction in disease activity; effects on serological markers appear to be more marked than clinical improvements in tender and swollen joints. The effects may be greater in patients with early disease; minocycline has been recommended[24] for those with low disease activity. Much research has been conducted into immunomodulators and immunotherapy. Although alternative immunosuppressants such as mycophenolate mofetil and tacrolimus have been tried, most interest in recent years has surrounded new biological therapies. The interleukin-6 receptor antagonist tocilizumab is given with methotrexate for the treatment of moderate to severe active rheumatoid arthritis in patients who have not responded to, or are intolerant of, conventional DMARDs or TNF-α inhibitors. It may also be given as monotherapy to patients who are unable to tolerate methotrexate or in whom methotrexate would otherwise be inappropriate. Matrix metalloproteinase inhibitors have proved disappointing, but modulators of B-cell function such as atacicept, belimumab, and epratuzumab are under investigation. In addition, denosumab is of interest for its potential to control joint destruction.[6] Other methods of treatment that are being or have been investigated include gene therapy and autologous bone marrow transplantation. A rheumatoid

arthritis vaccine is also in clinical trials. Induction of tolerance with collagen and other antigens given orally has also been tried, but results are reported to be variable.[34]

Many alternative and herbal therapies have been tried. Some studies suggest that addition of fish oils[35] and/or evening primrose oil to standard antirheumatic therapy might help to reduce pain and joint swelling. However, an evidence-based report[36] by the Arthritis Research Campaign in the UK of 21 alternative and complementary medicines used for rheumatoid arthritis, including collagen, evening primrose oil, fish oils, and green-lipped mussel, only found evidence of efficacy for fish oils.

There has been considerable interest in the possibility that statins such as atorvastatin may produce clinical improvements, albeit modest, in symptoms of rheumatoid arthritis,[37] as well as in any accompanying cardiovascular risk factors.

The importance of managing comorbidity in patients with rheumatoid arthritis has been emphasised;[1] in particular infection (especially pulmonary infection), cardiovascular disease, and osteoporosis require appropriate management and action to reduce risk factors.

The treatment of rheumatoid arthritis during **pregnancy** presents its own problems; some of the most effective DMARDs such as methotrexate and leflunomide have teratogenic properties, and for others, including the biological therapies, there is little evidence.[38,39] Hydroxychloroquine, and perhaps azathioprine and sulfasalazine, may be relatively safe to use, but it is important to weigh benefit against risk for each individual case.[38]

1. O'Dell JR. Therapeutic strategies for rheumatoid arthritis. *N Engl J Med* 2004; 350: 2591–2602.
2. Doan T, Massarotti E. Rheumatoid arthritis: an overview of new and emerging therapies. *J Clin Pharmacol* 2005; 45: 751–62.
3. Nurmohamed MT, Dijkmans BAC. Efficacy, tolerability and cost effectiveness of disease-modifying antirheumatic drugs and biologic agents in rheumatoid arthritis. *Drugs* 2005; 65: 661–94.
4. Klareskog L, *et al.* Rheumatoid arthritis. *Lancet* 2009; 373: 659–72.
5. Emery P. Treatment of rheumatoid arthritis. *BMJ* 2006; 332: 152–5.
6. Smolen JS, *et al.* New therapies for treatment of rheumatoid arthritis. *Lancet* 2007; 370: 1861–74.
7. National Collaborating Centre for Chronic Conditions/NICE. Rheumatoid arthritis: national clinical guideline for management and treatment in adults (issued February 2009). Available at: http://www.nice.org.uk/nicemedia/pdf/CG79FullGuideline.pdf (accessed 15/12/09)
8. Wienecke T, Gøtzsche PC. Paracetamol versus nonsteroidal anti-inflammatory drugs for rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 23/06/08).
9. MHRA. Updated advice on the safety of selective COX-2 inhibitors. Message from Professor G Duff, Chairman of Committee on Safety of Medicines (issued 17th February, 2005). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON019458&RevisionSelectionMethod=LatestReleased (accessed 23/06/08)
10. Luqmani R, *et al.* British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of rheumatoid arthritis (the first two years). *Rheumatology (Oxford)* 2006; 45: 1167–9. Full guideline available at: http://rheumatology.oxfordjournals.org/cgi/data/kel215a/DC1/1 (accessed 23/06/08)
11. Felson DT, *et al.* The comparative efficacy and toxicity of second-line drugs in rheumatoid arthritis. *Arthritis Rheum* 1990; 33: 1449–61.
12. Felson DT, *et al.* Use of short-term efficacy/toxicity tradeoffs to select second-line drugs in rheumatoid arthritis: a metaanalysis of published clinical trials. *Arthritis Rheum* 1992; 35: 1117–25.
13. Capell HA, *et al.* Second line (disease modifying) treatment in rheumatoid arthritis: which drug for which patient? *Ann Rheum Dis* 1993; 52: 423–8.
14. Tugwell P. International consensus recommendations on cyclosporin use in rheumatoid arthritis. *Drugs* 1995; 50: 48–56.
15. Cush JJ, *et al.* US consensus guidelines for the use of cyclosporin A in rheumatoid arthritis. *J Rheumatol* 1999; 26: 1176–86.
16. Donahue KE, *et al.* Systematic review: comparative effectiveness and harms of disease-modifying medications for rheumatoid arthritis. *Ann Intern Med* 2008; 148: 124–34.
17. Furst DE, *et al.* Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2007. *Ann Rheum Dis* 2007; 66 (suppl 3): iii2–iii22. Correction. *ibid.* 2008; 67: 280.
18. NICE. Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis (includes a review of technology appraisal guidance 36): Technology Appraisal Guidance 130 (issued October 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/TA130guidance.pdf (accessed 23/06/08)
19. Singh JA, *et al.* Biologics for rheumatoid arthritis: an overview of Cochrane reviews. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 15/12/09).
20. NICE. Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs: Technology Appraisal Guidance 225 (issued June 2011). Available at: http://www.nice.org.uk/nicemedia/live/13490/54929/54929.pdf (accessed 05/08/11)
21. NICE. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (part review of NICE technology appraisal guidance 36 and review of NICE technology appraisal guidance 126 and 141): Technology Appraisal Guidance 195 (issued August 2010). Available at: http://www.nice.org.uk/nicemedia/live/13108/50413/50413.pdf (accessed 04/11/10)
22. Ledingham J, Deighton C. British Society for Rheumatology Standards, Guidelines and Audit Working Group. Update on the British Society for Rheumatology guidelines for prescribing TNFα blockers in adults with rheumatoid arthritis (update of previous guidelines of April 2001). *Rheumatology (Oxford)* 2005; 44: 157–63. Also available at: http://rheumatology.oxfordjournals.org/cgi/reprint/44/2/157.pdf (accessed 23/06/08)
23. Meyer O, *et al.* Clinical practice format for choosing a second-line disease modifying anti-rheumatic drug in early rheumatoid arthritis after failure of 6 months' first-line DMARD therapy. *Joint Bone Spine* 2007; 74: 73–8.
24. Saag KG, *et al.* American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum* 2008; 59: 762–84. Also available at: http://www.rheumatology.org/publications/guidelines/recommendations.pdf (accessed 15/12/09)
25. Smolen JS, *et al.* Working Group on the Rituximab Consensus Statement. Consensus statement on the use of rituximab in patients with rheumatoid arthritis. *Ann Rheum Dis* 2007; 66: 143–50. Also available at: http://ard.bmj.com/cgi/reprint/66/2/143.pdf (accessed 24/06/08)
26. Anonymous. Combination therapy for early rheumatoid arthritis. *Drug Ther Bull* 2006; 44: 81–5.
27. Roberts LJ, *et al.* Early combination disease modifying antirheumatic drug treatment for rheumatoid arthritis. *Med J Aust* 2006; 184: 122–5.
28. Goekoop-Ruiterman YPM, *et al.* Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2007; 146: 406–15.
29. Capell H. Longterm maintenance therapy with disease modifying antirheumatic drugs. *J Rheumatol* 2002; 29 (suppl 66): 38–43.
30. Kirwan JR, *et al.* Effects of glucocorticoids on radiological progression in rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 23/06/08).
31. Gotzsche PC, Johansen HK. Short-term low-dose corticosteroids vs placebo and nonsteroidal antiinflammatory drugs in rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 23/06/08).
32. Criswell LA, *et al.* Moderate-term, low-dose corticosteroids for rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1998 (accessed 23/06/08).
33. Stone M, *et al.* Should tetracycline treatment be used more extensively for rheumatoid arthritis? Metaanalysis demonstrates clinical benefit with reduction in disease activity. *J Rheumatol* 2003; 30: 2112–22.
34. Toussirot ÉA. Oral tolerance in the treatment of rheumatoid arthritis. *Curr Drug Targets Inflamm Allergy* 2002; 1: 45–52.
35. Cleland LG, *et al.* The role of fish oils in the treatment of rheumatoid arthritis. *Drugs* 2003; 63: 845–53.
36. Arthritis Research Campaign. Complementary and alternative medicines for the treatment of rheumatoid arthritis, osteoarthritis and fibromyalgia (issued February 2009). Available at: http://www.arthritisresearchuk.org/Files/Complementary%20and%20alternative%20medicines_1101201015433 1.pdf (accessed 08/04/10)
37. McCarey DW, *et al.* Trial of Atorvastatin in Rheumatoid Arthritis (TARA): double-blind, randomised placebo-controlled trial. *Lancet* 2004; 363: 2015–21.
38. Vroom F, *et al.* Disease-modifying antirheumatic drugs in pregnancy: current status and implications for the future. *Drug Safety* 2006; 29: 845–63.
39. Golding A, *et al.* Rheumatoid arthritis and reproduction. *Rheum Dis Clin North Am* 2007; 33: 319–43, vi–vii.

Soft-tissue rheumatism

Soft-tissue rheumatism includes conditions such as:

- bursitis (e.g. housemaid's knee)
- fasciitis
- fibromyalgia (fibrositis, muscular rheumatism, myofascial pain)
- frozen shoulder
- humeral epicondylitis (e.g. tennis or golfer's elbow)
- sprains and strains
- tendinitis
- tenosynovitis
- Tietze's syndrome

Inflamed or displaced tissue may also impinge on nearby nerves and produce compression neuropathies such as carpal tunnel syndrome.

Some forms of soft-tissue rheumatism respond to selective rest of the affected region, massage, splinting, or application of heat, cold, or rubefacients.[1-3] Exercise is of value in neck pain,[3,4] fibromyalgia,[5-10] and frozen shoulder,[11] but its benefit in epicondylitis is unclear.[4]

For patients with epicondylitis oral or topical NSAIDs may offer short-term pain relief, but it is unclear if they are effective in producing longer term benefit.[3,4] They are of unknown benefit in frozen shoulder,[11] and are not thought to be helpful in fibromyalgia,[5,12,13] although some benefit has been reported with paracetamol and tramadol.[7,10,12-14]

Corticosteroid injections produce dose-dependent benefit for up to 9 months in shoulder pain such as that associated with rotator cuff tendinitis or frozen shoulder,[15] and oral corticosteroids may be of benefit for up to 6 weeks although it is not clear that benefit is subsequently maintained[16] (a study[17] in patients with epicondylitis suggested that benefits of corticosteroid injection in this group were paradoxically reversed after 6 weeks). Corticosteroid injections are often combined with a local anaesthetic; injection of a local anaesthetic alone has been shown to be of benefit in chronic neck pain.[4]

Botulinum toxin has been tried in epicondylitis[18] and myofascial pain.[19] There is evidence that nitric oxide plays a role in healing in patients with tendinitis, and topical application of a patch containing glyceryl trinitrate has proved of benefit in patients with epicondylitis or tendinitis.[20]

Fibromyalgia appears to be associated with abnormal pain responses, and some consider it a central pain syndrome rather than a rheumatic syndrome. There is strong evidence that low-dose tricyclic antidepressants are of benefit in many patients, as is the tricyclic compound cyclobenzaprine. Combination of amitriptyline with the SSRI fluoxetine also appears beneficial, although SSRIs alone have produced equivocal results: serotonin and noradrenaline reuptake inhibitors (SNRIs) such as duloxetine, milnacipran, or venlafaxine have also been reported to be of value. A meta-analysis[21] of antidepressants (the aforementioned drug groups and MAOIs) in the treatment of fibromyalgia found strong evidence for their efficacy in reducing pain, sleep disturbances, and depressed mood, and improving health-related quality of life; however, effect sizes were small. Nevertheless, the authors suggested using short-term amitriptyline (based on effect size) and duloxetine (based on number of patients studied) for the treatment of pain and sleep disturbances. The antiepileptics pregabalin and gabapentin have been shown to be of benefit in controlled studies.[5,6,8,10,12-14] Duloxetine, milnacipran, and pregabalin are now licensed in some countries for the treatment of fibromyalgia. Sodium oxybate has also been reported to show some benefit. Alternative and complementary therapies have been tried;[13] however, an evidence-based report[22] by the Arthritis Research Campaign in the UK of 4 such therapies, including ademetionine (the active derivative of methionine) and topical capsaicin, found no evidence of efficacy.

Surgery may be of benefit in some conditions such as epicondylitis and possibly shoulder pain.[3,4] Surgical decompression is also the definitive treatment for carpal tunnel syndrome,[23] although there is also evidence of benefit from splinting[2,24] and local corticosteroid injection[2,25] (although benefit may not be long term, and the procedure carries some risks[26]). A systematic review[27] concluded that surgical treatment was significantly better than splinting for symptomatic relief of carpal tunnel syndrome. However, further study is needed to determine if it is better than corticosteroid injection or for patients with mild symptoms. Oral corticosteroids and ultrasound have also shown benefit in patients with carpal tunnel syndrome.[24]

1. Reveille JD. Soft-tissue rheumatism: diagnosis and treatment. *Am J Med* 1997; 102 (suppl 1A): 23S–29S.
2. Shipley M, Wise E. Pain in the wrist and hand. In: Adebajo A, ed. *ABC of Rheumatology*. 4th ed. Chichester: Wiley-Blackwell, 2010: 5–11.
3. Buchbinder R, Mitchell C. Pain in the neck, shoulder and arm. In: Adebajo A, ed. *ABC of Rheumatology*. 4th ed. Chichester: Wiley-Blackwell, 2010: 12–20.
4. van Tulder M, *et al.* Repetitive strain injury. *Lancet* 2007; 369: 1815–22
5. Porseth KØ, Gran JT. Management of fibromyalgia: what are the best treatment choices? *Drugs* 2002; 62: 577–92.
6. Goldenberg DL, *et al.* Management of fibromyalgia syndrome. *JAMA* 2004; 292: 2388–95.
7. Busch AJ, *et al.* Exercise for treating fibromyalgia syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 16/12/09).
8. Rao SG, *et al.* Understanding the fibromyalgia syndrome. *Psychopharmacol Bull* 2007; 40: 24–67.
9. Goldenberg DL. Multidisciplinary modalities in the treatment of fibromyalgia. *J Clin Psychiatry* 2008; 69 (suppl 2): 30–4.
10. Staud R. Pharmacological treatment of fibromyalgia syndrome: new developments. *Drugs* 2010; 70: 1–14.
11. Dias R, *et al.* Frozen shoulder. *BMJ* 2005; 331: 1453–6.
12. Clauw DJ. Pharmacotherapy for patients with fibromyalgia. *J Clin Psychiatry* 2008; 69 (suppl 2): 25–9.
13. Abeles M, *et al.* Update on fibromyalgia therapy. *Am J Med* 2008; 121: 555–61.
14. Goldenberg DL. Pharmacological treatment of fibromyalgia and other chronic musculoskeletal pain. *Best Pract Res Clin Rheumatol* 2007; 21: 499–511.
15. Arroll B, Goodyear-Smith F. Corticosteroid injections for painful shoulder: a meta-analysis. *Br J Gen Pract* 2005; 55: 224–8.
16. Buchbinder R, *et al.* Oral steroids for adhesive capsulitis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 23/06/08).
17. Bisset L, *et al.* Mobilisation with movement and exercise, corticosteroid injection, or wait and see for tennis elbow: randomised trial. Abridged version: *BMJ* 2006; 333: 939–41. Full version: http://www.bmj.com/cgi/reprint/333/7575/939.pdf (accessed 23/06/08)
18. Wong SM, *et al.* Treatment of lateral epicondylitis with botulinum toxin: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2005; 143: 793–7.
19. Qerama E, *et al.* A double-blind, controlled study of botulinum toxin A in chronic myofascial pain. *Neurology* 2006; 67: 241–5.
20. Murrell GAC. Using nitric oxide to treat tendinopathy. *Br J Sports Med* 2007; 41: 227–31.
21. Häuser W, *et al.* Treatment of fibromyalgia syndrome with antidepressants: a meta-analysis. *JAMA* 2009; 301: 198–209.
22. Arthritis Research Campaign. Complementary and alternative medicines for the treatment of rheumatoid arthritis, osteoarthritis and fibromyalgia (issued February 2009). Available at: http://www.arthritisresearchuk.org/Files/Complementary%20and%20alternative%20medicines_1101201015433 1.pdf (accessed 08/04/10)
23. Bland JDP. Carpal tunnel syndrome. *BMJ* 2007; 335: 343–6.
24. O'Connor D, *et al.* Non-surgical treatment: (other than steroid injection) for carpal tunnel syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 23/06/08).
25. Marshall S, *et al.* Local corticosteroid injection for carpal tunnel syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 23/06/08).
26. Gooch CL, Mitten DJ. Treatment of carpal tunnel syndrome: is there a role for local corticosteroid injection? *Neurology* 2005; 64: 2006–7.
27. Verdugo RJ, *et al.* Surgical versus non-surgical treatment for carpal tunnel syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 16/12/09).

Spondyloarthropathies

The spondyloarthropathies are a group of seronegative arthritides which include ankylosing spondylitis, psoriatic arthritis, arthritis associated with inflammatory bowel disorders (enteropathic arthritis), and arthritis associated with infection as in reactive arthritis (aseptic arthritis).

Ankylosing spondylitis is characterised by arthritis of the spine and sacroiliac joints and sometimes there is also asymmetrical peripheral involvement. Axial spondyloarthritis is considered an early stage of ankylosing spondylitis. Males under 40 years of age are mainly affected. The aim of

management of the disease is to reduce pain and stiffness and to prevent spine and joint deformity, which is accomplished using a combination of active physical therapy and drug therapy. Exercises are used to strengthen muscles and to maintain a good posture and range of movement in joints. NSAIDs are used to relieve pain and inflammation, thus allowing the exercises to be performed; they do not influence the progression of the disease. Some patients may need to add other non-opioid analgesics such as paracetamol for additional pain control. Systemic corticosteroids are rarely indicated but intra-articular injections of corticosteroids may be beneficial when one or two peripheral joints are severely affected. The disease-modifying antirheumatic drug (DMARD) sulfasalazine is of benefit for peripheral arthritis, but not for spinal symptoms. The efficacy of most other DMARDs used in rheumatoid arthritis (see p. 13.2) remains to be shown. However, the TNF-α inhibitors adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab improve spinal pain, function, and peripheral joint disease. They produce rapid benefit (usually within 12 weeks) although most patients relapse once they are withdrawn. Treatment with a TNF-α inhibitor should be considered in patients with active disease despite conventional treatments. There is some evidence that early intervention may produce better remission rates, but it is yet unknown if this results in longer-lasting remission on withdrawal. Evidence is mostly lacking for other biological therapies, but no marked benefit has been seen in conflicting studies with the interleukin-1 receptor antagonist anakinra.

Psoriatic arthritis (or psoriatic arthropathy) is an inflammatory seronegative arthritis occurring in patients with psoriasis. In some patients the spine may be involved when the condition may be indistinguishable from ankylosing spondylitis. Less frequently some patients have a form of symmetrical arthritis resembling rheumatoid arthritis. The psoriasis (p. 1688.1) and the arthritis usually require separate treatment. Treatment of the arthritis is initially as for ankylosing spondylitis with NSAIDs and physical therapy. If these methods fail treatment with a DMARD may be instituted, although chloroquine and hydroxychloroquine should be avoided since they may precipitate skin reactions (see Psoriatic Arthritis, p. 653.2). There is most evidence to support the use of sulfasalazine or methotrexate. Leflunomide may be effective but is likely to be restricted by its toxicity and prolonged half-life. Ciclosporin is also restricted by its toxicity. As in ankylosing spondylitis, however, significant benefit has now been found with the TNF-α inhibitors, and treatment with these is recommended in patients with active disease despite treatment with NSAIDs and/or conventional (non-biological) DMARDs. Adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab are available and treatment should be individualised; a monoclonal antibody such as adalimumab or infliximab may be advocated in patients who also have inflammatory bowel disease. There is some suggestion that alefacept may also be of benefit in psoriatic arthritis. Systemic corticosteroids have little or no place in the management of psoriatic arthritis.

Reactive arthritis (aseptic arthritis) is characterised by sterile synovitis following 1 to 4 weeks after an infection, most commonly of the gastrointestinal or genito-urinary tract. Extra-articular features involving the skin, eyes, or genito-urinary tract may or may not be present. Reactive arthritis is also a feature of Reiter's syndrome. Reactive arthritis is treated with physical therapy and NSAIDs and, if indicated, intra-articular injections of corticosteroids; the role of antibacterials is less certain (see Bone and Joint Infections, p. 177.1).

References.

1. Jones G, *et al.* Interventions for treating psoriatic arthritis. Available in The Cochrane Database of Systematic Reviews: Issue 3. Chichester: John Wiley; 2000 (accessed 23/06/08).
2. Khan MA. Update on spondyloarthropathies. *Ann Intern Med* 2002; **136**: 896–907.
3. Lee RZ, Veale DJ. Management of spondyloarthropathy: new pharmacological treatment options. *Drugs* 2002; **62**: 2349–59.
4. Sieper J, *et al.* Ankylosing spondylitis: an overview. *Ann Rheum Dis* 2002; **61** (suppl III): iii8–iii18.
5. van der Horst-Bruinsma IE, *et al.* Treatment of ankylosing spondylitis with disease modifying antirheumatic drugs. *Clin Exp Rheumatol* 2002; **20** (suppl 28): S67–S70.
6. Brockbank J, Gladman D. Diagnosis and management of psoriatic arthritis. *Drugs* 2002; **62**: 2447–57.
7. Kyle S, *et al.* British Society for Rheumatology Standards Guidelines Audit Working Group. Guideline for anti-TNF-α therapy in psoriatic arthritis. *Rheumatology (Oxford)* 2005; **44**: 390–7. Corrections. *ibid.*; 569 and 701. Also available at: http://rheumatology.oxfordjournals.org/cgi/reprint/44/3/390.pdf (accessed 23/06/08)
8. Keat A, *et al.* British Society for Rheumatology Standards, Guidelines and Audit Working Group. BSR guidelines for prescribing TNF-α blockers in adults with ankylosing spondylitis. *Rheumatology (Oxford)* 2005; **44**: 939–47. Also available at: http://www.rheumatology.org.uk/guidelines/guidelines_as/tnfguideline_as (accessed 23/06/08)
9. Gladman DD. Traditional and newer therapeutic options for psoriatic arthritis: an evidence-based review. *Drugs* 2005; **65**: 1223–38.
10. Boulos P, *et al.* Pharmacological treatment of ankylosing spondylitis: a systematic review. *Drugs* 2005; **65**: 2111–27.
11. Reveille JD, Arnett FC. Spondyloarthritis: update on pathogenesis and management. *Am J Med* 2005; **118**: 592–603.
12. Petersel DL, Sigal LH. Reactive arthritis. *Infect Dis Clin North Am* 2005; **19**: 863–83.
13. Leirisalo-Repo M. Reactive arthritis. *Scand J Rheumatol* 2005; **34**: 251–9.
14. Gordon KB, Ruderman EM. The treatment of psoriasis and psoriatic arthritis: an interdisciplinary approach. *J Am Acad Dermatol* 2006; **54** (suppl 2): S85–S91.
15. McVeigh CM, Cairns AP. Diagnosis and management of ankylosing spondylitis. *BMJ* 2006; **333**: 581–5.
16. Zochling J, *et al.* ASsessment in AS' International Working Group. European League Against Rheumatism. ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann Rheum Dis* 2006; **65**: 442–52. Also available at: http://ard.bmj.com/cgi/reprint/65/4/442.pdf (accessed 23/06/08)
17. Anonymous. New drugs for peripheral joint psoriatic arthritis. *Drug Ther Bull* 2006; **44**: 1–5.
18. Furst DE, *et al.* Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2007. *Ann Rheum Dis* 2007; **66** (suppl 3): iii2–iii22. Correction. *ibid.* 2008; **67**: 280.
19. Braun J, Sieper J. Ankylosing spondylitis. *Lancet* 2007; **369**: 1379–90.
20. Pham T, *et al.* Club Rhumatismes et Inflammation (CRI/SFR). Recommendations of the French Society for Rheumatology regarding TNFα antagonist therapy in patients with ankylosing spondylitis or psoriatic arthritis: 2007 update. *Joint Bone Spine* 2007; **74**: 638–46.
21. Maksymowych WP. Update on the treatment of ankylosing spondylitis. *Ther Clin Risk Manag* 2007; **3**: 1125–33.
22. Ravindran V, *et al.* A systematic review and meta-analysis of efficacy and toxicity of disease modifying anti-rheumatic drugs and biological agents for psoriatic arthritis. *Ann Rheum Dis* 2008; **67**: 855–9.
23. Gottlieb A, *et al.* Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 2. Psoriatic arthritis: overview and guidelines of care for treatment with an emphasis on the biologics. *J Am Acad Dermatol* 2008; **58**: 851–64.
24. NICE. Adalimumab, etanercept and infliximab for ankylosing spondylitis: Technology Appraisal 143 (issued May 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA143Guidance.pdf (accessed 22/07/08)
25. Keat A, Inman R. Spondyloarthritides. In: Adebajo A, ed. *ABC of Rheumatology*. 4th ed. Chichester: Wiley-Blackwell, 2010: 79–84.
26. NICE. Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (review of technology appraisal guidance 104 and 125): Technology Appraisal Guidance 199 (issued August 2010). Available at: http://www.nice.org.uk/nicemedia/live/13110/50422/50422.pdf (accessed 19/10/10)
27. NICE. Golimumab for the treatment of psoriatic arthritis: Technology Appraisal Guidance 220 (issued April 2011). Available at: http://www.nice.org.uk/nicemedia/live/13441/54169/54169.pdf (accessed 05/08/11)

Still's disease

Adult-onset Still's disease is a syndrome characterised by high fever, with body temperature classically spiking daily or twice daily, an evanescent pink maculopapular rash, and arthritis (usually oligoarthritis initially). It is most common in patients aged 16 to 35 years.

Treatment has traditionally relied on NSAIDs, corticosteroids, and immunosuppressants or other DMARDs similar to those used in rheumatoid arthritis (p. 13.2).[1-3] A trial of NSAIDs is worthwhile in patients with mild disease, but most patients cannot be managed with NSAIDs alone.[2,3] Corticosteroids may be needed for initial therapy if manifestations are severe, but will eventually be needed in about 80% of cases.[2] DMARDs (generally methotrexate) are introduced when corticosteroid therapy fails to control the disease or when their adverse effects become problematic. Most patients will respond to methotrexate although liver function must be closely monitored. The value of other DMARDs is uncertain. Intravenous immunoglobulin is also frequently tried, although supporting evidence is lacking.[2,3]

The TNF-α inhibitors have also been tried,[2,3] but results have been variable.[2] There is, however, some evidence that interleukin-1 and interleukin-6 play a role in pathogenesis of the condition, and there have been a few reports of dramatic improvement with anakinra (an interleukin-1 receptor antagonist) in resistant disease, while tocilizumab (an interleukin-6 receptor antagonist) has also been suggested as an investigational therapy.[2,3]

The name Still's disease has also been used rather inconsistently to describe some types of juvenile idiopathic arthritis (p. 12.1).

1. Efthimiou P, Georgy S. Pathogenesis and management of adult-onset Still's disease. *Semin Arthritis Rheum* 2006; **36**: 144–52.
2. Pouchot J. How can we improve the management of adult-onset Still's disease? *Joint Bone Spine* 2007; **74**: 117–19.
3. Kontzias A, Efthimiou P. Adult-onset Still's disease: pathogenesis, clinical manifestations and therapeutic advances. *Drugs* 2008; **68**: 319–337.

Abatacept *(BAN, USAN, rINN)*

Abataceptum; BMS-188667; CTLA4-Ig; Абатацепт.

1-25-oncostatin M (human precursor) fusion protein with CTLA-4 (antigen) (human) fusion protein with immunoglobulin G1 (human heavy chain fragment), bimolecular (146→146')-disulfide.

CAS — 332348-12-6.

ATC — L04AA24.

ATC Vet — QL04AA24.

UNII — 7D0YB67S97.

Uses and Administration

Abatacept, a fusion protein, is a co-stimulation blocker. It prevents the activation of T-cells; activated T-cells have been found in the synovium of patients with rheumatoid arthritis. Abatacept is described as a biological disease-modifying antirheumatic drug (DMARD).

Abatacept is used in the treatment of moderate to severe active rheumatoid arthritis (below). In the UK, it is licensed for use in patients who have had an inadequate response to at least one other DMARD, including methotrexate or a TNF inhibitor; in the USA, it is licensed for use in early disease. In the UK, abatacept is licensed for use with methotrexate; however, in the USA it may be given alone or with other DMARDs (but see Interactions, p. 16.1).

Abatacept is given by *intravenous infusion* over a period of 30 minutes in the following doses, based on body-weight:

- 500 mg for patients weighing less than 60 kg
- 750 mg for those weighing 60 to 100 kg
- 1 g for those over 100 kg

The dose is repeated at 2 and 4 weeks, then every 4 weeks thereafter. If a response to treatment is not seen within 6 months, the benefits of continuing abatacept may need to be considered.

Abatacept may also be self-administered by *subcutaneous injection*. After a single intravenous loading dose given according to body-weight (as above), the first subcutaneous dose of 125 mg should be injected within a day; thereafter, 125 mg is injected once weekly. Patients who are unable to receive an infusion can start weekly subcutaneous injections without an intravenous loading dose. Those who are transferring from intravenous therapy should inject the first subcutaneous dose instead of receiving the next scheduled intravenous dose.

For the use of abatacept in children, and recommended doses, see below.

Abatacept is also being studied for other auto-immune diseases such as inflammatory bowel disease, psoriatic arthritis, and SLE.

Administration in children. Abatacept is licensed in the treatment of moderate to severe, active juvenile idiopathic arthritis in children aged 6 years and above; it may be used alone or with methotrexate. The dose is calculated according to body-weight and is given as an *intravenous infusion* over 30 minutes; those weighing less than 75 kg should be given 10 mg/kg initially, while heavier children may receive the appropriate adult intravenous dose (see above). Doses should be repeated at 2 and 4 weeks, and then every 4 weeks thereafter.

Rheumatoid arthritis. References to the use of abatacept in rheumatoid arthritis[1-9] (p. 13.2) and juvenile idiopathic arthritis[10-12] (p. 12.1).

1. Nogid A, Pham DQ. Role of abatacept in the management of rheumatoid arthritis. *Clin Ther* 2006; **28**: 1764–78.
2. Lundquist L. Abatacept: a novel therapy approved for the treatment of patients with rheumatoid arthritis. *Adv Therapy* 2007; **24**: 333–45.
3. Russell AS, *et al.* Abatacept improves both the physical and mental health of patients with rheumatoid arthritis who have inadequate response to methotrexate treatment. *Ann Rheum Dis* 2007; **66**: 189–94.
4. Bruce SP, Boyce EG. Update on abatacept: a selective costimulation modulator for rheumatoid arthritis. *Ann Pharmacother* 2007; **41**: 1153–62.
5. Maxwell L, Singh JA. Abatacept for rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 14/12/09).
6. NICE. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (part review of NICE technology appraisal guidance 36 and review of NICE technology appraisal guidance 126 and 141): Technology Appraisal Guidance 195 (issued August 2010). Available at: http://www.nice.org.uk/nicemedia/live/13108/50413/50413.pdf (accessed 04/11/10)
7. NICE. Abatacept for the treatment of rheumatoid arthritis after the failure of conventional disease-modifying anti-rheumatic drugs: Technology Appraisal Guidance 234 (issued August 2011). Available at: http://www.nice.org.uk/nicemedia/live/13562/56020/56020.pdf (accessed 08/03/12)
8. Genovese MC, *et al.* Subcutaneous abatacept versus intravenous abatacept: a phase IIIb noninferiority study in patients with an inadequate response to methotrexate. *Arthritis Rheum* 2011; **63**: 2854–64.
9. Kremer JM, *et al.* Long-term safety, efficacy and inhibition of radiographic progression with abatacept treatment in patients with rheumatoid arthritis and an inadequate response to methotrexate: 3-year results from the AIM trial. *Ann Rheum Dis* 2011; **70**: 1826–30.
10. Ruperto N, *et al.* Paediatric Rheumatology INternational Trials Organization (PRINTO). Pediatric Rheumatology Collaborative Study Group (PRCSG). Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. *Lancet* 2008; **372**: 383–91.
11. Ruperto N, *et al.* PRINTO. PRCSG. Long-term safety and efficacy of abatacept in children with juvenile idiopathic arthritis. *Arthritis Rheum* 2010; **62**: 1792–1802.
12. Goldzweig O, Hashkes PJ. Abatacept in the treatment of polyarticular JIA: development, clinical utility, and place in therapy. *Drug Des Devel Ther* 2011; **5**: 61–70.

Adverse Effects and Precautions

Reactions commonly occur within 1 hour of starting an infusion of abatacept. The most frequently reported infusion events are dizziness, headache, and hypertension; hypo-

tension and dyspnoea occur less commonly. Other acute events include nausea, flushing, pruritus, rash, and wheezing. Most events are usually mild to moderate although stopping treatment may be necessary in a few patients.

Other common adverse effects include headache, nasopharyngitis, nausea, dyspepsia, diarrhoea, dizziness, back pain, fatigue, cough, and abnormal liver function values. Antibodies to abatacept may develop and anaphylaxis or anaphylactic reactions have been reported rarely. Uncommon adverse reactions include paraesthesia, thrombocytopenia, and leucopenia.

Infections are frequent in patients treated with abatacept and most often affect the respiratory and urinary tracts. More serious infections such as pneumonia, sepsis, cellulitis, bronchitis, diverticulitis, and acute pyelonephritis have also been rarely associated with abatacept treatment; some of these infections have been fatal. Treatment should be stopped in patients who develop a serious infection. Since immunosuppressive therapy has been associated with progressive multifocal leukoencephalopathy (PML) treatment with abatacept should be discontinued if neurological symptoms suggestive of PML occur during use. Abatacept should not be given to patients with severe and uncontrolled infections such as sepsis and opportunistic infections. It should be used with caution in patients with a history of recurrent infections, with underlying conditions that may predispose to infections, or with chronic, latent, or localised infections. Patients should be screened for latent tuberculosis before starting treatment; those testing positive should be treated with standard chemoprophylaxis before beginning abatacept.

Some disease-modifying antirheumatic drugs have been associated with hepatitis B reactivation; licensed product information for abatacept recommends screening for viral hepatitis before starting treatment.

Adverse effects of abatacept are more frequent in patients with chronic obstructive pulmonary disease and may include a worsening of their respiratory symptoms.

Carcinogenicity. The role of abatacept in the onset of malignancies such as lymphoma in humans is not known.

In placebo-controlled studies the overall frequency of malignancies in patients treated with abatacept compared with those who received placebo was similar (1.4% and 1.1%, respectively). However, there were more cases of lung cancer and lymphomas in those given abatacept. In studies in *mice*, increases in lymphomas and mammary tumours have been noted, although these increases have not been seen in some studies with other mammals.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies abatacept as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 15/11/11)

Interactions

Live vaccines should not be given with abatacept, or within 3 months of stopping it, as its effect on vaccine efficacy or the risk of infection transmission is unknown. The use of TNF inhibitors with abatacept may increase the risk of serious infections (see under Infliximab, p. 77.3); such combinations are not recommended. Many of the serious infections reported have occurred in patients also receiving immunosuppressive therapy (see also p. 15.3). Use with anakinra or rituximab is also not recommended because of insufficient evidence to assess safety.

Pharmacokinetics

Abatacept is reported to have linear pharmacokinetics at usual dosages. After repeated intravenous doses, its mean terminal half-life is about 13 days. The mean terminal half-life after subcutaneous administration is about 14 days; bioavailability relative to intravenous use is about 79%.

Studies in *animals* suggest that abatacept is distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Orencia; ***Austral.***: Orencia; ***Austria***: Orencia; ***Belg.***: Orencia; ***Braz.***: Orencia; ***Canad.***: Orencia; ***Chile***: Orencia; ***Cz.***: Orencia; ***Denm.***: Orencia; ***Fr.***: Orencia; ***Ger.***: Orencia; ***Gr.***: Orencia; ***Hong Kong***: Orencia; ***Hung.***: Orencia; ***Irl.***: Orencia; ***Israel***: Orencia; ***Ital.***: Orencia; ***Jpn***: Orencia; ***Neth.***: Orencia; ***Norw.***: Orencia; ***NZ***: Orencia; ***Pol.***: Orencia; ***Port.***: Orencia; ***Singapore***: Orencia; ***Spain***: Orencia; ***Swed.***: Orencia; ***Switz.***: Orencia; ***Turk.***: Orencia; ***UK***: Orencia; ***USA***: Orencia.

Aceclofenac *(BAN, rINN)*

Acéclofénac; Aceclofenaco; Aceclofenacum; Aceklofenak; Aceklofenák; Aceklofenakas; Aseklofenaakki; Aseklofenak; Ацеклофенак.

[o-(2,6-Dichloroanilino)phenyl]acetate glycolic acid ester; 2-(2,6-Dichloroanalino)phenylacetoxyacetic acid.

$C_{16}H_{13}Cl_2NO_4$=354.2

CAS — 89796-99-6.

ATC — M01AB16; M02AA25.

ATC Vet — QM01AB16; QM02AA25.

UNII — RPK779R03H.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Aceclofenac). A white or almost white, crystalline powder. Practically insoluble in water; soluble in alcohol; freely soluble in acetone. Protect from light.

Uses and Administration

Aceclofenac, a phenylacetic acid derivative, is an NSAID (see p. 102.3) related to diclofenac (p. 48.3). It is used in the management of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis, in usual oral doses of 100 mg twice daily. Reduced doses should be used in patients with hepatic impairment, see below.

The sodium salt andaceclofenac betadex (aceclofenac betacyclodextrin) have been used similarly.

Reviews.

1. Dooley M, *et al.* Aceclofenac: a reappraisal of its use in the management of pain and rheumatic disease. *Drugs* 2001; 61: 1351–78.
2. Reginster JY, *et al.* Comment positionner l'acéclofénac au sein de l'arsenal thérapeutique des pathologies ostéo-articulaires chroniques? *Rev Med Liege* 2001; 56: 484–8.
3. Legrand E. Aceclofenac in the management of inflammatory pain. *Expert Opin Pharmacother* 2004; 5: 1347–57.
4. Lee J, *et al.* Formulation of microemulsion systems for transdermal delivery of aceclofenac. *Arch Pharm Res* 2005; 28: 1097–1102.

Administration in hepatic impairment. The initial oral dose of aceclofenac should be reduced to 100 mg daily in patients with hepatic impairment.

Adverse Effects and Treatment

As for NSAIDs in general, p. 104.3.

Hypersensitivity. Leucocytoclastic vasculitis, a type III hypersensitivity reaction, has been reported after therapy with aceclofenac.[1,2] Anaphylaxis has also occurred.[3]

1. Epelde F, Boada L. Leukocytoclastic vasculitis and hemoptysis after treatment with aceclofenac. *Ann Pharmacother* 1995; 29: 1168.
2. Morros R, *et al.* Hypersensitivity vasculitis related to aceclofenac. *Br J Rheumatol* 1997; 36: 503–4.
3. Rojas-Hijazo B, *et al.* Anaphylactic reaction after aceclofenac intake. *Allergy* 2006; 61: 511.

Precautions

As for NSAIDs in general, p. 107.1.

Aceclofenac should be avoided in patients with moderate to severe renal impairment.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies aceclofenac as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 23/10/11)

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Pharmacokinetics

Aceclofenac is well absorbed from the gastrointestinal tract and peak plasma concentrations occur 1 to 3 hours after an oral dose. Aceclofenac is more than 99% bound to plasma proteins. The plasma-elimination half-life is about 4 hours. About two-thirds of a dose is excreted in the urine, mainly as hydroxymetabolites. A small amount is converted to diclofenac.

It has been suggested[1] that low concentrations of diclofenac, a minor metabolite, may account for some of the actions of aceclofenac.

1. Hinz B, *et al.* Aceclofenac spares cyclooxygenase 1 as a result of limited but sustained biotransformation to diclofenac. *Clin Pharmacol Ther* 2003; 74: 222–35.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Berlofen; Urodulox; ***Belg.***: Air-Tal; Biofenac; ***Braz.***: Cecofene; Proflam; ***China***: Ai Fen (爱芬); AiFen (爱芬); Bei Su Qing (贝速清); Fen Ke Jing (分可靖); Ji Li Da (济力达); Lai Yi Fen (莱亿芬); Meinuofen (美诺芬); Wei Pu Fen (维朴芬); Xi Li Te (喜力特); ***Fr.***: Cartrex; ***Ger.***: Beofenac; ***Gr.***: Aceclonac; Arlina; Biofenac; Fractopon; Iasan; Sovipan; ***Hung.***: Acecgen; Aflamin; Flemac; ***India***: Abate-SR; Abdal; AC; ACB; Accept; Aceact; Acebloc; Acec; Aceclo; Acefen; Aceforce; Acelofan; Acelom; Acemove-SR; Acemove; Acenac; Acenez; Acent; Acerap; Acetuff; Acewin-SR; Acl-SR; Acicloflex; Acifact; Acifon; Acilex; Aciz; Aclo; Aclocta; Aclofen; Aclonac-SR; Acota; Afesan; Alnase; Aloo-SR; Alto; Altraflam; Arflur-100; Arflur; Aroff BCD; Aroff; Arrestin; Asiclo; Asonac; Atofen; Avir; Axsol SR; Canefo; Carnil AC; Catrix; Ceco; Celfast SR; Clonac; Cynac; Diplofen; Dipt; Dolochek; Dolokind; Dolostat; Dolour; Dolowin; Eclonac; Ecnac-SR; Elfenac-SR; Elven; Erinac; Fastnac SR; Fepra; Fico; Flamace; Flamtop-SR; Flaxinac-SR; Fornac; Fortafen; Genac; Hifenac; Hinac; Icenac; Icobit; Inane; Kairnac; Kinectine; Labace; Labonac; Letgo; Locet; Mahanac; Megadox; Micronac; Movace; Movexx; Moviz; Movon; Nacku; Naid; NBace-P; Neflo; Niplonac; Novo; Novoflam; Nusaid; Otonac; Painout; Panace; Zerodol; ***Ital.***: Airtal; Gladio; Kafenac; ***Mex.***: Bristaflam; Dexenac; Mycinadol; ***Neth.***: Biofenac; ***Philipp.***: Clanza; ***Port.***: Airtal; Biofenac; ***Rus.***: Airtal (Аэртал); Asinac (Асинак); ***Spain***: Aclocen; Airtal Difucrem; Airtal; Aracenac; Falcol; Gerbin; ***Turk.***: Biofenac; ***UAE***: Aceclofar; ***UK***: Preservex; ***Ukr.***: Airtal (Аэртал); Zerodol (Зеродол); ***Venez.***: Bristaflam.

Multi-ingredient Preparations. ***India***: Abate-CZ; Abate; Abdal Plus; Abdal-SP; AC Para; AC Sera; AC-Plus; AC2; ACB Plus; ACB-S; Accept-P; Accept-SP; Accept; Acceti-P; Ace-Proxyvon; Ace-Q-Para; Ace-X; Aceact-P; Acebloc-P; Acec Plus; Acec-P; Aceclo Plus; Aceclo-MR; Aceclo-Sera; Acecloren-P; Acecloren; Acedase-P; Acedase; Acefen-P; Acefen-SP; Aceflow-P; Aceforce-MR; Aceforce-P; Aceforce-SP; Acelofan Plus; Acelofan-SP; Acelom-P; Acelom-SP; Acemag-P; Acemiz-MR; Acemove Plus; Acemove-MR; Acemove-XT; Acemove; Acenac-P; Acenec; Acenez-P; Acent-MR; Acent-P; Acent-SD; Acent-TZ; Acent; Acepar-MR; Acepar; Acepara-S; Acepara; Acepil-P; Acerap-P; Aceroc-P; Acetal-SP; Acetech-P; Acetrop; Acetuff-MR; Acetuff-SP; Acewin; Aci-MR; Aciana-P; Acicloflex-MR; Acicloflex-SP; Acidol-P; Acifact-P; Acilex-P; Acimol-S; Aciz Plus; Aciz-SP; Aclocta-P; Aclodase; Aclofen Plus; Aclog-CX; Aclog-SD; Aclog; Aclomp-P; Aclomp-SP; Aclonac-P; Aclonac-SN; Aclonac-P; Acloson-SP; Aclozox; Acota-3; Acota-MR; Adifax-P; Adifax-SP; Afen-P; Afesan-CZ; Afesan-P; Afesan-SP; Alco-P; Alco-PS; Aleron; Algin-P; Alnase-P; Alnase-SP; Aloo; Alora; Alostar-SP; Alto P; Alto-3D; Alto; Altraflam-P; Anbrol-A; Ankare; Anodyne-P; Anthro; Ara; Arflur-3D; Arflur-MR; Arflur-P; Arflur; Arifnac-P; Aroff Plus; Aroff-EZ; Arrestin-P; Arrestin-SP; Arthocerin-A; Ascapar-P; Asflam; Asimol-AC; Asonac Forte; Asonac Plus; Asonac-SR Plus; Asonac-SR; Atofen Plus; Away-P; Axsol-P; Canefo-Plus; Carnil ACP; Catrix-P; Ceco Plus; Ceco-SP; Cedia-AC; Ceklif Plus; Celfast Plus; Celfast; Clobee-SP; Clofen-SP; Clonac Plus; Clonac-SP; Clophen-P; Combihext; Combodol; Conac-P; Conac-PT; Curejoint-AC; Cyka Plus; Cynac-MR; Cynac-P; Cynac-S; Cynac-SP; Decomb; Dersy-AP; Dinal-AP; Diplofen 3D; Diplofen-MR; Diplofen-P; Diplofen; Dipt-P; Diptase; Dolochek-P; Dolokind Plus; Dolokind-AA; Dolokind-MR; Doloral P; Doloral; Doloroff-AP; Doloroff-ASP; Dolostat-MR; Dolostat-PC; Dolour-X; Dolowin Forte; Dolowin Plus; Dolowin-MR; Dolowin; Dublace-P; Dublace-SP; Dycerin-A; Eclo-P; Eclonac-P; Ecnac-P; Elaxic-P; Elfenac Plus; Elfenac-MR; Elven-P; Erinac-P; Esnil; Essmol-3 Plus; Essmol-AF; Extranac; Fan-P; Fastnac; Fenbest MR; Fenbest P; Fenbest Plus; Fepra-P; Fico-P; Fico-SP; Flago; Flamace-MR; Flamace-P; Flamace-S; Flamace-SP; Flamtop; Flaxinac-SP; Flaxinac; Flexibel-AD; Flexidol-P; Flexidol; Flozen-AA; Fornac-CZ; Fornac-P; Fornac-SP; Fortafen Plus; Fortafen; Gag-PR; Genac-SP; Gesnac-P; Gramol-P; Gramol-SP; GS-AP; Hifenac-D; Hifenac-MR; Hifenac-P; Icenac-P; Icobit-MR; Icobit-P; Icobit-Plus; Icobit-S; Inane-P; Indofenac-P; Inflahit-P; Inflahit-SP; Inflameri; Isiko-Plus; Jacpar; Kairnac-P; Kinectine P; Kinectine-MR†; Klonac-P; Klonac-XS; Kudzu; Labace-P; Lacfen-P; Leofenac-MR; Leofenac-SP; Litonac-MR; Litonac-P; Litonac-SP; Locet-P; Lofen; Mahadol; Mahanac Pro; Masai; Maxinac; Maxoflam-A; MDace-P; MDace-SP; Micronac Plus; Micronac-MR; Micronac; Molsee; Morcet Plus; Morcet-MR; Morcet; Movace Plus; Movelite Plus; Mover; Movexx Plus; Moviz XP; Moviz-3D; Movon-MR; Movon-P; Movon-PT; Mumo; Nacku-P; Naid-P; Neflo-P; Nimopace A; Niplonac-MR; Niplonac-P; Nismol-S; Nismol; Novo-Plus; Novodase; Novoflam-Plus; Novonac-P; Novozox; Nusaid-MR; Nusaid-P; Nusaid-SP; Onspot; Opinac; Optiflam-P; Otonac-P; Pacinac; Pacinac; Panace-P; Panace; Panama Plus; Panama-SP; Paratel-AC; Paratel-ACP; Parclo-AP; Zerodol-MR; Zerodol-P.

Acemetacin *(BAN, rINN)*

Acemetacina; Acémétacine; Acemetacinum; Asemetasin; Bay-f-4975; Indometasinin Glikolik Asit Esteri; TVX-1322; Ацеметацин.

O-[(1-*p*-Chlorobenzoyl-5-methoxy-2-methylindol-3-yl)acetyl] glycolic acid.

$C_{21}H_{18}ClNO_6$=415.8

CAS — 53164-05-9.

ATC — M01AB11.

ATC Vet — QM01AB11.

UNII — 5V141XK28X.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*.

Ph. Eur. 8: (Acemetacin). A yellow or greenish-yellow, crystalline powder. It exhibits polymorphism. Practically insoluble in water; slightly soluble in anhydrous alcohol; soluble in acetone. Protect from light.

Uses and Administration

Acemetacin, a glycolic acid ester of indometacin, is an NSAID (p. 102.3). Its pharmacological activity is due to both acemetacin and its major metabolite, indometacin (p. 71.2). Acemetacin is used in rheumatoid arthritis, osteoarthritis, and low back pain, and for postoperative pain and inflammation. Usual oral doses are 120 to 180 mg daily in divided doses. Acemetacin is eliminated by both hepatic and renal routes, although pharmacokinetics are not affected by moderate renal or hepatic impairment and appear to be unchanged in the elderly.

References.
1. Jones RW, *et al.* Comparative pharmacokinetics of acemetacin in young subjects and elderly patients. *Br J Clin Pharmacol* 1991; 31: 543–5.
2. Hazleman B, Bernstein RM. Acemetacin in the long-term therapy of rheumatoid arthritis. *Curr Med Res Opin* 1993; 13: 119–26.
3. Chou CT, Tsai YY. A double-blind, randomized, controlled parallel group study evaluating the efficacy and safety of acemetacin for the management of osteoarthritis. *Int J Clin Pharmacol Res* 2002; 22: 1–6.
4. Leeb BF, *et al.* Behandlung der Gonarthrose: Wirksamkeit und Verträglichkeit von retardiertem Acemetacin im Vergleich zu Celecoxib. *Orthopade* 2004; 33: 1032–41.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3.

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Pharmacokinetics

Acemetacin is well absorbed after oral dosage. Its major metabolite is indometacin (p. 71.2) which, after repeated doses, is present at higher concentrations than those of acemetacin. Acemetacin is bound to plasma proteins to a slightly lesser extent than indometacin. It is eliminated via both the liver and the kidneys.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Rheutrop; ***China***: Rantudil (优妥); Shun Song (顺松); ***Cz.***: Rantudil†; ***Ger.***: Acemetadoc†; Rantudil; ***Gr.***: Gamespir; Rantudal; ***Hung.***: Rantudil; ***Jpn***: Rantudil; ***Malaysia***: Acemet; ***Mex.***: Rantudil; ***Philipp.***: Rantudil†; ***Pol.***: Rantudil; ***Port.***: Rantudil; ***Switz.***: Tilur; ***Turk.***: Rantudil; ***UK***: Emflex; ***Venez.***: Pranex.

Multi-ingredient Preparations. ***Arg.***: Rucaten Forte; Rucaten Prednisolona; ***Thai.***: Aceo.

Acetanilide

Acetanilid; Acetanilida; Acétanilide; Antifebrin; Asetanilidi; Ацетанилид; Антифебрин.

N-Phenylacetamide.

C_8H_9NO=135.2

CAS — 103-84-4.

UNII — SP86R356CC.

Pharmacopoeias. In *Fr.*

Profile

Acetanilide, a para-aminophenol derivative related to paracetamol (p. 115.1), has analgesic and antipyretic properties. It was replaced by safer analgesics.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. ***Fr.***: Neurocynesine†; ***Neth.***: Neurocynesine†.

Actarit *(rINN)*

Actaritum; MS-932; Актарит.

(*p*-Acetamidophenyl)acetic acid.

$C_{10}H_{11}NO_3$=193.2

CAS — 18699-02-0.

UNII — HW5B6351RZ.

Profile

Actarit is reported to be a disease-modifying antirheumatic drug. It has been given in the treatment of rheumatoid arthritis in a usual oral dose of 100 mg three times daily.

Adverse effects. A photosensitivity reaction developed in a 52-year-old woman one month after starting actarit and doxycycline.[1] Photopatch tests for both drugs were only positive for the patches containing actarit.

1. Kawada A, *et al.* Photosensitivity due to actarit. *Contact Dermatitis* 1997; 36: 175–6.

Use. References.

1. Nakamura H, *et al.* Clinical effects of actarit in rheumatoid arthritis: improvement of early disease activity mediated by reduction of serum concentrations of nitric oxide. *Clin Exp Rheumatol* 2000; 18: 445–50.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: An Ji Xin (安吉欣)†; Kai Mai Si (凯迈思); ***Jpn***: Mover; Orcl.

Adalimumab *(BAN, USAN, rINN)*

Adalimumabum; D2E7; LU-200134; Адалимумаб.

Immunoglobulin G1 (human monoclonal D2E7 heavy chain anti-human tumor necrosis factor), disulfide with human monoclonal D2E7κ-chain, dimer.

CAS — 331731-18-1.

ATC — L04AB04.

ATC Vet — QL04AB04.

UNII — FYS6T7F842.

Uses and Administration

Adalimumab is a recombinant human monoclonal TNF antibody that binds specifically to TNF-α and blocks its interaction with endogenous cell-surface TNF receptors. It also modulates biological responses that are induced or regulated by TNF. Elevated levels of TNF have been found in the affected tissues and fluids of patients with rheumatoid arthritis (p. 18.1), axial spondyloarthritis, ankylosing spondylitis, and psoriatic arthritis (see Spondyloarthropathies, p. 18.1), plaque psoriasis (below), and Crohn's disease and ulcerative colitis (see Inflammatory Bowel Disease, below). Adalimumab is described as a biological disease-modifying antirheumatic drug (DMARD).

Adalimumab is used in the treatment of moderate to severe, active **rheumatoid arthritis** and active and progressive **psoriatic arthritis**. In the UK, it is licensed for use in patients who have had an inadequate response to standard DMARDs, although in severe progressive rheumatoid arthritis it may be used in patients not previously treated with methotrexate; in the USA, it is licensed for use in early disease. Adalimumab is also used in the treatment of active **ankylosing spondylitis**: UK licensed product information recommends that it should only be used in patients with severe disease who have had an inadequate response to conventional treatment; however, in the USA it may be used in early disease. In the UK, it is also used in the treatment of severe **axial spondyloarthritis** without radiographic evidence of ankylosing spondylitis in patients who have had an inadequate response to, or are intolerant of, NSAIDs. For all the above indications, it is given by subcutaneous injection in a dose of 40 mg every other week. In the treatment of rheumatoid arthritis, UK licensed product information recommends that adalimumab should be given with methotrexate, although monotherapy may be used where treatment with methotrexate would be inappropriate. When used as monotherapy in rheumatoid arthritis, some patients may benefit from increasing the dose to 40 mg every week. In the UK, NICE recommends that adalimumab be stopped if there is no adequate response after 6 months for the treatment of rheumatoid arthritis, and after 12 weeks for psoriatic arthritis or ankylosing spondylitis.

Adalimumab is used in the treatment of moderate to severe, active **Crohn's disease** and **ulcerative colitis** unresponsive to conventional treatment; it may also be used in patients with Crohn's disease who have relapsed while taking infliximab. For both these indications, patients may be given an initial dose of 160 mg subcutaneously on day 1 (given as four 40-mg injections in one day or two 40-mg injections daily for 2 consecutive days), followed by 80 mg two weeks later (day 15). After a further two weeks (day 29), a maintenance dose of 40 mg every other week may be started. There is a high risk of adverse effects associated with the above induction dose, consequently, in those with Crohn's disease who do not require a more rapid response to therapy, UK licensed product information advises that a lower dose of 80 mg may be given initially, followed by 40 mg 2 weeks later; thereafter, usual maintenance doses may be given. A clinical response is usually seen within 8 or 12 weeks of starting treatment for ulcerative colitis or Crohn's disease, respectively; for both indications, those patients who relapse while on adalimumab may benefit from increasing the maintenance dose to 40 mg every week.

In the treatment of moderate to severe chronic **plaque psoriasis** in patients unresponsive to, or intolerant of, conventional systemic therapy including phototherapy, the recommended initial dose of adalimumab is 80 mg subcutaneously; this may be followed by a maintenance dose of 40 mg subcutaneously on alternate weeks, starting 1 week after the initial dose. A clinical response is usually seen within 16 weeks of starting treatment.

For the uses of adalimumab in children, and recommended doses, see below.

Administration in children. Adalimumab is used in the treatment of active polyarticular **juvenile idiopathic arthritis** in children. In the UK, it is licensed for use in those aged 2 years and older who have had an inadequate response to standard disease-modifying antirheumatic drugs (DMARDs). The dose in children aged 2 to 12 years is calculated according to body-surface and is given subcutaneously: 24 mg/m^2 up to a maximum dose of 20 mg in those younger than 4 years of age and 40 mg in those aged 4 to 12 years may be given every other week. Older children may receive 40 mg every other week regardless of body-surface area. Licensed product information also recommends that it should be given with methotrexate, although monotherapy may be used where treatment with methotrexate is inappropriate. In the USA, adalimumab is licensed for use in children aged 4 to 17 years to reduce the signs and symptoms of moderately to severely active disease; the dose is calculated according to body-weight and is given subcutaneously: those weighing 15 kg to less than 30 kg should be given 20 mg every other week, while heavier children may receive 40 mg every other week.

In the UK, adalimumab is also licensed for the treatment of severe, active **Crohn's disease** in children aged 6 years and older who have had an inadequate response to conventional therapy, or who have contra-indications for or are intolerant of such treatments. The dose is given subcutaneously, according to body-weight: those weighing less than 40 kg should be given an initial dose of 80 mg on day 1, followed by 40 mg 2 weeks later (day 15). After a further 2 weeks (day 29), a maintenance dose of 20 mg every other week may be started. There is a high risk of adverse effects associated with the above induction dose, consequently, in those who do not require a more rapid response to therapy, licensed product information advises that a lower dose of 40 mg may be given initially, followed by 20 mg 2 weeks later; thereafter, usual maintenance doses may be given. Patients who have an insufficient response may benefit from increasing the maintenance dose to 20 mg every week. Heavier children may be given the usual adult dose (see above) for this indication.

Hidradenitis suppurativa. For mention of adalimumab having been used in the treatment of hidradenitis suppurativa, see under Infliximab, p. 75.1.

Inflammatory bowel disease. Adalimumab is used in the management of inflammatory bowel disease (p. 1811.3) such as Crohn's disease and ulcerative colitis.[1-9] It has also been tried in children.[10-12]

1. Plosker GL, Lyseng-Williamson KA. Adalimumab: in Crohn's disease. *BioDrugs* 2007; 21: 125–32.
2. NICE. Infliximab (review) and adalimumab for the treatment of Crohn's disease (includes a review of NICE technology appraisal guidance 40): Technology Appraisal Guidance 187 (issued May 2010). Available at: http://www.nice.org.uk/nicemedia/live/12985/48552/48552.pdf (accessed 19/10/10)
3. Huang ML, *et al.* Efficacy and safety of adalimumab in Crohn's disease: meta-analysis of placebo-controlled trials. *J Dig Dis* 2011; 12: 165–72.
4. Guidi L, *et al.* Update on the management of inflammatory bowel disease: specific role of adalimumab. *Clin Exp Gastroenterol* 2011; 4: 163–72.
5. Wasan SK, Kane SV. Adalimumab for the treatment of inflammatory bowel disease. *Expert Rev Gastroenterol Hepatol* 2011; 5: 679–84.
6. Reinisch W, *et al.* Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. *Gut* 2011; 60: 780–7.
7. Sandborn WJ, *et al.* Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2012; 142: 257–65.e1–3.
8. Burness CB, Keating GM. Adalimumab: a review of its use in the treatment of patients with ulcerative colitis. *BioDrugs* 2013; 27: 247–62.
9. Panaccione R, *et al.* Adalimumab maintains remission of Crohn's disease after up to 4 years of treatment: data from CHARM and ADHERE. *Aliment Pharmacol Ther* 2013; 38: 1236–47.
10. Viola F, *et al.* Efficacy of adalimumab in moderate-to-severe pediatric Crohn's disease. *Am J Gastroenterol* 2009; 104: 2566–71.
11. Russell RK, *et al.* A British Society of Paediatric Gastroenterology, Hepatology and Nutrition survey of the effectiveness and safety of adalimumab in children with inflammatory bowel disease. *Aliment Pharmacol Ther* 2011; 33: 946–53.
12. Hyams JS, *et al.* Safety and efficacy of adalimumab for moderate to severe Crohn's disease in children. *Gastroenterology* 2012; 143: 365–74. e2.

Psoriasis. Adalimumab is used in the treatment of plaque psoriasis[1-7] (p. 1688.1).

1. NICE. Adalimumab for the treatment of adults with psoriasis: Technology Appraisal Guidance 146 (issued June 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA146Guidance.pdf (accessed 25/07/08)
2. Papoutsaki M, *et al.* Adalimumab for the treatment of severe psoriasis and psoriatic arthritis. *Expert Opin Biol Ther* 2008; 8: 363–70.
3. Traczewski P, Rudnicka L. Adalimumab in dermatology. *Br J Clin Pharmacol* 2008; 66: 618–25.
4. Croom KF, McCormack PL. Adalimumab: in plaque psoriasis. *Am J Clin Dermatol* 2009; 10: 43–50.
5. Iaconi A, *et al.* Psoriasis and its treatment with adalimumab. *Expert Opin Biol Ther* 2010; 10: 133–52.
6. Leonardi C, *et al.* Efficacy, safety and medication cost implications of adalimumab 40 mg weekly dosing in patients with psoriasis with

suboptimal response to 40 mg every other week dosing: results from an open-label study. *Br J Dermatol* 2012; 167: 658–67.
7. Saraceno R, *et al.* Adalimumab in the treatment of plaque-type psoriasis and psoriatic arthritis. *Expert Opin Biol Ther* 2013; 13: 1325–34.

Rheumatoid arthritis. Some references[1-9] to the use of adalimumab in rheumatoid arthritis (p. 13.2) and juvenile idiopathic arthritis (p. 12.1).

1. Navarro-Sarabia F, *et al.* Adalimumab for treating rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 13/06/08).
2. Cvetković RS, Scott LJ. Adalimumab: a review of its use in adult patients with rheumatoid arthritis. *BioDrugs* 2006; 20: 293–311.
3. Chen Y-F, *et al.* NHS Health Technology Assessment Programme. A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness (issued November 2006). Available at: http://www.hta.ac.uk/fullmono/mon1042.pdf (accessed 31/10/08)
4. Mease PJ. Adalimumab in the treatment of arthritis. *Ther Clin Risk Manag* 2007; 3: 133–48.
5. NICE. Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis (includes a review of technology appraisal guidance 36): Technology Appraisal Guidance 130 (issued October 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/TA130guidance.pdf (accessed 03/11/08)
6. Lovell DJ, *et al.* Pediatric Rheumatology Collaborative Study Group. Pediatric Rheumatology International Trials Organisation. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. *N Engl J Med* 2008; 359: 810–20.
7. NICE. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (part review of NICE technology appraisal guidance 36 and review of NICE technology appraisal guidance 126 and 141): Technology Appraisal Guidance 195 (issued August 2010). Available at: http://www.nice.org.uk/nicemedia/live/13108/50413/50413.pdf (accessed 04/11/10)
8. Wiens A, *et al.* Meta-analysis of the efficacy and safety of adalimumab, etanercept, and infliximab for the treatment of rheumatoid arthritis. *Pharmacotherapy* 2010; 30: 339–53.
9. Poddubnyy D, Rudwaleit M. Efficacy and safety of adalimumab treatment in patients with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis. *Expert Opin Drug Safety* 2011; 10: 655–73.

Spondyloarthropathies. References[1-13] to the use of adalimumab in ankylosing spondylitis, axial spondyloarthritis, and psoriatic arthritis (p. 14.3).

1. Simpson D, Scott LJ. Adalimumab: in psoriatic arthritis. *Drugs* 2006; 66: 1487–96.
2. McLeod C, *et al.* NHS Health Technology Assessment Programme. Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation (issued August 2007). Available at: http://www.hta.ac.uk/fullmono/mon1128.pdf (accessed 31/10/08)
3. Mease PJ. Adalimumab in the treatment of arthritis. *Ther Clin Risk Manag* 2007; 3: 133–48.
4. Papoutsaki M, *et al.* Adalimumab for the treatment of severe psoriasis and psoriatic arthritis. *Expert Opin Biol Ther* 2008; 8: 363–70.
5. NICE. Adalimumab, etanercept and infliximab for ankylosing spondylitis: Technology Appraisal Guidance 143 (issued May 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA143Guidance.pdf (accessed 31/10/08)
6. Mease PJ, *et al.* Adalimumab for long-term treatment of psoriatic arthritis: 2-year data from the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT). *Ann Rheum Dis* 2009; 68: 702–9.
7. van der Heijde D, *et al.* ATLAS Study Group. Adalimumab effectiveness for the treatment of ankylosing spondylitis is maintained for up to 2 years: long-term results from the ATLAS trial. *Ann Rheum Dis* 2009; 68: 922–9.
8. Poddubnyy DA, Rudwaleit M. Adalimumab for the treatment of psoriatic arthritis. *Expert Rev Clin Immunol* 2009; 5: 671–81.
9. NICE. Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (review of technology appraisal guidance 104 and 125): Technology Appraisal Guidance 199 (issued August 2010). Available at: http://www.nice.org.uk/nicemedia/live/13110/50422/50422.pdf (accessed 19/10/10)
10. Poddubnyy D, Rudwaleit M. Efficacy and safety of adalimumab treatment in patients with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis. *Expert Opin Drug Safety* 2011; 10: 655–73.
11. Sieper J, *et al.* Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). *Ann Rheum Dis* 2012. Available at: doi:10.1136/annrheumdis-2012-201766
12. Burness CB, Deeks ED. Adalimumab: in non-radiographic axial spondyloarthritis. *Drugs* 2012; 72: 2385–95.
13. Saraceno R, *et al.* Adalimumab in the treatment of plaque-type psoriasis and psoriatic arthritis. *Expert Opin Biol Ther* 2013; 13: 1325–34.

Uveitis. Adalimumab has been tried with some success in the treatment of idiopathic uveitis[1,2] (p. 1615.1). Uveitis can also develop as a complication of other inflammatory disorders such as rheumatoid arthritis; treatment with adalimumab may improve ocular symptoms in addition to its effect on the primary disorder.

1. Vazquez-Cobian LB, *et al.* Adalimumab therapy for childhood uveitis. *J Pediatr* 2006; 149: 572–5.
2. Biester S, *et al.* Adalimumab in the therapy of uveitis in childhood. *Br J Ophthalmol* 2007; 91: 319–24.

Adverse Effects, Treatment, and Precautions

As for Infliximab, p. 75.3.

Injection site reactions including erythema, itching, pain, and swelling are the most common adverse reactions with adalimumab; however, most reactions are mild and do not result in drug withdrawal. Other common reactions include headache, rashes, back pain, hypertension, paraesthesias, increased alkaline phosphate levels, and cough.

Autoantibodies to adalimumab have been detected.

References.
1. Burmester GR, *et al.* Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. *Ann Rheum Dis* 2012. Available at: doi:10.1136/annrheumdis-2011-201244

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies adalimumab as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 15/11/11)

Interactions

As for Infliximab, p. 77.3.

Methotrexate is reported to reduce the clearance of adalimumab by up to 44% but licensed product information for the latter states that dosage adjustment for either drug does not appear to be necessary.

Pharmacokinetics

Adalimumab is reported to have linear pharmacokinetics at usual dosages. After subcutaneous injection peak concentrations are reached in about 3 to 8 days and bioavailability is estimated to be 64%. The mean terminal half-life is about 2 weeks. Adalimumab crosses the placenta and is distributed into breast milk.

References.
1. Nestorov I. Clinical pharmacokinetics of tumor necrosis factor antagonists. *J Rheumatol* 2005; 74 (suppl): 13–18.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Humira; *Austral.*: Humira; *Austria*: Humira; *Belg.*: Humira; *Braz.*: Humira; *Canad.*: Humira: *Chile*: Humira; *China*: Humira (修美乐); *Cz.*: Humira; *Denm.*: Humira; *Fin.*: Humira; *Fr.*: Humira; *Ger.*: Humira; *Gr.*: Humira: Trudexa; *Hong Kong*: Humira; *Hung.*: Humira; *Irl.*: Humira; *Israel*: Humira; *Ital.*: Humira; *Jpn*: Humira; *Malaysia*: Humira; *Mex.*: Humira; *Neth.*: Humira; *Norw.*: Humira; *NZ*: Humira; *Pol.*: Humira; *Port.*: Humira; *Rus.*: Humira (Хумира); *S.Afr.*: Humira; *Singapore*: Humira; *Spain*: Humira; *Swed.*: Humira; *Switz.*: Humira; *Turk.*: Humira; *UK*: Humira; *Ukr.*: Humira (Хумира); *USA*: Humira; *Venez.*: Humira.

Alfentanil Hydrochloride

(BANM, USAN, rINNM) ⊗

Alfentanilihydrokloridi; Alfentanil, Chlorhydrate d'; Alfentanil Hidroklorür; Alfentanil-hidroklorid; Alfentanilhydrochlorid; Alfentanil-hydrochlorid; Alfentanilhydroklorid; Alfentanili Hydrochloridum; Alfentanilio hidrochloridas; Alfentanilo, hidrocloruro de; Hidrocloruro de alfentanilo; R-39209; Альфентанила Гидрохлорид.

N-[1-[2-(4-Ethyl-5-oxo-2-tetrazolin-1-yl)ethyl]-4-(methoxymethyl)-4-piperidyl]propionanilide hydrochloride.

$C_{21}H_{32}N_6O_3$,HCl=453.0

CAS — 71195-58-9 (alfentanil); 69049-06-5 (anhydrous alfentanil hydrochloride); 70879-28-6 (alfentanil hydrochloride monohydrate).

ATC — N01AH02.

ATC Vet — QN01AH02.

UNII — 11S92G0TIW.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Alfentanil Hydrochloride). A white or almost white powder. Freely soluble in water, in alcohol, and in methyl alcohol. Protect from light.

USP 36: (Alfentanil Hydrochloride). A white to almost white powder. Soluble in water; freely soluble in alcohol, in chloroform, and in methyl alcohol; sparingly soluble in acetone. Store in airtight containers.

Uses and Administration

Alfentanil is a short-acting opioid analgesic (p. 108.1) related to fentanyl (p. 60.2).

Alfentanil is used in surgical procedures as an analgesic and adjunct to general anaesthetics or as a primary anaesthetic. It is also used as an analgesic and respiratory depressant in the management of mechanically ventilated patients under intensive care.

Alfentanil is given intravenously as the hydrochloride although doses are expressed in terms of the base. Alfentanil hydrochloride 108.8 micrograms is equivalent to about 100 micrograms of alfentanil. A peak effect may be seen within 1.5 to 2 minutes of an injection and analgesia can be expected to last for up to 10 minutes; dose supplements are therefore required if it is to be used for more prolonged surgical procedures. It may be given by continuous intravenous infusion in ventilated patients.

The dosage of alfentanil used depends on whether the patient has spontaneous respiration or assisted ventilation and on the expected duration of anaesthesia. Doses are adjusted according to the needs of the patient. Children may require higher or more frequent doses than adults, whereas the elderly or debilitated patients may require lower or less frequent doses. Obese patients may require doses based on their ideal (lean) body-weight.

When used as an adjunct in the **maintenance of general anaesthesia** the initial licensed dose in the UK is as follows:

- in patients with *spontaneous respiration*, up to 500 micrograms may be given slowly over about 30 seconds with supplementary doses of 250 micrograms
- *ventilated* patients may be given 30 to 50 micrograms/kg with supplements of 15 micrograms/kg. When given by infusion to ventilated patients there is an initial loading dose of 50 to 100 micrograms/kg given as a bolus or by infusion over 10 minutes, followed by infusion at a rate of 0.5 to 1 microgram/kg per minute

Typical doses that have been used in the USA are as follows:

- for *short surgical procedures of less than 1 hour* in patients with spontaneous respiration or assisted ventilation, the dose is 8 to 20 micrograms/kg; this may be followed by supplementary doses of 3 to 5 micrograms/kg every 5 to 20 minutes or an infusion of 0.5 to 1 microgram/kg per minute. Alternatively patients with assisted or controlled ventilation may be given an initial dose of 20 to 50 micrograms/kg, followed by supplementary doses of 7 to 15 micrograms/kg every 5 to 20 minutes
- in *general surgical procedures* in patients with assisted or controlled ventilation, an initial dose of 50 to 75 micrograms/kg may be followed by an infusion of 0.5 to 3 micrograms/kg per minute. If alfentanil has been given in anaesthetic doses (see below) for the induction of anaesthesia, infusion rates may need to be reduced by 30 to 50% during the first hour of maintenance

Maintenance infusions of alfentanil should be stopped 10 to 30 minutes before the anticipated end of surgery.

The dose for the **induction of anaesthesia** in patients with assisted ventilation undergoing procedures of at least 45 minutes is 130 to 245 micrograms/kg, followed by an inhalation anaesthetic or maintenance doses of alfentanil of 0.5 to 1.5 micrograms/kg per minute.

For details of doses in children, see below.

In the UK, *ventilated* patients in **intensive care** may be given alfentanil initially at an infusion rate of 2 mg/hour or a loading dose of 5 mg may be given in divided doses over 10 minutes or more slowly if hypotension or bradycardia occur. Thereafter a suitable rate of infusion should be determined for each patient (rates of 0.5 to 10 mg/hour have been used); patients should be carefully monitored and the duration of treatment should not generally exceed 4 days. During continuous infusion additional bolus injections of 0.5 to 1 mg may be given if required to provide analgesia for short painful procedures that may be carried out in intensive care.

Alfentanil is also used as an analgesic in patients with *spontaneous respiration* receiving monitored anaesthesia care; in the USA, an initial dose of 3 to 8 micrograms/kg may be followed by supplementary doses of 3 to 5 micrograms/kg every 5 to 20 minutes or an infusion of 0.25 to 1 microgram/kg per minute.

Administration. Alfentanil is usually given by intravenous injection or infusion, but has also been given intramuscularly,[1,2] intrathecally,[3] or epidurally (see Pain, p. 19.1).

1. Arendt-Nielsen L, *et al.* Analgesic efficacy of im alfentanil. *Br J Anaesth* 1990; 65: 164–8.
2. Virkkilä M, *et al.* Pharmacokinetics and effects of i.m. alfentanil as premedication for day-case ophthalmic surgery in elderly patients. *Br J Anaesth* 1993; 71: 507–11.
3. Hughes DA, Hill DA. Intrathecal alfentanil with and without bupivacaine for analgesia in labour. *Anaesthesia* 2000; 55: 1116–21.

Administration in children. In the UK, the *BNFC* recommends the use of intravenous alfentanil in *ventilated* children as an analgesic and adjunct to general anaesthetics; the following doses, given according to age, are suggested:

for **short procedures** in patients with assisted ventilation by *injection* over 30 seconds

- neonates, 5 to 20 micrograms/kg initially, followed by supplementary doses of up to 10 micrograms/kg
- 1 month to 18 years, 10 to 20 micrograms/kg initially, followed by supplementary doses of up to 10 micrograms/kg

for **longer procedures** in patients with assisted ventilation by *infusion*

- neonates, 10 to 50 micrograms/kg over 10 minutes initially, followed by 0.5 to 1 microgram/kg per minute
- 1 month to 18 years, 50 to 100 micrograms/kg over 10 minutes initially, followed by 0.5 to 2 micrograms/kg

per minute (or 1 microgram/kg per minute when used with an intravenous anaesthetic)

Similar doses are licensed in the UK for use in children with spontaneous respiration or assisted ventilation although age ranges are not specified: equipment for assisted ventilation should be available for use, even for short procedures in those who are breathing spontaneously.

Anaesthesia. Alfentanil, like fentanyl (p. 61.2), appears to produce fewer circulatory changes than morphine and may be preferred for anaesthetic use, especially in cardiovascular surgery. It is generally considered to have a shorter duration of action than fentanyl. It has been used with propofol to facilitate intubation, and for total intravenous anaesthesia.

For a discussion of the drugs used to facilitate intubation and of opioids such as alfentanil used to control the pressor response and the rise of intra-ocular pressure associated with intubation, see Anaesthesia, p. 2028.1. For reference to a study indicating that pretreatment with alfentanil can reduce the pain associated with injection of propofol, see p. 1914.3.

CAESAREAN SECTION. UK licensed product information contra-indicates the use of alfentanil before clamping the cord during caesarean section because of the risk of respiratory depression in the neonate. A study of alfentanil 30 micrograms/kg in women undergoing caesarean section was abandoned after massive respiratory depression had occurred in 4 of 5 neonates.[1] Another study[2] in patients undergoing elective caesarean section found that although maternal haemodynamic responses to intubation were minimised when alfentanil 10 micrograms/kg was given intravenously immediately before induction, neonates in the alfentanil group had lower Apgar scores compared with those in the placebo group.

However, alfentanil has been used successfully to minimise haemodynamic responses to intubation and surgery in patients with severe cardiovascular disorders undergoing caesarean section.[3,4] A baby delivered after the successful use of alfentanil 35 micrograms/kg in a mother with severe aortic stenosis[5] was apnoeic and unresponsive with poor muscle tone; the baby responded rapidly to naloxone. Alfentanil 10 micrograms/kg immediately before induction attenuated the cardiovascular response to intubation in patients with severe pregnancy-induced hypertension[4] and was considered a suitable alternative to fentanyl 2.5 micrograms/kg; no effect on neonatal mortality could be attributed to anaesthetic technique. However, it has been suggested that the use of smaller doses of alfentanil of 7.5 micrograms/kg with magnesium sulfate 30 mg/kg may provide better cardiovascular control.[5]

1. Leuwer M, *et al.* Pharmacokinetics and pharmacodynamics of an equipotent fentanyl and alfentanil dose in mother and infant during caesarean section. *Br J Anaesth* 1990; **64**: 398P–399P.
2. Gin T, *et al.* Alfentanil given immediately before the induction of anesthesia for elective cesarean delivery. *Anesth Analg* 2000; **90**: 1167–72.
3. Redfern N, *et al.* Alfentanil for caesarean section complicated by severe aortic stenosis: a case report. *Br J Anaesth* 1987; **59**: 1309–12.
4. Rout CC, Rocke DA. Effects of alfentanil and fentanyl on induction of anaesthesia in patients with severe pregnancy-induced hypertension. *Br J Anaesth* 1990; **65**: 468–74.
5. Ashton WB, *et al.* Attenuation of the pressor response to tracheal intubation by magnesium sulphate with and without alfentanil in hypertensive proteinuric patients undergoing caesarean section. *Br J Anaesth* 1991; **67**: 741–7.

PHAEOCHROMOCYTOMA. Alfentanil does not release histamine and was of value in the anaesthetic management of patients with phaeochromocytoma.[1] It has a very rapid onset of action, good vasodilating properties, and a relatively short elimination half-life. These patients are often very somnolent for the first 48 hours after surgery and postoperative opioid dosage requirements may be less than expected. Alfentanil infusion continued into the postoperative period allows careful titration of dosage.

1. Hull CJ. Phaeochromocytoma: diagnosis, preoperative preparation and anaesthetic management. *Br J Anaesth* 1986; **58**: 1453–68.

Pain. *POSTOPERATIVE ANALGESIA.* Continuous on-demand epidural infusions of alfentanil 200 micrograms/hour or fentanyl 20 micrograms/hour provided comparable analgesia to morphine 200 micrograms/hour in the early postoperative period;[1] alfentanil (16 minutes) and fentanyl (13 minutes) had the advantage of more rapid onset of analgesia than morphine (44 minutes). However, some considered that there was no overall advantage of epidural over intravenous alfentanil either as patient-controlled analgesia[2] or by continuous infusion.[3]

1. Chrubasik J, *et al.* Relative analgesic potency of epidural fentanyl, alfentanil, and morphine in treatment of postoperative pain. *Anesthesiology* 1988; **68**: 929–33.
2. Chauvin M, *et al.* Equivalence of postoperative analgesia with patient-controlled intravenous or epidural alfentanil. *Anesth Analg* 1993; **76**: 1251–8.
3. van den Nieuwenhuyzen MCO, *et al.* Epidural vs intravenous infusion of alfentanil in the management of postoperative pain following laparotomies. *Acta Anaesthesiol Scand* 1996; **40**: 1112–18.

Dependence and Withdrawal

As for Opioid Analgesics, p. 109.1.

Adverse Effects and Treatment

As for Opioid Analgesics in general, p. 110.1, and for Fentanyl, p. 62.1.

Effects on the cardiovascular system. Sinus arrest had occurred[1] during intubation in 2 patients given alfentanil 30 micrograms/kg.

1. Maryniak JK, Bishop VA. Sinus arrest after alfentanil. *Br J Anaesth* 1987; **59**: 390–1.

Effects on mental function. Like fentanyl, alfentanil 7.5 or 15 micrograms/kg intravenously had no effect on memory in healthy subjects.[1] In another study impairment of memory for new facts did occur 2 hours after operation in patients anaesthetised with alfentanil 7.5 micrograms/kg, but not in those given fentanyl;[2] methohexital might have contributed to the impairment.

1. Scamman FL, *et al.* Ventilatory and mental effects of alfentanil and fentanyl. *Acta Anaesthesiol Scand* 1984; **28**: 63–7.
2. Kennedy DJ, Ogg TW. Alfentanil and memory function: a comparison with fentanyl for day case termination of pregnancy. *Anaesthesia* 1985; **40**: 537–40.

Effects on the respiratory system. Alfentanil, like other opioid agonists, causes dose-related respiratory depression; it is significant with doses of more than 1 mg. Recovery has been reported to be faster after alfentanil than after fentanyl (see p. 62.2),[1,2] possibly reflecting the shorter elimination half-life of alfentanil. Even so, accumulation of alfentanil is possible with large doses over a prolonged period. Profound analgesia is accompanied by marked respiratory depression which may persist or recur postoperatively.

Sudden respiratory arrest usually within an hour after the end of alfentanil infusion has been reported in patients who initially appeared to have made a rapid recovery from anaesthesia;[3-5] all responded to treatment with naloxone. Close monitoring of respiration in the initial postoperative period was recommended and this was reinforced by the manufacturers;[6] factors such as hyperventilation and the use of opioid premedication might enhance or prolong the respiratory depressant effects of alfentanil.

1. Andrews CJH, *et al.* Ventilatory effects during and after continuous infusion of fentanyl or alfentanil. *Br J Anaesth* 1983; **55**: 211S–16S.
2. Scamman FL, *et al.* Ventilatory and mental effects of alfentanil and fentanyl. *Acta Anaesthesiol Scand* 1984; **28**: 63–7.
3. Sebel PS, *et al.* Respiratory depression after alfentanil infusion. *BMJ* 1984; **289**: 1581–2.
4. Krane BD, *et al.* Alfentanil and delayed respiratory depression: cases studies and review. *Anesth Analg* 1990; **70**: 557–61.
5. Sternlo JEG, Sandin RH. Recurrent respiratory depression after total intravenous anaesthesia with propofol and alfentanil. *Anaesthesia* 1998; **53**: 378–81.
6. Waldron HA, Cookson RF. Respiratory depression after alfentanil infusion. *BMJ* 1985; **290**: 319.

Precautions

As for Opioid Analgesics in general, p. 110.3.

Children. Alfentanil given to preterm infants undergoing paralysis and mechanical ventilation for respiratory distress syndrome resulted in a rapid and significant fall in heart rate and blood pressure, emphasising that proper evaluation of the pharmacological and clinical effects was necessary.[1]

The half-life of alfentanil is prolonged in neonates and accumulation is likely with prolonged use; muscle rigidity may occur and the use of muscle relaxants may be required.

1. Marlow N, *et al.* Hazards of analgesia for newborn infants. *Arch Dis Child* 1988; **63**: 1293.

The elderly. EEG changes suggested that elderly patients had increased brain sensitivity to alfentanil,[1] and that lower doses might be indicated in older patients for pharmacodynamic rather than pharmacokinetic reasons. See also under Pharmacokinetics, p. 20.1.

1. Scott JC, Stanski DR. Decreased fentanyl and alfentanil dose requirements with age: a simultaneous pharmacokinetic and pharmacodynamic evaluation. *J Pharmacol Exp Ther* 1987; **240**: 159–66.

Handling. Avoid contact with the skin and the inhalation of particles of alfentanil hydrochloride.

Inflammatory bowel disease. Patients with Crohn's disease required higher doses of alfentanil than control patients[1] although there were no differences in alfentanil pharmacokinetics between the 2 groups of patients.

1. Gesink-van der Veer BJ, *et al.* Influence of Crohn's disease on the pharmacokinetics and pharmacodynamics of alfentanil. *Br J Anaesth* 1993; **71**: 827–34.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies alfentanil as probably not porphyrinogenic: it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/10/11)

Pregnancy. UK licensed product information contra-indicates the use of alfentanil in labour, or before clamping of the cord during caesarean section, because placental transfer means there is a risk of neonatal respiratory depression.

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

Drugs that depress the heart or increase vagal tone, such as beta blockers and anaesthetic drugs, may predispose patients given alfentanil to develop bradycardia and hypotension. Use of alfentanil with non-vagolytic neuromuscular blockers may produce bradycardia and possibly asystole.

The metabolism of alfentanil via the cytochrome P450 isoenzyme CYP3A4 may be reduced by potent inhibitors of this isoenzyme, resulting in a risk of prolonged or delayed respiratory depression. Reduced doses of alfentanil may be required if given with a CYP3A4 inhibitor such as cimetidine, diltiazem, erythromycin, fluconazole, itraconazole, ketoconazole, or ritonavir.

Antibacterials. The elimination half-life of alfentanil was increased and clearance decreased when given after a 7-day course of oral *erythromycin* in healthy subjects.[1] Prolonged respiratory depression has also occurred in a 32-year-old man given alfentanil during anaesthesia after three 1-g doses of erythromycin in the 24 hours before surgery.[2] In another study of healthy subjects, the clearance (three-compartment model) of alfentanil was reduced by 70% in those given oral *troleandomycin*.[3]

Other hepatic enzyme inhibitors and drugs interfering with hepatic blood flow might also affect the clearance of alfentanil.

1. Bartkowski RR, *et al.* Inhibition of alfentanil metabolism by erythromycin. *Clin Pharmacol Ther* 1989; **46**: 99–102.
2. Bartkowski RR, McDonnell TE. Prolonged alfentanil effect following erythromycin administration. *Anesthesiology* 1990; **73**: 566–8.
3. Kharasch ED, *et al.* The role of cytochrome P450 3A4 in alfentanil clearance: implications for interindividual variability in disposition and perioperative drug interactions. *Anesthesiology* 1997; **87**: 36–50.

Antifungals. Azole antifungals such as *fluconazole, ketoconazole,* or *voriconazole* can inhibit the metabolism of alfentanil. In a study,[1] giving alfentanil 1 hour after intravenous or oral fluconazole decreased the clearance of alfentanil by 60 and 55%, respectively and increased the mean half-life of alfentanil from 1.5 hours to 2.7 and 2.5 hours, respectively. Similarly, another study[2] found that giving alfentanil 1 hour after oral voriconazole decreased the clearance of alfentanil by 85% and increased the mean half-life of alfentanil to 6.6 hours.

1. Palkama VJ, *et al.* The effect of intravenous and oral fluconazole on the pharmacokinetics and pharmacodynamics of intravenous alfentanil. *Anesth Analg* 1998; **87**: 190–4.
2. Saari TI, *et al.* Voriconazole, but not terbinafine, markedly reduces alfentanil clearance and prolongs its half-life. *Clin Pharmacol Ther* 2006; **80**: 502–8.

Pharmacokinetics

After parenteral doses alfentanil hydrochloride has a rapid onset and short duration of action. Alfentanil is about 90% protein bound and has a small volume of distribution. Its terminal elimination half-life is about 1 to 2 hours. It is metabolised in the liver; oxidative *N*- and *O*-dealkylation by the cytochrome P450 isoenzyme CYP3A4 leads to inactive metabolites, which are excreted in the urine. Alfentanil crosses the blood-brain barrier and the placenta and has been detected in colostrum.

Alfentanil is less lipid-soluble than fentanyl, but more so than morphine. It is highly bound to plasma proteins, mainly to α_1-acid glycoprotein. Decreased lipid solubility can be expected to limit penetration of the blood-brain barrier when compared with fentanyl, but the majority of unbound alfentanil is unionised and can rapidly gain access to the CNS. Alfentanil has a smaller volume of distribution than fentanyl and its elimination half-life is shorter. The manufacturers have given values for a three-compartment pharmacokinetic model with a distribution half-life of 0.4 to 3.1 minutes, a redistribution half-life of 4.6 to 21.6 minutes, and a terminal elimination half-life of 64.1 to 129.3 minutes after single bolus injections of 50 or 125 micrograms/kg. Accumulation is less likely than with fentanyl, but can occur after repeated or continuous dosage especially in patients with reduced clearance. The mean elimination half-life reported is usually about 90 minutes, but this is reduced in children (p. 20.1) and increased in the elderly and neonates (p. 20.1), in hepatic impairment (p. 20.2), in the obese (p. 20.2), and during cardiopulmonary bypass (p. 20.1).

Reviews.
1. Hull CJ. The pharmacokinetics of alfentanil in man. *Br J Anaesth* 1983; 55 (suppl 2): 157S–164S.
2. Mather LE. Clinical pharmacokinetics of fentanyl and its newer derivatives. *Clin Pharmacokinet* 1983; 8: 422–46.
3. Davis PJ, Cook DR. Clinical pharmacokinetics of the newer intravenous anaesthetic agents. *Clin Pharmacokinet* 1986; 11: 18–35.
4. Bodenham A, Park GR. Alfentanil infusions in patients requiring intensive care. *Clin Pharmacokinet* 1988; 15: 216–26.
5. Scholz J, *et al.* Clinical pharmacokinetics of alfentanil, fentanyl and sufentanil. *Clin Pharmacokinet* 1996; 31: 275–92.

Administration. *CONTINUOUS INTRAVENOUS INFUSION.* Small studies of alfentanil by continuous intravenous infusion[1-3] have found pharmacokinetic parameters to be similar to those after a single bolus injection, but with some conflicting results. In 29 patients undergoing orthopaedic surgery an initial bolus intravenous injection of alfentanil 50 micrograms/kg was followed by intravenous infusion of 1 microgram/kg per minute, continued for 44 to 445 minutes; a second bolus injection of 50 micrograms/kg was given immediately before incision and an additional bolus injection of 1 mg given if necessary.[4] The time course of the plasma-alfentanil concentration fitted a two-compartmental model in 26 patients. Terminal half-lives varied widely from 56 to 226 minutes (mean 106 minutes), the highest values being mainly in patients over 60 years. There was no significant correlation between pharmacokinetic parameters and the duration of the infusion or the total dose. Plasma clearance and volumes of distribution did not correlate significantly with body-weight although steady-state volume of distribution was enlarged with increasing age. The mean estimated steady-state concentration was 293 nanograms/mL (range 147 to 636 nanograms/mL).

1. Fragen RJ, *et al.* Pharmacokinetics of the infusion of alfentanil in man. *Br J Anaesth* 1983; 55: 1077–81.
2. Shafer A, *et al.* Pharmacokinetics and pharmacodynamics of alfentanil infusions during general anesthesia. *Anesth Analg* 1986; 65: 1021–8.
3. Reitz JA, *et al.* The pharmacokinetics of alfentanil in gynecologic surgical patients. *J Clin Pharmacol* 1986; 26: 60–4.
4. van Beem H, *et al.* Pharmacokinetics of alfentanil during and after a fixed rate infusion. *Br J Anaesth* 1989; 62: 610–15.

INTRAMUSCULAR. See The Elderly, below.

Burns. The volume of distribution and total clearance of alfentanil were reduced and its elimination half-life prolonged in patients with burns.[1] This was due, in part, to raised concentrations of α_1-acid glycoprotein leading to increased protein binding.

1. Macfie AG, *et al.* Disposition of alfentanil in burns patients. *Br J Anaesth* 1992; 69: 447–50.

Cardiopulmonary bypass. The elimination half-life of alfentanil increased from 72 minutes before cardiopulmonary bypass to 195 minutes afterwards in 5 patients.[1] This was attributed to an increase in volume of distribution, based in part on a dilution-induced decrease in plasma protein binding. Others[2,3] found that on starting cardiopulmonary bypass total serum concentrations of alfentanil were halved, mainly because of dilution of α_1-acid glycoprotein and an increase in unbound alfentanil.

1. Hug CC, *et al.* Alfentanil pharmacokinetics in patients before and after cardiopulmonary bypass. *Anesth Analg* 1983; 62: 266.
2. Kumar K, *et al.* The effect of cardiopulmonary bypass on plasma protein binding of alfentanil. *Eur J Clin Pharmacol* 1988; 35: 47–52.
3. Hynynen M, *et al.* Plasma concentration and protein binding of alfentanil during high-dose infusion for cardiac surgery. *Br J Anaesth* 1994; 72: 571–6.

Children. Alfentanil has been shown to have a shorter elimination half-life (about 40 minutes) and a smaller volume of distribution in children than in adults.[1] However, the half-life of alfentanil is prolonged in neonates. See also Hepatic Impairment, below.

1. Meistelman C, *et al.* A comparison of alfentanil pharmacokinetics in children and adults. *Anesthesiology* 1987; 66: 13–16.

The elderly. Plasma clearance of alfentanil after a single intravenous dose of 50 micrograms/kg was reduced in patients more than 65 years old when compared with that in healthy young adults.[1] Mean elimination half-life was 137 minutes in the elderly and 83 minutes in the young adults. Volumes of distribution were similar and it was considered that reduced clearance might be due to decreased hepatic metabolism in the elderly. In a study in male patients the terminal elimination half-life of alfentanil increased with age, although clearance was not significantly affected.[2] In patients given alfentanil 1 microgram/kg per minute by continuous intravenous infusion during orthopaedic surgery,[3] terminal half-life increased linearly with age in those older than 40 years and steady-state volume of distribution was enlarged with increasing age; clearance did not correlate significantly with age and was thought to be more variable during a continuous infusion in long-term surgery than after a single bolus injection. Others have reported[4] that the effects of age on alfentanil pharmacokinetics are dependent on gender. In this study total plasma clearance decreased and terminal half-life increased with increasing age in women, but not in men. It has been suggested that this effect in women may be more dependent on menopausal status than on age.[5]

In a study[6] in elderly patients plasma concentrations of alfentanil were greater and the maximum concentration occurred earlier when alfentanil was injected into the deltoid muscle compared with injection into the gluteal muscle.

1. Helmers H, *et al.* Alfentanil kinetics in the elderly. *Clin Pharmacol Ther* 1984; 36: 239–43.
2. Scott JC, Stanski DR. Decreased fentanyl and alfentanil dose requirements with age: a simultaneous pharmacokinetic and pharmacodynamic evaluation. *J Pharmacol Exp Ther* 1987; 240: 159–66.
3. van Beem H, *et al.* Pharmacokinetics of alfentanil during and after a fixed rate infusion. *Br J Anaesth* 1989; 62: 610–15.
4. Lemmens HJM, *et al.* Influence of age on the pharmacokinetics of alfentanil: gender dependence. *Clin Pharmacokinet* 1990; 19: 416–22.
5. Rubio A, Cox C. Sex, age and alfentanil pharmacokinetics. *Clin Pharmacokinet* 1991; 21: 81.
6. Virkkilä M, *et al.* Pharmacokinetics and effects of i.m. alfentanil as premedication for day-case ophthalmic surgery in elderly patients. *Br J Anaesth* 1993; 71: 507–11.

Hepatic impairment. Total plasma clearance and protein binding of alfentanil were decreased in patients with alcoholic cirrhosis when compared with control subjects. Elimination half-life was prolonged from 90 to 219 minutes in the cirrhotic patients following a single intravenous dose of 50 micrograms/kg and was attributed in part to alterations in binding sites of α_1-acid glycoprotein.[1] There might be different effects on alfentanil disposition in patients with non-alcoholic cirrhosis or other liver disorders.[2] The pharmacokinetics of alfentanil were apparently not affected in children with cholestatic hepatic disease whereas clearance was reduced postoperatively in 3 patients who had undergone liver transplantation.[3]

1. Ferrier C, *et al.* Alfentanil pharmacokinetics in patients with cirrhosis. *Anesthesiology* 1985; 62: 480–4.
2. Bower S, *et al.* Effects of different hepatic pathologies on disposition of alfentanil in anaesthetized patients. *Br J Anaesth* 1992; 68: 462–5.
3. Davis PJ, *et al.* Effects of cholestatic hepatic disease and chronic renal failure on alfentanil pharmacokinetics in children. *Anesth Analg* 1989; 68: 579–83.

Obesity. The pharmacokinetics of alfentanil are reportedly altered in obesity.[1] Elimination half-life was 172 minutes in 6 obese patients compared with 92 minutes in 7 who were not obese. Plasma clearance of alfentanil was also decreased, although others[2] found that obesity had no effect on clearance, but it did have a direct relationship with the volume of the central compartment.

1. Bentley JB, *et al.* Obesity and alfentanil pharmacokinetics. *Anesth Analg* 1983; 62: 251.
2. Maitre PO, *et al.* Population pharmacokinetics of alfentanil: the average dose-plasma concentration relationship and interindividual variability in patients. *Anesthesiology* 1987; 66: 3–12.

Renal impairment. The pharmacokinetics of alfentanil were not affected significantly in adults[1] or children[2] with chronic renal failure. In another study[3] increased volume of distribution of alfentanil at steady state was associated with decreased plasma protein binding in patients with chronic renal failure.

1. Van Peer A, *et al.* Alfentanil kinetics in renal insufficiency. *Eur J Clin Pharmacol* 1986; 30: 245–7.
2. Davis PJ, *et al.* Effects of cholestatic hepatic disease and chronic renal failure on alfentanil pharmacokinetics in children. *Anesth Analg* 1989; 68: 579–83.
3. Chauvin M, *et al.* Pharmacokinetics of alfentanil in chronic renal failure. *Anesth Analg* 1987; 66: 53–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Brevafen; *Austral.*: Rapifen; *Austria*: Rapifen; *Belg.*: Rapifen; *Braz.*: Alfast; Rapifen; *Chile*: Rapifen; *Cz.*: Rapifen; *Denm.*: Rapifen; *Fin.*: Rapifen; *Fr.*: Rapifen; *Ger.*: Rapifen; *Gr.*: Rapifen; *Hong Kong*: Rapifen; *Hung.*: Rapifen†; *Irl.*: Rapifen; *Israel*: Rapifen†; *Ital.*: Fentalim; *Mex.*: Rapifen; *Neth.*: Rapifen; *Norw.*: Rapifen; *NZ*: Rapifen; *Port.*: Rapifen; *S.Afr.*: Rapifen; *Singapore*: Rapifen; *Spain*: Fanaxal†; Limifen; *Swed.*: Rapifen; *Switz.*: Rapifen; *Turk.*: Rapifen; *UK*: Rapifen; *USA*: Alfenta; *Venez.*: Rapifen.

Pharmacopoeial Preparations
USP 36: Alfentanil Injection.

Alminoprofen *(rINN)*

Alminoprofène; Alminoprofeno; Alminoprofenum; Альминопрофен.

4-[(2-Methylallyl)amino]hydratropic acid.

$C_{13}H_{17}NO_2$=219.3

CAS — 39718-89-3.

ATC — M01AE16.

ATC Vet — QM01AE16.

UNII — 025SAHR9GJ.

Pharmacopoeias. In *Jpn.*

Profile

Alminoprofen, a propionic acid derivative related t ibuprofen (p. 68.2), is an NSAID (p. 102.3). It has beer used in inflammatory and rheumatic disorders in oral dose of up to 900 mg daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Minalfene.

Aloxiprin *(BAN, rINN)*

Acetilsalicilato de polioxoaluminio; Aloksipriini; Aloxiprina; Aloxiprine; Aloxiprinum; Алоксиприн.

CAS — 9014-67-9.

ATC — B01AC15; N02BA02.

ATC Vet — QB01AC15; QN02BA02.

UNII — 6QT214X4XU.

Pharmacopoeias. In *Br.*

BP 2014: (Aloxiprin). A polymeric condensation product of aluminium oxide and aspirin. A fine, white or slightly pink powder, odourless or almost odourless. It contains not less than 7.5% and not more than 8.5% of aluminium and not less than 79.0% and not more than 87.4% of total salicylates, calculated as aspirin, $C_9H_8O_4$, both calculated with reference to the dried substance. Practically insoluble in water, in alcohol, and in ether; slightly soluble in chloroform.

Profile

Aloxiprin, a polymeric condensation product of aluminium oxide and aspirin, has actions similar to those of aspirin (p. 22.2); aloxiprin 600 mg is equivalent to about 500 mg o aspirin. Aloxiprin has been used as an analgesic and anti-inflammatory in musculoskeletal and joint disorders. It has also been used in the treatment and prevention of thromboembolic disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Superpyrin.

Multi-ingredient Preparations. *UK*: Askit†.

Pharmacopoeial Preparations
BP 2014: Aloxiprin Tablets.

Aluminium Aspirin

Acetilsalicilato de aluminio; Aluminum Acetylsalicylate; Aluminum Aspirin; Aluminum Bis(acetylsalicylate); Aspirin Aluminium; Аспирин Алюминий; Алюминий Аспирина.

Bis(2-acetoxybenzoato-*O*')hydroxyaluminium.

$C_{18}H_{15}AlO_9$=402.3

CAS — 23413-80-1.

UNII — E33TS05V68.

Pharmacopoeias. In *Jpn.*

Profile

Aluminium aspirin is a salicylic acid derivative (see Aspirin, p. 22.2) that has been given orally in the management of fever, pain, and musculoskeletal and joint disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Indon.*: Remasal†.

Amfenac Sodium *(BANM, USAN, rINNM)*

AHR-5850; AHR-5850D; Amfénac Sodique; Amfenaco sódico; Natrii Amfenacum; Натрий Амфенак.

Sodium (2-amino-3-benzoylphenyl)acetate monohydrate.

$C_{15}H_{12}NNaO_3.H_2O$=295.3

CAS — 51579-82-9 (amfenac); 61618-27-7 (amfenac sodium).

UNII — PPF9V8J28Y.

Profile

Amfenac sodium, an arylacetic derivative, is an NSAID (p. 102.3). It has been given orally for the relief of pain and inflammation.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Fenazox.

Aminophenazone (rINN)

Amidazofen; Amidopyrine; Amidopyrine-Pyramidon; Aminofenatsoni; Aminofenazon; Aminofenazona; Aminophénazone; Aminophenazonum; Aminopyrine; Dimethylaminoantipyrine; Dimethylaminophenazone; Аминофеназон.
4-Dimethylamino-1,5-dimethyl-2-phenyl-4-pyrazolin-3-one.
$C_{13}H_{17}N_3O$=231.3
CAS — 58-15-1.
ATC — N02BB03.
ATC Vet — QN02BB03.
UNII — 01704YP3MO.

Pharmacopoeias. In *It.*

Profile

Aminophenazone, a pyrazolone derivative, is an NSAID (p. 102.3), but the risk of agranulocytosis is sufficiently great to render it unsuitable for systemic use. Onset of agranulocytosis may be sudden and unpredictable. Aminophenazone has been used as salts or complexes, including topically as the salicylate.

Precautions. *CARCINOGENICITY.* Aminophenazone may be regarded as a potential carcinogen because it has reacted readily with nitrous acid to form dimethylnitrosamine.[1] The reaction was catalysed by thiocyanate present in the saliva particularly in smokers.

1. Boyland E, Walker SA. Catalysis of the reaction of aminopyrine and nitrite by thiocyanate. *Arzneimittelforschung* 1974; 24: 1181–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Hung.*: Germicid.

Multi-ingredient Preparations. *Hung.*: Antineuralgica; Demalgon; Demalgonil†; Dolor†; Germicid-C; Kefalgin; Meristin; *Ital.*: Virdex; *Mex.*: Flumil.

Ammonium Salicylate

Salicilato de amonio; Аммоний Салицилат.
$C_7H_9NO_3$=155.2
CAS — 528-94-9.
UNII — 0T3Q181657.

Profile

Ammonium salicylate is a salicylic acid derivative used topically in rubefacient preparations similarly to methyl salicylate (p. 92.1) for the relief of pain in musculoskeletal and joint disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *UK*: Radian-B.

Ampiroxicam (BAN, rINN)

Ampiroxicamum; CP-65703; Ампироксикам.
4-[1-(Ethoxycarbonyloxy)ethoxy]-2-methyl-N^2-pyridyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide.
$C_{20}H_{21}N_3O_7S$=447.5
CAS — 99464-64-9.
UNII — 0PV32JZB1J.

Profile

Ampiroxicam is an NSAID (p. 102.3) that is reported to be metabolised to piroxicam (p. 125.3). It has been given orally for the relief of pain and inflammation particularly in musculoskeletal disorders such as rheumatoid arthritis and osteoarthritis.

Adverse effects. Photosensitivity reactions have occurred during ampiroxicam treatment.[1-3]

1. Kurumaji Y. Ampiroxicam-induced photosensitivity. *Contact Dermatitis* 1996; 34: 298–9.
2. Toyohara A, *et al.* Ampiroxicam-induced photosensitivity. *Contact Dermatitis* 1996; 35: 101–2.
3. Chishiki M, *et al.* Photosensitivity due to ampiroxicam. *Dermatology* 1997; 195: 409–10.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Flucam.

Amtolmetin Guacil (rINN)

Amtolmetina guacilo; Amtolmétine Guacil; Amtolmetinum Guacilum; MED-15; ST-679; Амтолметин Гуацил.
N-[(1-Methyl-5-*p*-toluoylpyrrol-2-yl)acetyl]glycine *o*-methoxyphenyl ester.
$C_{24}H_{24}N_2O_5$=420.5
CAS — 87344-06-7.
UNII — 323A00CRO9.

Profile

Amtolmetin guacil is an NSAID (p. 102.3) that is an ester prodrug of tolmetin (p. 139.1). It is used in painful and inflammatory disorders in oral doses of 600 to 1200 mg daily.

References.

1. Biasi G, Marcolongo R. Efficacia e tollerabilità dell'amtolmetina guacil nel trattamento dell'artrosi in fase di riacutizzazione. *Minerva Med* 2001; 92: 315–24.
2. Jajic Z, *et al.* Gastrointestinal safety of amtolmetin guacyl in comparison with celecoxib in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2005; 23: 809–18.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Artricol; Artromed; Eufans.

Amyl Salicylate

Isoamyl Salicylate; Isopentyl Salicylate; Salicilato de isoamilo; Salicilato de isopentilo; Амилсалицилат.
3-Methylbutyl 2-hydroxybenzoate.
$C_{12}H_{16}O_3$=208.3
CAS — 87-20-7.
UNII — M25E4ZMR0N.

Pharmacopoeias. In *Fr.*

Profile

Amyl salicylate is a salicylic acid derivative used topically in rubefacient preparations similarly to methyl salicylate (p. 92.1) for its analgesic and anti-inflammatory actions. It has also been used in perfumery.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Atomo Desinflamante C; Atomo Desinflamante Familiar; Atomo Desinflamante: Rati Salil Crema; *Fr.*: Baume Saint-Bernard.

Anakinra (BAN, USAN, rINN)

Anakinrum; rhIL-1ra; r-metHuIL-1ra; Анакинра.
N^2-L-Methionylinterleukin 1 receptor antagonist (human isoform x reduced).
CAS — 143090-92-0.
ATC — L04AC03.
ATC Vet — QL04AC03.
UNII — 9013DUQ28K.

Uses and Administration

Anakinra is a recombinant receptor antagonist of interleukin-1 (p. 2533.3), an inflammatory mediator found in the plasma and synovial fluid of patients with rheumatoid arthritis. Anakinra is described as a biological disease-modifying antirheumatic drug (DMARD).

Anakinra is used for the treatment of the signs and symptoms of moderate to severely active **rheumatoid arthritis** in patients who have had an inadequate response to methotrexate or another DMARD alone (but see below). In the UK, it is only licensed for use with methotrexate; however, in the USA, it may be given either alone or with another DMARD, although not one that inhibits TNF (see Interactions, p. 22.1). The usual dose is 100 mg once daily by subcutaneous injection. The dose should be given at about the same time each day.

Anakinra is also used in the management of **cryopyrin-associated periodic syndromes** (CAPS) including neonatal-onset multisystem inflammatory disease (NOMID) [also known as chronic infantile neurological, cutaneous, articular syndrome (CINCA)], familial cold auto-inflammatory syndrome (FCAS), and Muckle-Wells syndrome (MWS), which are rare inherited auto-inflammatory disorders (below) in adults and children from 8 months of age who weigh at least 10 kg. The usual initial dose is 1 to 2 mg/kg daily by subcutaneous injection; patients with mild disease may be maintained on this dose. In those with severe disease, the dose may be increased if necessary, after 1 to 2 months in steps of 0.5 to 1 mg/kg; the usual maintenance dose is 3 to 4 mg/kg daily. A maximum dose of 8 mg/kg daily should not be exceeded. Once-daily injections are recommended; however, the dose may be divided to give twice daily. In severe CAPS, evaluation of clinical symptoms, inflammatory markers, and inflammation of the CNS including the inner ear and eyes are recommended after the first 3 months of therapy and every 6 months thereafter until patients are well controlled, at which point, CNS and ophthalmological monitoring may then be carried out annually.

For use of anakinra in patients with renal impairment, see below.

Anakinra has been tried in septic shock and graft-versus-host disease in transplant recipients, but results were disappointing.

Administration in children. Anakinra is licensed for use in children and adolescents for the treatment of cryopyrin-associated periodic syndromes (CAPS). For doses see Uses and Administration, above.

Administration in renal impairment. Caution may be advisable if anakinra is used in patients with renal impairment. A study[1] in patients with varying degrees of renal function indicated that no dosage adjustment was needed for anakinra in patients with mild or moderate renal impairment but dosage on alternate days appeared advisable in those with severe renal impairment. US licensed product information also recommends alternate-day dosing in patients with severe impairment or end-stage disease (creatinine clearance less than 30 mL/minute). However, in the UK, licensed product information contra-indicates use in those with this degree of impairment.

Dialysis does not affect anakinra concentrations to any significant degree.

1. Yang B-B, *et al.* Pharmacokinetics of anakinra in subjects with different levels of renal function. *Clin Pharmacol Ther* 2003; 74: 85–94.

Cryopyrin-associated periodic syndromes. Anakinra is a recombinant interleukin-1 (IL-1) receptor antagonist that inhibits the binding of the proinflammatory cytokines, IL-1α and IL-1β, to IL-1 receptors, thus ameliorating systemic and organ inflammation. It is used in the treatment of cryopyrin-associated periodic syndromes (CAPS), which are rare inherited auto-inflammatory disorders associated with excessive production of IL-1.[1-4]

1. Neven B, *et al.* Long-term efficacy of the interleukin-1 receptor antagonist anakinra in ten patients with neonatal-onset multisystem inflammatory disease/chronic infantile neurologic, cutaneous, articular syndrome. *Arthritis Rheum* 2010; 62: 258–67.
2. Kuemmerle-Deschner JB, *et al.* Efficacy and safety of anakinra therapy in pediatric and adult patients with the autoinflammatory Muckle-Wells syndrome. *Arthritis Rheum* 2011; 63: 840–9.
3. Rigante D, *et al.* Long-term response after 6-year treatment with anakinra and onset of focal bone erosion in neonatal-onset multisystem inflammatory disease (NOMID/CINCA). *Rheumatol Int* 2011; 31: 1661–4.
4. Sibley CH, *et al.* Sustained response and prevention of damage progression in patients with neonatal-onset multisystem inflammatory disease treated with anakinra: a cohort study to determine three- and five-year outcomes. *Arthritis Rheum* 2012; 64: 2375–86.

Familial Mediterranean fever. For mention of anakinra having been tried in familial Mediterranean fever, see p. 605.1.

Rheumatoid arthritis. In the UK, anakinra is licensed for the treatment of rheumatoid arthritis[1-10] (p. 13.2) in patients with an inadequate response to methotrexate alone; however, NICE[11] does not recommend its use except in the context of a controlled, long-term clinical study.

1. Bresnihan B, *et al.* Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. *Arthritis Rheum* 1998; 41: 2196–2204.
2. Cohen S, *et al.* Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist, in combination with methotrexate: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2002; 46: 614–24.
3. Nuki G, *et al.* Long-term safety and maintenance of clinical improvement following treatment with anakinra (recombinant human interleukin-1 receptor antagonist) in patients with rheumatoid arthritis: extension phase of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2002; 46: 2838–46.
4. Fleischmann RM, *et al.* Anakinra, a recombinant human interleukin-1 receptor antagonist (r-metHuIL-1ra), in patients with rheumatoid arthritis: a large, international, multicenter, placebo-controlled trial. *Arthritis Rheum* 2003; 48: 927–34.
5. Schiff MH. Durability and rapidity of response to anakinra in patients with rheumatoid arthritis. *Drugs* 2004; 64: 2493–2501.
6. Waugh J, Perry CM. Anakinra: a review of its use in the management of rheumatoid arthritis. *BioDrugs* 2005; 19: 189–202.
7. Reiff A. The use of anakinra in juvenile arthritis. *Curr Rheumatol Rep* 2005; 7: 434–40.
8. den Broeder AA, *et al.* Observational study on efficacy, safety, and drug survival of anakinra in rheumatoid arthritis patients in clinical practice. *Ann Rheum Dis* 2006; 65: 760–2.
9. Burger D, *et al.* Is IL-1 a good therapeutic target in the treatment of arthritis? *Best Pract Res Clin Rheumatol* 2006; 20: 879–96.
10. Mertens M, Singh JA. Anakinra for rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009 (accessed 20/10/09).
11. National Collaborating Centre for Chronic Conditions/NICE. Rheumatoid arthritis: national clinical guideline for management and treatment in adults (issued February 2009). Available at: http://www.nice.org.uk/nicemedia/pdf/CG79FullGuideline.pdf (accessed 20/10/09)

Adverse Effects and Precautions

Mild to moderate injection site reactions with symptoms of erythema, bruising, swelling, and pain are common with anakinra particularly in the first month of treatment. Other common reactions include headache, nausea, diarrhoea, and abdominal pain. Antibodies to anakinra may develop. Allergic reactions such as rashes have been reported rarely; if a severe allergic reaction occurs, anakinra should be stopped and appropriate treatment given.

Serious infections have been reported with anakinra, particularly in patients with asthma. These infections are mainly bacterial, such as cellulitis, pneumonia, and bone and joint infections. More rarely, opportunistic infections involving fungal, mycobacterial, and viral pathogens have also been seen. Anakinra should be stopped in those who develop a serious infection. In addition, therapy should not be started in patients with active infections, including chronic or localised infections; caution is recommended in those with a history of recurrent infections or with underlying conditions that may predispose to infections.

A small decrease in absolute neutrophil count (ANC) is commonly seen with anakinra treatment; however, true neutropenia (ANC < 1500 cells/mm^3) is rare. Licensed product information recommends that neutrophil counts should be taken before starting anakinra and periodically throughout treatment. UK licensed information recommends monthly monitoring during the first 6 months and then quarterly thereafter; US licensed information requires monthly monitoring for the first 3 months and then quarterly monitoring for a period of up to 1 year. Anakinra should not be started in patients with neutropenia. Small reductions in the total white blood cell and platelets counts and a small increase in eosinophils have also been noted. Anakinra is also associated with an increased incidence of lymphoma in patients with rheumatoid arthritis.

For caution in patients with renal impairment see under Uses and Administration, p. 21.3.

Effects on the cardiovascular system. A 29-year-old woman with refractory adult-onset Still's disease developed shortness of breath, which progressed to cardiorespiratory failure, 3 months after being started on anakinra;[1] although resuscitation was tried, the patient died. The authors considered that the role of anakinra in this event was unclear, particularly as the patient had shown some evidence of myocardial or pulmonary dysfunction before starting the drug.

1. Ruiz PJ, *et al.* Cardiac death in a patient with adult-onset Still's disease treated with the interleukin 1 receptor inhibitor anakinra. *Ann Rheum Dis* 2007; 66: 422–3.

Effects on the skin. Inflammatory lesions at injection sites were reported in 5 patients after anakinra use.[1] The lesions were erythematous, oedematous, painful, and itchy plaques, and were seen within 16 days of starting treatment. Treatment with anakinra was completely stopped in 1 patient and interrupted in 2 other patients; when reintroduced, one patient developed abdominal pain, dyspnoea, and facial and abdominal erythema with pruritus.

A patient with rheumatoid arthritis developed psoriasis 9 months after starting anakinra therapy;[2] the lesions improved significantly when the drug was stopped and with topical corticosteroids and vitamin D therapy.

1. Vila AT, *et al.* Adverse cutaneous reactions to anakinra in patients with rheumatoid arthritis: clinicopathological study of five patients. *Br J Dermatol* 2005; 153: 417–23.
2. González-López MA, *et al.* New-onset psoriasis following treatment with the interleukin-1 receptor antagonist anakinra. *Br J Dermatol* 2008; 158: 1146–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies anakinra as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 15/11/11)

Interactions

Live vaccines should not be given with anakinra as its effect on vaccine efficacy or the risk of infection transmission is unknown.

The risk of serious infection and neutropenia is increased when anakinra and etanercept are used together (see under Infliximab, p. 77.3); a similar effect may occur with other TNF antagonists. The use of anakinra with etanercept or other TNF inhibitors is not recommended.

Pharmacokinetics

After subcutaneous doses, peak plasma concentrations of anakinra occur in 3 to 7 hours. Its terminal half-life is about 4 to 6 hours. Anakinra is excreted mainly in the urine.

References.

1. Urien S, *et al.* Anakinra pharmacokinetics in children and adolescents with systemic-onset juvenile idiopathic arthritis and autoinflammatory syndromes. *BMC Pharmacol Toxicol* 2013; 14: 40. Available at: http://www.biomedcentral.com/content/pdf/2050-6511-14-40.pdf (accessed 08/11/13)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Kineret; *Austria*: Kineret; *Canad.*: Kineret; *Cz.*: Kineret; *Denm.*: Kineret; *Fin.*: Kineret; *Fr.*: Kineret; *Ger.*: Kineret; *Gr.*: Kineret; *Irl.*: Kineret; *Israel*: Kineret; *Ital.*: Kineret; *Neth.*: Kineret; *Norw.*: Kineret; *Pol.*: Kineret; *Port.*: Kineret; *Spain*: Kineret; *Swed.*: Kineret; *UK*: Kineret; *USA*: Kineret.

Anileridine *(BAN, rINN)*

Anileridiini; Anileridin; Anileridina; Anilératine; Anileridinum; Анилеридин.

Ethyl 1-(4-aminophenethyl)-4-phenylpiperidine-4-carboxylate.

$C_{22}H_{28}N_2O_2$=352.5

CAS — 144-14-9.

ATC — N01AH05.

ATC Vet — QN01AH05.

UNII — 71Q1A3O279.

Pharmacopoeias. In *US.*

USP 36: (Anileridine). A white to yellowish-white, odourless or practically odourless, crystalline powder. When exposed to light and air it oxidises and darkens in colour. It exhibits polymorphism, and of two crystalline forms observed, one melts at about 80 degrees and the other at about 89 degrees. Very slightly soluble in water; soluble 1 in 2 of alcohol and 1 in 1 of chloroform; soluble in ether but solutions may be turbid. Store in airtight containers. Protect from light.

Anileridine Hydrochloride *(BANM, rINNM)*

Anileridina, hidrocloruro de; Anilératine, Chlorhydrate d'; Anileridini Hydrochloridum; Hidrocloruro de anileridina; Анилеридина Гидрохлорид.

$C_{22}H_{28}N_2O_2$,2HCl=425.4

CAS — 126-12-5.

UNII — 915Q054DLC.

Pharmacopoeias. In *US.*

USP 36: (Anileridine Hydrochloride). A white or nearly white odourless crystalline powder. Soluble 1 in 5 of water and 1 in 80 of alcohol; practically insoluble in chloroform and in ether. pH of a 5% solution in water is 2.5 to 3.0. Store in airtight containers. Protect from light.

Anileridine Phosphate *(BANM, rINNM)*

Anilératine, Phosphate d'; Anileridini Phosphas; Fosfato de anileridina; Анилеридина Фосфат.

$C_{22}H_{28}N_2O_2$,H_3PO_4=450.5

CAS — 4268-37-5.

UNII — 3584484N8V.

Profile

Anileridine, a phenylpiperidine derivative, is an opioid analgesic (p. 108.1) chemically related to pethidine (p. 121.3) and with similar actions. It has been used as the hydrochloride in the management of moderate to severe pain. Anileridine has also been given by injection as the phosphate.

Preparations

Pharmacopoeial Preparations

USP 36: Anileridine Hydrochloride Tablets; Anileridine Injection.

Aspirin *(BAN)*

Acetilsalicílico, ácido; Acetilsalicilo rūgštis; Acetilszalicilsav; Acetylsal. Acid; Acetylsalicylic Acid; Acetylsalicylsäure; Acetylsalicylsyra; Acide acétylsalicylique; Acidum Acetylsalicylicum; Asetilsalisilik Asit; Asetyylisalisyylihappo; Kwas acetylosalicylowy; Kyselina acetylsalicylová; Polopiryna; Salicylic Acid Acetate; Аспирин.

O-Acetylsalicylic acid; 2-Acetoxybenzoic acid.

$C_9H_8O_4$=180.2

CAS — 50-78-2.

ATC — A01AD05; B01AC06; N02BA01.

ATC Vet — QA01AD05; QB01AC06; QN02BA01.

UNII — R16CO5Y76E.

NOTE. The use of the name Aspirin is limited; in some countries it is a trade-mark.

Compounded preparations of aspirin may be represented by the following names:

- Co-codaprin (*BAN*)—aspirin 50 parts and codeine phosphate 1 part (w/w)
- Co-codaprin (*PEN*)—aspirin and codeine phosphate.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Acetylsalicylic Acid; Aspirin BP 2014). White or almost white, crystalline powder or colourless crystals. Slightly soluble in water; freely soluble in alcohol. Store in airtight containers.

USP 36: (Aspirin). White crystals, commonly tubular or needle-like, or white crystalline powder; odourless or has a faint odour. Is stable in dry air; in moist air it gradually hydrolyses to salicylic and acetic acids. Soluble 1 in 300 of water, 1 in 5 of alcohol, 1 in 17 of chloroform, and 1 in 10 to 15 of ether; sparingly soluble in absolute ether. Store in airtight containers.

Uses and Administration

Aspirin is a salicylate NSAID and has many properties in common with non-aspirin NSAIDs (p. 102.3). Aspirin and other salicylates have analgesic, anti-inflammatory, and antipyretic properties; they act as inhibitors of the enzyme cyclo-oxygenase, which results in the direct inhibition of the biosynthesis of prostaglandins and thromboxanes from arachidonic acid (see p. 2598.1). Aspirin also inhibits platelet aggregation; non-acetylated salicylates do not.

Aspirin is used for the relief of mild to moderate pain such as headache, dysmenorrhoea, myalgias, and dental pain. It has also been used in the management of pain and inflammation in acute and chronic rheumatic disorders such as rheumatoid arthritis, juvenile idiopathic arthritis, osteoarthritis, and ankylosing spondylitis. In the treatment of minor febrile conditions, such as colds or influenza, aspirin can reduce temperature and relieve headache and joint and muscle pains.

Aspirin is also used for its antiplatelet activity in the initial treatment of cardiovascular disorders such as angina pectoris and myocardial infarction and for the prevention of cardiovascular events in patients at risk. Other such uses include the treatment and prevention of cerebrovascular disorders such as stroke. For further details see Antiplatelet Therapy, below.

Aspirin is usually taken orally. Gastric irritation may be reduced by taking doses after food. Various dosage forms are available including plain uncoated tablets, buffered tablets, dispersible tablets, enteric-coated tablets, and modified-release tablets. In some instances aspirin may be given rectally by suppository.

The usual oral dose of aspirin as an analgesic and antipyretic is 300 to 900 mg, repeated every 4 to 6 hours according to clinical needs, to a maximum of 4 g daily. The dose as suppositories is 450 to 900 mg every 4 hours to a maximum of 3.6 g daily.

Plasma-salicylate concentrations of 150 to 300 micrograms/mL are required for optimal anti-inflammatory activity (but see also Adverse Effects, p. 24.2). Doses need to be adjusted individually to achieve optimum concentrations. Generally doses of about 4 to 8 g daily in divided doses are used for acute rheumatic disorders such as rheumatoid arthritis or osteoarthritis. Doses of up to 5.4 g daily in divided doses may be sufficient in chronic conditions.

Indications for aspirin therapy in children are extremely limited because of the risk of Reye's syndrome (see under Adverse Effects, p. 25.3), but include Kawasaki disease (see p. 23.3), and juvenile idiopathic arthritis and Still's disease (see Rheumatic Disorders, p. 24.1).

Sodium aspirin has also been used for the treatment of pain and fever.

Homoeopathy

Aspirin has been used in homoeopathic medicines under the following names: Acetylsalicylicum acidum; Acetylsal. ac.

Administration in children. Indications for aspirin therapy in children are extremely limited because of the risk of Reye's syndrome (see under Adverse Effects, p. 25.3). For further information, including some doses, see Antiplatelet Therapy, Kawasaki Disease, and Rheumatic Disorders, below, p. 23.3, and p. 24.1, respectively.

Antiplatelet therapy. Aspirin is an inhibitor of the enzyme cyclo-oxygenase, the action being considered to be due to an irreversible acetylation process.

- In blood platelets such enzyme inhibition prevents the synthesis of thromboxane A_2, a compound which is a vasoconstrictor, causes platelet aggregation, and is thus potentially thrombotic.
- In blood vessel walls the enzyme inhibition prevents the synthesis of prostacyclin, which is a vasodilator, has

anti-aggregating properties, and is thus potentially anti-thrombotic.

Aspirin therefore appears to have opposing biological effects. The duration of these effects, however, may differ, with the *effects on the vascular tissue generally being shorter than the effects on the platelets* (although the *animal* species studied, the type of blood vessel used, and the prevailing experimental conditions may alter the results). The difference may be explained by the fact that vascular cells regain the ability to regenerate prostacyclin in a few hours but platelets are unable to re-synthesise cyclo-oxygenase, which results in no new thromboxane A_2 being produced for about 24 hours until more platelets are released by the bone marrow; as platelet activity in bone marrow may also be affected by aspirin it is generally considered that aspirin only needs to be given once daily for inhibition of platelet aggregation to occur. The inhibitory effect on thromboxane is rapid and unrelated to serum concentrations of aspirin, probably because of the inactivation of cyclo-oxygenase in platelets in the presystemic circulation. Since the effect is unrelated to systemic bioavailability, modified-release and dermal delivery preparations which do not achieve high systemic concentrations of aspirin are being developed to limit extraplatelet effects of aspirin. Inhibition is cumulative on repeated dosage, and it has been estimated that a daily dose of 20 to 50 mg will result in virtually complete suppression of platelet thromboxane synthesis within a few days. Large doses of 150 to 300 mg can produce maximum suppression almost instantaneously.

Uses. Aspirin's antiplatelet activity has led to its use for the treatment or prevention of a variety of disorders.[1-7]

- It is used as part of the initial **treatment** of unstable *angina* (p. 1254.3) and is given in the early treatment of *myocardial infarction* (p. 1257.1); it is also of benefit in the initial treatment of acute *ischaemic stroke* (p. 1269.2).
- Aspirin is used for its combination of anti-inflammatory, antipyretic, and antiplatelet activity in the treatment of *Kawasaki disease* (see below). It is also used to treat thrombotic symptoms associated with *antiphospholipid syndrome*, such as occurs in patients with SLE (p. 1613.3), and has been recommended for prophylactic use in pregnant patients with antiphospholipid antibodies who are at risk of fetal loss. The thrombolytic action of aspirin has also led to its use in *thrombotic thrombocytopenic purpura* (see Thrombotic Microangiopathies, p. 1159.1). Aspirin provides a modest reduction in risk of *pre-eclampsia* and its complications (see Hypertension, p. 1251.1) and is recommended in some women.
- It is of value for the **prevention** of cardiovascular events in patients at high risk, including those with stable or unstable angina, current or previous myocardial infarction, ischaemic stroke, or transient ischaemic attack[8,9] (see Cardiovascular Risk Reduction, p. 1246.1). It has also been used in the long-term management of atrial fibrillation (see Cardiac Arrhythmias, p. 1266.1) for the prevention of stroke in patients with contra-indications to warfarin or if there are no other risk factors for stroke.
- The value of aspirin for **primary prevention** of cardiovascular events, particularly *myocardial infarction* and *stroke* depends upon the accurate estimation of overall cardiovascular risk but routine use is probably not justified in healthy individuals.[7-12] Published evidence of unequivocal benefit with low-dose aspirin in such patients is lacking; furthermore, there is an increased risk of gastrointestinal haemorrhage with long-term treatment.

  Although evidence suggests aspirin may provide some protection against *venous thromboembolism* (p. 1274.1) in hospitalised patients, anticoagulants are preferred since they are much more effective. However, it is recommended for use in preventing thrombotic complications associated with procedures such as angioplasty and coronary bypass grafting (see Reperfusion and Revascularisation Procedures, p. 1259.2). Aspirin has been given as an adjunct to patients with *peripheral arterial thromboembolism* (p. 1273.3) to prevent propagation of the clot and also to prevent postoperative complications. Antiplatelet therapy is recommended as part of aggressive cardiovascular risk reduction measures in patients with *peripheral arterial occlusive disease* (p. 1272.3), although a meta-analysis[13] of small and short-term studies did not find a statistically significant benefit (i.e. 12% relative risk reduction) of its use on cardiovascular events when compared with placebo or dipyridamole.

  The benefit of aspirin for the primary prevention of cardiovascular events in patients with *diabetes mellitus* and who have no other cardiovascular risk factors remains to be determined. Use may be recommended in those at increased risk (see Diabetes-associated Cardiovascular Disease, p. 465.3 for further details).

  The value of adding aspirin to anticoagulants for the prophylaxis of thromboembolism in patients with *prosthetic heart valves* (see Valvular Heart Disease, p. 1264.3) is also still to be firmly established. It is usually recommended as an adjunct in patients with other risk factors. Aspirin alone may be considered in patients with bioprosthetic valves who do not require anticoagulation.

Several pharmacological studies have attempted to find a dose of aspirin that would inhibit synthesis of platelet thromboxane A_2 while sparing the effect on prostacyclin production[14-16] but it has been pointed out[3] that in patients with vascular disease accompanying or caused by endothelial dysfunction, such as in atherosclerosis, a selective sparing of vascular prostacyclin production may not be obtained at any effective antiplatelet dose. However, the clinical relevance of inhibiting the synthesis of prostacyclin may have been exaggerated.[17] Experimental evidence indicates that aspirin is thrombogenic only at extremely high doses (200 mg/kg), far exceeding the minimum dose required to inhibit prostacyclin production. Also aspirin is clinically effective as an antithrombotic drug at doses that inhibit the synthesis of prostacyclin. Further support for the lack of importance of inhibition of prostacyclin synthesis comes from epidemiological studies in patients with arthritis given large doses of aspirin and patients with congenital cyclo-oxygenase deficiency; neither of these groups of patients have experienced an excess of thrombotic episodes.

In a meta-analysis conducted by the Antithrombotic Trialists' Collaboration[8] daily doses of 75 to 325 mg appeared to be equally effective for their antiplatelet effect; doses greater than 500 mg did not appear to be superior and caused more gastrointestinal adverse effects. Whether doses less than 75 mg offer the same efficacy with reduced gastrointestinal toxicity is unknown (see Effects on the Gastrointestinal Tract, p. 24.3). The meta-analysis concluded that for the long-term prevention of serious vascular events in high-risk patients, a daily dose of aspirin in the range of 75 to 150 mg should be effective; if an immediate effect is required as in the initial treatment of acute myocardial infarction, acute ischaemic stroke, or unstable angina, a loading dose of 150 to 300 mg may be given. Other analyses[18] have made similar dose recommendations. However, another review[19] has suggested that doses as low as 75 or 80 mg daily may be inadequate for the primary prevention of stroke and myocardial infarction; it was considered that the most appropriate dose of aspirin for primary prevention was 160 mg daily. Aspirin should be chewed or dispersed in water; chewing a tablet of aspirin ensures that some buccal absorption occurs.

The use of aspirin in **children** is limited because of the risk of Reye's syndrome (see under Adverse Effects, p. 25.3); however, it may be specifically indicated in those at risk of clot formation after cardiac surgery or for the prophylaxis of stroke in high-risk children. The *BNFC* has suggested oral doses of 1 to 5 mg/kg (up to a usual maximum of 75 mg) once daily in neonates and children up to 12 years of age; older children may be given 75 mg daily.

1. Patrono C. Aspirin as an antiplatelet drug. *N Engl J Med* 1994; 330: 1287–94.
2. Lutomski DM, *et al.* Pharmacokinetic optimisation of the treatment of embolic disorders. *Clin Pharmacokinet* 1995; 28: 67–92.
3. Schrör K. Antiplatelet drugs: a comparative review. *Drugs* 1995; 50: 7–28.
4. Hung J. Aspirin for cardiovascular disease prevention. *Med J Aust* 2003; 179: 147–52.
5. Saseen JJ. ASHP therapeutic position statement on the daily use of aspirin for preventing cardiovascular events. *Am J Health-Syst Pharm* 2005; 62: 1398–1405.
6. Patrono C, *et al.* Low-dose aspirin for the prevention of atherothrombosis. *N Engl J Med* 2005; 353: 2373–83.
7. US Preventive Services Task Force. Aspirin for the prevention of cardiovascular disease: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2009; 150: 396–404.
8. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002; 324: 71–86. Correction. *ibid.*: 141.
9. Baigent C, *et al.* Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009; 373: 1849–60.
10. Sanmuganathan PS, *et al.* Aspirin for primary prevention of coronary heart disease: safety and absolute benefit related to coronary risk derived from meta-analysis of randomised trials. *Heart* 2001; 85: 265–71.
11. Anonymous. Aspirin for primary prevention of cardiovascular disease? *Drug Ther Bull* 2009; 47: 122–5. Correction. *ibid.* 2010; 48: 24.
12. Barnett H, *et al.* Don't use aspirin for primary prevention of cardiovascular disease. *BMJ* 2010; 340: 920–2.
13. Berger JS, *et al.* Aspirin for the prevention of cardiovascular events in patients with peripheral artery disease: a meta-analysis of randomized trials. *JAMA* 2009; 301: 1909–19.
14. Patrignani P, *et al.* Selective cumulative inhibition of platelet thromboxane production by low-dose aspirin in healthy subjects. *J Clin Invest* 1982; 69: 1366–72.
15. Weksler BB, *et al.* Differential inhibition by aspirin of vascular and platelet prostaglandin synthesis in atherosclerotic patients. *N Engl J Med* 1983; 308: 800–5.
16. McLeod LJ, *et al.* The effects of different doses of some acetylsalicylic acid formulations on platelet function and bleeding times in healthy subjects. *Scand J Haematol* 1986; 36: 379–84.
17. Hirsh J, *et al.* Aspirin and other platelet active drugs: relationship among dose, effectiveness, and side effects. *Chest* 1989; 95 (suppl 2): 12S–18S.
18. Campbell CL, *et al.* Aspirin dose for the prevention of cardiovascular disease: a systematic review. *JAMA* 2007; 297: 2018–24.
19. Dalen JE. Aspirin to prevent heart attack and stroke: what's the right dose? *Am J Med* 2006; 119: 198–202.

Behçet's syndrome. For reference to the use of aspirin in the management of vasculitic symptoms of Behçet's syndrome, see p. 1601.1.

Cataract. Evidence to support or disprove the hypothesis that aspirin has a protective effect against cataract formation is considered inconclusive. A study in the USA in over 22 000 males concluded that low-dose aspirin (325 mg on alternate days) for 5 years was unlikely to have a major effect on cataract formation but that a slightly decreased risk for cataract extraction could not be excluded.[1] In a later study[2] in the UK ophthalmic examination of over 1800 patients who were receiving 300 mg to 1.2 g of aspirin daily for transient ischaemic attacks failed to confirm any protective effect. Re-analysis[3] of the results of the original US study identified additional cases of cataract formation or extraction although these cases did not affect the overall conclusions of the original study. However, when the study patients were followed up over 15 years, observational data[4] suggested that the use of low-dose aspirin may, in fact, increase the risk of cataract development. It was considered that further studies were needed to establish the role of long-term aspirin in cataract prevention.

1. Seddon JM, *et al.* Low dose aspirin and risks of cataract in a randomised trial of US physicians. *Arch Ophthalmol* 1991; 109: 252–5.
2. UK-TIA Study Group. Does aspirin affect the rate of cataract formation? Cross-sectional results during a randomised double-blind placebo controlled trial to prevent serious vascular events. *Br J Ophthalmol* 1992; 76: 259–61.
3. Christen WG, *et al.* Low-dose aspirin and risk of cataract and subtypes in a randomized trial of U.S. physicians. *Ophthalmic Epidemiol* 1998; 5: 133–42.
4. Christen WG, *et al.* Aspirin use and risk of cataract in posttrial follow-up of Physicians' Health Study I. *Arch Ophthalmol* 2001; 119: 405–12.

Dysmenorrhoea. Drugs such as aspirin and other NSAIDs that inhibit prostaglandin production through inhibition of cyclo-oxygenase are effective drugs in the treatment of dysmenorrhoea (p. 8.2).

Fever. Methods for controlling fever (see p. 11.3) include the use of antipyretics and/or physical cooling methods (although the value of the latter is questionable). Paracetamol, salicylates such as aspirin, and some other NSAIDs are the main antipyretics used. However, salicylates are generally contra-indicated for the management of fever in children because of the possible link between their use and the development of Reye's syndrome (see under Adverse Effects, p. 25.3).

Headache. Aspirin is often used for the symptomatic treatment of various types of headache including migraine (see p. 670.3) and tension-type headache (see p. 671.3). Aspirin given at the onset of symptoms can successfully treat an acute attack of migraine. However, absorption may be poor due to gastric stasis which is commonly present in migraine. For this reason dispersible and effervescent preparations and compound preparations containing drugs such as metoclopramide which relieve gastric stasis have been advocated.

References.
1. Tfelt-Hansen P, Olesen J. Effervescent metoclopramide and aspirin (Migravess) versus effervescent aspirin or placebo for migraine attacks: a double-blind study. *Cephalalgia* 1984; 4: 107–11.
2. Buring JE, *et al.* Low-dose aspirin for migraine prophylaxis. *JAMA* 1990; 264: 1711–13.
3. MacGregor EA, *et al.* Mouth-dispersible aspirin in the treatment of migraine: a placebo-controlled study. *Headache* 2002; 42: 249–55.
4. Steiner TJ, *et al.* Aspirin in episodic tension-type headache: placebo-controlled dose-ranging comparison with paracetamol. *Cephalalgia* 2003; 23: 59–66.
5. Lipton RB, *et al.* Aspirin is efficacious for the treatment of acute migraine. *Headache* 2005; 45: 283–92.
6. Diener HC, *et al.* Aspirin in the treatment of acute migraine attacks. *Expert Rev Neurother* 2006; 6: 563–73.

Kawasaki disease. Aspirin has been given in regimens with normal immunoglobulins to children with Kawasaki disease (p. 2405.2) because of its anti-inflammatory, antipyretic, and antiplatelet activity.[1-4]

The usual practice is to use an anti-inflammatory regimen until the fever has settled and then convert to an antithrombotic regimen. The *BNFC* recommends an oral dose of aspirin 30 to 50 mg/kg daily in 4 divided doses in children aged 1 month and over (neonates may be given 32 mg/kg daily in 4 divided doses); this should be continued until the patient is afebrile or for the first 14 days after the onset of symptoms. Once fever and signs of inflammatory disease resolve, the aspirin dose is reduced to 2 to 5 mg/kg daily (neonates may be given 5 mg/kg daily) as a single dose for its antiplatelet effect. Aspirin may be stopped 6 to 8 weeks after the onset of illness but is usually continued for at least one year if coronary abnormalities are present and is continued indefinitely if coronary aneurysms persist. Similar regimens[3,4] are used in the USA although the initial dose of aspirin is more usually 80 to 100 mg/kg daily.

Despite this widespread use the optimum dose and duration of treatment have not been clearly established, and the value of aspirin in the initial management of Kawasaki disease has been questioned. In a meta-analysis[5] fever duration was significantly shorter in those on high-dose aspirin; however, other studies[6] have not shown such a benefit. Meta-analyses[5,7] have also shown that the incidence of coronary artery abnormalities is not significantly different for regimens using high (over 80 mg/kg daily) or low doses of aspirin. Furthermore, a retrospective study[8] suggested that aspirin use (irrespective of dose) in the acute phase of the disease may be unnecessary as its addition to immunoglobulin treatment had no effect on the rate of coronary artery abnormalities. A more recent review[9] found that evidence from comparative studies failed to show that aspirin reduced the rate of coronary artery abnormalities; a lack of good quality randomised controlled studies prevented any recommendations on the use of aspirin in the treatment of Kawasaki disease.

1. Williams RV, *et al.* Pharmacological therapy for patients with Kawasaki disease. *Paediatr Drugs* 2001; 3: 649–60.
2. Brogan PA, *et al.* Kawasaki disease: an evidence based approach to diagnosis, treatment, and proposals for future research. *Arch Dis Child* 2002; 86: 286–90.
3. Newburger JW, *et al.* Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Pediatrics* 2004; 114: 1708–33. Correction. *ibid.* 2005; 115: 1118. Also available at: http://pediatrics.aappublications.org/cgi/reprint/114/6/1708.pdf (accessed 12/04/07) Also published in *Circulation* 2004; 110: 2747–71. Also available at: http://circ.ahajournals.org/cgi/reprint/110/17/2747.pdf (accessed 12/04/07)
4. Freeman AF, Shulman ST. Kawasaki disease: summary of the American Heart Association guidelines. *Am Fam Physician* 2006; 74: 1141–8.
5. Terai M, Shulman ST. Prevalence of coronary artery abnormalities in Kawasaki disease is highly dependent on gamma globulin dose but independent of salicylate dose. *J Pediatr* 1997; 131: 888–93.
6. Saulsbury FT. Comparison of high-dose and low-dose aspirin plus intravenous immunoglobulin in the treatment of Kawasaki syndrome. *Clin Pediatr (Phila)* 2002; 41: 597–601.
7. Durongpisitkul K, *et al.* The prevention of coronary artery aneurysm in Kawasaki disease: a meta-analysis on the efficacy of aspirin and immunoglobulin treatment. *Pediatrics* 1999; 96: 1057–61.
8. Hsieh K-S, *et al.* Treatment of acute Kawasaki disease: aspirin's role in the febrile stage revisited. Abstract: *Pediatrics* 2004; 114: 689. Full version: http://pediatrics.aappublications.org/cgi/reprint/114/6/e689 (accessed 27/11/06)
9. Baumer JH, *et al.* Salicylate for the treatment of Kawasaki disease in children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 27/11/06).

Leg ulcers. A 4-month placebo-controlled study[1] in 20 patients suggested that aspirin 300 mg daily aided healing of chronic venous leg ulcers; the mechanism of action was unclear.[2] However, the validity of the findings has been challenged.[3] The management of leg ulcers is discussed on p. 1690.1.

1. Layton AM, *et al.* Randomised trial of oral aspirin for chronic venous leg ulcers. *Lancet* 1994; 344: 164–5.
2. Ibbotson SH, *et al.* The effect of aspirin on haemostatic activity in the treatment of chronic venous leg ulceration. *Br J Dermatol* 1995; 132: 422–6.
3. Ruckley CV, Prescott RJ. Treatment of chronic leg ulcers. *Lancet* 1994; 344: 1512–13.

Malignant neoplasms. For references to studies suggesting that regular use of aspirin and other NSAIDs may reduce the risk of developing malignant neoplasms of the gastrointestinal tract, see under NSAIDs, p. 104.1.

Myeloproliferative disorders. Aspirin in low doses may be used to provide symptomatic relief for erythromelalgia (burning pain and erythema of the hands and feet) in patients with polycythaemia vera (p. 695.2) and primary thrombocythaemia (p. 695.2).

Pain. Aspirin, along with other NSAIDs and paracetamol, may be used for treating mild or moderate pain (see Choice of Analgesic, p. 4.2) and is also used in moderate or severe pain to potentiate the effects of opioids. It is suitable for use in acute or chronic pain. Aspirin should not be used for pain relief in children because of its association with Reye's syndrome (see under Adverse Effects, p. 25.3).

Dependence and tolerance are not a problem with non-opioid analgesics such as aspirin, but there is a ceiling of efficacy, above which increasing the dose has no further therapeutic effect.

References.

1. Rees J, *et al.* Single dose oral aspirin for acute pain. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 1999 (accessed 27/11/06).
2. Hersch EV, *et al.* Over-the-counter analgesics and antipyretics: a critical assessment. *Clin Ther* 2000; 22: 500–48.
3. Vergne P, *et al.* Aspirine, douleurs et inflammation. *Rev Med Interne* 2000; 21 (suppl 1): 89s–96s.

Rheumatic disorders. Aspirin was once widely used in the treatment of rheumatoid arthritis (p. 13.2) but has been superseded by better tolerated NSAIDs; however, juvenile idiopathic arthritis (p. 12.1) including Still's disease are among the limited number of indications for aspirin use in children. The *American Hospital Formulary Service*[1] suggests that children weighing 25 kg or less may be given an initial oral dose of 60 to 130 mg/kg daily in divided doses; heavier children should be started on 2.4 to 3.6 g daily. Alternatively, an initial oral dose of 1.5 g/m^2 daily may be given in divided doses. The usual maintenance dose is 80 to 100 mg/kg daily although up to 130 mg/kg daily may be required in some children; however, because of the risk of toxicity, it is recommended that children weighing over 25 kg should not receive doses of 100 mg/kg daily or above.

1. McEvoy GK (ed), AHFS Drug Information. online] Bethesda, MD: American Society of Health-System Pharmacists. Available at: http://www.medicinescomplete.com (accessed 13/01/10)

Adverse Effects and Treatment

Aspirin has many properties in common with the non-aspirin NSAIDs, the adverse effects of which are described on p. 104.3.

The most common adverse effects of therapeutic doses of aspirin are gastrointestinal disturbances such as nausea, dyspepsia, and vomiting. Gastrointestinal symptoms may be minimised by giving aspirin with food. Irritation of the gastric mucosa with erosion, ulceration, haematemesis, and melaena may occur. Histamine H_2-antagonists, proton pump inhibitors, and prostaglandin analogues such as misoprostol may be used in the management of NSAID-induced ulceration (see Peptic Ulcer Disease, p. 1816.2), including that caused by aspirin. Slight blood loss, which is often asymptomatic, may occur in about 70% of patients; it is not usually of clinical significance but may, in a few patients, cause iron-deficiency anaemia during long-term therapy. Such occult blood loss is not affected by giving aspirin with food but may be reduced by use of enteric-coated or other modified-release tablets, H_2-antagonists, or high doses of antacids. Major upper gastrointestinal bleeding occurs rarely.

Some persons, especially those with asthma, chronic urticaria, or chronic rhinitis, exhibit notable hypersensitivity to aspirin (see also p. 25.2), which may provoke reactions including urticaria and other skin eruptions, angioedema, rhinitis, and severe, even fatal, paroxysmal bronchospasm and dyspnoea. Persons sensitive to aspirin often have cross-sensitivity to other NSAIDs.

Aspirin increases bleeding time, decreases platelet adhesiveness, and, in large doses, can cause hypoprothrombinaemia. It may cause other blood disorders, including thrombocytopenia.

Aspirin and other salicylates may cause hepatotoxicity, particularly in patients with juvenile idiopathic arthritis or other connective tissue disorders. In children the use of aspirin has been implicated in some cases of Reye's syndrome, leading to severe restrictions on the indications for aspirin therapy in children. For further details, see Reye's Syndrome, p. 25.3.

Aspirin given rectally may cause local irritation; anorectal stenosis has been reported.

Mild chronic salicylate intoxication, or salicylism, usually occurs only after repeated use of large doses. Salicylism can also occur following excessive topical application of salicylates. Symptoms include dizziness, tinnitus, deafness, sweating, nausea and vomiting, headache, and confusion, and may be controlled by reducing the dosage. Tinnitus can occur at the plasma concentrations of 150 to 300 micrograms/mL required for optimal anti-inflammatory activity; more serious adverse effects occur at concentrations above 300 micrograms/mL. Symptoms of more severe intoxication or of acute poisoning following overdosage include hyperventilation, fever, restlessness, ketosis, and respiratory alkalosis and metabolic acidosis. Depression of the CNS may lead to coma; cardiovascular collapse and respiratory failure may also occur. In children drowsiness and metabolic acidosis commonly occur; hypoglycaemia may be severe.

In acute oral salicylate overdosage the UK National Poisons Information Service (NPIS) recommends that an oral dose of activated charcoal be given if the patient is suspected of ingesting more than 125 mg/kg of salicylate or any amount of methyl salicylate, within 1 hour of presentation. Activated charcoal not only prevents the absorption of any salicylate remaining in the stomach but also aids the elimination of any that has been absorbed. Gastric lavage should be considered in patients who have ingested more than 500 mg/kg of salicylate within 1 hour of presentation.

Measurement of plasma-salicylate concentration should be carried out in patients who have ingested more than 125 mg/kg of aspirin, or any amount of methyl salicylate or salicylamide, although the severity of poisoning cannot be estimated from plasma concentrations alone. Absorption of aspirin can be delayed by reduced gastric emptying, formation of concretions in the stomach, or as a result of ingestion of enteric-coated preparations. In consequence, plasma concentrations should be measured at least 2 hours (symptomatic patients) or 4 hours (asymptomatic patients) after ingestion and repeated 2 hours later. A second dose of activated charcoal may be given to those whose plasma-salicylate concentration continues to rise or those who have ingested enteric-coated preparations. If necessary, measurements should be repeated every 3 hours until the concentrations fall.

Fluid and electrolyte management is essential to correct acidosis, hyperpyrexia, hypokalaemia, and dehydration. Intravenous sodium bicarbonate is given to enhance urinary salicylate excretion if plasma-salicylate concentrations exceed 500 micrograms/mL (350 micrograms/mL in children). Haemodialysis or haemoperfusion are also effective methods of removing salicylate from the plasma. The *BNF* considers haemodialysis the method of choice in severe poisoning; it should be seriously considered when the plasma-salicylate concentration is more than 700 micrograms/mL or if there is severe metabolic acidosis. Vulnerable patients such as children (aged under 10 years) or the elderly (aged over 70 years) may require dialysis at an earlier stage.

References to salicylate toxicity and its management.

1. Notarianni L. A reassessment of the treatment of salicylate poisoning. *Drug Safety* 1992; 7: 292–303.
2. Woods D, *et al.* Acute toxicity of drugs: salicylates. *Pharm J* 1993; 250: 576–8.
3. Collee GG, Hanson GC. The management of acute poisoning. *Br J Anaesth* 1993; 70: 562–73.
4. Watson JE, Tagupa ET. Suicide attempt by means of aspirin enema. *Ann Pharmacother* 1994; 28: 467–9.
5. Dargan PI, *et al.* An evidence based flowchart to guide the management of acute salicylate (aspirin) overdose. *Toxicol Rev* 2002; 21: 89–97.
6. Rivera W, *et al.* Delayed salicylate toxicity at 35 hours without early manifestations following a single salicylate ingestion. *Ann Pharmacother* 2004; 38: 1186–8. Correction. *ibid.* 2006; 40: 999.

Effects on the blood. Although it has beneficial effects on platelets, aspirin can cause adverse blood effects. An indication of this toxicity is given by an early reference[1] to reports submitted to the UK CSM. There were 787 reports of adverse reactions to aspirin reported to the CSM between June 1964 and January 1973. These included 95 reports of blood disorders (17 fatal) including thrombocytopenia (26; 2 fatal), aplastic anaemia (13; 7 fatal), and agranulocytosis or pancytopenia (10; 2 fatal). Aspirin has also been associated with haemolytic anaemia in patients with G6PD deficiency.[2]

1. Cuthbert MF. Adverse reactions to non-steroidal antirheumatic drugs. *Curr Med Res Opin* 1974; 2: 600–9.
2. Magee P, Bexley L. Drug-induced blood dyscrasias. *Pharm J* 1991; 246: 396–7.

Effects on the cardiovascular system. Salicylate poisoning may result in cardiovascular collapse but details of such cases have not been widely reported. In 2 patients with salicylate intoxication asystole developed after intravenous diazepam.[1] It was suggested that diazepam-induced respiratory depression affected the acid–base balance so that the concentration of non-ionised membrane-penetrating fraction of salicylate was increased. Fatal aspirin intoxication in a 5-year-old child was marked by hypotension and rapidly progressive cardiac symptoms including ventricular tachycardia and AV block.[2] Extensive myocardial necrosis was found at autopsy.

For reference to the effects of aspirin on blood pressure compared with other NSAIDs, see p. 105.1.

1. Berk WA, Andersen JC. Salicylate-associated asystole: report of two cases. *Am J Med* 1989; 86: 505–6
2. Peña-Alonso YR, *et al.* Aspirin intoxication in a child associated with myocardial necrosis: is this a drug-related lesion? *Pediatr Dev Pathol* 2003; 6: 342–7.

Effects on the gastrointestinal tract. Clinical and epidemiological evidence suggests that aspirin produces dose related gastrointestinal toxicity[1,2] that is sometimes, but rarely, fatal.[2] Meta-analysis[3] suggests that the risk of gastrointestinal bleeding is not significantly lowered with the use of oral low-dose aspirin (less than 300 mg daily). A systematic review[4] of observational epidemiologic studies also concurred with this finding. Another systematic review[5] of randomised, controlled studies found that although low-dose aspirin (up to 325 mg daily) increased the risk of major bleeding including gastrointestinal bleeding by twofold when compared with placebo, the actual risk of bleeding was modest; for every 833 patients taking low-dose aspirin for cardiovascular prophylaxis only 1 additional major bleeding episode will occur annually. In a population-based study,[6] the annual excess risk of upper gastrointestinal complications was about an extra 5 cases per 1000 patients; however, the excess risk varied with underlying gastrointestinal risk factors such as old age and might exceed an extra 10 cases per 1000 patients in a higher-risk group comprising over 10% of aspirin users. It has been suggested that very small doses of aspirin can produce prophylactic benefits in cardiovascular disease without the risk of gastrointestinal toxicity,[7] although others have reported gastric injury even with doses of 10 mg daily.[8]

There appears to be no convincing evidence that the risk of major gastrointestinal bleeding associated with a 75-mg

dose is reduced by using enteric-coated or modified-release formulations rather than soluble aspirin,[3,4,9] although individual studies have reported a reduction in acute mucosal injury with enteric coating.[10]

All known NSAIDs have the potential for causing acute damage to the gastric mucosa (see p. 105.3), and comparative studies of acute gastric mucosal damage caused by such drugs consistently associate aspirin with the most severe lesions.[1] Gastric mucosal injury can occur even with cutaneous application.[11]

1. Graham DY, Smith JL. Aspirin and the stomach. *Ann Intern Med* 1986; **104:** 390–8.
2. Roderick PJ, *et al.* The gastrointestinal toxicity of aspirin: an overview of randomised controlled trials. *Br J Clin Pharmacol* 1993; **35:** 219–26.
3. Derry S, Loke YK. Risk of gastrointestinal haemorrhage with long term use of aspirin: meta-analysis. *BMJ* 2000; **321:** 1183–7.
4. García Rodríguez LA, *et al.* Association between aspirin and upper gastrointestinal complications: systematic review of epidemiologic studies. *Br J Clin Pharmacol* 2001; **52:** 563–71.
5. McQuaid KR, Laine L. Systematic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. *Am J Med* 2006; **119:** 624–38.
6. Hernández-Díaz S, García Rodríguez LA. Cardioprotective aspirin users and their excess risk of upper gastrointestinal complications. *BMC Med* 2006; **4:** 22. Available at: http://www.biomedcentral.com/content/pdf/1741-7015-4-22.pdf (accessed 11/12/06)
7. Lee M, *et al.* Dose effects of aspirin on gastric prostaglandins and stomach mucosal injury. *Ann Intern Med* 1994; **120:** 184–9.
8. Cryer B, Feldman M. Effects of very low dose daily, long-term aspirin therapy on gastric, duodenal, and rectal prostaglandin levels and on mucosal injury in healthy humans. *Gastroenterology* 1999; **117:** 17–25.
9. Anonymous. Which prophylactic aspirin? *Drug Ther Bull* 1997; **35:** 7–8.
10. Cole AT, *et al.* Protection of human gastric mucosa against aspirin—enteric coating or dose reduction? *Aliment Pharmacol Ther* 1999; **13:** 187–93.
11. Cryer B, *et al.* Effects of cutaneous aspirin on the human stomach and duodenum. *Proc Assoc Am Physicians* 1999; **111:** 448–56.

Effects on hearing. Studies have shown that tinnitus develops at serum-salicylate concentrations above 200 micrograms/mL.[1] However, there appears to be considerable intersubject variation in the response of the ear to salicylate;[2] tinnitus may occur at lower concentrations, whereas patients with pre-existing hearing loss may not have tinnitus despite serum-salicylate concentrations of 311 to 677 micrograms/mL.[1] A graded increase in intensity of ototoxicity with increasing salicylate dose and plasma concentration has been shown.[2] For example, at an average total plasma-salicylate concentration of 110 micrograms/mL, the hearing loss at any given frequency was about 12 decibels; such a deficit might be relevant to patients with pre-existing hearing impairment.[2]

1. Mongan E, *et al.* Tinnitus as an indication of therapeutic serum salicylate levels. *JAMA* 1973; **226:** 142–5.
2. Day RO, *et al.* Concentration-response relationships for salicylate-induced ototoxicity in normal volunteers. *Br J Clin Pharmacol* 1989; **28:** 695–702.

Effects on the kidneys. Although abuse of combined analgesic preparations containing aspirin has been implicated in the development of analgesic nephropathy, kidney damage associated with the therapeutic use of aspirin alone appears to be comparatively rare. Many studies have failed to find an increased risk of renal damage in patients taking aspirin.[1-9]

1. New Zealand Rheumatism Association Study. Aspirin and the kidney. *BMJ* 1974; **1:** 593–6.
2. Walker BR, *et al.* Aspirin and renal function. *N Engl J Med* 1977; **297:** 1405.
3. Akyol SM, *et al.* Renal function after prolonged consumption of aspirin. *BMJ* 1982; **284:** 631–2.
4. Bonney SL, *et al.* Renal safety of two analgesics used over the counter: ibuprofen and aspirin. *Clin Pharmacol Ther* 1986; **40:** 373–7.
5. Sandler DP, *et al.* Analgesic use and chronic renal disease. *N Engl J Med* 1989; **320:** 1238–43.
6. Pommer W, *et al.* Regular analgesic intake and the risk of end-stage renal failure. *Am J Nephrol* 1989; **9:** 403–12.
7. Dubach UC, *et al.* An epidemiologic study of abuse of analgesic drugs: effects of phenacetin and salicylate on mortality and cardiovascular morbidity (1968 to 1987). *N Engl J Med* 1991; **324:** 155–60.
8. Perneger TV, *et al.* Risk of kidney failure associated with the use of acetaminophen, aspirin, and nonsteroidal antiinflammatory drugs. *N Engl J Med* 1994; **331:** 1675–9.
9. Rexrode K, *et al.* Analgesic use and renal function in men. *JAMA* 2001; **286:** 315–21.

Effects on the liver. Aspirin-induced hepatic injury is generally mild and manifests as a mild to moderate elevation in aminotransferase values; however, there is a risk of severe liver injury.[1] One review[2] reported an increase in aminotransferase values in 59 of 439 patients given aspirin; the increase was considered to be probably related to aspirin in 23. Hepatotoxicity appears to be correlated with serum-salicylate concentrations greater than 150 micrograms/mL and with active rheumatoid disease. Aspirin-induced liver injury is usually reversible on stopping the drug.[2]

See also under Reye's Syndrome, below.

1. Lewis JH. Hepatic toxicity of nonsteroidal anti-inflammatory drugs. *Clin Pharm* 1984; **3:** 128–38.
2. Freeland GR, *et al.* Hepatic safety of two analgesics used over the counter: ibuprofen and aspirin. *Clin Pharmacol Ther* 1988; **43:** 473–9.

Effects on the mouth. Aspirin burn (ulceration of the mucosal layer of the lips) developed in a 26-year-old woman after taking an aspirin-containing powder for a migraine.[1] The woman had swallowed the powder undissolved rather than adding to water.

1. Dellinger TM, Livingston HM. Aspirin burn of the oral cavity. *Ann Pharmacother* 1998; **32:** 1107.

Hypersensitivity. The main clinical features of patients who have aspirin hypersensitivity include middle-age, female gender, diagnoses of asthma or rhinitis, a personal or family history of atopy, and a history of nasal polyps.[1,2] Aspirin sensitivity occurring with asthma and nasal polyps has been referred to in some reports as the 'aspirin triad'. Other sensitivities often found concomitantly include allergy to food dyes such as tartrazine and to drugs such as other NSAIDs.

The prevalence of aspirin-induced asthma can vary according to the method used to measure it. A systematic review[3] calculated the prevalence of aspirin-induced asthma to be 21% in the general adult asthma population and 5% in children when determined by oral provocation testing. However, when based on medical history alone it was only 2.7% in adults and 2% in children. In another study[4] using data from patient questionnaires the prevalence of aspirin-induced asthma was 10 to 11% in patients with asthma and 2.5% in non-asthmatics.

There is considerable cross-reactivity between aspirin and other NSAIDs and it is generally recommended that patients who have had a hypersensitivity reaction to aspirin or any other NSAID should avoid all NSAIDs. In a systematic review[3] cross-sensitivity to other non-selective NSAIDs (ibuprofen, diclofenac, and naproxen) occurred in over 90% of those patients with aspirin-induced asthma. A review of the literature[5] found little evidence of cross-reactivity with selective cyclo-oxygenase-2 (COX-2) inhibitors and aspirin particularly in patients with aspirin-induced asthma; however, although there have been isolated reports of asthma in such patients after taking celecoxib or rofecoxib. About 4% of patients with aspirin-induced skin reactions may develop a cutaneous reaction when challenged with a COX-2 selective NSAID. Paracetamol is usually safe in patients sensitive to aspirin and cross-sensitivity to paracetamol has been calculated as about 7%.[3] Based on these figures, it is considered that less than 2% of asthmatic patients would be likely to react to both paracetamol and aspirin.

The response to individual NSAIDs is believed to be closely linked to the extent to which they inhibit prostaglandin synthesis.[6,7] There may be a dose threshold below which no detectable symptoms occur and patients who may be tolerant of regular low-dose aspirin can develop symptoms when they take larger doses.[7] Some[7] use a formal challenge with a 300-mg oral dose of aspirin to confirm a diagnosis of NSAID sensitivity but others[8] consider this to be a dangerous technique and use inhalation of lysine aspirin which they consider to be a safer and more predictable alternative. Intranasal challenge with lysine aspirin has also been used.[9,10]

1. Kwoh CK, Feinstein AR. Rates of sensitivity reactions to aspirin: problems in interpreting the data. *Clin Pharmacol Ther* 1986; **40:** 494–505.
2. Schiavino D, *et al.* The aspirin disease. *Thorax* 2000; **55** (suppl 2): S66–S69.
3. Jenkins C, *et al.* Systematic review of prevalence of aspirin induced asthma and its implications for clinical practice. *BMJ* 2004; **328:** 434–7.
4. Vally H, *et al.* The prevalence of aspirin intolerant asthma (AIA) in Australian asthmatic patients. *Thorax* 2002; **57:** 569–74.
5. Knowles SR, *et al.* Management options for patients with aspirin and nonsteroidal antiinflammatory drug sensitivity. *Ann Pharmacother* 2007; **41:** 1191–1200.
6. Power L. Aspirin-induced asthma. *Br J Anaesth* 1993; **71:** 619–21.
7. Frew A. Selected side-effects: 13. non-steroidal anti-inflammatory drugs and asthma. *Prescribers' J* 1994; **34:** 74–7.
8. Davies BH. NSAIDs and asthma. *Prescribers' J* 1994; **34:** 163–4.
9. Casadevall J *et al.* Intranasal challenge with aspirin in the diagnosis of aspirin intolerant asthma: evaluation of nasal response by acoustic rhinometry. *Thorax* 2000; **55:** 921–4.
10. Alonso-Llamazares A, *et al.* Nasal provocation test (NPT) with aspirin: a sensitive and safe method to diagnose aspirin-induced asthma (AIA). *Allergy* 2002; **57:** 632–5.

DESENSITISATION. Successful desensitisation has been achieved using oral aspirin challenge protocols.[1-6] Incremental doses of aspirin (traditionally starting at 30 mg) are given until an allergic response occurs; aspirin is readministered at the dose that caused the response and again incremental doses are given until finally a 650-mg dose is tolerated.[1,2] After desensitisation, an interruption of continuous aspirin dosage results in the reappearance of sensitivity. Desensitisation has been maintained indefinitely with as little as 81 mg daily of aspirin.[6]

1. Asad SI, *et al.* Effect of aspirin in "aspirin sensitive" patients. *BMJ* 1984; **288:** 745–8.
2. Stevenson DD. Desensitization of aspirin-sensitive asthmatics: a therapeutic alternative? *J Asthma* 1983; **20:** 31–8.
3. Gollapudi RR, *et al.* Aspirin sensitivity: implications for patients with coronary artery disease. *JAMA* 2004; **292:** 3017–23.
4. Cormican LJ, *et al.* Improvements in an oral aspirin challenge protocol for the diagnosis of aspirin hypersensitivity. *Clin Exp Allergy* 2005; **35:** 717–22.
5. Pfaar O, Klimek L. Aspirin desensitization in aspirin intolerance: update on current standards and recent improvements. *Curr Opin Allergy Clin Immunol* 2006; **6:** 161–6.
6. Knowles SR, *et al.* Management options for patients with aspirin and nonsteroidal antiinflammatory drug sensitivity. *Ann Pharmacother* 2007; **41:** 1191–1200.

Hypoglycaemia. A review of the literature[1] on drug-induced hypoglycaemia highlighted the fact that overdosage with salicylates could produce hypoglycaemia in children. Although therapeutic doses of salicylates in adults can lower blood-glucose concentrations in diabetic and non-diabetic subjects alike, opinion on the clinical significance of this effect varies. Salicylates have been implicated in a few cases of hypoglycaemia in adults[1] and some[2] suggest that patients with renal impairment or those receiving large doses, such as in the treatment of rheumatoid arthritis, may be at risk. Hypoglycaemia has been reported in a patient with renal failure after excessive application of a topical preparation containing salicylic acid.[3]

1. Seltzer HS. Drug-induced hypoglycemia: a review of 1418 cases. *Endocrinol Metab Clin North Am* 1989; **18:** 163–83.
2. Pandit MK, *et al.* Drug-induced disorders of glucose tolerance. *Ann Intern Med* 1993; **118:** 529–39.
3. Raschke R, *et al.* Refractory hypoglycemia secondary to topical salicylate intoxication. *Arch Intern Med* 1991; **151:** 591–3.

Reye's syndrome. Reye's syndrome is a disorder characterised by acute encephalopathy and fatty degeneration of the liver. It occurs almost exclusively in young children although cases have been seen[1] in patients over the age of 12. Many factors may be involved in its aetiology but it typically occurs after a viral infection such as chickenpox or influenza and may be precipitated by a chemical trigger. Several large studies, as well as individual case reports, have found a link between Reye's syndrome and the prior ingestion of aspirin;[2-7] the evidence for other salicylates could not be adequately evaluated.[4] More recently, *in-vitro* studies have shown biological plausibility for the role of aspirin in the development of Reye's syndrome.[6]

Although a causal relationship remains to be established, the use of aspirin and other acetylated salicylates as analgesics or antipyretics is generally considered contra-indicated in children under the age of 12 years and, in some countries, in teenagers. For example, the UK MHRA has recommended that all children aged under 16 years should not take aspirin.[8] (This advice superseded their earlier recommendations to avoid aspirin during fever or viral infection in children under 16 years of age; this advice was considered too complex for products on general sale and, given the wide availability of other analgesic preparations, there was no need to expose this age group to any risk.) Some countries also extend these recommendations to non-acetylated salicylates. In the UK, the MHRA[9] contra-indicates the use of topical oral pain relief preparations containing salicylates in children under 16 years of age due to the theoretical risk of Reye's syndrome (for details, see Choline Salicylate, p. 39.3).

One group of workers[10] who re-examined some of the original studies suggested that there might also be a link between Reye's syndrome and the use of antiemetics, phenothiazines, and some other antihistamines, but their conclusions have been criticised.[11] More recently, others[12] have suggested that Reye's syndrome was caused by a viral mutation or the result of misdiagnoses of metabolic disorders but again these conclusions have been questioned.[6,13]

1. Hall SM, Lynn R. Reye's syndrome. *N Engl J Med* 1999; **341:** 845–6.
2. Waldman RJ, *et al.* Aspirin as a risk factor in Reye's syndrome. *JAMA* 1982; **247:** 3089–94.
3. Halpin TJ, *et al.* Reye's syndrome and medication use. *JAMA* 1982; **248:** 687–91.
4. Hurwitz ES, *et al.* Public health service study of Reye's syndrome and medications: report of the main study. *JAMA* 1987; **257:** 1905–11.
5. Hall SM, *et al.* Preadmission antipyretics in Reye's syndrome. *Arch Dis Child* 1988; **63:** 857–66.
6. Glasgow JFT. Reye's syndrome: the case for a causal link with aspirin. *Drug Safety* 2006; **29:** 1111–21.
7. Schrör K. Aspirin and Reye syndrome: a review of the evidence. *Pediatr Drugs* 2007; **9:** 195–204.
8. MHRA. Aspirin and Reye's syndrome: questions and answers (issued 4th April, 2003). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON0195128&RevisionSelectionMethod=LatestReleased (accessed 29/11/06)
9. MHRA. Press release: new advice on oral salicylate gels in under 16s (issued 23rd April, 2009). Available at: http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON044014 (accessed 24/04/09)
10. Casteels-Van Daele M, Eggermont E. Reye's syndrome. *BMJ* 1994; **308:** 919–20.
11. Hall SM. Reye's syndrome. *BMJ* 1994; **309:** 411.
12. Orlowski JP, *et al.* Is aspirin a cause of Reye's syndrome? A case against. *Drug Safety* 2002; **25:** 225–31.
13. Waller P, Suvarna R. Is aspirin a cause of Reye's syndrome? *Drug Safety* 2004; **27:** 71–3.

Precautions

Aspirin has many properties in common with the non-aspirin NSAIDs, the precautions of which are described on p. 107.1.

Aspirin should be used cautiously, if at all, in patients prone to dyspepsia or known to have a lesion of the gastric mucosa. It should not be given to patients with haemophilia or other haemorrhagic disorders, nor to treat patients with gout (since low doses increase urate concentrations).

Aspirin should be used with caution in patients with asthma or allergic disorders. It should not be given to patients with a history of sensitivity reactions to aspirin or other NSAIDs, including those in whom attacks of asthma, angioedema, urticaria, or rhinitis have been precipitated by such drugs (for further details of risk factors see Hypersensitivity under Adverse Effects, p. 25.2).

Caution is necessary when renal or hepatic function is impaired; aspirin should be avoided in severe renal or hepatic impairment. Aspirin should be used cautiously in dehydrated patients and in the presence of uncontrolled hypertension.

High doses may precipitate acute haemolytic anaemia in patients with G6PD deficiency. Aspirin may interfere with insulin and glucagon control in diabetics (see Hypoglycaemia under Adverse Effects, p. 25.3).

The use of aspirin in children is extremely limited because of the risk of Reye's syndrome (see under Adverse Effects, p. 25.3, and Uses and Administration, p. 22.3).

Although low-dose aspirin might be used in some pregnant patients, analgesic doses of aspirin should not be used at term as they may be associated with delayed onset and prolongation of labour and with maternal and neonatal bleeding. High doses may cause closure of fetal ductus arteriosus *in utero* and possibly persistent pulmonary hypertension in the newborn (but see Pregnancy, below); kernicterus may occur in jaundiced neonates.

Continuous prolonged use of aspirin should be avoided in the elderly because of the risk of gastrointestinal bleeding.

Aspirin should be stopped several days before scheduled surgical procedures (see below).

Aspirin and other salicylates can interfere with thyroid function tests.

Breast feeding. The American Academy of Pediatrics[1] considers that salicylates should be given with caution to breast-feeding mothers, since aspirin has been associated with metabolic acidosis in the infant.[2] The *BNF* also recommends that aspirin should be avoided in breast-feeding mothers because of the possible risk of Reye's syndrome in nursing infants; they also advise that infants with neonatal vitamin K deficiency may be at risk of hypoprothrombinaemia after the regular use of high doses of aspirin in breast-feeding mothers. However, a prospective study[3] found no adverse effects in 15 breast-fed infants whose mothers were receiving aspirin.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 23/11/06)
2. Clark JH, Wilson WG. A 16-day-old breast-fed infant with metabolic acidosis caused by salicylate. *Clin Pediatr (Phila)* 1981; 20: 53–4.
3. Ito S, *et al.* Prospective follow-up of adverse reactions in breast-fed infants exposed to maternal medication. *Am J Obstet Gynecol* 1993; 168: 1393–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies aspirin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Pregnancy. The potential adverse effects of aspirin when used during pregnancy have been reviewed.[1] Salicylates readily cross the placenta and have been shown to be teratogenic in *animals*. Although some studies and anecdotal reports have implicated aspirin in the formation of congenital abnormalities, most large studies[2-4] have failed to find any significant risk or evidence of teratogenicity. Analysis of data collected by the Slone Epidemiology Unit Birth Defects Study suggests that use of aspirin during the early months of pregnancy, when the fetal heart is developing, is not associated with an increased risk of cardiac defects.[5] The ability of aspirin, however, to alter platelet function may be a potential risk. There have been a few reports of haemorrhagic disorders in infants whose mothers had consumed aspirin during pregnancy[6] and of salicylate-associated haemorrhagic complications in mothers.[7] However, no clinically significant adverse effects on maternal or neonatal bleeding or on fetal ductus flow were reported in a meta-analysis[8] of 6 controlled studies which evaluated low-dose aspirin (less than 325 mg daily) in pregnancy-induced hypertension. Two more recent placebo-controlled studies[9,10] have also found no clinically significant adverse effects on neonatal bleeding with low-dose aspirin. It appeared that the degree of cyclo-oxygenase inhibition produced by aspirin was unlikely to be great enough to cause premature closure of the ductus arteriosus or to affect the pulmonary blood vessels.[1] However, in some studies in patients considered to have high-risk pregnancies the risk of abruptio placentae[11] or consequent perinatal death[12] was increased by maternal dosage with aspirin.

For reference to a possible association between aspirin and other NSAIDs and persistent pulmonary hypertension of the newborn, and a possible association between simple analgesics including aspirin and congenital cryptorchidism, see under NSAIDs, p. 107.2.

Although aspirin has the potential to inhibit uterine contractions of labour it was considered that intermittent or low-dose aspirin was unlikely to inhibit cyclo-oxygenase for long enough to prolong pregnancy or labour.[1]

See also Surgical Procedures, below.

1. de Swiet M, Fryers G. The use of aspirin in pregnancy. *J Obstet Gynaecol* 1990; 10: 467–82.
2. Slone D, *et al.* Aspirin and congenital malformations. *Lancet* 1976; I: 1373–5.
3. Shapiro S, *et al.* Perinatal mortality and birth-weight in relation to aspirin taken during pregnancy. *Lancet* 1976; I: 1375–6.
4. Winship KA, *et al.* Maternal drug histories and central nervous system anomalies. *Arch Dis Child* 1984; 59: 1032–60.
5. Werler MM, *et al.* The relation of aspirin use during the first trimester of pregnancy to congenital cardiac defects. *N Engl J Med* 1989; 321: 1639–42.
6. Bleyer WA, Breckenridge RT. Studies on the detection of adverse drug reactions in the newborn II: the effects of prenatal aspirin on newborn hemostasis. *JAMA* 1970; 213: 2049–53.
7. Collins E, Turner G. Maternal effects of regular salicylate ingestion in pregnancy. *Lancet* 1975; II: 335–7.
8. Imperiale TF, Petrulis AS. A meta-analysis of low-dose aspirin for the prevention of pregnancy-induced hypertensive disease. *JAMA* 1991; 266: 261–4.
9. Louden KA, *et al.* Neonatal platelet reactivity and serum thromboxane B_2 production in whole blood: the effect of maternal low dose aspirin. *Br J Obstet Gynaecol* 1994; 101: 203–8.
10. Dasari R, *et al.* Effect of maternal low dose aspirin on neonatal platelet function. *Indian Pediatr* 1998; 35: 507–11.
11. Sibai BM, *et al.* Prevention of preeclampsia with low-dose aspirin in healthy, nulliparous pregnant women. *N Engl J Med* 1993; 329: 1213–18.
12. Hamid R, *et al.* Low dose aspirin in women with raised maternal serum alpha-fetoprotein and abnormal Doppler waveform patterns from the uteroplacental circulation. *Br J Obstet Gynaecol* 1994; 101: 481–4.

Resistance. Some patients given aspirin for the management of cardiovascular disease do not respond to treatment, a phenomenon that has been described as aspirin resistance. At present, aspirin resistance is poorly understood and further studies are needed to define it.

References

1. Sanderson S, *et al.* Narrative review: aspirin resistance and its clinical implications. *Ann Intern Med* 2005; 142: 370–80.
2. Hankey GJ, Eikelboom JW. Aspirin resistance. *Lancet* 2006; 367: 606–17.
3. Michos ED, *et al.* Aspirin and clopidogrel resistance. *Mayo Clin Proc* 2006; 81: 518–26.
4. Undas A, *et al.* Antithrombotic properties of aspirin and resistance to aspirin: beyond strictly antiplatelet actions. *Blood* 2007; 109: 2285–92.
5. Dalen JE. Aspirin resistance: is it real? Is it clinically significant? *Am J Med* 2007; 120: 1–4.
6. Hovens MMC, *et al.* Prevalence of persistent platelet reactivity despite use of aspirin: a systematic review. *Am Heart J* 2007; 153: 175–81.
7. Krasopoulos G, *et al.* Aspirin "resistance" and risk of cardiovascular morbidity: systematic review and meta-analysis. *BMJ* 2008; 336: 195–8.
8. Gasparyan AY, *et al.* The role of aspirin in cardiovascular prevention: implications of aspirin resistance. *J Am Coll Cardiol* 2008; 51: 1829–43.

Surgical procedures. Aspirin prolongs bleeding time, mainly by inhibiting platelet aggregation. This effect is irreversible and new platelets must be released into the circulation before bleeding time can return to normal. Therefore aspirin therapy should be stopped several days before surgical procedures. In some clinical situations, aspirin may have been given shortly before a surgical procedure. When emergency coronary bypass surgery is required for myocardial infarction, most patients would have received aspirin as part of the initial treatment for infarction. Perioperative bleeding, transfusion requirements, and surgical re-exploration rates may be increased when aspirin is given.[1] However, some studies[2,3] have shown that the increase in bleeding is not significant; in addition, there have been reports that pre-operative aspirin may reduce the rate of perioperative myocardial infarction (with aprotinin),[4] improve oxygenation,[5] and even decrease mortality.[3,6] Desmopressin may reduce the risk of perioperative bleeding (see under Haemorrhagic Disorders, p. 2355.3).

Aspirin is sometimes given during the second and third trimester for the prevention of pregnancy-induced hypertensive disease (see under Hypertension, p. 1251.1). Studies indicate that when given in a dose of 325 mg daily or less, clinically significant effects on maternal or neonatal bleeding do not occur.[7] Some have suggested that aspirin therapy may increase the risk of formation of extradural haematoma thus making epidural anaesthesia inadvisable[8] but a subsequent study[9] found that low-dose aspirin during pregnancy did not increase the risk of bleeding complications during epidural anaesthesia.

Patients on low-dose aspirin, in whom tourniquets are used for nerve blocks or other procedures, may be at increased risk of developing purpuric rash.[10]

It has been suggested that in patients undergoing dermatological,[11] or minor dental[12] surgery, aspirin need only be stopped before surgery in those patients with a prolonged bleeding time, whereas patients with a normal bleeding time could continue therapy.

1. Goldman S, *et al.* Improvement in early saphenous vein graft patency after coronary artery bypass surgery with antiplatelet therapy: results of a Veterans Administration Cooperative Study. *Circulation* 1988; 77: 1324–32.
2. Reich DL, *et al.* Aspirin does not increase homologous blood requirements in elective coronary bypass surgery. *Anesth Analg* 1994; 79: 4–8.
3. Dacey LJ, *et al.* Effect of preoperative aspirin use on mortality in coronary artery bypass grafting patients. *Ann Thorac Surg* 2000; 70: 1986–90.
4. Klein M, *et al.* Aprotinin counterbalances an increased risk of perioperative hemorrhage in CABG patients pre-treated with aspirin. *Eur J Cardiothorac Surg* 1998; 14: 360–6.
5. Gerrah R, *et al.* Preoperative aspirin administration improves oxygenation in patients undergoing coronary artery bypass grafting. *Chest* 2005; 127: 1622–6.
6. Bybee KA, *et al.* Preoperative aspirin therapy is associated with improved postoperative outcomes in patients undergoing coronary artery bypass grafting. *Circulation* 2005; 112 (suppl I): I286–I292.
7. Imperiale TF, Petrulis AS. A meta-analysis of low-dose aspirin for the prevention of pregnancy-induced hypertensive disease. *JAMA* 1991; 266: 260–4.
8. Macdonald R. Aspirin and extradural blocks. *Br J Anaesth* 1991; 66: 1–3.
9. Sibai BM, *et al.* Low-dose aspirin in nulliparous women: safety of continuous epidural block and correlation between bleeding time and maternal-neonatal bleeding complications. *Am J Obstet Gynecol* 1995; 172: 1553–7.
10. Runcie CJ, *et al.* Aspirin and intravenous regional blocks. *Br J Hosp Med* 1990; 43: 229–30.
11. Lawrence C, *et al.* Effect of aspirin and nonsteroidal antiinflammatory drug therapy on bleeding complications in dermatologic surgical patients. *J Am Acad Dermatol* 1994; 31: 988–92.
12. Madan GA, *et al.* Minor oral surgery without stopping daily low-dose aspirin therapy: a study of 51 patients. *J Oral Maxillofac Surg* 2005; 63: 1262–5.

Interactions

Aspirin has many properties in common with the non-aspirin NSAIDs, the interactions of which are described on p. 107.3.

Some of the effects of aspirin on the gastrointestinal tract are enhanced by alcohol. Use of gold compounds with aspirin may exacerbate aspirin-induced liver damage.

Use of aspirin with dipyridamole may result in an increase in plasma-salicylate concentrations. Drugs such as metoclopramide in patients with migraine headache result in earlier absorption of aspirin and higher peak plasma-salicylate concentrations. Metoprolol may also increase peak plasma-salicylate concentrations. Salicylate intoxication has occurred in patients on high-dose salicylate regimens and carbonic anhydrase inhibitors.

Plasma-salicylate concentrations may be reduced by corticosteroids. This interaction is likely to be important in patients receiving high-dose long-term salicylate treatment. Conversely, salicylate toxicity may occur if corticosteroids are withdrawn. Also the risk of gastrointestinal bleeding and ulceration associated with aspirin is increased when used with corticosteroids. Antacids may increase the excretion of aspirin in alkaline urine.

Aspirin may increase the activity of coumarin anticoagulants, sulfonylurea hypoglycaemic drugs, zafirlukast, methotrexate, phenytoin, and valproate. Aspirin diminishes the effects of uricosurics such as probenecid and sulfinpyrazone. The manufacturer of mifepristone advises of a theoretical risk that prostaglandin synthetase inhibition by aspirin or NSAIDs may alter the efficacy of mifepristone.

Use of aspirin with other NSAIDs should be avoided because of the increased risk of adverse effects; the cardioprotective effects of aspirin may be abolished by ibuprofen and possibly other NSAIDS. Aspirin may decrease the plasma concentration of some other NSAIDs, for example, fenbufen, indometacin, and piroxicam.

References.

1. Miners JO. Drug interactions involving aspirin (acetylsalicylic acid) and salicylic acid. *Clin Pharmacokinet* 1989; 17: 327–44.
2. Abebe W. Herbal medication: potential for adverse interactions with analgesic drugs. *J Clin Pharm Ther* 2002; 27: 391–401.
3. Gaziano JM, Gibson CM. Potential for drug-drug interactions in patients taking analgesics for mild-to-moderate pain and low-dose aspirin for cardioprotection. *Am J Cardiol* 2006; 97: 23–9.

ACE inhibitors. For a discussion of aspirin and other NSAIDs reducing the activity of ACE inhibitors, see p. 1288.3.

Anagrelide. For the potential effect of aspirin in patients taking anagrelide, see p. 2443.1.

Antiepileptics. Aspirin may inhibit the metabolism of *valproate*; for further details, see Analgesics, p. 557.2.

Antifungals. Plasma-salicylate concentrations in an 8-year-old child receiving long-term aspirin therapy for rheumatic heart disease were markedly reduced when treatment with *griseofulvin* was started.[1] It was suggested that griseofulvin might interfere with absorption of aspirin.

1. Phillips KR, *et al.* Griseofulvin significantly decreases serum salicylate concentrations. *Pediatr Infect Dis J* 1993; 12: 350–2.

Calcium-channel blockers. The antiplatelet effects of aspirin and calcium-channel blockers may be increased when they are used together; there have been isolated reports[1,2] of disturbed haemostasis including abnormal

bruising, prolonged bleeding times, and ecchymosis in patients taking aspirin and *verapamil* concurrently.

1. Ring ME, *et al.* Clinically significant antiplatelet effects of calcium-channel blockers. *J Clin Pharmacol* 1986; 26: 719–20.
2. Verzino E, *et al.* Verapamil-aspirin interaction. *Ann Pharmacother* 1994; 28: 536–7.

General anaesthetics. For the effect of aspirin on *thiopental* anaesthesia, see p. 1919.3.

NSAIDs. It has been suggested that *ibuprofen* and possibly other *NSAIDs* may reduce the cardioprotective effect of aspirin. A study[1] involving 7107 patients found that cardiovascular mortality was increased in patients taking low-dose aspirin for cardiovascular disease when also taking ibuprofen (adjusted hazard ratio 1.73 times that of patients not taking ibuprofen). Another study[2] found that although taking low-dose aspirin or NSAIDs alone decreased the incidence of myocardial infarction, there was a non-significant increase in the risk of myocardial infarction when both were taken. Another large study also found the risk to be increased in those taking regular rather than intermittent NSAID treatment with aspirin.[3] However, a study[4] involving 14 098 patients concluded that the risk of myocardial infarction was reduced in patients taking ibuprofen and aspirin when compared with those taking aspirin alone. Furthermore, a study[5] in 70 316 patients found that the risk of death in patients prescribed aspirin and ibuprofen was comparable to that of patients prescribed aspirin alone or with another NSAID.

The timing of doses may be important; a study[6] has shown that irreversible platelet aggregation occurred when a single daily dose of ibuprofen was given 2 hours after aspirin; however, when ibuprofen was given before aspirin as a single daily dose or given three times daily, platelet aggregation was reversible which may limit the cardioprotective effects of aspirin.

There are limitations to all these studies and further studies are needed before any recommendations can be made.[7-11]

1. MacDonald TM, Wei L. Effect of ibuprofen on cardioprotective effect of aspirin. *Lancet* 2003; 361: 573–4.
2. Kimmel SE, *et al.* The effects of nonselective non-aspirin non-steroidal anti-inflammatory medications on the risk of nonfatal myocardial infarction and their interaction with aspirin. *J Am Coll Cardiol* 2004; 43: 985–90.
3. Kurth T, *et al.* Inhibition of clinical benefits of aspirin on first myocardial infarction by nonsteroidal antiinflammatory drugs. *Circulation* 2003; 108: 1191–5.
4. Patel TN, Goldberg KC. Use of aspirin and ibuprofen compared with aspirin alone and the risk of myocardial infarction. *Arch Intern Med* 2004; 164: 852–6.
5. Curtis JP, *et al.* Aspirin, ibuprofen, and mortality after myocardial infarction: retrospective cohort study. *BMJ* 2003; 327: 1322–3.
6. Catella-Lawson F, *et al.* Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *N Engl J Med* 2001; 345: 1809–17.
7. Etminan M, Samii A. Effect of ibuprofen on cardioprotective effect of aspirin. *Lancet* 2003; 361: 1558–9.
8. Kimmel SE, Strom BL. Giving aspirin and ibuprofen after myocardial infarction. *BMJ* 2003; 327: 1298–9.
9. Curtis JP, Krumholz HM. The case for an adverse interaction between aspirin and non-steroidal anti-inflammatory drugs: is it time to believe the hype? *J Am Coll Cardiol* 2004; 43: 991–3.
10. Cheema AA. Should people on aspirin avoid ibuprofen? A review of the literature. *Cardiol Rev* 2004; 12: 174–6.
11. Corman SL, *et al.* Impact of nonsteroidal antiinflammatory drugs on the cardioprotective effects of aspirin. *Ann Pharmacother* 2005; 39: 1073–9.

Spironolactone. For the effect of aspirin in patients taking spironolactone, see p. 1502.2.

Pharmacokinetics

Aspirin and other salicylates are absorbed rapidly from the gastrointestinal tract when taken orally but absorption after rectal doses is less reliable. Aspirin and other salicylates can also be absorbed through the skin.

After oral doses, absorption of non-ionised aspirin occurs in the stomach and intestine. Some aspirin is hydrolysed to salicylate in the gut wall. Once absorbed, aspirin is rapidly converted to salicylate, but during the first 20 minutes after an oral dose aspirin is the main form of the drug in the plasma. Aspirin is 80 to 90% bound to plasma proteins and is widely distributed; its volume of distribution is reported to be 170 mL/kg in adults. As plasma-drug concentrations increase, the binding sites on the proteins become saturated and the volume of distribution increases. Both aspirin and salicylate have pharmacological activity although only aspirin has an anti-platelet effect. Salicylate is extensively bound to plasma proteins and is rapidly distributed to all body parts. Salicylate appears in breast milk and crosses the placenta.

Salicylate is mainly eliminated by hepatic metabolism; the metabolites include salicyluric acid, salicyl phenolic glucuronide, salicylic acyl glucuronide, gentisic acid, and gentisuric acid. The formation of the major metabolites, salicyluric acid and salicyl phenolic glucuronide, is easily saturated and follows Michaelis-Menten kinetics; the other metabolic routes are first-order processes. As a result, steady-state plasma-salicylate concentrations increase disproportionately with dose. After a 325-mg aspirin dose, elimination is a first-order process and the plasma-salicylate half-life is about 2 to 3 hours; at high aspirin doses, the half-life increases to 15 to 30 hours. Salicylate is also excreted unchanged in the urine; the amount excreted by this route increases with increasing dose and also depends on urinary pH, about 30% of a dose being excreted in alkaline urine compared with 2% of a dose in acidic urine. Renal excretion involves glomerular filtration, active renal tubular secretion, and passive tubular reabsorption.

Salicylate is removed by haemodialysis.

References.
1. Needs CJ, Brooks PM. Clinical pharmacokinetics of the salicylates. *Clin Pharmacokinet* 1985; 10: 164–77.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aspirina; Aspirinetas; Bayaspirina; Cardioaspirina; Desenfriolito; Ecotrin; Geniol Prevencion; Geniol SC sin Cafeina; Lafeaspirina; Nuevapina; Vipirina Ginsex Corazon; ***Austral.***: Aspro Protect†; Aspro; Astrix; Cardiprin; Cartia; Disprin Direct; Disprin; Solprin; ***Austria***: Acekapton†; Aspirin Protect; Aspro; ASS; CorProtect; Herz ASS; Herzschutz ASS; Thrombo ASS; Thrombostad; Togal Mono†; ***Belg.***: Acenterine; Alka-Seltzer; Asaflow; Aspaxa; Aspirine; Cardioaspirine; Cardiphar; Dispril†; Sedergine; ***Braz.***: AAS; Aceticil; Analgesin; Antifebrin; Aspirina; Bufferin; Cardio AAS; Cimaas; Ecasil; Hipotermal†; Salicetil; Salicil; Salicin; Salipirin; Salisvit; Salitil; Sifaas; Somalgin; ***Canad.***: Apo-Asa; ASA; Asadol†; Asaphen; Asatab; Aspergum; Aspirin with Stomach Guard; Bufferin; Entrophen; Equate Daily Low-Dose; Life Brand Daily Low Dose ASA†; Lowprin; Novasen; PMS-ASA; Pro-AAS; Relief ASA; Rivasa; Tri-Buffered ASA†; ***Chile***: Aspirina; Cardioaspirina; Corvasol; Disgren; Ecotrin; Fluicor; Hassapirin; Thrombo AS; ***China***: An Ni Tuo (安尼妥); Bamyl (巴米尔); Bayaspirin Protect (拜阿司匹灵); Bo Ji (伯基); Jie Ning (介宁); Sai Ning (塞宁); Shi Tai Le (施泰乐); Si Er Li (司尔利); Xie Mei Da (协美达); Xin Dong (欣动); Yixinxue (益欣雪); ***Cz.***: Acylpyrin; Anopyrin; Axanum; Godasal; ***Denm.***: Carnyl†; Hjerdyl; Hjertealbyl; Hjertemagnyl; Hjertemin; Idotyl†; Magnyl; ***Fin.***: Aspirin Cardio; Aspirin Zipp; Disperin; Primaspan; Thrombo ASA; ***Fr.***: Aspirine pH8; Aspirine; Aspirisucre†; Aspro; ***Ger.***: Acesal; ASS; Axanum; Godamed; HerzASS; Miniasal†; Togal ASS; ***Gr.***: Alka-Seltzer N; Apyr; Ascriptin; Bufferin; Measurin; Neospir; Salospir; Upsalgin-N; ***Hong Kong***: Aspilets; Astrix†; Bokey; Cardiprin; Disprin; Ecotrin†; Glyprin; LAsprin†; Propirin; Uni-Acetil†; ***Hung.***: Aspirin Protect; Astrix; Colfarit†; Kalmopyrin; ***India***: Alpyrin; ASA; Ascad; Asicom; Aspent; Aspicot†; Aspin; Aspisol; Colsprin; Cotasprin; CV-Sprin; Delisprin; Disprin; E-Prin; Ecosprin; Gra; Insprin-ER; LDA; Linzi; Loprin; Manospirin; Mazoral; Nusprin; Od-Prin; Optaz; Otaspirin; ***Indon.***: Aptor; Ascardia; Aspilets; Aspitrom; Astika; Bodrexin; Cardio Aspirin; Contrexyn; Farmasal; Inzana†; Miniaspi; Minigrip; Naspro; Procardin†; Proxime; Restor; Rheumapill†; Thrombo Aspilets; ***Irl.***: Asacard; Aspro†; Caprin; Disprin Direct; Disprin Extra Strength; Disprin; Lowasa†; Nu-Seals; Nuasa; Nuprin; Resprin†; ***Israel***: Acetosal; Alka-Seltzer†; Aspirin Cardio; Buffered Pirin†; Cardiopirin; Cartia; Godamed; Micropirin; Tevapirin; ***Ital.***: Ascriptin; Aspiglicina; Aspirina 03; Aspirina; Aspirinetta; Aspro; Cardioaspirin; ***Malaysia***: Aceprin; Aspirin Cardio; Cardiprin; Casprin; Disprin; Glyprin; ***Mex.***: Acetil-A; Acetin†; Acitab; Antacsal; ASA; Ascriptin; Aspirina Protect; Disprina†; Doloquim; Ecotrin†; Midolen; Vastecel; ***Neth.***: Asacard; Aspirine Protect; Aspro; Axanum; Cardioral; Togal†; ***Norv.***: Acetyratio†; Albyl-E; Axanum; Globoid; Magnyl-E†; ***NZ***: Aspec; Aspro; Cartia; Disprin; Ecotrin†; Solprin; ***Philipp.***: Aceprin; Anthrom; Asaprim; Aspec; Aspen; Aspilets; Asthromed; Astrix; Bayprin; Cor-30; Cortal; Enteroprin; Tromcor; ***Pol.***: Acard; Acesan; Alka-Prim; Alka-Seltzer; ASA†; Asaltec; Aspimag; Aspirin Protect; Asprocard†; Asprocol; Bestpirin; Calcipiryna†; Cardiofil; Encopirin; Galocard†; Hascopiryn; Nipas; Polocard; Polopiryna S; Polopiryna; Proficar†; Salpirin; Upsarin; ***Port.***: AAS; Actipiril; Asacard; ASP; Aspirina; Cartia; DuoCover; DuoPlavin; Migraspirina; Toldex; Tromalyt; ***Rus.***: Acecardol (Ацекардол); Alka-Prim (Алька-Прим); Asa-Cardio (Аск-Кардио); Aspikor (Аспикор); Aspinat (Аспинат); Aspinat Cardio (Аспинат Кардио); Aspirin Cardio (Аспирин Кардио); CardiASK (КардиАСК); Cardiomagnyl (Кардиомагнил); Cardiopyrin (Кардиопирин); Nextrim Fast (Некстрим Фаст); Taspir (Таспир); Thrombo ASS (Тромбо АСС); Trombopol (Тромбопол); Upsarin (Упсарин); ***S.Afr.***: Coprin; Disprin; Ecotrin; Myoprin; ***Singapore***: Aspro†; Astrix†; Bokey; Cardiprin; Disprin; Dusil†; Glyprin; Platet†; ***Spain***: AAS; Adiro; Aspirina; Bioplak; Okal†; Okaldol; Rhonal†; Sedergine; Tromalyt; ***Swed.***: Albyl minor; Bamyl; Magnecyl; Trombyl; ***Switz.***: ASA; Asperivo; Aspirine Cardio; Aspro; ASS Cardio; Axanum; Cardiax-ASS; Thrombace Neo†; Tiatral 100 SR; Togal ASS; ***Thai.***: Actorin†; Anassa; Arpisine; ASA; Asatab; Ascot; Aspaco; Aspent; Aspilets; Aspipac; Aspirine; Asrina; B-Aspirin; Buntaopoad-Bura; Caparin; Cardiprin; Empirin; Entrarin; Pirin; Seferin; SP; V-AS†; ***Turk.***: Algo Bebe; Algo†; Asabrin; Asinpirine; Aspapirine; Aspimirin; Aspinal; Ataspin; Babyprin; Coraspin; Dispril; Ecopirin; Isaspin; Notras; Opon; Pharmaspirin; ***UAE***: Jusprin; ***UK***: Alka; Angettes†; Aspro: Caprin; Disprin Direct; Disprin; Enprin; Flamasacard; Micropirin; Nu-Seals; Pure Health; ***Ukr.***: Acecardin (Ацекардин); Acecor Cardio (Ацекор Кардио); Alka-Prim (Алька-Прим); Aspecard (Аспекард); Aspeter (Аспетер)†; Aspirin Cardio (Аспирин Кардио); Cardiomagnyl (Кардиомагнил); Combi-ASA (Комби-АСК); Ecorin (Экорин)†; Godasal (Годасал); Magnikor (Магникор); Polocard (Полокард); ***USA***: Adprin-B; Arthritis Pain Formula; Ascriptin; Aspergum†; AspirLow; Bayer Low Adult Strength; Bufferin; Buffex; Cama Arthritis Pain Reliever; Easprin; Ecotrin; Emprin; Extra Strength Bayer Plus; Genprin; Halfprin; Miniprin; Norwich Extra Strength; Norwich Regular Strength; Regular Strength Bayer; St. Joseph Adult Chewable; ZORprin; ***Venez.***: Asaprol; Ascriptin; Azacard; Cardipirina; Coraspirina.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

BP 2014: Aspirin and Caffeine Tablets; Aspirin Tablets; Co-codaprin Tablets; Dispersible Aspirin Tablets; Dispersible Co-codaprin Tablets; Effervescent Soluble Aspirin Tablets; Gastro-resistant Aspirin Tablets;

USP 36: Acetaminophen and Aspirin Tablets; Acetaminophen, Aspirin, and Caffeine Tablets; Aspirin and Codeine Phosphate Tablets; Aspirin Capsules; Aspirin Delayed-release Capsules; Aspirin Delayed-release Tablets; Aspirin Effervescent Tablets for Oral Solution; Aspirin Extended-release Tablets; Aspirin Suppositories; Aspirin Tablets; Aspirin, Alumina, and Magnesia Tablets; Aspirin, Alumina, and Magnesium Oxide Tablets; Buffered Aspirin Tablets; Butalbital and Aspirin Tablets; Butalbital, Aspirin, and Caffeine Capsules; Butalbital, Aspirin, and Caffeine Tablets; Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules; Carisoprodol and Aspirin Tablets; Carisoprodol, Aspirin, and Codeine Phosphate Tablets; Orphenadrine Citrate, Aspirin, and Caffeine Tablets; Oxycodone and Aspirin Tablets; Pentazocine and Aspirin Tablets; Propoxyphene Hydrochloride, Aspirin, and Caffeine Capsules; Propoxyphene Napsylate and Aspirin Tablets.

Auranofin *(BAN, USAN, rINN)*

Auranofiini; Auranofina; Auranofine; Auranofinum; Oranofin; SKF-39162; SKF-D-39162; Ауранофин.

(1-Thio-β-D-glucopyranosato)(triethylphosphine)gold 2,3,4,6-tetra-acetate.

$C_{20}H_{34}AuO_9PS$=678.5

CAS — 34031-32-8.

ATC — M01CB03.

ATC Vet — QM01CB03.

UNII — 3H04W2810V.

Uses and Administration

Auranofin is a gold compound with a gold content of about 29%; it has similar actions and uses to those of sodium aurothiomalate (p. 130.2). It is given orally in active progressive rheumatoid arthritis (p. 28.1); such oral treatment is less toxic than intramuscular gold but is also much less effective. The usual initial dose of auranofin is 6 mg daily given in two divided doses at first, then, if tolerated, as a single dose. Treatment should be continued for at least 6 months to assess the response; the dose may be increased after 6 months, if the response is inadequate, to 3 mg three times daily. If the response is still inadequate after 3 months at this dosage, then treatment should be stopped.

Asthma. A systematic review[1] found that oral or parenteral gold compounds reduced corticosteroid requirements in the management of asthma (p. 1195.2); however, it was considered that the effect was probably of limited clinical significance and, given the adverse effects and monitoring requirements of gold compounds, their use in asthma could not be recommended.

1. Evans DJ, *et al.* Gold as an oral corticosteroid sparing agent in stable asthma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 11/01/11).

Lupus. Since the introduction of less toxic drugs gold compounds are now rarely used in the treatment of SLE, however, there have been anecdotal reports suggesting that auranofin may be of use in patients with discoid lupus erythematosus[1] or cutaneous lupus erythematosus[2] refractory to conventional treatment.

1. Dalziel K, *et al.* Treatment of chronic discoid lupus erythematosus with an oral gold compound (auranofin). *Br J Dermatol* 1986; 115: 211–16.
2. Farrell AM, Bunker CB. Oral gold therapy in cutaneous lupus erythematosus (revisited). *Br J Dermatol* 1996; 135 (suppl 47): 41.

Pemphigus. A patient with long-standing pemphigus foliaceus being treated with prednisolone and hydroxychloroquine had healing of his lesions within 6 months of auranofin being substituted for the hydroxychloroquine.[1]

1. Bagheri MM, *et al.* Pemphigus foliaceus presenting as eruptive seborrheic keratosis and responding to oral gold treatment. *J Drugs Dermatol* 2002; 1: 333–4.

Psoriasis. Although topical auranofin has been shown in a placebo-controlled study[1] to be effective in the treatment of plaque-type psoriasis (p. 1688.1) the high incidence of

adverse skin reactions, such as contact dermatitis, was thought to outweigh any benefit.

1. Helm KF, *et al.* Topical auranofin ointment for the treatment of plaque psoriasis. *J Am Acad Dermatol* 1995; **33**: 517–19.

Rheumatic disorders. Gold compounds are among the disease-modifying antirheumatic drugs (DMARDs) that may be used in the treatment of rheumatoid arthritis (p. 13.2). Oral gold is less toxic than intramuscular gold but is also much less effective. Gold compounds may also be of benefit in psoriatic arthritis (see under Spondyloarthropathies, p. 14.3) and have been used in juvenile idiopathic arthritis (p. 12.1).

References.

1. Suarez-Almazor ME, *et al.* Auranofin versus placebo in rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2000 (accessed 11/01/11).

Adverse Effects and Treatment

The most common adverse effects of auranofin involve the gastrointestinal tract and include nausea, abdominal pain, and sometimes vomiting, but most often diarrhoea, which can affect up to 50% of patients and may be severe enough to cause patients to withdraw from treatment. Other adverse effects are similar to those of sodium aurothiomalate (p. 131.1), although they appear to be less troublesome since fewer patients stop treatment with auranofin than with injectable gold. As with other gold salts, treatment of adverse effects is generally symptomatic (see p. 131.3). Modifying the diet to increase bulk, use of a bulking agent such as bran, or a temporary reduction in auranofin dosage, may help the diarrhoea (but see Effects on the Gastrointestinal Tract, below).

Reviews.

1. Tozman EC5, Gottlieb NL. Adverse reactions with oral and parenteral gold preparations. *Med Toxicol* 1987; **2**: 177–89.

Effects on the gastrointestinal tract. Diarrhoea and abdominal pain are common with auranofin. The mechanism of gastrointestinal toxicity has not been established but may be associated with a reversible defect in intestinal permeability.[1] Although some have suggested that diarrhoea may occur in up to 50% of patients taking auranofin, a study in 269 patients given the drug for rheumatoid arthritis found that only about 15% had loose and watery stools over a 6-month period.[2] Although bulking agents have been recommended in the management of auranofin-induced diarrhoea, no overall difference in incidence was seen between patients given prophylactic psyllium and those given placebo; however, patients given psyllium had slightly fewer days with loose and watery stools.

Gold-induced colitis has also been reported in patients taking auranofin.[3,4]

1. Behrens R, *et al.* Investigation of auranofin-induced diarrhoea. *Gut* 1986; **27**: 59–65.
2. van Beusekom HJ, *et al.* The moderate intestinal side effects of auranofin do not require prophylactic therapy with a bulkforming agent. Dutch Ridaura Study Group. *Clin Rheumatol* 1997; **16**: 471–6.
3. Michet CJ, *et al.* Auranofin-associated colitis and eosinophilia. *Mayo Clin Proc* 1987; **62**: 142–4.
4. Langer HE, *et al.* Gold colitis induced by auranofin treatment of rheumatoid arthritis: case report and review of the literature. *Ann Rheum Dis* 1987; **46**: 787–92.

Effects on the kidneys. In a retrospective review[1] of 1283 patients given auranofin for treatment of rheumatoid arthritis 41 (3.2%) were found to have developed proteinuria. In most cases proteinuria was treated by stopping auranofin therapy. Long-term follow-up of 36 patients indicated that proteinuria had resolved in 31 within 2 years and in 29 within 1 year. Seven of 8 patients later rechallenged with auranofin had no relapses. In a further review of 2 comparative double-blind studies using gold compounds in the treatment of rheumatoid arthritis, proteinuria was found to have developed in 27% (23 of 85) of patients treated with sodium aurothiomalate, in 17% (42 of 247) of those treated with auranofin, and in 17% (36 of 210) of those receiving placebo. All patients were receiving NSAIDs.

1. Katz WA, *et al.* Proteinuria in gold-treated rheumatoid arthritis. *Ann Intern Med* 1984; **101**: 176–9.

Precautions

As for Sodium Aurothiomalate, p. 131.3. Urine and blood tests should be carried out before starting auranofin and monthly thereafter; licensed product information advises that auranofin should be withdrawn if the platelet count falls below 100 000 cells/mm^3 or if signs and symptoms suggestive of thrombocytopenia, leucopenia, or aplastic anaemia occur. Licensed product information states that baseline renal and liver function levels should also be established before starting auranofin therapy. Auranofin should be used with caution in patients with inflammatory bowel disease.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies auranofin as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 20/07/11)

Interactions

As for Sodium Aurothiomalate, p. 132.1.

Pharmacokinetics

Auranofin is incompletely absorbed from the gastrointestinal tract, only about 25% of the gold being absorbed. Gold from auranofin is bound to plasma proteins as well as to red blood cells. After 2 to 3 months of treatment the steady-state concentration of gold in the blood is reported to be about 700 nanograms/mL. The average terminal plasma half-life of gold at steady state is about 26 days while the biological half-life is 80 days. Tissue retention and total gold accumulation in the body are less than with intramuscular gold. Gold from auranofin penetrates into synovial fluid.

Most of a dose of auranofin appears in the faeces due to its poor absorption. About 60% of the absorbed gold from auranofin is excreted in the urine and the remainder in the faeces.

Reviews.

1. Blocka KLN, *et al.* Clinical pharmacokinetics of oral and injectable gold compounds. *Clin Pharmacokinet* 1986; **11**: 133–43.
2. Beun HP, *et al.* Pharmacokinetics of auranofin: a single dose study in man. *J Rheumatol* 1990; **17**: 466–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Ridaura; *Austria*: Ridaura; *Belg.*: Ridaura; *Canad.*: Ridaura; *China*: Ridaura (瑞得); *Denm.*: Ridaura; *Fin.*: Ridaura; *Gr.*: Ridaura; *Hong Kong*: Ridaura; *India*: Goldar; *Irl.*: Ridaura†; *Israel*: Ridaura; *Ital.*: Ridaura; *Norw.*: Ridaura†; *NZ*: Ridaura: *Port.*: Ridaura; *Rus.*: Auropan (Ауропан)†; *S.Afr.*: Ridaura†; *Spain*: Ridaura†; *Swed.*: Ridaura: *UK*: Ridaura†; *USA*: Ridaura.

Aurothioglucose

1-Aurothio-D-glucopyranose; Aurotioglucosa; (D-Glucosylthio)gold; Gold Thioglucose; Ауротиоглюкоза.
(1-Thio-D-glucopyranosato)gold.
$C_6H_{11}AuO_5S$=392.2
CAS — 12192-57-3.
ATC — M01CB04.
ATC Vet — QM01CB04.
UNII — 2P2V9Q0E78.

Pharmacopoeias. In *US.*

USP 36: (Aurothioglucose). A yellow odourless or practically odourless powder. An aqueous solution is unstable on long standing. It is stabilised by the addition of a small amount of sodium acetate. pH of a 1% solution in water is about 6.3. Freely soluble in water; practically insoluble in alcohol, in acetone, in chloroform, and in ether. Store in airtight containers. Protect from light.

Profile

Aurothioglucose is a gold compound with a gold content of about 50%; it has similar actions and uses to those of sodium aurothiomalate (p. 130.2). It has been used intramuscularly in the treatment of active rheumatoid arthritis and juvenile idiopathic arthritis.

For comment on the relative efficacy and tolerability of aurothioglucose and aurothiomalate, see Rheumatic Disorders, under Sodium Aurothiomalate, p. 130.3.

Effects on the blood. Thrombocytopenia developed in 2 patients treated with intramuscular aurothioglucose.[1]

1. Levin M-D, *et al.* Two patients with acute thrombocytopenia following gold administration and five-year follow-up. *Neth J Med* 2003; **61**: 223–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Solganal†.

Pharmacopoeial Preparations
USP 36: Aurothioglucose Injectable Suspension.

Aurotioprol

Aurothiopropanol Sodium Sulfonate; Aurothiopropanolsulfonate de Sodium; Aurotiopropanol Sodium Sulfonate; Ауротиопрол.
Sodium 3-aurothio-2-hydroxypropane-1-sulphonate.
$C_3H_6AuNaO_4S_2$=390.2
CAS — 27279-43-2.
ATC — M01CB05.
ATC Vet — QM01CB05.
UNII — G7097J63E9.

Profile

Aurotioprol is a gold compound with a gold content of about 50%; it has similar actions and uses to those of sodium aurothiomalate (p. 130.2). It is given by intramuscular injection for the treatment of rheumatoid arthritis (p. 13.2). The initial dose is 25 mg weekly, increased to 50 to 100 mg weekly, until a total dose of 1.2 to 1.5 g has been given. If improvement has occurred with no signs of toxicity, this may be followed by a dose of 50 to 100 mg intramuscularly every month.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Allochrysine.

Azapropazone (BAN, rINN)

AHR-3018; Apazone (USAN); Atsapropatsoni; Azapropazon; Azapropazona; Azapropazonum; Mi85; NSC-102824; Азапропазон.
5-Dimethylamino-9-methyl-2-propylpyrazolo[1,2-*a*][1,2,4]benzotriazine-1,3(2*H*)-dione.
$C_{16}H_{20}N_4O_2$=300.4
CAS — 13539-59-8.
ATC — M01AX04.
ATC Vet — QM01AX04.
UNII — K2VOT966ZI.

Pharmacopoeias. *Br.* includes the dihydrate.

BP 2014: (Azapropazone). The dihydrate is a white to pale yellow crystalline powder. Very slightly soluble in water and in chloroform; soluble in alcohol; dissolves in solutions of alkali hydroxides.

Profile

Azapropazone is an NSAID (see p. 102.3), structurally related to phenylbutazone (p. 125.1). It also has uricosuric properties. Because azapropazone appears to be associated with a higher incidence of adverse effects than with some other NSAIDs, its use was restricted to the treatment of rheumatoid arthritis, ankylosing spondylitis, and acute gout in patients for whom other NSAIDs have been ineffective.

Breast feeding. Small quantities of azapropazone are excreted into breast milk.[1] However, the American Academy of Pediatrics[2] states that there have been no reports of any clinical effect on the infant associated with the use of azapropazone by breast-feeding mothers, and that therefore it may be considered to be usually compatible with breast feeding.

1. Bald R, *et al.* Excretion of azapropazone in human breast milk. *Eur J Clin Pharmacol* 1990; **39**: 271–3.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 01/11/07)

Effects on the blood. Auto-immune haemolytic anaemia, occasionally fatal, often with pulmonary infiltration, allergic alveolitis, pulmonary fibrosis, or fibrosing alveolitis, has been reported in patients receiving azapropazone.[1-3]

1. Chan-Lam D, *et al.* Red cell antibodies and autoimmune haemolysis after treatment with azapropazone. *BMJ* 1986; **293**: 1474.
2. Albazzaz MK, *et al.* Alveolitis and haemolytic anaemia induced by azapropazone. *BMJ* 1986; **293**: 1537–8.
3. Montgomery RD, Babb RG. Alveolitis and haemolytic anaemia induced by azapropazone. *BMJ* 1987; **294**: 375.

Effects on the gastrointestinal tract. In a review[1] of the relative safety of 7 oral NSAIDs, the UK CSM commented that azapropazone was associated with the highest risk of gastrointestinal reactions in both epidemiological studies and an analysis of spontaneous reporting of adverse reactions. Although it appeared that some patients over 60 years of age had received doses exceeding those recommended for this age group, it was considered that even when this was taken into account a marked difference remained between gastrointestinal reactions for azapropazone compared with other NSAIDs.

The CSM recommended that azapropazone should be restricted to use in rheumatoid arthritis, ankylosing spondylitis, and acute gout and only when other NSAIDs have been ineffective. Its use in patients with a history of peptic ulceration was contra-indicated. It was also recommended that when used in patients over 60 years of age for rheumatoid arthritis or ankylosing spondylitis the dose should be reduced.

Azapropazone has been withdrawn in many countries including the UK.

1. CSM/MCA. Relative safety of oral non-aspirin NSAIDs. *Current Problems* 1994; 20: 9–11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015615&RevisionSelectionMethod=LatestReleased (accessed 01/11/07)

Effects on the skin. Of 917 reports of adverse reactions associated with azapropazone forwarded to the WHO Collaborating Centre for International Drug Monitoring[1] before September 1984, 190 (21%) were of photosensitivity. Of 154 reports of photosensitivity evaluated, a causal relationship to use of azapropazone was considered certain in 6, probable in 138, and possible in 10. In May 1994 the UK CSM stated[2] that since 1976 they had received 464 reports of photosensitivity reactions associated with azapropazone and commented that, when corrected for prescription volume, reporting of this reaction was 50 times greater than with other commonly prescribed NSAIDs. They recommended that patients should be advised to avoid direct exposure to sunlight or to use sunblock preparations.

1. Olsson S, *et al.* Photosensitivity during treatment with azapropazone. *BMJ* 1985; 291: 939.
2. CSM/MCA. Photosensitivity associated with azapropazone (Rheumox). *Current Problems* 1994; 20: 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015616&RevisionSelectionMethod=LatestReleased (accessed 01/11/07)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Prolixan; *S.Afr.*: Rheumox†; *Turk.*: Prodisan.

Pharmacopoeial Preparations
BP 2014: Azapropazone Capsules; Azapropazone Tablets.

Bendazac *(BAN, USAN, rINN)*

AF-983; Bendazaco; Bendazacum; Bindazac; Бендазак.
(1-Benzyl-1*H*-indazol-3-yloxy)acetic acid.
$C_{16}H_{14}N_2O_3$=282.3
CAS — 20187-55-7.
ATC — M02AA11; S01BC07.
ATC Vet — QM02AA11; QS01BC07.
UNII — G4AG71204O.

Bendazac Lysine *(BANM, rINNM)*

AF-1934; Bendazac lisina; Bendazaco de lisina; Bendazacum Lysinum; Бендазак Лизин.
L-Lysine-(1-benzyl-1*H*-indazol-3-yloxy)acetic acid.
$C_{22}H_{28}N_4O_5$=428.5
CAS — 81919-14-4.
ATC — S01BC07.
ATC Vet — QS01BC07.
UNII — CL7T957EGC.

Pharmacopoeias. In *Chin.*

Profile

Bendazac is an NSAID (p. 102.3) structurally related to indometacin (p. 71.2). It has been used topically in preparations containing 1 or 3% for the treatment of various inflammatory skin disorders.

Bendazac lysine has been used in the management of cataract, eye drops containing 0.5% being instilled three times daily.

Hepatotoxicity has been reported.

References.
1. Balfour JA, Clissold SP. Bendazac lysine: a review of its pharmacological properties and therapeutic potential in the management of cataracts. *Drugs* 1990; 39: 575–96.
2. Prieto de Paula JM, *et al.* Hepatotoxicidad por bendazaco: análisis de 16 casos. *Rev Clin Esp* 1995; 195: 387–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Sha Pu Ai Si (莎普爱思); *Gr.*: Bendalina; Versalba; Zebinor; *Ital.*: Bendalina; Versus; *Philipp.*: Bendalina; *Port.*: Bendalina; *Venez.*: Bendalina.

Benorilate *(BAN, rINN)*

Benorilaatti; Benorilat; Bénorilate; Benorilato; Benorilatum; Benorylate; FAW-76; Fenasprate; Win-11450; Бенорилат.
4-Acetamidophenyl *O*-acetylsalicylate.
$C_{17}H_{15}NO_5$=313.3
CAS — 5003-48-5.
ATC — N02BA10.
ATC Vet — QN02BA10.
UNII — W1QX9DV96G.

Pharmacopoeias. In *Br.* and *Chin.*

BP 2014: (Benorilate). A white or almost white, odourless or almost odourless, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol and in methyl alcohol; soluble in acetone and in chloroform.

Profile

Benorilate is an aspirin-paracetamol ester with analgesic, anti-inflammatory, and antipyretic properties. After absorption, it is rapidly metabolised to salicylate and paracetamol. It has been used orally in the treatment of mild to moderate pain and fever. It has also been used in osteoarthritis, rheumatoid arthritis, and soft-tissue rheumatism.

When an overdose of benorilate is suspected, it has been suggested that plasma concentrations of both salicylate and paracetamol should be measured since a normal plasma-paracetamol concentration cannot necessarily be assumed from a normal plasma-salicylate measurement.

References.
1. Aylward M. Toxicity of benorylate. *BMJ* 1973; 2: 118.
2. Symon DNK, *et al.* Fatal paracetamol poisoning from benorylate therapy in child with cystic fibrosis. *Lancet* 1982; ii: 1153–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Beilijin (贝利金); YiNuo (益诺).

Multi-ingredient Preparations. *China*: Bei Shu (备硫).

Pharmacopoeial Preparations
BP 2014: Benorilate Oral Suspension; Benorilate Tablets.

Benzydamine Hydrochloride

(BANM, USAN, rINNM)

AF-864; Bencidamina, hidrocloruro de; Benzidamin Hidroklorür; Benzindamine Hydrochloride; Benzydamine, Chlorhydrate de; Benzydamini Hydrochloridum; Benzydaminy chlorowodorek; Hidrocloruro de bencidamina; Бензидамина Гидрохлорид.
3-(1-Benzyl-1*H*-indazol-3-yloxy)-*NN*-dimethylpropylamine hydrochloride.
$C_{19}H_{23}N_3O$,HCl=345.9
CAS — 642-72-8 (benzydamine); 132-69-4 (benzydamine hydrochloride).
ATC — A01AD02; G02CC03; M01AX07; M02AA05.
ATC Vet — QA01AD02; QG02CC03; QM01AX07; QM02AA05.
UNII — K2GI407R4Q.

Pharmacopoeias. In *Br.* and *Pol.*

BP 2014: (Benzydamine Hydrochloride). A white crystalline powder. Very soluble in water; freely soluble in alcohol and in chloroform; practically insoluble in ether. A 10% solution in water has a pH of 4.0 to 5.5.

Uses and Administration

Benzydamine hydrochloride is an NSAID (p. 102.3). It is used topically on the skin in concentrations of 3 to 5% in painful musculoskeletal and soft-tissue disorders. Benzydamine hydrochloride is also used as a mouthwash or spray in concentrations of 0.15% for the relief of inflammatory conditions of the mouth and throat. It has been given orally or rectally for the relief of painful and inflammatory conditions, and as a topical solution for vaginal irrigation.

Benzydamine salicylate (benzasal) has been used topically on the skin as a 6% cream or spray.

Mouth disorders. Results of a randomised placebo-controlled study in patients undergoing radiotherapy for oropharyngeal cancer indicated that benzydamine as an oral rinse was effective in reducing the area and severity of mucositis.[1] Benzydamine is also used locally for the management of mouth ulcers (p. 1814.2) although an early study[2] found it no more useful than placebo.

1. Epstein JB, *et al.* Benzydamine HCl for prophylaxis of radiation-induced oral mucositis: results from a multicenter, randomized, double-blind, placebo-controlled clinical trial. *Cancer* 2001; 92: 875–85.
2. Matthews RW, *et al.* Clinical evaluation of benzydamine, chlorhexidine, and placebo mouthwashes in the management of recurrent aphthous stomatitis. *Oral Surg Oral Med Oral Pathol* 1987; 63: 189–91.

Adverse Effects

After topical application to the skin local reactions such as erythema or rash may occur and photosensitivity has been reported. After use as mouth and throat preparations, numbness or stinging sensations of the oral mucosa have been reported; hypersensitivity reactions including urticaria, photosensitivity, and bronchospasm may also occur rarely.

Effects on the kidneys. A 57-year-old woman who had used 400 g of a topical cream containing benzydamine hydrochloride 3% over a period of 4 months was found to have raised plasma concentrations of creatinine and urea consistent with a substantial reduction in glomerular filtration rate.[1]

1. O'Callaghan CA, *et al.* Renal disease and use of topical non-steroidal anti-inflammatory drugs. *BMJ* 1994; 308: 110–11.

Effects on the skin. Photoallergic contact dermatitis developed on the hands of a 65-year-old woman after the use of a genital wash containing benzydamine 0.1% for several years.[1] The lesions disappeared once the patient stopped using the solution.

1. Lasa Eigezua O, *et al.* Photoallergic hand eczema due to benzydamine. *Eur J Dermatol* 2004; 14: 69–70.

Overdose. A 6-year old girl had hallucinations[1] after receiving 500 mg of benzydamine orally; it had been intended as a vaginal douche for pruritus vulvae; recovery was spontaneous.

1. Gómez-López L, *et al.* Acute overdose due to benzydamine. *Hum Exp Toxicol* 1999; 18: 471–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Actifedrin†; Bencifem; Ernex; Sandival Desleible; *Austral.*: Difflam Anti-inflammatory Throat Spray; Difflam Solution; Difflam; *Austria*: Tantum; *Braz.*: Benflogin; Benzidrol; Benziflex; Benzitrat; Ciflogex; Flogo-Rosa; Flogolab; Flogomin; Flogoral; Fonergoral; Gargojuice; Neoflogin; *Canad.*: Sun-Benz; Tantum; *Cz.*: Rosalgin; Tantum; *Denm.*: Andolex; Zyx; *Fin.*: Zyx; *Fr.*: Opalgyne; *Ger.*: Tantum Rosa; Tantum Verde; *Gr.*: Tantum; *Hong Kong*: Dantum; Difflam Anti-inflammatory Lozenges; Difflam; Verax†; *Hung.*: Rosalgin; Tantum Lemon; Tantum Verde; *Indon.*: Tanflex; Tantum; *Irl.*: Difflam; Tantum Verde; *Israel*: Easy Gel; Tantum Rosa; *Ital.*: Afloben†; Ginesal; Saniflor Collutorio; Tantum; Verax; Xentafid; *Malaysia*: Difflam Anti-inflammatory Lozenges; Difflam Forte Anti-Inflammatory Throat Spray; Difflam Solution†; *Mex.*: Artroben; Beniflant; Ciflnir; Lonol; Vantal; *Neth.*: Tantum; *NZ*: Difflam; *Philipp.*: Difflam; *Pol.*: Hascosept; Septolux; Tantum; *Port.*: Flogoraft; Flogoral; Momen; Rosalgin; Tantum Rosa; Tantum Verde; Tantum Verde; Tantum; *Rus.*: Tantum Rose (Тантум Роза); Tantum Verde (Тантум Верде); *S.Afr.*: Andolex; Andosept; *Singapore*: Difflam; *Spain*: Fulgium; Rosalgin; Tantum Verde; Tantum; *Swed.*: Andolex; Zyx; *Switz.*: Bucco-Tantum; *Thai.*: Difflam; *Turk.*: Beniflex; Benzidan; Farengil; Tanflex; Tantum; Ternex; *UK*: Difflam; *Ukr.*: Tantum Rose (ТантумРоза); Tantum Verde (Тантум Верде); *Venez.*: Azutan; Bevi Dam; Biozendi; Flodont; Tantum Verde; Tantum; Zydan.

Multi-ingredient Preparations. *Arg.*: Buchex; Ernex Duo; Espectocural; *Austral.*: Difflam Anti-inflammatory Lozenges with Cough Suppressant; Difflam Lozenges; Difflam Mouth Gel; Difflam-C; Logicin Rapid Relief; *Braz.*: Angino-Rub; *Hong Kong*: Difflam Anti-inflammatory Antibacterial Lozenges; Difflam Mouth Gel; Difflam-C; Kloroben; Logicin Rapid Relief; *Hung.*: Tantum Rosa†; *Ital.*: Gola Action; Linea F; Tantum Orosan; *Malaysia*: Difflam Anti-inflammatory Lozenges (with Antibacterial); Difflam Anti-Inflammatory Lozenges (with cough suppressant); Difflam Mouth Gel; Difflam-C; *Mex.*: Lonol Sport; *NZ*: Difflam Anti-inflammatory Antibacterial Lozenges; Difflam Cough; Difflam Mouth Gel; Difflam-C; *Philipp.*: Difflam Orange; *Port.*: Benoral; Gartun; Tantum Verde; *S.Afr.*: Andolex-C; Andolex-C; Andosept-Co; *Singapore*: Difflam Anti-inflammatory Anti-Bacterial Lozenges; Difflam Anti-Inflammatory Throat Spray; Difflam Cough Lozenges; Difflam Mouth Gel; Difflam-C; Logicin Rapid Relief; *Spain*: Eternol Antitusivo†; Mentamida†; Prosturol; Tantum†; Vinciseptil Otico; *Turk.*: Cloder Plus; Farhex; Geral; Klodamin; Kloroben; Oroheks Plus; *Venez.*: Amicets; Gencivol Compuesto; Solunovar Compuesto.

Pharmacopoeial Preparations
BP 2014: Benzydamine Cream; Benzydamine Mouthwash; Benzydamine Oromucosal Spray.

Benzyl Nicotinate

Bensylnikotinat; Bentsyylinikotinaatti; Benzil Nikotinat; Benzyli Nicotinas; Nicotinato de bencilo; Бензил Никотинат.
Benzyl pyridine-3-carboxylate.
$C_{13}H_{11}NO_2$=213.2
CAS — 94-44-0.
UNII — S497LCF9C9.

Pharmacopoeias. In *Ger.*

Profile

Benzyl nicotinate is used in topical preparations as a rubefacient.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Pernionin Thermo Teilbad; Pernionin Thermo Vollbad; Rubriment-BN†; Rubriment†.

Multi-ingredient Preparations. *Arg.*: Oxa Sport; Pergalen; *Austria*: Ambenat†; Derivon; Mobilisin plus; Rheumex†; Rilfit-Rheumasalbe; Rubriment; Thermo-Rheumon; Thrombophob; *Braz.*: Trombofob; *Fin.*: Trombosol; *Fr.*: Lumbalgine; *Ger.*: Camphopin†; Pelvichthol N†; Rubriment†; *Gr.*: Air Salonpas; Bayolin; Ehrlich; Striafissan; Thermo-Roiplon; *Hong Kong*: Salomethyl†; *Hung.*: Air Salonpas; *India*: Arjet; Beparine; Thrombophob; *Indon.*: Stop X; Thrombophob; Zeropain; *Ital.*: Salonpas; Sloan†; *Mex.*: Bayro Termo; *Pol.*: Lumbolin†; Thermo-Rheumon; *Port.*: Balsamo Analgesico; Medalginan; *Rus.*: Capsicam (Капсикам); Heparin Ointment (Гепариновая Мазь); *Switz.*: Assan thermo; Dolo Demotherm†; Histalgane; Marament-N; Sportusal assan thermo; *Turk.*: Thermo-Doline; Thermo-Rheumon; Thermoflex; Thermove; *UK*: Salonair†; *Ukr.*: Capsicam (Капсикам); Kamfart (Камфарт); *Venez.*: Ehrlich Balsamo.

Beta-aminopropionitrile

β-Aminopropionitrile; Aminopropionitrile; β-Aminopropionitrilo; BAPN; Beta-aminopropionityrile; Бета-аминопропионитрил.

3-Aminopropionitrile.

$C_3H_6N_2$=70.10

CAS — 151-18-8 (beta-aminopropionitrile); 1119-28-4 (beta-aminopropionitrile fumarate).

ATC Vet — QM01AX91.

UNII — 38D5LJ4KH2.

Profile

Beta-aminopropionitrile, a lysyl oxidase inhibitor, is an anti-inflammatory used as the fumarate in veterinary medicine for the treatment of tendinitis.

Bornyl Salicylate

Borneol Salicylate; Salicilato de bornilo; Борнилсалицилат.

2-Hydroxybenzoic acid 1,7,7-trimethylbicyclo[2.2.1]hept-2-yl ester.

$C_{17}H_{22}O_3$=274.4

CAS — 560-88-3.

Profile

Bornyl salicylate is a salicylic acid derivative that has been used topically in rubefacient preparations similarly to methyl salicylate (p. 92.1) for the relief of pain in musculoskeletal and joint disorders.

Bromfenac Sodium *(USAN, rINNM)*

AHR-10282; AHR-10282B; Bromfénac Sodique; Bromfenaco sódico; Natrii Bromfenacum; Натрий Бромфенак.

Sodium [2-amino-3-(*p*-bromobenzoyl)phenyl]acetate sesquihydrate.

$C_{15}H_{11}BrNNaO_3$,1½H_2O=383.2

CAS — 91714-94-2 (bromfenac); 91714-93-1 (bromfenac sodium); 120638-55-3 (bromfenac sodium).

ATC — S01BC11.

ATC Vet — QS01BC11.

UNII — 8ECVS71Y37.

Profile

Bromfenac, a phenylacetic acid derivative related to diclofenac (p. 48.3), is an NSAID (p. 102.3) used for ocular pain and inflammation including postoperative inflammation in patients who have undergone cataract extraction. It is given as the sodium salt although the eye drop strength may be expressed in terms of the free acid; 1 mg of bromfenac sodium is equivalent to about 0.9 mg of bromfenac. Eye drops containing the equivalent of 0.09% bromfenac are instilled twice daily in inflammatory ocular conditions. When used postoperatively, drops containing the equivalent of 0.07% or 0.09% bromfenac are instilled once daily starting one day before, and continuing until 14 days after, surgery. Alternatively, twice daily administration of 0.09% bromfenac drops are started the day after surgery and continued for the next 14 days.

It was formerly given orally in the management of acute pain but was withdrawn from the market after reports of severe and sometimes fatal hepatic failure.

Effects on the eyes. Severe corneal melting (ulceration) was seen in 3 patients after topical use of bromfenac sodium.[1] All patients recovered after bromfenac was withdrawn. Similar effects have been reported with other ophthalmic NSAID preparations; for further details see under Adverse Effects of Diclofenac, p. 50.1.

1. Asai T, *et al.* Three cases of corneal melting after instillation of a new nonsteroidal anti-inflammatory drug. *Cornea* 2006; **25**: 224–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Natax; *Denm.*: Yellox; *Fr.*: Yellox; *Ger.*: Yellox; *Irl.*: Yellox; *Jpn*: Bronuck; *Neth.*: Yellox; *Norw.*: Yellox; *Spain*: Yellox; *Swed.*: Yellox; *UK*: Yellox; *USA*: Bromday; Prolensa; Xibrom†.

Bufexamac *(BAN, rINN)*

Bufeksamaakki; Bufeksamakas; Bufexamaco; Bufexamacum; Bufexamak; Bufexamák; Буфексамак.

2-(4-Butoxyphenyl)acetohydroxamic acid.

$C_{12}H_{17}NO_3$=223.3

CAS — 2438-72-4.

ATC — M01AB17; M02AA09.

ATC Vet — QM01AB17; QM02AA09.

UNII — 4T3C38J78L.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.*

Ph. Eur. 8: (Bufexamac). A white or almost white, crystalline powder. Practically insoluble in water; soluble in dimethylformamide; slightly soluble in ethyl acetate and in methyl alcohol. Protect from light.

Profile

Bufexamac is an NSAID (p. 102.3) that is applied topically in concentrations of 5% in various skin disorders. Stinging and burning may occur after application; hypersensitivity reactions have been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Parfenac; *China*: Kerun (科润); *Fr.*: Parfenact; *Ger.*: Haemo-Exhirud Bufexamact; Jomaxt; Parfenact; Windolt; *Ital.*: Fansamac; *Port.*: Parfenact; *Switz.*: Parfenac; *Turk.*: Isoderm.

Multi-ingredient Preparations. *Austral.*: Paraderm Plus†; Resolve; *Cz.*: Mastu S†; *Ger.*: Anaesthesin akut†; Faktu akut†; Hamoratiopharm N†; Hamoagil plus†; Hexamon Bufexamac†; Mastu akut†; *Hong Kong*: Fungo Soothing Balm†; Mastu S†; *Hung.*: Mastu S†; *NZ*: Paraderm Plus†; *Rus.*: Proctosan (Проктозан); *Thai.*: Mastu S†; *Ukr.*: Proctosan (Проктозан).

Bumadizone Calcium *(rINNM)*

Bumadizona cálcica; Bumadizone Calcique; Calcii Bumadizonum; Кальций Бумадизон.

Calcium 2-(1,2-diphenylhydrazinocarbonyl)hexanoate hemihydrate.

$(C_{19}H_{21}N_2O_3)_2Ca$,½H_2O=699.9

CAS — 3583-64-0 (bumadizone); 34461-73-9 (bumadizone calcium).

ATC — M01AB07.

ATC Vet — QM01AB07.

UNII — 7PSH384AJD (bumadizone calcium hemihydrate); 142R7TU2TN (anhydrous bumadizone calcium).

Profile

Bumadizone calcium is an NSAID (p. 102.3) that is metabolised to phenylbutazone (p. 125.1) and oxyphenbutazone (p. 114.3). Use has been limited by the risk of agranulocytosis and other haematological adverse effects.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Mex.*: Desflam.

Buprenorphine *(BAN, rINN)* ⊗

Buprenorfiini; Buprenorfin; Buprenorfina; Buprenorfinas; Buprenorphin; Buprénorphine; Buprenorphinum; RX-6029-M; Бупренорфин.

(6*R*,7*R*,14*S*)-17-Cyclopropylmethyl-7,8-dihydro-7-[(1*S*)-1-hydroxy-1,2,2-trimethylpropyl]-6-*O*-methyl-6,14-ethano-17-normorphine; (2*S*)-2-[(–)-(5*R*,6*R*,7*R*,14*S*)-9a-Cyclopropylmethyl-4,5-epoxy-3-hydroxy-6-methoxy-6,14-ethanomorphinan-7-yl]-3,3-dimethylbutan-2-ol.

$C_{29}H_{41}NO_4$=467.6

CAS — 52485-79-7.

ATC — N02AE01; N07BC01.

ATC Vet — QN02AE01; QN07BC01.

UNII — 40D3SCR4GZ.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of buprenorphine:

TEM; Tems.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Buprenorphine). A white or almost white crystalline powder. Very slightly soluble in water; freely soluble in acetone; slightly soluble in cyclohexane; soluble in methyl alcohol. It dissolves in dilute solutions of acids. Protect from light.

Buprenorphine Hydrochloride

(BANM, USAN, rINNM) ⊗

Buprenorfiinihydrokloridi; Buprenorfina, hidrocloruro de; Buprenorfin-hidroklorid; Buprenorfin-hydrochlorid; Buprenorfinhydroklorid; Buprenorfino hidrochloridas; Buprenorphine, Chlorhydrate de; Buprenorphinhydrochlorid; Buprenorphini Hydrochloridum; CL-112302; Hidrocloruro de buprenorfina; NIH-8805; UM-952; Бупренорфина Гидрохлорид.

$C_{29}H_{41}NO_4$,HCl=504.1

CAS — 53152-21-9.

UNII — 56W8MW3EN1.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Buprenorphine Hydrochloride). A white or almost white crystalline powder. Sparingly soluble in water; soluble in alcohol; practically insoluble in cyclohexane; freely soluble in methyl alcohol. Protect from light.

USP 36: (Buprenorphine Hydrochloride). pH of a 1% solution in water is between 4.0 and 6.0. Store in airtight containers. Protect from light.

Uses and Administration

Buprenorphine is an opioid analgesic (p. 108.1) classified as an opioid agonist and antagonist. It is used for the relief of moderate to severe pain and as an adjunct to anaesthesia. Buprenorphine is also used in the treatment of opioid dependence.

Buprenorphine has a relatively slow onset but prolonged duration of action. On intramuscular injection analgesia is apparent within 15 minutes and lasts up to 6 hours. A slower, more prolonged response is achieved after sublingual doses. The analgesic effects of buprenorphine after transdermal application may not be seen for at least 12 to 24 hours or up to 72 hours in the case of the once-weekly patch.

Buprenorphine is usually given by intramuscular or intravenous injection or sublingually as the hydrochloride or as transdermal patches as the base. For all routes doses are expressed in terms of the base. Buprenorphine hydrochloride 107.8 micrograms is equivalent to about 100 micrograms of buprenorphine.

Buprenorphine is given by all the above routes for opioid analgesia in moderate to severe pain.

- The dose by intramuscular or slow intravenous injection is 300 to 600 micrograms repeated every 6 to 8 hours as required
- By the sublingual route, doses of 200 to 400 micrograms may be repeated every 6 to 8 hours as required
- For opioid treatment of chronic pain in patients aged 18 years and over transdermal patches delivering varying amounts of buprenorphine are available. Doses should be individually titrated for each patient according to previous opioid usage. During transfer to treatment with buprenorphine patches previous opioid analgesic therapy should be phased out gradually in order to allow for the gradual increase in plasma-buprenorphine concentrations. Depending on dose required up to 2 patches may be applied, however, this should be done at the same time to avoid confusion. Buprenorphine patches are not appropriate for acute pain. In the UK and USA, transdermal buprenorphine patches are available as follows:

  Transtec (*Napp, UK*) delivering buprenorphine in a range of 35 to 70 micrograms/hour. Initial dosages should not exceed 35 micrograms/hour in *opioid-naive* patients. For *patients who have been receiving a strong opioid analgesic* the initial dose should be based on the previous 24-hour opioid requirement. Use of a patch providing 35 micrograms/hour of buprenorphine is roughly equivalent to 30 to 60 mg daily of oral morphine sulfate. Patches should be replaced every 96 hours at the latest with the new patch being applied to a different site; use of the same area of the skin should be avoided for at least the next 2 applications.

  BuTrans (*Napp, UK*) and *Butrans* (*Purdue, USA*) delivering buprenorphine in a range of 5 to 20 micrograms/hour. UK licensed product information states that initial dosages should not exceed 5 micrograms/hour in *all* patients, whereas in the USA, this dose is licensed for the initial treatment of *opioid-naive* patients or those who have been receiving a strong opioid analgesic whose daily dose is *less than 30 mg of oral morphine* or its equivalent. US licensed information recommends an

initial dose of 10 micrograms/hour for opioid-tolerant patients whose daily dose is *between 30 and 80 mg of oral morphine* or its equivalent. In those requiring *more than 80 mg daily of oral morphine* or its equivalent the use of patches providing 20 micrograms/hour of buprenorphine may not provide adequate analgesia; however, application of multiple patches to provide doses greater than 20 micrograms/hour is not licensed in the USA (see Adverse Effects and Treatment, below). Patches should be replaced every 7 days with the new patch being applied to a different site; use of the same area of the skin should be avoided for the next 3 to 4 weeks.

When used in balanced **anaesthesia** 300 micrograms may be given intramuscularly or 400 micrograms sublingually for premedication; 300 to 450 micrograms may be given intravenously as a perioperative analgesic supplement.

For the treatment of **opioid dependence** in patients aged 16 years and over, the initial dose is 0.8 to 4 mg sublingually once daily. The dose may be increased as necessary but maintenance doses should not exceed 32 mg daily. Once the patient has been stabilised, the dosage should be reduced gradually to a lower maintenance dose; treatment may eventually be stopped if appropriate. For addicts who have not undergone opioid withdrawal before starting buprenorphine, the first dose of buprenorphine should not be given until the first signs of craving appear or until at least 4 (USA) or 6 (UK) hours after the last opioid use. In those already receiving methadone replacement, the dose of methadone should be reduced to a maximum of 30 mg daily before starting buprenorphine therapy. As a deterrent to abuse, combined sublingual preparations of buprenorphine hydrochloride and naloxone hydrochloride are available in some countries for the treatment of opioid dependence. Naloxone may also increase the analgesic effect of buprenorphine, see Administration with Buprenorphine, under Naloxone, p. 1563.3.

For details of doses in **children**, see below.

Action. Buprenorphine is generally described as a mixed agonist-antagonist acting mainly as a partial agonist at μ opioid receptors, with some antagonist activity at κ receptors. It has also been shown to bind at μ, δ, and κ opioid binding sites and to have high affinity for the μ and δ receptors and lesser affinity for the κ receptor.[1] Buprenorphine, like fentanyl, has high lipid solubility, but has a lower intrinsic activity than fentanyl. Differences between buprenorphine and pure μ opioid agonists such as fentanyl, including relatively slow onset of action, prolonged duration of action, resistance to antagonism by naloxone, and lack of correlation between plasma concentrations and analgesic effects, have been explained by differences in the way buprenorphine binds to opioid receptors. In a study *in vitro* buprenorphine had slow rates of association and dissociation from the opioid receptor when compared with fentanyl.[2]

1. Bovill JG. Which potent opioid? Important criteria for selection. *Drugs* 1987; 33: 520–30.
2. Boas RA, Villiger JW. Clinical actions of fentanyl and buprenorphine: the significance of receptor binding. *Br J Anaesth* 1985; 57: 192–6.

Administration in children. Buprenorphine is used for the relief of moderate to severe **pain** in children. In the UK, those aged from 6 months to 12 years may be given 3 to 6 micrograms/kg by *intramuscular* or slow *intravenous* injection every 6 to 8 hours; up to 9 micrograms/kg may be given if required in refractory cases. In the USA, parenteral buprenorphine is licensed in children aged 2 years and over; usual doses of 2 to 6 micrograms/kg may be given intramuscularly or intravenously every 4 to 6 hours to those up to 12 years old.

The *sublingual* route is licensed in the UK in children aged from 6 to 12 years and the following doses are given every 6 to 8 hours according to body-weight:

- 16 to 25 kg: 100 micrograms
- 25 to 37.5 kg: 100 to 200 micrograms
- 37.5 to 50 kg: 200 to 300 micrograms

Older children requiring pain relief may be given the usual adult dose (see p. 30.3) for all the above routes.

Buprenorphine is also used in the treatment of **opioid dependence**; adolescents aged 16 years and over may be given the usual adult dose (see p. 30.3).

Opioid dependence. Buprenorphine is used in the treatment of opioid dependence (p. 109.2). Its agonist-antagonist properties may mean that it has a lower potential for dependence and a lower risk of respiratory depression in overdose than pure agonists such as methadone. Buprenorphine can be used as substitution therapy in patients with moderate opioid dependence for acute management of withdrawal and in maintenance treatment as an alternative to or with methadone. However, in patients dependent on high doses of opioids buprenorphine may precipitate withdrawal due to its partial antagonist properties; the daily opioid dose should be reduced gradually in such patients before beginning buprenorphine. Abuse of the preparation, as with other substitution therapies, may be a problem. A combined sublingual preparation of buprenorphine hydrochloride and naloxone hydrochloride is available in some countries as a deterrent to abuse.

References.

1. Kakko J, *et al.* 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomised, placebo-controlled trial. *Lancet* 2003; 361: 662–8.
2. Fudala PJ, *et al.* Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. *N Engl J Med* 2003; 349: 949–58.
3. Montoya ID, *et al.* Randomized trial of buprenorphine for treatment of concurrent opiate and cocaine dependence. *Clin Pharmacol Ther* 2004; 75: 34–48.
4. Fiellin DA, *et al.* Consensus statement on office-based treatment of opioid dependence using buprenorphine. *J Subst Abuse Treat* 2004; 27: 153–9.
5. Donaher PA, Welsh C. Managing opioid addiction with buprenorphine. *Am Fam Physician* 2006; 73: 1573–8.
6. Sung S, Conry JM. Role of buprenorphine in the management of heroin addiction. *Ann Pharmacother* 2006; 40: 501–5.
7. Robinson SE. Buprenorphine-containing treatments: place in the management of opioid addiction. *CNS Drugs* 2006; 20: 697–712.
8. NICE. Methadone and buprenorphine for the management of opioid dependence: Technology Appraisal Guidance 114 (issued January 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/TA114Niceguidance.pdf (accessed 26/06/08)
9. Boothby LA, Doering PL. Buprenorphine for the treatment of opioid dependence. *Am J Health-Syst Pharm* 2007; 64: 266–72.
10. Mattick RP, *et al.* Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 26/06/08).
11. Sullivan LE, Fiellin DA. Narrative review: buprenorphine for opioid-dependent patients in office practice. *Ann Intern Med* 2008; 148: 662–70.
12. Schottenfeld RS, *et al.* Maintenance treatment with buprenorphine and naltrexone for heroin dependence in Malaysia: a randomised, double-blind, placebo-controlled trial. *Lancet* 2008; 371: 2192–2200.
13. Woody GE, *et al.* Extended vs short-term buprenorphine-naloxone for treatment of opioid-addicted youth: a randomized trial. *JAMA* 2008; 300: 2003–11. Correction. *ibid.* 2009; 301: 830.
14. Orman JS, Keating GM. Buprenorphine/naloxone: a review of its use in the treatment of opioid dependence. *Drugs* 2009; 69: 577–607.
15. Gowing L, *et al.* Buprenorphine for the management of opioid withdrawal. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2009 (accessed 30/10/09).

Pain. *ACUTE PAIN.* The *BNF* considers that buprenorphine may antagonise the analgesic effect of other opioids and is generally not recommended for the management of *post-operative* pain. Nonetheless, it can be given intramuscularly, intravenously, or sublingually for this purpose, although the intravenous route may be preferred for acute pain relief. The epidural route[1] and continuous subcutaneous infusion[2] have also been used; an intranasal formulation of buprenorphine has been investigated for the management of postoperative pain.[1] Patient-controlled analgesia with intravenous[3] and intramuscular[4] buprenorphine is effective although its long half-life may limit such use.

Buprenorphine had no adverse cardiovascular effects when given intravenously after open-heart surgery,[5] suggesting that it was a suitable analgesic for patients with unstable circulation. Epidural analgesia with buprenorphine has also been used after cardiac surgery.[6] Buprenorphine was also considered suitable for the relief of pain in *myocardial infarction*.[7]

1. Miwa Y, *et al.* Epidural administered buprenorphine in the perioperative period. *Can J Anaesth* 1996; 43: 907–13.
2. Kawamata T, *et al.* Pain management after lumbar spinal fusion surgery using continuous subcutaneous infusion of buprenorphine. *J Anesth* 2005; 19: 199–203.
3. Dingus DJ, *et al.* Buprenorphine versus morphine for patient-controlled analgesia after cholecystectomy. *Surg Gynecol Obstet* 1993; 177: 1–6.
4. Harmer M, *et al.* Intramuscular on demand analgesia: double blind controlled trial of pethidine, buprenorphine, morphine, and meptazinol. *BMJ* 1983; 286: 680–2.
5. Rosenfeldt FL, *et al.* Haemodynamic effects of buprenorphine after heart surgery. *BMJ* 1978; 2: 1602–3.
6. Mehta Y, *et al.* Lumbar versus thoracic epidural buprenorphine for postoperative analgesia following coronary artery bypass graft surgery. *Acta Anaesthesiol Scand* 1999; 43: 388–93.
7. Hayes MJ, *et al.* Randomised trial comparing buprenorphine and diamorphine for chest pain in suspected myocardial infarction. *BMJ* 1979; 2: 300–2.

CHRONIC PAIN. Transdermal buprenorphine is used for chronic intractable cancer pain.[1-5] It has also been used successfully in chronic non-cancer pain including neuropathic pain;[1-3,5-7] however, licensed product information states that this route is not suitable for the treatment of acute pain.

1. Böhme K. Buprenorphine in a transdermal therapeutic system—a new option. *Clin Rheumatol* 2002; 21 (suppl 1): S13–S16.
2. Evans HC, Easthope SE. Transdermal buprenorphine. *Drugs* 2003; 63: 1999–2010.
3. Sittl R. Transdermal buprenorphine in the treatment of chronic pain. *Expert Rev Neurother* 2005; 5: 315–23.
4. Sittl R. Transdermal buprenorphine in cancer pain and palliative care. *Palliat Med* 2006; 20 (suppl 1): S25–S30.
5. Kress HG. Clinical update on the pharmacology, efficacy and safety of transdermal buprenorphine. *Eur J Pain* 2009; 13: 219–30.
6. Bálint G. Buprenorphine treatment of patients with non-malignant musculoskeletal diseases. *Clin Rheumatol* 2002; 21 (suppl 1): S17–S18.
7. Hans G. Buprenorphine—a review of its role in neuropathic pain. *J Opioid Manag* 2007; 3: 195–206.

Dependence and Withdrawal

As for Opioid Analgesics, p. 109.1.

Buprenorphine may have a lower potential for producing dependence than pure agonists such as morphine. However, it has been subject to abuse (see under Precautions, p. 32.2). Abrupt withdrawal of buprenorphine is said to produce only a mild abstinence syndrome, which may be delayed in onset.

Buprenorphine is used for substitution therapy in the management of opioid dependence (see under Uses and Administration, above).

Adverse Effects and Treatment

As for Opioid Analgesics in general, p. 110.1.

Acute hepatotoxicity, including elevated liver enzyme values, hepatitis with jaundice, hepatic failure, necrosis, and encephalopathy, and hepatorenal syndrome, has been reported in opioid-dependent addicts; these reactions have also occurred after the misuse of buprenorphine, particularly after high doses or intravenous use.

Local reactions such as rash, erythema, and itching have been reported with the transdermal patches. In isolated cases delayed local allergic reactions with marked signs of inflammation have occurred; the patches should be withdrawn in such cases. US licensed product information for *Butrans (Purdue, USA)* also warns that prolongation of the QT interval has occurred with transdermal buprenorphine when given at a dose of 40 micrograms/hour.

Treatment of adverse effects is similar to that for other opioid analgesics (p. 110.3). The effects of buprenorphine are only partially reversed by naloxone (see Effects on the Respiratory System, p. 32.1) but use of the latter is still recommended.

Incidence of adverse effects. Adverse effects reported[1] after *parenteral* buprenorphine in 8187 patients were nausea (8.8%), vomiting (7.4%), drowsiness (4.3%), sleeping (1.9%), dizziness (1.2%), sweating (0.98%), headache (0.55%), confusion (0.53%), lightheadedness (0.38%), blurred vision (0.28%), euphoria (0.27%), dry mouth (0.11%), depression (0.09%), and hallucinations (0.09%). Some studies[2,3] have reported nausea, vomiting, and dizziness to be more troublesome with buprenorphine than with morphine.

In a study[4] of *sublingual* buprenorphine, 50 of 141 cancer patients withdrew because of adverse effects, especially dizziness, nausea, vomiting, and drowsiness; constipation was not reported. A woman developed[5] a painless ulcer on the upper surface of her tongue after she had put sublingual buprenorphine tablets on rather than under her tongue.

Shock occurred[6] in 2 patients 2 hours after receiving *epidural* buprenorphine 300 micrograms; treatment with naloxone was unsuccessful but symptoms disappeared spontaneously after 2 to 3 hours.

In a multicentre study[7] of *transdermal* buprenorphine, 252 of 1223 patients with moderate to severe cancer pain or non-cancer pain withdrew due to adverse effects. The most commonly reported were nausea (11%), vomiting (9.2%), constipation (7.8%), dizziness (7.5%), drowsiness (4.0%), retching (3.7%), generalised pruritus (2.0%), and headache (1.6%); local adverse effects included pruritus (1.4%), dermatitis (1.3%), and erythema (1.3%). Another study[8] reported oedema, headache, nausea, palpitation, and difficulty concentrating as causes for therapy withdrawal in 4 out of 90 patients.

1. Harcus AW, *et al.* Methodology of monitored release of a new preparation: buprenorphine. *BMJ* 1979; 2: 163–5.
2. Sear JW, *et al.* Buprenorphine for postoperative analgesia. *Br J Anaesth* 1979; 51: 71.
3. Kjaer M, *et al.* A comparative study of intramuscular buprenorphine and morphine in the treatment of chronic pain of malignant origin. *Br J Clin Pharmacol* 1982; 13: 487–92.
4. Robbie DS. A trial of sublingual buprenorphine in cancer pain. *Br J Clin Pharmacol* 1979; 7 (suppl 3): 315S–317S.
5. Lockhart SP, Baron JH. Tongue ulceration after lingual buprenorphine. *BMJ* 1984; 288: 1346.
6. Christensen FR, Andersen LW. Adverse reaction to extradural buprenorphine. *Br J Anaesth* 1982; 54: 476.
7. Muriel C, *et al.* Effectiveness and tolerability of the buprenorphine transdermal system in patients with moderate to severe chronic pain: a multicenter, open-label, uncontrolled, prospective, observational clinical study. *Clin Ther* 2005; 27: 451–62.
8. Sorge J, Sittl R. Transdermal buprenorphine in the treatment of chronic pain: results of a phase III, multicenter, randomized, double-blind, placebo-controlled study. *Clin Ther* 2004; 26: 1808–20.

Effects on the heart. For a report of myocardial infarction associated with abuse of buprenorphine, see Abuse under Precautions, p. 32.2.

Effects on mental function. Psychotomimetic effects have been relatively uncommon with buprenorphine. Hallucinations were reported[1] in only 7 of 8147 patients (0.09%) given buprenorphine by injection. There have been reports of hallucinations after sublingual[2] or epidural[3] use.

1. Harcus AW, *et al.* Methodology of monitored release of a new preparation: buprenorphine. *BMJ* 1979; 2: 163–5.
2. Paraskevaides EC. Near fatal auditory hallucinations after buprenorphine. *BMJ* 1988; 296: 214.
3. MacEvilly M, O'Carroll C. Hallucinations after epidural buprenorphine. *BMJ* 1989; 298: 928–9.

Effects on the respiratory system. There have been varying reports on the occurrence of respiratory depression with buprenorphine. It may be subject to a 'ceiling effect' in which respiratory depression does not increase further above doses of about 3 micrograms/kg.[1] However, high doses of 30 or 40 micrograms/kg given as sole intravenous analgesic in balanced anaesthesia have been associated with severe respiratory depression.[2]

Respiratory depression may be delayed in onset and more prolonged than with morphine and is only partially reversed by naloxone, possibly because buprenorphine is very firmly bound to opioid receptors. A study of sublingual buprenorphine for postoperative pain relief was abandoned when 3 of the first 16 patients showed signs of late-onset respiratory depression after the second dose of buprenorphine; the respiratory depression did not respond to naloxone.[3] Successful reversal has been shown in healthy subjects with buprenorphine-induced respiratory depression given large doses of naloxone 5 or 10 mg, but not with 1 mg; reversal was gradual in onset and decreased the duration of the normally prolonged respiratory depression.[4] Other studies found that lower doses of naloxone 2 to 4 mg given over 30 minutes,[5,6] or bolus doses of 2 to 3 mg followed by a continuous infusion of 4 mg/hour,[6] were effective in reversing buprenorphine-induced respiratory depression. The authors of both these studies suggested that a longer duration of naloxone infusion may be needed for reversal of respiratory depression caused by high doses of buprenorphine. The respiratory depressant and analgesic effects of buprenorphine were decreased by the *concomitant* use of naloxone.[7] It should be noted that a combined sublingual preparation of buprenorphine hydrochloride and naloxone hydrochloride is available in some countries for the treatment of opioid dependence.

1. Dahan A, *et al.* Comparison of the respiratory effects of intravenous buprenorphine and fentanyl in humans and rats. *Br J Anaesth* 2005; **94:** 825–34.
2. Schmidt JP, *et al.* Postoperative pain relief with naloxone: severe respiratory depression and pain after high dose buprenorphine. *Anaesthesia* 1985; **40:** 583–6.
3. Thörn S-E, *et al.* Prolonged respiratory depression caused by sublingual buprenorphine. *Lancet* 1988; **i:** 179–80.
4. Gal TJ. Naloxone reversal of buprenorphine-induced respiratory depression. *Clin Pharmacol Ther* 1989; **45:** 66–71.
5. Dahan A. Opioid-induced respiratory effects: new data on buprenorphine. *Palliat Med* 2006; **20** (suppl 1): 53–58.
6. van Dorp E, *et al.* Naloxone reversal of buprenorphine-induced respiratory depression. *Anesthesiology* 2006; **105:** 51–7.
7. Lehmann KA, *et al.* Influence of naloxone on the postoperative analgesic and respiratory effects of buprenorphine. *Eur J Clin Pharmacol* 1988; **34:** 343–52.

Overdosage. A small case series reported[1] acute buprenorphine intoxication in 5 children, aged from 15 to 22 months, after accidental ingestion of sublingual tablets; of these, 4 had ingested a combined preparation containing naloxone (*Suboxone; Reckitt Benckiser, USA*). Symptoms included drowsiness and miosis; decreased respiratory rates were reported in 4. All 5 children required hospital admission; 4 were treated with naloxone and 1 needed mechanical ventilation. Accidental poisoning has also been reported[2] in a 9-month-old infant who ingested *Suboxone*; his symptoms were reversed by naloxone. A retrospective review[3] of buprenorphine overdoses in children under 6 years of age reported by US poison centres to a national surveillance system from November 2002 to December 2005 concluded that overdosage is generally well tolerated. Out of 86 reports, 54 children developed symptoms of toxicity. Such symptoms included: drowsiness or lethargy (55%), vomiting (21%), miosis (21%), respiratory depression (7%), agitation or irritability (5%), pallor (3%), and coma (2%). There were no fatalities, and significant CNS and respiratory depression occurred in 7%. *Suboxone* preparations were the most commonly ingested products. The authors considered that any child who has ingested more than 2 mg and any aged under 2 years who has had more than a lick or taste should be referred to the emergency department.

During the years 1980 to 2002, buprenorphine was mentioned in 43 cases of adult fatalities in the UK.[4] Of these, 27 deaths were confirmed to have involved buprenorphine including 7 cases where it was taken alone. In those deaths where multiple drugs were involved sedatives or benzodiazepines were detected in 23 cases and other opioids were found in 17 cases; alcohol had also been taken in 10 cases. The authors also found an increase in buprenorphine-related fatalities since 1999 when the high-dose formulation became available.

1. Geib A-J, *et al.* Adverse effects in children after unintentional buprenorphine exposure. *Pediatrics* 2006; **118:** 1746–51.
2. Cho CS, *et al.* Exploratory buprenorphine ingestion in an infant. *Ann Emerg Med* 2006; **48:** 109.
3. Hayes BD, *et al.* Toxicity of buprenorphine overdoses in children. Abstract: *Pediatrics* 2008; **121:** 807–8. Full version: http://pediatrics.aappublications.org/cgi/reprint/121/4/e782 (accessed 22/07/08)
4. Schifano F, *et al.* Buprenorphine mortality, seizures and prescription data in the UK, 1980–2002. *Hum Psychopharmacol* 2005; **20:** 343–8.

Precautions

As for Opioid Analgesics in general, p. 110.3.

Buprenorphine has opioid antagonist actions and may precipitate withdrawal symptoms if given to patients physically dependent on opioids.

Respiratory depression, if it occurs, is relatively slow in onset and of prolonged duration; it may be only partially reversed by naloxone.

Licensed product information states that baseline liver function levels should be established before starting buprenorphine therapy, and periodic monitoring of liver function should be performed throughout therapy in patients being treated for opioid dependence. It should be used with caution in all patients with pre-existing hepatic impairment.

Absorption of buprenorphine from transdermal patches may be increased as the temperature rises and patients should therefore avoid exposing the patch to external heat; similarly, patients with fever may require monitoring because of increased absorption. It may take up to 30 hours for plasma concentrations of buprenorphine to decrease by 50% after removal of a patch; patients who have had adverse effects should be monitored during this period. US licensed product information for *Butrans (Purdue, USA)* recommends that transdermal buprenorphine should be avoided in patients with a personal or family history of QT interval prolongation and used with caution in those with hypokalaemia or unstable cardiac disease such as atrial fibrillation, congestive heart failure, or myocardial ischaemia.

Abuse. A 22-year-old man had chest pains on each of two occasions after he had inhaled crushed buprenorphine tablets.[1] An ECG taken after the second episode suggested that the patient had suffered a myocardial infarction. Intravenous injection of crushed sublingual tablets was associated with rhabdomyolysis and sciatic neuropathy in 2 patients.[2] A case series[3] of 4 patients reported severe limb and digit complications, such as ischaemia and gangrene, from parenteral abuse of sublingual buprenorphine tablets; intra-arterial injection in 2 cases resulted in amputation of the affected digits or limb. The use of adulterants in illicit preparations may also cause adverse effects: 4 patients on substitution treatment developed candida endophthalmitis after intravenously injecting sublingual buprenorphine diluted with lemon juice.[4]

Hepatotoxicity has been seen in opioid-dependent addicts after buprenorphine abuse (see Adverse Effects and Treatment, p. 31.3).

1. Cracowski J-L, *et al.* Myocardial infarction associated with buprenorphine. *Ann Intern Med* 1999; **130:** 537.
2. Seet RCS, Lim ECH. Intravenous use of buprenorphine tablets associated with rhabdomyolysis and compressive sciatic neuropathy. *Ann Emerg Med* 2006; **47:** 396–7.
3. Loo HW, *et al.* Severe upper limb complications from parenteral abuse of Subutex. *Ann Acad Med Singapore* 2005; **34:** 575–8.
4. Cassoux N, *et al.* Presumed ocular candidiasis in drug misusers after intravenous use of oral high dose buprenorphine (Subutex). *Br J Ophthalmol* 2002; **86:** 940–1.

Breast feeding. From a study[1] of a breast-feeding mother who was receiving sublingual buprenorphine 4 mg daily, it was estimated that at the age of 4 weeks the total amount ingested by the infant during a 24-hour period was 3.28 micrograms for buprenorphine and 330 nanograms for norbuprenorphine. Another study[2] found that buprenorphine, also taken sublingually, was present in the breast milk of a breast-feeding mother with a maternal milk-to-plasma ratio of about one. The authors of both studies considered the amount absorbed through breast feeding to be low.

Some licensed product information state that buprenorphine, regardless of route, should not be given to mothers who are breast feeding. However, the *BNF* permits breast feeding and recommends that breast-fed infants should be monitored for opioid-induced adverse effects.

Studies in *rats* have shown that it may inhibit lactation.

1. Marquet P, *et al.* Buprenorphine withdrawal syndrome in a newborn. *Clin Pharmacol Ther* 1997; **62:** 569–71.
2. Johnson RE, *et al.* Buprenorphine treatment of pregnant opioid-dependent women: maternal and neonatal outcomes. *Drug Alcohol Depend* 2001; **63:** 97–103.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies buprenorphine as not porphyrinogenic: it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/10/11)

Pregnancy. An infant born to a mother who was being treated with sublingual buprenorphine 4 mg daily for diamorphine addiction suffered a minor withdrawal syndrome 2 days after birth.[1] The infant rapidly recovered without any treatment. No further signs of withdrawal occurred when breast feeding was abruptly stopped at the age of 8 weeks. In another report[2] of 15 opioid-dependent mothers who had received buprenorphine maintenance sublingually during their pregnancies, withdrawal symptoms were either absent or mild in 12 of the neonates. The remaining 3 neonates required treatment with morphine. There appeared to be no correlation between the buprenorphine dose and the degree of withdrawal symptoms. A literature review[3] found that of about 309 infants born to opioid-dependent mothers maintained on buprenorphine (sublingual dose range: 0.4 to 24 mg daily) 193 developed neonatal abstinence syndrome; of these, 149 required treatment. More than 40% of treated cases were confounded by misuse of other drugs. Onset of symptoms occurred within the first 12 to 48 hours and peaked within about 72 to 96 hours; duration of symptoms was about 120 to 168 hours although in some infants, it was reported to last for 6 to 10 weeks.

The 67 pregnancies of 66 women using sublingual buprenorphine have been followed in a prospective study.[4] The incidences of premature birth, caesarean section, and low Apgar scores in buprenorphine-exposed neonates were no greater than those seen in the general population although the mean birth-weight of the exposed neonates was significantly lower. In the exposed group, 91% of neonates needed intensive care treatment: 76% had neonatal abstinence syndrome and 57% needed opioid replacement therapy. There were also 2 cases of sudden infant deaths in the exposed group, which was considered to be higher than that generally expected.

1. Marquet P, *et al.* Buprenorphine withdrawal syndrome in a newborn. *Clin Pharmacol Ther* 1997; **62:** 569–71.
2. Fischer G, *et al.* Treatment of opioid-dependent pregnant women with buprenorphine. *Addiction* 2000; **95:** 239–44.
3. Johnson RE, *et al.* Use of buprenorphine in pregnancy: patient management and effects on the neonate. *Drug Alcohol Depend* 200: 70 (suppl 2): S87–S101.
4. Kahila H, *et al.* A prospective study on buprenorphine use during pregnancy: effects on maternal and neonatal outcome. *Acta Obstet Gynecol Scand* 2007; **86:** 185–90.

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

Buprenorphine is metabolised by the cytochrome P450 isoenzyme CYP3A4; consequently, use with other drugs that induce or inhibit this isoenzyme may result in changes in plasma concentrations of buprenorphine and, possibly adverse effects. Some manufacturers state that dosage adjustment of buprenorphine may be necessary when used with such drugs. The UK licensed product information for one sublingual formulation (*Subutex; Schering-Plough*) recommends that the dose of buprenorphine should be halved when starting treatment with the potent CYP3A4 inhibitor, ketoconazole.

There have been reports of respiratory and cardiovascular collapse in patients given therapeutic doses of intravenous buprenorphine and diazepam.

Use with other potentially hepatotoxic drugs may increase the risk of liver damage.

Analgesics. There is a risk that, with opioid agonist-antagonists such as buprenorphine, their antagonistic effects might impair more effective analgesic therapy. This appeared to happen in 2 cancer patients both of whom were given sublingual buprenorphine that was later substituted by *morphine*.[1] Conventional doses of morphine were inadequate and in one patient raising the dose of morphine proved fatal.

1. Overweg-van Kinis J, Stricker BHC. Falende pijnbestrijding tijdens sublinguaal gebruik van buprenorfine. *Ned Tijdschr Geneeskd* 1987; **13:** 1973–4.

Antivirals. Various HIV-protease inhibitors and NNRTIs can inhibit or induce cytochrome P450 isoenzymes, and most are also substrates for CYP3A4; thus, they have the potential to interact with buprenorphine. A pharmacokinetic study[1] found that usual doses of *nelfinavir, ritonavir* and *lopinavir-ritonavir* given to HIV-negative patients taking buprenorphine with naloxone for opiate dependence did not produce any clinically significant interactions: ritonavir increased the area under the concentration-time curve (AUC) of buprenorphine by about 57%, although no adverse effects were seen. Another pharmacokinetic study[2] in a similar group of patients also found no clinically significant interactions between buprenorphine with naloxone and *delavirdine* or *efavirenz*: delavirdine increased the AUC of buprenorphine fourfold, and efavirenz decreased it by about 50%, but no adverse effects were seen. However, a small case series[3] of 3 opioid-dependent patients reported symptoms of buprenorphine toxicity, such as dizziness, daytime somnolence, and decreased mental functioning, with concomitant *atazanavir* and ritonavir therapy.

Buprenorphine does not appear to significantly affect the pharmacokinetics of antiretrovirals.[1,2]

1. McCance-Katz EF, *et al.* Interactions between buprenorphine and antiretrovirals: I—The nonnucleoside reverse-transcriptase inhibitors efavirenz and delavirdine. *Clin Infect Dis* 2006; 43 (suppl 4): S224–S234.
2. McCance-Katz EF, *et al.* Interactions between buprenorphine and antiretrovirals: II—The protease inhibitors nelfinavir, lopinavir/ritonavir, and ritonavir. *Clin Infect Dis* 2006; 43 (suppl 4): S235–S246.
3. Bruce RD, Altice FL. Three case reports of a clinical pharmacokinetic interaction with buprenorphine and atazanavir plus ritonavir. *AIDS* 2006; 20: 783–4.

Pharmacokinetics

After intramuscular injection, buprenorphine rapidly reaches peak plasma concentrations. Absorption also takes place through the buccal mucosa after sublingual doses and peak plasma concentrations occur after 90 minutes. Transdermal application results in absorption through the skin; the minimum effective concentration is reached in 12 to 24 hours and peak plasma concentrations occur after about 60 hours. However, there is a lack of correlation between plasma concentrations and analgesic activity. Buprenorphine is about 96% bound to plasma proteins.

Elimination of buprenorphine is bi- or triphasic; metabolism takes place in the liver by oxidation via the cytochrome P450 isoenzyme CYP3A4 to the pharmacologically active metabolite *N*-dealkylbuprenorphine (norbuprenorphine), and by conjugation to glucuronide metabolites. Buprenorphine is subject to considerable first-pass metabolism after oral doses. However, when given by the usual routes buprenorphine is excreted mainly unchanged in the faeces; there is some evidence for enterohepatic recirculation. Plasma elimination half-lives have ranged from 1.2 to 7.2 hours after intravenous injection; elimination half-lives after sublingual or transdermal use are longer and may range from 20 to 36 hours or more. Metabolites are excreted in the urine, but very little unchanged drug is excreted in this way. Buprenorphine crosses the placenta and small amounts are distributed into breast milk.

References.
1. Elkader A, Sproule B. Buprenorphine: clinical pharmacokinetics in the treatment of opioid dependence. *Clin Pharmacokinet* 2005; 44: 661–80.

Administration. *BUCCAL ROUTE.* Absorption of sublingual buprenorphine is relatively slow. In a 10-hour study[1] plasma concentrations after 400 or 800 micrograms given sublingually peaked at about 200 minutes (range 90 to 360 minutes) and buprenorphine was still detected in plasma at the end of the study. Systemic availability was about 55% (range 16 to 94%) and absorption was more or less complete 5 hours after a dose. However, the authors of a subsequent study[2] considered that this was an overestimation, possibly due to methodological flaws. The later study results indicated that the bioavailability of sublingual buprenorphine is about 30% and that sublingual holding times between 3 and 5 minutes are bioequivalent. Another single-dose study[3] found that the bioavailability of sublingual buprenorphine was 50% less from a tablet than from a liquid formulation. Later studies[4,5] noted that the bioavailability of buprenorphine from a sublingual tablet relative to a sublingual liquid formulation was about 70% after daily dosing for 7 days. One of these studies[4] also found that the bioavailability of sublingual buprenorphine from a tablet formulation containing naloxone was higher than from a single-ingredient tablet formulation and similar to that seen with liquid formulations.

1. Bullingham RES, *et al.* Sublingual buprenorphine used postoperatively: ten hour plasma drug concentration analysis. *Br J Clin Pharmacol* 1982; 13: 665–73.
2. Mendelson J, *et al.* Bioavailability of sublingual buprenorphine. *J Clin Pharmacol* 1997; 37: 31–7.
3. Nath RP, *et al.* Buprenorphine pharmacokinetics: relative bioavailability of sublingual tablet and liquid formulations. *J Clin Pharmacol* 1999; 39: 619–23.
4. Strain EC, *et al.* Relative bioavailability of different buprenorphine formulations under chronic dosing conditions. *Drug Alcohol Depend* 2004; 74: 37–43.
5. Compton P, *et al.* Pharmacokinetics, bioavailability and opioid effects of liquid versus tablet buprenorphine. *Drug Alcohol Depend* 2006; 82: 25–31.

Children. The terminal elimination half-life of buprenorphine was only about 1 hour in small children aged 4 to 7 years given 3 micrograms/kg intravenously as premedication, but could not be estimated reliably because of the rapid decline in plasma-buprenorphine concentrations.[1] Clearance values did, however, appear higher than in adults; steady-state volume of distribution was similar. Premature neonates (gestational age 27 to 32 weeks) given a similar dose followed by an infusion of 720 nanograms/kg per hour had a considerably lower clearance rate and had a mean elimination half-life of 20 hours.[2] Although this dosing regimen appeared to be safe, sedation was judged to be inadequate in 4 of the 12 neonates studied. It was suggested that as buprenorphine given by infusion might not produce consistent sedation and analgesia in premature neonates, it could not be recommended for use in neonatal care.

1. Olkkola KT, *et al.* Pharmacokinetics of intravenous buprenorphine in children. *Br J Clin Pharmacol* 1989; 28: 202–4.
2. Barrett DA, *et al.* The pharmacokinetics and physiological effect of buprenorphine infusion in premature neonates. *Br J Clin Pharmacol* 1993; 36: 215–19.

Renal impairment. Buprenorphine clearance appears to occur mainly by hepatic extraction and metabolism and would not be expected to be related to renal function, whereas metabolites are excreted in urine. In a study, buprenorphine kinetics were similar in anaesthetised healthy patients to those in patients with renal impairment, with a mean elimination half-life of 398 and 239 minutes, respectively.[1] Plasma concentrations of the metabolites norbuprenorphine and buprenorphine-3-glucuronide were increased about 4 times and 15 times, respectively in patients with renal impairment,[1] but significant pharmacological activity was unlikely since norbuprenorphine has little analgesic activity compared with the parent compound and buprenorphine-3-glucuronide has none.

1. Hand CW, *et al.* Buprenorphine disposition in patients with renal impairment: single and continuous dosing, with special reference to metabolites. *Br J Anaesth* 1990; 64: 276–82.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Restiva; *Austral.*: Norspan; Suboxone; Subutex; Temgesic; *Austria*: Suboxone; Subutex; Temgesic; Transtec; Triquisic; *Belg.*: Suboxone; Subutex; Temgesic; Transtec; *Braz.*: Temgesic; *Canad.*: BuTrans; Suboxone; *Chile*: Transtec; *China*: Sha Fei (沙菲); Shumeifen (舒美芬); *Cz.*: Norspan; Ravata; Suboxone; Subutex; Temgesic; Transtec; Trapamaphin; *Denm.*: Buprenotex; Norspan; Norvipren; Suboxone; Subutex; Temgesic; Transtec; *Fin.*: Norspan; Subutex†; Temgesic; *Fr.*: Suboxone; Subutex; Temgesic; *Ger.*: Cras; Norspan; Suboxone; Subutex; Temgesic; Transtec; *Gr.*: Prenorvine; Suboxone; Subutex; *Hong Kong*: Suboxone; Subutex†; Temgesic; *Hung.*: Buprenf†; Suboxone; Transtec; *India*: Addnok; Bunogesic; Buprigesic; Buprinor; Norphin; Pentorel; Tidigesic; *Indon.*: Suboxone; Subutex; *Irl.*: BuTrans; Centradol†; Suboxone; Subutex; Temgesic; Transtec; *Israel*: BuTrans; Nopan†; SBT; Subutex; *Ital.*: Suboxone; Subutex; Temgesic; Transtec; *Jpn*: Norspan; *Malaysia*: Suboxone; *Mex.*: Brospina; Temgesic; Transtec; *Neth.*: BuTrans; Suboxone; Subutex†; Temgesic; Transtec; *Norw.*: Norspan; Suboxone; Subutex; Temgesic; *NZ*: Norspan; Suboxone; Temgesic; *Philipp.*: Norspan; *Pol.*: Bunondol; Suboxone; Transtec; *Port.*: Buprex; Norspan†; Suboxone; Subutex; Transtec; Trapamafin; Triquisic; *Rus.*: Bupranal (Бупранал); Nopan (Нопан); Transtec (Трансгек); *S.Afr.*: Subutex; Temgesic; *Singapore*: Temgesic; *Spain*: Buprex; Suboxone; Transtec; *Swed.*: Buprenotex; Norspan; Suboxone; Subutex; Temgesic; *Switz.*: Subutex; Temgesic; Transtec; *Thai.*: Buprinef†; *Turk.*: Suboxone; *UK*: BuTrans; Hapoctasin; Suboxone; Subutex; Temgesic; Tephine; Transtec; *USA*: Buprenex; Butrans; Suboxone; Subutex†.

Multi-ingredient Preparations. *USA*: Zubsolv.

Pharmacopoeial Preparations

BP 2014: Buprenorphine Injection; Buprenorphine Sublingual Tablets; Buprenorphine Transdermal Patches.

Butorphanol Tartrate *(BANM, USAN, rINNM)*

Butorfanol, tartrato de; Butorfanolitartraatti; Butorfanoltartrat; Butorphanol, Tartrate de; Butorphanoli Tartras; *levo*-BC-2627 (butorphanol); Tartrato de butorfanol; Буторфанола Тартрат.

(-)-17-(Cyclobutylmethyl)morphinan-3,14-diol hydrogen tartrate.

$C_{21}H_{29}NO_2.C_4H_6O_6$=477.6

CAS — 42408-82-2 (butorphanol); 58786-99-5 (butorphanol tartrate).

ATC — N02AF01.

ATC Vet — QN02AF01.

UNII — 2L7I72RUHN.

Pharmacopoeias. In *US.*

USP 36: (Butorphanol Tartrate). A white powder. Its solutions are slightly acidic. Sparingly soluble in water; insoluble in alcohol, in chloroform, in ether, in ethyl acetate, and in hexane; slightly soluble in methyl alcohol; soluble in dilute acids. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Butorphanol tartrate, a phenanthrene derivative, is an opioid analgesic (p. 108.1) with opioid agonist and antagonist properties; it is pharmacologically similar to pentazocine (p. 120.3). Butorphanol is used for the relief of moderate to severe pain, including the pain of labour, and as an adjunct to anaesthesia. Onset of analgesia occurs within 15 minutes of intramuscular injection or an intranasal dose and may last for 3 to 4 hours after parenteral doses or for 4 to 5 hours after intranasal doses.

For the relief of moderate to severe pain, butorphanol tartrate is given in doses of 1 to 4 mg (usually 2 mg) by intramuscular injection or in doses of 0.5 to 2 mg (usually 1 mg) by intravenous injection every 3 to 4 hours. It may also be given as a nasal spray, in usual doses of 1 mg (1 spray in 1 nostril), repeated after 60 to 90 minutes, if necessary. This sequence may be repeated after 3 to 4 hours as needed. An initial dose of 2 mg (1 spray in each nostril) may be given for severe pain, but should not be repeated until 3 to 4 hours later.

In *obstetric analgesia* 1 to 2 mg may be given by intramuscular or intravenous injection during early labour in women at term. This dose may be repeated after 4 hours if necessary but an alternative analgesic should be used if delivery is expected within 4 hours.

In **anaesthesia**, 2 mg may be given intramuscularly for premedication 60 to 90 minutes before surgery. For use in balanced anaesthesia, a usual dose is 2 mg given intravenously shortly before induction and/or 0.5 to 1 mg given intravenously in increments during anaesthesia. The total dose needed varies but most patients require 4 to 12.5 mg.

Dosage adjustment may be needed in the elderly. When given by injection the initial dose of butorphanol for pain should be half the usual initial adult dose. Subsequent doses should be determined by the patient's response; a dosage interval of at least 6 hours has been recommended. For nasal use the initial dose should be limited to 1 mg followed by 1 mg after 90 to 120 minutes if necessary; subsequent doses if required should generally be given at intervals of not less than 6 hours. Similar recommendations have also been made for patients with hepatic or renal impairment, see below.

References.
1. Atkinson BD, *et al.* Double-blind comparison of intravenous butorphanol (Stadol) and fentanyl (Sublimaze) for analgesia during labor. *Am J Obstet Gynecol* 1994; 171: 993–8.
2. Gillis JC, *et al.* Transnasal butorphanol: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in acute pain management. *Drugs* 1995; 50: 157–75.
3. Commiskey S, *et al.* Butorphanol: effects of a prototypical agonist-antagonist analgesic on κ -opioid receptors. *J Pharmacol Sci* 2005; 98: 109–16.

Administration in hepatic or renal impairment. The dosage of butorphanol may need to be adjusted in patients with hepatic or renal impairment. When given by injection the initial dose for pain should be half the usual initial dose (see above). Subsequent doses should be determined by the patient's response; a dosage interval of at least 6 hours has been recommended. For nasal use the initial dose should be limited to 1 mg followed by 1 mg after 90 to 120 minutes if necessary; subsequent doses if required should generally be given at intervals of not less than 6 hours.

Headache. Butorphanol has been advocated for use as a nasal spray in the treatment of migraine, but there have been problems with abuse and dependence (see p. 34.1) and its place in therapy, if any, still remains to be established. See also Antimigraine Drugs, under Interactions, p. 34.2.

References.
1. Freitag FG. The acute treatment of migraine with transnasal butorphanol (TNB). *Headache Q* 1993; 4 (suppl 3): 22–8.
2. Hoffert MJ, *et al.* Transnasal butorphanol in the treatment of acute migraine. *Headache* 1995; 35: 65–9.
3. Melanson SW, *et al.* Transnasal butorphanol in the emergency department management of migraine headache. *Am J Emerg Med* 1997; 15: 57–61.

Pruritus. Results from a small study[1] of 6 patients with severe opioid-induced pruritus unresponsive to diphenhydramine, and from a case series of 5 patients with intractable pruritus from other causes,[2] suggest that intranasal butorphanol may be an effective treatment. Doses have ranged from 1 mg every other day to 2 mg every 4 to 6 hours.

1. Dunteman E, *et al.* Transnasal butorphanol for the treatment of opioid-induced pruritus unresponsive to antihistamines. *J Pain Symptom Manage* 1996; 12: 255–60.
2. Dawn AG, Yosipovitch G. Butorphanol for treatment of intractable pruritus. *J Am Acad Dermatol* 2006; 54: 527–31.

Dependence and Withdrawal

As for Opioid Analgesics, p. 109.1.

Butorphanol may have a lower potential for producing dependence than pure agonists such as morphine. However, it has been subject to abuse (see under Precautions, p. 34.1). Abruptly stopping chronic butorphanol has produced a less severe withdrawal syndrome than with morphine.

Adverse Effects and Treatment

As for Opioid Analgesics in general, p. 110.1, and for Pentazocine, p. 121.1.

Headache, and feelings of floating may also occur. Hallucinations and other psychotomimetic effects are rare and have been reported less frequently than with pentazocine. In addition insomnia and nasal congestion may occur frequently when butorphanol is given intranasally.

Because butorphanol has opioid agonist and antagonist activity, naloxone is the recommended antagonist for the treatment of overdosage.

Effects on the respiratory system. Butorphanol 2 mg produces a similar degree of respiratory depression to morphine 10 mg, but a ceiling effect is apparent with higher doses of butorphanol.[1] It has been reported to be a less potent respiratory depressant than fentanyl,[2] but more potent than nalbuphine.[3]

1. Nagashima H, *et al.* Respiratory and circulatory effects of intravenous butorphanol and morphine. *Clin Pharmacol Ther* 1976; 19: 738–45.
2. Dryden GE. Voluntary respiratory effects of butorphanol and fentanyl following barbiturate induction: a double-blind study. *J Clin Pharmacol* 1986; 26: 203–7.
3. Zucker JR, *et al.* Respiratory effects of nalbuphine and butorphanol in anesthetized patients. *Anesth Analg* 1987; 66: 879–81.

Precautions

As for Opioid Analgesics in general, p. 110.3.

Although cardiovascular effects may be less than with pentazocine, butorphanol should generally be avoided after myocardial infarction.

Butorphanol may precipitate withdrawal symptoms if given to patients physically dependent on opioids. The dosage regimen of butorphanol may need to be adjusted in the elderly and in patients with hepatic or renal impairment.

Abuse. A WHO expert committee considered in 2006 that the likelihood of butorphanol abuse was low and was not great enough to warrant international control.[1] Abuse had been reported infrequently and only in a few countries. The committee also commented that, pharmacologically, intranasal preparations of butorphanol do not appear to differ in their abuse potential from parenteral preparations; however, other factors such as availability and usage patterns may affect the likelihood of abuse. Indeed, US licensed product information states that there have been more reports of abuse with intranasal preparations than with injectable ones.

Cases of butorphanol abuse have been published[2,3] including a report of fibrous myopathy associated with chronic intramuscular abuse.

1. WHO. WHO expert committee on drug dependence: thirty-fourth report. *WHO Tech Rep Ser* 942 2006. Also available at: http://libdoc.who.int/trs/WHO_TRS_942_eng.pdf (accessed 26/06/08)
2. Wagner JM, Cohen S. Fibrous myopathy from butorphanol injections. *J Rheumatol* 1991; 18: 1934–5.
3. Loder E. Post-marketing experience with an opioid nasal spray for migraine: lessons for the future. *Cephalalgia* 2006; 26: 89–97.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were given butorphanol, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

In a study[2] of 12 women, butorphanol was detected in breast milk after both intramuscular and oral doses. However, the milk-to-plasma ratio after a 2-mg intramuscular dose (0.7) was significantly less than that after an 8-mg oral dose (1.9). Although the mothers were not breast feeding at the time of the study, the authors concluded that the potential for any adverse effects on nursing infants after maternal butorphanol use would be minimal.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *Ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/06/08)
2. Pittman KA, *et al.* Human perinatal distribution of butorphanol. *Am J Obstet Gynecol* 1980; 138: 797–800.

Pregnancy. Two instances of sinusoidal fetal heart rate pattern were noted out of 188 consecutive cases of butorphanol use in active-phase labour.[1] Visual hallucinations and paranoid delusions developed in a woman on receiving a 1-mg intravenous injection of butorphanol early in labour; the psychosis had resolved 40 hours after the injection and was not noted on follow-up 2 weeks later.[2]

1. Welt SI. Sinusoidal fetal heart rate and butorphanol administration. *Am J Obstet Gynecol* 1985; 152: 362–3.
2. Davis A, *et al.* Acute psychosis associated with butorphanol. *J Neuropsychiatr Clin Neurosci* 1998; 10: 236–7.

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

Antimigraine drugs. No pharmacokinetic interactions were reported when butorphanol nasal spray and subcutaneous *sumatriptan* were used within a minute of each other in healthy subjects.[1] However, another study[2] in healthy subjects found that the AUC and peak plasma concentration of intranasal butorphanol were reduced by about 29% and 38%, respectively when given 1 minute after intranasal sumatriptan. No such effect was noted when administration was separated by 30 minutes. It was suggested that sumatriptan may reduce butorphanol absorption by inducing transient nasal vasoconstriction.

1. Srinivas NR, *et al.* Lack of pharmacokinetic interaction between butorphanol tartrate nasal spray and sumatriptan succinate. *J Clin Pharmacol* 1995; 35: 432–7.
2. Vachharajani NN, *et al.* A pharmacokinetic interaction study between butorphanol and sumatriptan nasal sprays in healthy subjects: importance of the timing of butorphanol administration. *Cephalalgia* 2002; 22: 282–7.

Pharmacokinetics

Butorphanol is absorbed from the gastrointestinal tract but it undergoes extensive first-pass metabolism. Peak plasma concentrations occur 0.5 to 1 hour after intramuscular and intranasal doses and 1 to 1.5 hours after oral doses. Butorphanol has a plasma elimination half-life of about 4.5 hours. About 80% is bound to plasma proteins.

Butorphanol is extensively metabolised in the liver through hydroxylation, *N*-dealkylation, and conjugation; only 5% being excreted unchanged. Excretion is mainly in the urine; about 15% of a parenteral dose is excreted in the bile. It crosses the placenta and is distributed into breast milk.

Administration. *INTRANASAL ROUTE.* References.

1. Davis GA, *et al.* Pharmacokinetics of butorphanol tartrate administered from single-dose intranasal sprayer. *Am J Health-Syst Pharm* 2004; 61: 261–6.
2. Davis GA, *et al.* Bioavailability of intranasal butorphanol administered from a single-dose sprayer. *Am J Health-Syst Pharm* 2005; 62: 48–53.
3. Wermeling DP, *et al.* Pharmacokinetics, bioequivalence, and spray weight reproducibility of intranasal butorphanol after administration with 2 different nasal spray pumps. *J Clin Pharmacol* 2005; 45: 969–73.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China:* Nuo Yang (诺扬); *India:* Butodol; Butrum; *Mex.:* Stadol; *Philipp.:* Stadol†; *Rus.:* Stadol (Стадол); *USA:* Stadol.

Pharmacopoeial Preparations

USP 36: Butorphanol Tartrate Injection; Butorphanol Tartrate Nasal Solution.

Canakinumab *(BAN, USAN, rINN)*

ACZ-885; Canakinumabum; Канакинумаб.

immunoglobulin G1, anti-[*Homo sapiens* interleukin 1, beta (IL1B)] human monoclonal ACZ885; gamma1 heavy chain (*Homo sapiens* VH-IGHG1*03) (221-214″)-disulfide with kappa light chain (*Homo sapiens* V-KAPPA-IGKC*01); (227-227″,230-230″)-bisdisulfide dimer.

CAS — 914613-48-2 (canakinumab); 402710-27-4 (light chain); 402710-25-2 (heavy chain).

ATC — L04AC08.

ATC Vet — QL04AC08.

UNII — 37CQ2C7X93.

Uses and Administration

Canakinumab is a recombinant human monoclonal interleukin-1β antibody used for the symptomatic treatment of frequent gouty arthritis attacks (defined as at least 3 attacks in the previous 12 months) when the use of NSAIDs and colchicine are contra-indicated, not tolerated, or produce an inadequate response, and repeated courses of corticosteroids are inappropriate. Canakinumab may be used for the treatment of juvenile idiopathic arthritis. It is also used in the management of cryopyrin-associated periodic syndromes (CAPS) including familial cold auto-inflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS), which are rare inherited auto-inflammatory disorders.

For the treatment of gouty arthritis attacks, canakinumab should be used as on-demand therapy; hyperuricaemia should be managed with appropriate urate-lowering therapy (see Gout and Hyperuricaemia, p. 600.1). The recommended dose is 150 mg given by subcutaneous injection as a single dose as soon as possible after the onset of an attack. Patients who do not respond to initial treatment should not be re-treated with canakinumab. Those who respond may be given another dose at least 12 weeks after the initial dose.

For the treatment of CAPS, canakinumab is given by subcutaneous injection as a single dose; patients with a body-weight greater than 40 kg may be given an initial dose of 150 mg, followed by a usual maintenance dose of 150 mg every 8 weeks. A second dose of 150 mg may be given 7 days after the initial dose if the response has been unsatisfactory; if this produces a full response after 7 days, the dose should be maintained at 300 mg every 8 weeks. If the response has been unsatisfactory, a third dose of 300 mg may be given 7 days after the second dose and if this produces a full response after 7 days, the dose should be maintained at 600 mg every 8 weeks.

For details of use and dosage in children, including use in juvenile idiopathic arthritis, see Administration in Children, below.

References.

1. Lachmann HJ, *et al.* Use of canakinumab in the cryopyrin-associated periodic syndrome. *N Engl J Med* 2009; 360: 2416–25.
2. Koné-Paut I, *et al.* Canakinumab in CAPS Study Group. Sustained remission of symptoms and improved health-related quality of life in patients with cryopyrin-associated periodic syndrome treated with canakinumab: results of a double-blind placebo-controlled randomized withdrawal study. *Arthritis Res Ther* 2011; 13: R202.
3. Schlesinger N, *et al.* Canakinumab for acute gouty arthritis in patients with limited treatment options: results from two randomised, multicentre, active-controlled, double-blind trials and their initial extensions. *Ann Rheum Dis* 2012; 71: 1839–48.
4. Ruperto N, *et al.* PRINTO, PRCSG. Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. *N Engl J Med* 2012; 367: 2396–2406.

Administration in children. Canakinumab may be used in children for the treatment of cryopyrin-associated periodic syndromes (CAPS) including familial cold auto-inflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS). It is given by subcutaneous injection as a single dose, according to age and body-weight. In the UK, the following regimen is used in children aged 2 years or older:

- ≥ 2 years, weighing ≥ 7.5 kg and < 15 kg: 4 mg/kg initially, followed by a usual maintenance dose of 4 mg/kg every 8 weeks; a second dose of 4 mg/kg may be given 7 days after the initial dose if the response has been unsatisfactory, and if this produces a full response after 7 days, the dose should be maintained at 8 mg/kg every 8 weeks
- ≥ 4 years, weighing ≥ 15 kg and ≤ 40 kg: 2 mg/kg initially, followed by a usual maintenance dose of 2 mg/kg every 8 weeks; a second dose of 2 mg/kg may be given 7 days after the initial dose if the response has been unsatisfactory, and if this produces a full response after 7 days, the dose should be maintained at 4 mg/kg every 8 weeks. If the response has been unsatisfactory, a third dose of 4 mg/kg may be given 7 days after the second dose and if this produces a full response after 7 days, the dose should be maintained at 8 mg/kg every 8 weeks
- ≥ 4 years, weighing > 40 kg: the usual adult dose (see Uses and Administration, above) may be given

Similar initial doses are used in the USA in children aged 4 years and over, and weighing at least 15 kg; a dose of 3 mg/kg has been suggested for those with an inadequate response.

Canakinumab is also licensed for the treatment of active systemic juvenile idiopathic arthritis (p. 12.1) in children aged 2 years or older. The recommended dose in those weighing 7.5 kg or more is 4 mg/kg (maximum of 300 mg) given as a single subcutaneous injection every 4 weeks.

Adverse Effects and Precautions

The adverse effects reported most commonly with canakinumab are headache, nasopharyngitis, nausea, diarrhoea, respiratory-tract infections including influenza, and vertigo. Injection site reactions have also occurred.

Canakinumab has been associated with an increased incidence of serious infections and it should therefore be given with caution to patients with active infections, a history of recurring infections, or underlying conditions that may predispose them to developing infections. Canakinumab treatment should not be started or continued in patients with severe infections that require treatment. Patients should be screened for active and latent tuberculosis infection before starting canakinumab treatment. Patients should be up to date with appropriate immunisation schedules, including pneumococcal vaccine and inactivated influenza, before starting treatment with canakinumab; live vaccines should not be given at the same time as canakinumab unless the benefits clearly outweigh the risks (see also Interactions, p. 35.1).

Treatment with canakinumab should not be started in patients with neutropenia, and it is recommended that neutrophil counts should be taken before starting treatment, 1 to 2 months later, and periodically thereafter.

Patients who have vertigo during treatment with canakinumab should avoid driving or operating machinery.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies canakinumab as possibly porphyrinogenic; it should be used only when no

safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Interactions

There are no formal interaction studies with canakinumab; however, it is recommended that live vaccines should not be given at the same time as canakinumab as its effect on vaccine efficacy or the risk of infection transmission is unknown. If use together is unavoidable, live vaccines should not be given until at least 3 months after the last, and before the next, dose of canakinumab.

The use of TNF inhibitors with canakinumab may increase the risk of serious infections and neutropenia; such combinations are not recommended. A similar effect may also occur when used with other interleukin-1 antagonists.

During inflammation the expression of cytochrome P450 isoenzymes is suppressed by cytokines such as interleukin-1β, and cytochrome P450 expression may therefore be normalised when treatment with a cytokine inhibitor such as canakinumab is started. This becomes clinically significant for cytochrome P450 isoenzyme substrates that have narrow therapeutic ratios where the dose has to be individually adjusted (e.g. warfarin). Therefore when starting or stopping therapy with canakinumab, patients being treated with such drugs should be monitored as doses of these drugs may need to be adjusted.

Pharmacokinetics

Peak serum concentrations occur about 7 days after a single subcutaneous injection of canakinumab; the mean terminal half-life is about 26 days. The absolute bioavailability was estimated to be 66%.

References.

1. Chakraborty A, *et al.* Pharmacokinetic and pharmacodynamic properties of canakinumab, a human anti-interleukin-1 β monoclonal antibody. *Clin Pharmacokinet* 2012; 51: e1–e18.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Ilaris; *Austria*: Ilaris; *Braz.*: Ilaris; *Canad.*: Ilaris; *Cz.*: Ilaris; *Denm.*: Ilaris; *Fr.*: Ilaris; *Ger.*: Ilaris; *Gr.*: Ilaris; *Irl.*: Ilaris; *Israel*: Ilaris; *Ital.*: Ilaris; *Jpn*: Ilaris; *Neth.*: Ilaris; *Norw.*: Ilaris; *NZ*: Ilaris; *Pol.*: Ilaris; *Port.*: Ilaris; *Spain*: Ilaris; *Swed.*: Ilaris; *Switz.*: Ilaris; *Turk.*: Ilaris; *UK*: Ilaris; *USA*: Ilaris.

Capsaicin

Capsaicina; Capsaicinum; Kapsaicin; Kapsaicyna; Kapsaisiini; Капсаицин.

(*E*)-8-Methyl-*N*-vanillylnon-6-enamide.

$C_{18}H_{27}NO_3$=305.4

CAS — 404-86-4.

ATC — M02AB01; N01BX04.

ATC Vet — QM02AB01; QN01BX04.

UNII — S07O44R1ZM.

NOTE. Do not confuse capsaicin with capsicin, which is capsicum oleoresin (see Capsicum, p. 2469.3).

Pharmacopoeias. In *US*.

USP 36: (Capsaicin). An off-white powder. M.p. 57 degrees to 66 degrees. Practically insoluble in cold water; soluble in alcohol, in chloroform, and in benzene; slightly soluble in carbon disulfide. Store in a cool place in airtight containers. Protect from light.

Uses and Administration

Capsaicin is the active principle of the dried ripe fruits of *Capsicum* spp. It is used as a topical analgesic (p. 6.3) in peripheral neuropathic pain including postherpetic neuralgia after the lesions have healed and diabetic neuropathy (see Neuropathic Pain, below), and in osteoarthritis and rheumatoid arthritis (see Rheumatic Disorders, below).

Capsaicin is usually applied sparingly 3 or 4 times daily (and not more often than every 4 hours) as a 0.025% or 0.075% *cream*; in the UK these creams are not licensed for use in children, but in the USA they may be used in children over 2 years of age. A more concentrated cream containing 0.25% capsaicin is available in some countries.

Capsaicin cream should be rubbed well into the skin until little or no residue is left on the surface. Therapeutic response may not be evident for 1 to 2 weeks for arthritic disorders, or 2 to 4 weeks for neuralgias (or even longer if the head or neck are involved). For the management of painful diabetic neuropathy, UK licensed product information recommends that capsaicin should only be used under specialist supervision and that treatment should be reviewed after the first 8 weeks and regularly re-evaluated thereafter.

Although not a counter-irritant itself, capsaicin has been included in rubefacient preparations for the relief of muscular and rheumatic pain.

A high-concentration *transdermal patch* containing capsaicin 8% (equivalent to 179 mg in total) is available for the treatment of peripheral neuropathic pain in non-diabetic patients, either as monotherapy or as an adjunct. The treatment area and surrounding 1 to 2 cm should be pretreated with a topical anaesthetic before applying the patch, for example, topical lidocaine 4% left for 60 minutes. Up to a maximum of 4 patches may be applied to the most painful areas of the skin and left in place for 30 minutes on the feet (e.g. in HIV-associated neuropathy) or for 60 minutes on other locations (e.g. in postherpetic neuralgia). Treatment may be repeated every 90 days if necessary.

A long-acting *topical solution* has been investigated for painful conditions such as postoperative, musculoskeletal, and trauma-induced neuropathic pain including interdigital neuroma.

Action. The action of capsaicin and related compounds (vanilloids) are complex and still being investigated. Capsaicin has been found to produce burning pain[1-3] by activating specific vanilloid receptors such as TRPV1 (transient receptor potential channel, vanilloid subfamily member 1) which are also stimulated by heat and acids. TRPV1 is expressed by nerves and other tissues such as the keratinocytes of the epidermis, bladder urothelium and smooth muscle, and liver.

The analgesic effect of capsaicin has been suggested to be due to both depletion of substance P from local sensory C-type nerve fibres[4-8] and to the desensitisation of vanilloid receptors.[1-3,9] Since the effect of capsaicin does not rely on vasodilatation in the skin it is therefore not considered to be a traditional counter-irritant.

1. Szallasi A, Blumberg PM. Vanilloid (capsaicin) receptors and mechanisms. *Pharmacol Rev* 1999; 51: 159–211.
2. Cortright DN, Szallasi A. Biochemical pharmacology of the vanilloid receptor TRPV1: an update. *Eur J Biochem* 2004; 271: 1814–19.
3. Wang Y. The functional regulation of TRPV1 and its role in pain sensitization. *Neurochem Res* 2008; 33: 2008–12.
4. Rumsfield JA, West DP. Topical capsaicin in dermatologic and peripheral pain disorders. *DICP Ann Pharmacother* 1991; 25: 381–7.
5. Cordell GA, Araujo OE. Capsaicin: identification, nomenclature, and pharmacotherapy. *Ann Pharmacother* 1993; 27: 330–6.
6. Winter J, *et al.* Capsaicin and pain mechanisms. *Br J Anaesth* 1995; 75: 157–68.
7. Del Bianco E, *et al.* The effects of repeated dermal application of capsaicin to the human skin on pain and vasodilatation induced by intradermal injection of acid and hypertonic solutions. *Br J Clin Pharmacol* 1996; 41: 1–6.
8. Fusco BM, Giacovazzo M. Peppers and pain: the promise of capsaicin. *Drugs* 1997; 53: 909–14.
9. Tominaga M, Julius D. Capsaicin receptor in the pain pathway. *Jpn J Pharmacol* 2000; 83: 20–4.

Administration in children. In the USA, capsaicin cream is licensed in children, for details see above.

Headache. Prevention of attacks of *cluster headache* (p. 670.1) by repeated application of capsaicin to the nasal mucosa has been reported.[1] The Z-isomer (zucapsaicin; civamide) has also been found to be modestly effective.[2]

Repeated nasal application of capsaicin has also been found to be effective in *chronic migraine*[3] (p. 670.3).

1. Fusco BM, *et al.* Preventative effect of repeated nasal applications of capsaicin in cluster headache. *Pain* 1994; 59: 321–5.
2. Saper JR, *et al.* Intranasal civamide for the treatment of episodic cluster headaches. *Arch Neurol* 2002; 59: 990–4.
3. Fusco BM, *et al.* Repeated intranasal capsaicin applications to treat chronic migraine. *Br J Anaesth* 2003; 90: 812.

Micturition disorders. Intravesical instillation of capsaicin or its analogue resiniferatoxin have been tried for painful bladder disorders and to treat bladder detrusor hyperreflexia.[1-9] Results have been variable, and they are considered to be of limited use.[10,11] Instillation into the ureter has also been tried in the management of the loin pain/haematuria syndrome[12] but pain relief appears to be at best short-term and its use is associated with significant adverse effects.[13]

1. Lazzeri M, *et al.* Intravesical capsaicin for treatment of severe bladder pain: a randomized placebo controlled study. *J Urol (Baltimore)* 1996; 156: 947–52.
2. de Sèze M, *et al.* Capsaicin and neurogenic detrusor hyperreflexia: a double-blind placebo-controlled study in 20 patients with spinal cord lesions. *Neurourol Urodyn* 1998; 17: 513–23.
3. Petersen T, *et al.* Intravesical capsaicin in patients with detrusor hyperreflexia: a placebo-controlled cross-over study. *Scand J Urol Nephrol* 1999; 33: 104–10.
4. de Sèze M, *et al.* Intravesical instillation of capsaicin in urology: a review of the literature. *Eur Urol* 1999; 36: 267–77.
5. de Sèze M, *et al.* Capsaicine intravésicale et hyperréflexie du détrusor: expérience de 100 instillations sur une période de cinq ans. *Ann Readapt Med Phys* 2001; 44: 514–24.
6. Szallasi A, Fowler CJ. After a decade of intravesical vanilloid therapy: still more questions than answers. *Lancet Neurol* 2002; 1: 167–72.
7. El-Mahrouky AS, *et al.* The effect of intravesical capsaicin and resiniferatoxin in neurogenic bladder dysfunction. *Adv Exp Med Biol* 2003; 539: 359–79.
8. de Sèze M, *et al.* Intravesical capsaicin versus resiniferatoxin for the treatment of detrusor hyperreflexia in spinal cord injured patients: a double-blind, randomized, controlled study. *J Urol (Baltimore)* 2004; 171: 251–5.
9. Lazzeri M, *et al.* Intravesical vanilloids and neurogenic incontinence: ten years experience. *Urol Int* 2004; 72: 145–9.
10. Andersson K-E, *et al.* Pharmacological treatment of overactive bladder: report from the International Consultation on Incontinence. *Curr Opin Urol* 2009; 19: 380–94.
11. Yamaguchi O, *et al.* Neurogenic Bladder Society. Clinical guidelines for overactive bladder. *Int J Urol* 2009; 16: 126–42.
12. Bultitude MI. Capsaicin in treatment of loin pain/haematuria syndrome. *Lancet* 1995; 345: 921–2.
13. Uzoh CC, *et al.* The use of capsaicin in loin pain-haematuria syndrome. *BJU Int* 2009; 103: 236–9.

Neuropathic pain. Capsaicin has been tried topically in various types of pain including neuropathic pain, which does not generally respond to conventional systemic analgesics. Topical capsaicin cream (in a usual strength of 0.075%) is used in the management of diabetic neuropathy (p. 8.2) and postherpetic neuralgia (p. 10.3). A high-concentration transdermal capsaicin patch 8% is also available for the treatment of peripheral neuropathic pain in non-diabetic patients. A systematic review[1] suggested that capsaicin, given as either a repeated dose of the cream or a single application of the patch, was of benefit in neuropathic pain, although limited data and inconsistent definition of outcomes meant that estimates of benefit and harm were not robust. Other types of pain syndrome for which capsaicin has been tried include reflex sympathetic dystrophy (see Complex Regional Pain Syndrome, p. 8.1), postmastectomy neuroma, amputation stump pain, chronic neck pain, and the pain of oral mucositis.[2]

See also Rheumatic Disorders, below, for use in musculoskeletal pain.

1. Derry S, *et al.* Topical capsaicin for chronic neuropathic pain in adults. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 29/01/10).
2. Hautkappe M, *et al.* Review of the effectiveness of capsaicin for painful cutaneous disorders and neural dysfunction. *Clin J Pain* 1998; 14: 97–106.

Pruritus. Substance P is a possible mediator of itch sensations and since capsaicin acts as a depletor of substance P it has been tried in the relief of pruritus (p. 1687.3) associated with various diseases and haemodialysis.[1-8] It has also been used to provide relief from pruritus induced by hetastarch[9] and for the itch and pain associated with PUVA therapy.[10,11] However, a systematic review[12] in 2010 considered that there was currently no convincing evidence that topical capsaicin was effective for the treatment of pruritus in any medical condition.

1. Breneman DL, *et al.* Topical capsaicin for treatment of hemodialysis-related pruritus. *J Am Acad Dermatol* 1992; 26: 91–4.
2. Leibsohn E. Treatment of notalgia paresthetica with capsaicin. *Cutis* 1992; 49: 335–6.
3. Hautmann G, *et al.* Aquagenic pruritus, PUVA and capsaicin treatments. *Br J Dermatol* 1994; 131: 920–1.
4. Föister-Holst R, Brasch J. Effect of topically applied capsaicin on pruritus in patients with atopic dermatitis. *J Dermatol Treat* 1996; 7: 13–15.
5. Hautkappe M, *et al.* Review of the effectiveness of capsaicin for painful cutaneous disorders and neural dysfunction. *Clin J Pain* 1998; 14: 97–106.
6. Ständer S, *et al.* Treatment of prurigo nodularis with topical capsaicin. *J Am Acad Dermatol* 2001; 44: 471–8.
7. Lysy J, *et al.* Topical capsaicin—a novel and effective treatment for idiopathic intractable pruritus ani: a randomised, placebo controlled, crossover study. *Gut* 2003; 52: 1323–6.
8. Makhlough A. Topical capsaicin therapy for uremic pruritus in patients on hemodialysis. *Iran J Kidney Dis* 2010; 4: 137–40.
9. Szelmies R-M, *et al.* Successful treatment of hydroxyethyl starch-induced pruritus with topical capsaicin. *Br J Dermatol* 1994; 131: 380–2.
10. Burrows NP, Norris PG. Treatment of PUVA-induced skin pain with capsaicin. *Br J Dermatol* 1994; 131: 584–5.
11. Kirby B, Rogers S. Treatment of PUVA itch with capsaicin. *Br J Dermatol* 1997; 137: 152.
12. Gooding SM, *et al.* Systematic review of topical capsaicin in the treatment of pruritus. *Int J Dermatol* 2010; 49: 858–65.

Psoriasis. Since substance P has been implicated in the pathophysiology of several inflammatory dermatological processes, capsaicin, a substance P depletor, has been tried with some benefit in some skin disorders including psoriasis.[1-3]

The usual management of psoriasis is discussed on p. 1688.1.

1. Bernstein JE, *et al.* Effects of topically applied capsaicin on moderate and severe psoriasis vulgaris. *J Am Acad Dermatol* 1986; 15: 504–7.
2. Ellis CN, *et al.* A double-blind evaluation of topical capsaicin in pruritic psoriasis. *J Am Acad Dermatol* 1993; 29: 438–42.
3. Hautkappe M, *et al.* Review of the effectiveness of capsaicin for painful cutaneous disorders and neural dysfunction. *Clin J Pain* 1998; 14: 97–106.

Rheumatic disorders. Topical capsaicin is used for the temporary relief of the pain of arthritis. From the results of a meta-analysis[1] of randomised, double-blind, placebo-controlled studies and later studies[2,3] it appears that capsaicin is effective in easing the pain of osteoarthritis (p. 12.3). Based on these results, the Arthritis Research Campaign in the UK[4] considered topical capsaicin to be safe and can be effective in reducing pain and tenderness in the affected joints. Published evidence[5] for efficacy in rheumatoid arthritis (p. 13.2) appears to be limited. A review of use in both neuropathic and musculoskeletal chronic pain concluded that its benefits were at best moderate, but noted that in a minority of patients unrespon-

sive to, or intolerant of, other treatments it might be useful.[6] Capsaicin may be a useful therapy for pain associated with primary fibromyalgia[4,7] (see Soft Tissue Rheumatism, p. 14.2),. which responds poorly to conventional treatment.

1. Zhang WY, Li Wan Po A. The effectiveness of topically applied capsaicin. *Eur J Clin Pharmacol* 1994; **46**: 517–22.
2. Altman RD, *et al.* Capsaicin cream 0.025% as monotherapy for osteoarthritis: a double-blind study. *Semin Arthritis Rheum* 1994; **23** (suppl 3): 25–33.
3. McCleane G. The analgesic efficacy of topical capsaicin is enhanced by glyceryl trinitrate in painful osteoarthritis: a randomized, double blind, placebo controlled study. *Eur J Pain* 2000; **4**: 355–60.
4. Arthritis Research Campaign. Complementary and alternative medicines for the treatment of rheumatoid arthritis, osteoarthritis and fibromyalgia (Issued February 2009). Available at: http://www.arthritisresearchuk.org/pdf/Complementary%20and%20alternative%20medicines_110120101543 31.pdf (accessed 28/07/10)
5. Deal CL, *et al.* Treatment of arthritis with topical capsaicin: a double-blind trial. *Clin Ther* 1991; **13**: 383–95.
6. Mason L, *et al.* Systematic review of topical capsaicin for the treatment of chronic pain. *BMJ* 2004; **328**: 991–4.
7. McCarty DJ, *et al.* Treatment of pain due to fibromyalgia with topical capsaicin: a pilot study. *Semin Arthritis Rheum* 1994; **23** (suppl 3): 41–7.

Adverse Effects

A warm, stinging, or burning sensation may occur at the site of application; this usually disappears after a few days of use but may persist for longer if applications are less frequent than recommended (see Uses and Administration, p. 35.1). This sensation may be particularly painful in patients receiving the high-concentration transdermal patches; in some cases, the treatment-related increase in pain has led to transient increases in blood pressure.

Coughing, sneezing, runny eyes, or other signs of irritation may occur if vapours or dried residue from topical preparations are inhaled. There have been a few reports of dyspnoea, wheezing, and exacerbation of asthma.

Precautions

Capsaicin should be handled with care. Particles should not be inhaled nor come into contact with any part of the body.

For topical application, contact with eyes and broken or irritated skin should be avoided. Thick applications of the *cream* should be avoided. The hands should be washed after application of the cream, unless the hands are the treated areas, in which case, they should be washed 30 minutes after application. If bandages are used to cover treated areas they should not be wound too tightly. Nitrile gloves should be worn when handling the high-concentration *transdermal patch* and when cleansing treatment areas; after careful removal of the patch, the cleansing gel supplied by the manufacturer should be applied liberally to the treatment area and left for at least 1 minute before wiping off and the area washed with soap and water. Heating pads should not be used with capsaicin, and patients should avoid taking a hot bath or shower immediately before or after application, as the burning sensation may be exacerbated.

Patients who develop increased pain with the high-concentration transdermal patch should be given supportive treatment such as local cooling or oral analgesics; however, those who are already taking high-dose opioid analgesics may not respond to oral opioids given for acute pain during and after the treatment procedure. Blood pressure should be monitored during the treatment procedure with transdermal patches.

Minor and temporary changes in sensory function such as heat detection have been reported with capsaicin; patients at risk from such effects should be cautious when using capsaicin.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies capsaicin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/07/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Zostrix; ***Austria***: Hansaplast Warme-Creme; Qutenza; ***Belg.***: Hansamedic Warmtepleister; ***Braz.***: Moment; ***Canad.***: Rub A-535 Antiphlogistine Capsaicin; Zoderm; Zostrix; Zuacta; ***Chile***: Presyc; ***China***: Jin Lang (劲朗); Ou Tong (欧通); ***Cz.***: Qutenza; ***Denm.***: Qutenza; ***Fr.***: Qutenza; ***Ger.***: Qutenza; ***Gr.***: Arthralgon; Capser; Gelcen; Qutenza; Sensocaps; Zacin; ***India***: Capsain-P; ***Indon.***: Capzacin; ***Irl.***: Axsain; Qutenza; Zacin; ***Israel***: Zostrix; ***Ital.***: Cerotto Bertelli; Dolpyc; ***Malaysia***: Menzza NP; Menzza OA; ***Mex.***: Capsidol; ***Neth.***: Qutenza; ***Norw.***: Capsina; Qutenza; ***NZ***: Zostrix; ***Pol.***: Qutenza; ***Port.***: Hansaplast Emplastro Termico; Hansaterm; Qutenza; ***Singapore***: Menzza OA; Thetagen; ***Spain***: Arafarmadol†; Capsicin; Capsicum Farmaya†; Capsidol; Gelcen†; Hansaterm; Picasum; Qutenza; Sensedol; ***Swed.***: Capsina; Qutenza; ***Switz.***: Isola Capsicum N; Qutenza; ***Thai.***: Capsika; ***UK***: Axsain; Qutenza; Zacin; ***USA***: Axsain; Capsin; Capzasin-HP; Capzasin-P; Doublecap†; No Pain-HP; Qutenza; R-Gel†; Rid-a-Pain HP; Theragen†; Zostrix.

Multi-ingredient Preparations. ***Arg.***: Atomo Desinflamante C; Rati Salil Crema; Rati Salil Flex; ***Canad.***: Menthacin; Rub A-535 Extra Strength Arthritis; Tiger Balm Patch Warm; ***Cz.***: Capsicolle; ***Fr.***: Capsaine; Capsic†; ***Gr.***: Ponostop; ***Hong Kong***: Salomethyl†; ***Hung.***: Inno Rheuma Forte; Nicoflex; Salonpas Liniment; ***India***: Accept; Acent; Alto; Arflur; Arthrill; Axane; Capsidol; Diclomax Power Gel; Diplofen; Diptase; Divexx; Dofec Plus; Dolowin; Mahadol; Myolaxin-D; Nam; Nelsid; Niclofen; Nimulid Nugel; Nise Gel; Onspot; Opinac; ***Indon.***: Flexozin; Nostren; ***Ital.***: Perfluxi Cremagel; Remystick; ***Pol.***: Capsigel N; Neo-Capsiderm; ***Rus.***: Nicoflex (Никофлекс); ***Switz.***: DUL-X warm; Isola Capsicum N Plus; ***UK***: NatraFlex; ***Ukr.***: Nizer (Найзер)†; ***USA***: Aspercreme Max; Bio-Therm Pain Relieving Lotion; Capzasin Quick Relief; Dendracin Neurodendtraxcin; Exoten-C; Gold Bond Foot Pain Relieving; Gold Bond Pain Relieving Foot Roll-On; Heet; Icy Hot PM; LidoPro; Medi-Derm; Medrox; Menthacin; New Terocin; Pain Doctor; Ultracin; Ziks; Zostrix Hot & Cold Therapy System.

Carbasalate Calcium *(BAN, rINN)*

Calcium Acetylsalicylate Carbamide; Calcium Carbaspirin; Carbasalat-Calcium; Carbasalate Calcique; Carbasalato cálcico; Carbasalatum Calcicum; Carbasalatum Calcium; Carbaspirin Calcium (USAN); Karbasalaattikalsium; Karbasalát vápenatá sůl; Karbasalatkalcium; Karbasalato kalcio druska; Karbaszalát-kálcium; Карбасалат Кальций.

Calcium bis[2-(acetoxy)benzoate]—urea.

$C_{19}H_{18}CaN_2O_9$=458.4

CAS — 5749-67-7.

ATC — B01AC08; N02BA15.

ATC Vet — QB01AC08; QN02BA15.

UNII — N667F17JP1.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Carbasalate Calcium). A white or almost white, crystalline powder. It contains not less than 99.0% and not more than the equivalent of 101.0% of an equimolecular compound of calcium di[2-(acetyloxy)benzoate] and urea, calculated with reference to the anhydrous substance. Freely soluble in water and in dimethylformamide; practically insoluble in acetone and in anhydrous methyl alcohol. Store in airtight containers.

Uses and Administration

Carbasalate calcium is a 1:1 complex of calcium acetylsalicylate and urea. It is metabolised to aspirin after absorption and thus has the actions of aspirin (p. 22.3). Carbasalate calcium 100 mg is equivalent to about 78 mg of aspirin. Carbasalate calcium is given in oral doses equivalent to about 400 to 800 mg of aspirin every 4 to 8 hours up to a maximum of about 3 g daily for pain or fever. Carbasalate calcium has also been used in the management of thromboembolic disorders.

Adverse Effects, Treatment, and Precautions

As for Aspirin, p. 24.2.

Carbasalate calcium, like aspirin, should not generally be given to children because of the risk of Reye's syndrome.

Effects on hearing. As of June 2006 the Netherlands Pharmacovigilance Centre[1] database contained 8 reports of tinnitus and 1 of ototoxicity associated with use of low oral doses of carbasalate calcium (38 or 100 mg usually once daily). The association between low-dose carbasalate calcium and tinnitus was considered to be disproportional.

1. Nederlands Bijwerkingen Centrum. Low dosage carbasalate calcium and tinnitus. Available at: http://www.lareb.nl/documents/kwb_2006_3_carbas.pdf (accessed 12/04/07)

Interactions

For interactions associated with aspirin, see p. 26.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Iromin; Vascal†; ***Irl.***: Ascal; ***Neth.***: Ascal; ***Port.***: Ascal; ***Switz.***: Alcacyl.

Multi-ingredient Preparations. ***Austria***: Irocopar c C†; Irocophan; Iromin Vitamin C; Iromin-Chinin-C†; ***Switz.***: Alca-C; ***Turk.***: Alca-C.

Carfentanil Citrate *(USAN, rINNM)* ⊗

Carfentanil, Citrate de; Carfentanili Citras; Carfentanilo, citrato de; Citrato de carfentanilo; R-33799; Карфентанила Цитрат. Methyl 1-phenethyl-4-(*N*-phenylpropionamido)isonipecotate citrate.

$C_{24}H_{30}N_2O_3.C_6H_8O_7$=586.6

CAS — 59708-52-0 (carfentanil); 61380-27-6 (carfentanil citrate).

UNII — 7LG286J8GV.

Profile

Carfentanil citrate is an opioid analgesic related to fentanyl (p. 60.1). It is used in veterinary medicine.

Carprofen *(BAN, USAN, rINN)*

C-5720; Carprofène; Carprofeno; Carprofenum; Karprofeen; Karprofen; Ro-20-5720/000; Карпрофен.

(±)-2-(6-Chlorocarbazol-2-yl)propionic acid.

$C_{15}H_{12}ClNO_2$=273.7

CAS — 53716-49-7.

ATC Vet — QM01AE91.

UNII — FFL0D546HO.

Pharmacopoeias. In *Eur.* (see p. vii) and *US* for veterinary use only.

Ph. Eur. 8: (Carprofen for Veterinary Use). A white or almost white, crystalline powder. Practically insoluble in water; freely soluble in acetone; soluble in methyl alcohol; slightly soluble in isopropyl alcohol. It exhibits polymorphism. Protect from light.

USP 36: (Carprofen). A white crystalline powder. Practically insoluble in water; freely soluble in acetone, in ether, in ethyl acetate, and in solutions of sodium carbonate and of sodium hydroxide. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Profile

Carprofen, a propionic acid derivative, is an NSAID (p. 102.3) used in veterinary medicine.

Adverse effects. Pruritic, erythematous, eczematous eruptions have been seen in workers after occupational exposure to carprofen.[1,2] Patch testing showed a strong positive photoallergic reaction to carprofen.

1. Walker SL, *et al.* Occupational photoallergic contact dermatitis in a pharmaceutical worker manufacturing carprofen, a canine nonsteroidal anti-inflammatory drug. *Br J Dermatol* 2006; **154**: 569–70.
2. Kerr AC, *et al.* Occupational carprofen photoallergic contact dermatitis. *Br J Dermatol* 2008; **159**: 1303–8.

Preparations

Pharmacopoeial Preparations

USP 36: Carprofen Tablets.

Celecoxib *(BAN, USAN, rINN)*

Célécoxib; Celecoxibum; Celekoksyb; Celekoxib; SC-58635; Selekoksib; Selekoksibi; YM-177; Целекоксиб.

p-[5-*p*-Tolyl-3-(trifluoromethyl)pyrazol-1-yl]benzenesulfonamide.

$C_{17}H_{14}F_3N_3O_2S$=381.4

CAS — 169590-42-5.

ATC — L01XX33; M01AH01.

ATC Vet — QL01XX33; QM01AH01.

UNII — JCX84Q7J1L.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Celecoxib). A white or almost white, crystalline or amorphous powder. It shows polymorphism. Practically insoluble in water; freely soluble to soluble in dehydrated alcohol; soluble in dichloromethane.

USP 36: (Celecoxib). A white or almost white, crystalline or amorphous powder. Practically insoluble in water; soluble to freely soluble in alcohol; soluble in dichloromethane. Store in airtight containers. Protect from light and moisture.

Uses and Administration

Celecoxib is an NSAID (p. 102.3) reported to be a selective inhibitor of cyclo-oxygenase-2 (COX-2). It is licensed for the treatment of rheumatoid arthritis including juvenile idiopathic arthritis, osteoarthritis, and ankylosing spondylitis. In the USA, celecoxib is also licensed for use in the management of acute pain and dysmenorrhoea. Celecoxib has also been used as an adjunct to standard therapy to reduce the number of adenomatous colorectal polyps in patients with familial adenomatous polyposis (see p. 37.1).

For **osteoarthritis** the recommended oral dose is 200 mg daily given as a single dose or in 2 divided doses. If necessary a dose of 200 mg twice daily may be used. For **rheumatoid arthritis** the dose is 100 to 200 mg given twice daily. Celecoxib is also used for **ankylosing spondylitis** in an initial oral dose of 200 mg daily, as a single dose or in 2 divided doses. In the USA, the dose may be increased to 400 mg daily after 6 weeks, although if no

response is seen at this dose after a further 6 weeks, alternative treatments should be considered; a similar increase is also permitted in the UK. However, for all the above indications, UK licensed product information recommends that if ineffective, the higher dose should only be continued for 2 weeks before considering alternative treatments.

For doses in children with **juvenile idiopathic arthritis**, see below.

In the treatment of **pain** and **dysmenorrhoea**, an initial oral dose of 400 mg followed by an additional dose of 200 mg, if necessary, is recommended on the first day; thereafter the dose is 200 mg twice daily.

Reduced doses are recommended in patients with hepatic impairment (see below) and in those also taking fluconazole, a potent inhibitor of the cytochrome P450 isoenzyme CYP2C9 (see Interactions, p. 38.3). The dose of celecoxib should be reduced to half the lowest recommended dose in patients who are deficient in CYP2C9 and hence poor metabolisers of celecoxib.

Reviews.

1. Clemett D, Goa KL. Celecoxib: a review of its use in osteoarthritis, rheumatoid arthritis and acute pain. *Drugs* 2000; **59**: 957–80.
2. Frampton JE, Keating GM. Celecoxib: a review of its use in the management of arthritis and acute pain. *Drugs* 2007; **67**: 2433–72.

Administration in children. In the USA, celecoxib is licensed for the treatment of juvenile idiopathic arthritis in children aged 2 years and over. The recommended oral doses, based on body-weight, are:

- 10 to 25 kg: 50 mg twice daily
- over 25 kg: 100 mg twice daily

Licensed product information recommends that the contents of a celecoxib capsule may be sprinkled onto apple sauce if a patient has difficulty swallowing the capsules. The sprinkled capsule should be taken immediately; however, it remains stable at a temperature of between 2 degrees to 8 degrees for up to 6 hours.

Administration in hepatic impairment. Licensed product information recommends that doses of celecoxib should be reduced by 50% in patients with moderate hepatic impairment (Child-Pugh category B); its use is contra-indicated in those with severe impairment (Child-Pugh category C or a score of 10 or more).

Familial adenomatous polyposis. Celecoxib has been used in the treatment of familial adenomatous polyposis, an inherited syndrome known to predispose sufferers to the development of colonic cancer. An early randomised study[1,2] found that treatment with celecoxib in an oral dose of 400 mg twice daily reduced the number of colonic polyps; the authors considered celecoxib to be a useful adjunct to the standard therapy of colectomy.

Marketing authorisations for the use of celecoxib as adjunctive treatment in familial adenomatous polyps were issued in the USA and the EU with the requirement that further data on safety and efficacy were provided; however, in 2011, the manufacturer, *Pfizer*, voluntarily withdrew this indication as it had been unable to fulfill this requirement due to slow enrolment into clinical studies.

1. Steinbach G, *et al.* The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. *N Engl J Med* 2000; **342**: 1946–52.
2. Phillips RKS, *et al.* A randomised, double blind, placebo controlled study of celecoxib, a selective cyclooxygenase 2 inhibitor, on duodenal polyposis in familial adenomatous polyposis. *Gut* 2002; **50**: 857–60.

Malignant neoplasms. Celecoxib is under investigation as adjuvant therapy in the treatment of cancer;[1-9] preliminary results have been variable. It has also been investigated for chemoprevention of malignancy[10-13] (see also Familial Adenomatous Polyposis, above), but a large study for the prevention of colon cancer was terminated early because of increased cardiovascular risk.[11,12]

1. Dang CT, *et al.* Phase II study of celecoxib and trastuzumab in metastatic breast cancer patients who have progressed after prior trastuzumab-based treatments. *Clin Cancer Res* 2004; **10**: 4062–7.
2. Reardon DA, *et al.* Phase II trial of irinotecan plus celecoxib in adults with recurrent malignant glioma. *Cancer* 2005; **103**: 329–38.
3. Nugent FW, *et al.* Docetaxel and cyclooxygenase-2 inhibition with celecoxib for advanced non-small cell lung cancer progressing after platinum-based chemotherapy: a multicenter phase II trial. *Lung Cancer* 2005; **48**: 267–73.
4. Gasparini G, *et al.* The combination of the selective cyclooxygenase-2 inhibitor celecoxib with weekly paclitaxel is a safe and active second-line therapy for non-small cell lung cancer: a phase II study with biological correlates. *Cancer J* 2005; **11**: 209–16.
5. Prince HM, *et al.* A multicenter phase II trial of thalidomide and celecoxib for patients with relapsed and refractory multiple myeloma. *Clin Cancer Res* 2005; **11**: 5504–14.
6. Pan CX, *et al.* A phase II trial of irinotecan, 5-fluorouracil and leucovorin combined with celecoxib and glutamine as first-line therapy for advanced colorectal cancer. *Oncology* 2005; **69**: 63–70.
7. Csiki I, *et al.* Targeting cyclooxygenase-2 in recurrent non-small cell lung cancer: a phase II trial of celecoxib and docetaxel. *Clin Cancer Res* 2005; **11**: 6634–40.
8. Chow LWC, *et al.* Serum lipid profiles in patients receiving endocrine treatment for breast cancer—the results from the Celecoxib And Aromatase Neoadjuvant (CAAN) Trial. *Biomed Pharmacother* 2005; **59** (suppl 2): S302–S305.
9. Ferrari V, *et al.* Gemcitabine plus celecoxib (GECO) in advanced pancreatic cancer: a phase II trial. *Cancer Chemother Pharmacol* 2006; **57**: 185–90.
10. Limburg PJ, *et al.* Randomized, placebo-controlled, esophageal squamous cell cancer chemoprevention trial of selenomethionine and celecoxib. *Gastroenterology* 2005; **129**: 863–73.
11. Solomon SD, *et al.* Adenoma Prevention with Celecoxib (APC) Study Investigators. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med* 2005; **352**: 1071–80.
12. Bertagnolli MM, *et al.* Celecoxib for the prevention of sporadic colorectal adenomas. *N Engl J Med* 2006; **355**: 873–84.
13. Arber N, *et al.* Celecoxib for the prevention of colorectal adenomatous polyps. *N Engl J Med* 2006; **355**: 885–95.

Musculoskeletal and joint disorders. Celecoxib is used in the treatment of osteoarthritis (p. 12.3) and rheumatoid arthritis (p. 13.2) including juvenile idiopathic arthritis (p. 12.1). However, in the UK it is recommended that the use of celecoxib and other selective cyclo-oxygenase-2 (COX-2) inhibitors be limited to those patients considered to be at high risk of developing serious gastrointestinal problems if given a non-selective NSAID and who do not have pre-existing cardiovascular risk factors (see Adverse Effects, below).

Celecoxib is also used in the treatment of ankylosing spondylitis (see Spondyloarthropathies, p. 14.3).

References.

1. Bensen WG, *et al.* Treatment of osteoarthritis with celecoxib, a cyclooxygenase-2 inhibitor: a randomized controlled trial. *Mayo Clin Proc* 1999; **74**: 1095–1105.
2. Simon LS, *et al.* Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis: a randomized controlled trial. *JAMA* 1999; **282**: 1921–28.
3. Emery P, *et al.* Celecoxib versus diclofenac in long-term management of rheumatoid arthritis: randomised double-blind comparison. *Lancet* 1999; **354**: 2106–11.
4. Dougados M, *et al.* Efficacy of celecoxib, a cyclooxygenase 2-specific inhibitor, in the treatment of ankylosing spondylitis: a six-week controlled study with comparison against placebo and against a conventional nonsteroidal antiinflammatory drug. *Arthritis Rheum* 2001; **44**: 180–5.
5. Stengaard-Pedersen K, *et al.* Celecoxib 200 mg qd is efficacious in the management of osteoarthritis of the knee or hip regardless of the time of dosing. *Rheumatology (Oxford)* 2004; **43**: 592–5.
6. Schnitzer TJ, *et al.* VACT-1 and VACT-2 (Protocols 106 and 150) Study Groups. Efficacy of rofecoxib, celecoxib, and acetaminophen in patients with osteoarthritis of the knee: a combined analysis of the VACT studies. *J Rheumatol* 2005; **32**: 1093–1105.
7. Singh G, *et al.* Celecoxib versus naproxen and diclofenac in osteoarthritis patients: SUCCESS-I Study. *Am J Med* 2006; **119**: 255–66.
8. Barkhuizen A, *et al.* Celecoxib is efficacious and well tolerated in treating signs and symptoms of ankylosing spondylitis. *J Rheumatol* 2006; **33**: 1805–12.
9. Luyten FP, *et al.* A prospective randomised multicentre study comparing continuous and intermittent treatment with celecoxib in patients with osteoarthritis of the knee or hip. *Ann Rheum Dis* 2007; **66**: 99–106.
10. Foeldvari I, *et al.* A prospective study comparing celecoxib with naproxen in children with juvenile rheumatoid arthritis. *J Rheumatol* 2009; **36**: 174–82.

Palmar-plantar erythrodysesthesia syndrome. Celecoxib has been investigated in the treatment of capecitabine-induced hand-foot (palmar-plantar erythrodysesthesia) syndrome; for references, see under Adverse Effects and Precautions of Capecitabine, p. 758.3.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3.

Serious skin reactions such as exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported with celecoxib. Other hypersensitivity reactions, including anaphylaxis and angioedema, have also occurred. Celecoxib should be stopped at the first signs of hypersensitivity. Some of these reactions have been seen in patients with a history of allergic reactions to sulfonamides and licensed product information contra-indicates the use of celecoxib in such patients (but see also Hypersensitivity, under Sulfamethoxazole, p. 367.3).

Celecoxib should not be used after coronary artery bypass surgery as there may be an increased risk of adverse effects such as myocardial infarction and stroke. It should be used with caution, if at all, in patients with a history of ischaemic heart disease, peripheral arterial disease, or cerebrovascular disease; it should also be used with caution in patients with significant risk factors for cardiovascular disease such as hypertension, hyperlipidaemia, and diabetes mellitus. For further details, see Effects on the Cardiovascular System, below.

Therapy is contra-indicated in patients with moderate to severe heart failure (NYHA class II to IV), inflammatory bowel disease, and renal impairment associated with a creatinine clearance of less than 30 mL/minute. Celecoxib should also not be used in patients with severe hepatic impairment (Child-Pugh category C). Caution is recommended when using celecoxib in dehydrated patients; rehydration may be advisable before giving celecoxib.

Celecoxib treatment may need to be stopped if signs or symptoms of organ toxicity develop.

Poor metabolisers of celecoxib (see Pharmacokinetics, p. 38.3) may have an increased risk of adverse reactions.

Incidence of adverse effects. A prescription-event monitoring study[1] conducted after the introduction of celecoxib in England in May 2000 found that the most common adverse events reported were gastrointestinal effects including dyspepsia (4.7% of all events), abdominal pain (1.8%), nausea or vomiting (1.6%), and diarrhoea (1.4%). Rash (1.2%) was also common. Uncommon events included anaemia, cough, anxiety, hypertension, visual disturbances, and insomnia. Blood dyscrasias, gastrointestinal bleeds, myocardial infarction, heart failure, abnormal liver function tests, nephritis, confusion, hallucinations, serious skin disorders, anaphylaxis, and bronchospasm were rare.

1. Layton D, *et al.* Safety profile of celecoxib as used in general practice in England: results of a prescription-event monitoring study. *Eur J Clin Pharmacol* 2004; **60**: 489–501.

Breast feeding. No adverse effects were noted in 2 older infants (aged 17 and 22 months) whose mothers took celecoxib while breast feeding.[1] The authors of this report also measured celecoxib plasma concentrations in 2 other women; from these values, the average milk-to-plasma ratio was calculated to be 0.23 and infant exposure was estimated at about 0.3% of the weight-adjusted maternal dose. Similar values have also been estimated from a study of blood and milk concentrations of celecoxib in 6 women.[2] Nonetheless, UK licensed product information contra-indicates the use of celecoxib in breast-feeding women.

1. Hale TW, *et al.* Transfer of celecoxib into human milk. *J Hum Lact* 2004; **20**: 397–403.
2. Gardiner SJ, *et al.* Quantification of infant exposure to celecoxib through breast milk. *Br J Clin Pharmacol* 2006; **61**: 101–4.

Effects on the blood. Severe methaemoglobinaemia has been reported in an elderly patient after taking celecoxib for 1 month.[1]

1. Kaushik P, *et al.* Celecoxib-induced methemoglobinemia. *Ann Pharmacother* 2004; **38**: 1635–8.

Effects on the cardiovascular system. Prelicensing studies did not report any increased risk of serious cardiovascular effects in patients given celecoxib.[1,2] Nonetheless, by February 2001 the UK CSM had received a small number of reports[3] of *myocardial infarction* or *ischaemia* associated with the selective cyclo-oxygenase-2 (COX-2) inhibitors. There were also 3 cases of *torsade de pointes* associated with celecoxib use.[4] Subsequently, in September 2004, the COX-2 inhibitor rofecoxib was generally withdrawn worldwide by the manufacturer after further reports of cardiovascular adverse effects (see p. 128.3) and this has prompted re-evaluation of the safety of other selective COX-2 inhibitors.

In December 2004 a large study of celecoxib for prevention of colon polyps (the APC study) was halted because of an increased risk of cardiovascular events (including death from cardiovascular causes, myocardial infarction, stroke, and heart failure) in patients receiving the drug compared with those receiving placebo.[5] The results of this long-term study suggested that there was a 2.8-fold increase in the risk of such events in patients taking either celecoxib 400 or 800 mg daily and that the increase was dose-related. The possibility of a dose-adverse effect relationship was supported by some at-the-time unpublished studies, the PreSAP and ADAPT studies, that showed no increase in the risk of cardiovascular effects with celecoxib 400 mg daily when compared with placebo.[6] These studies[7,8] have since been published and their finished reports were less reassuring than initially thought. The risk of serious cardiovascular events was found to be increased in the celecoxib group when compared with the placebo group although the difference was not significant. In addition, an update[9] of the original APC study confirmed that the risk of adverse cardiovascular events was significantly increased for both high-dose (800 mg daily) and low-dose (400 mg daily) celecoxib when compared with placebo treatment; however, high-dose treatment was associated with the greatest risk. Increases in blood pressure were also more likely with both celecoxib groups than with placebo. An analysis[10] using pooled data from 6 randomised placebo-controlled studies, including the APC, PreSap, and ADAPT studies, found the following relationship between dose and adverse cardiovascular effect, in descending order of risk: 400 mg twice daily (adjusted hazard ratio 3.1 times that of placebo), 200 mg twice daily (hazard ratio 1.8), and 400 mg once daily (hazard ratio 1.1). (The result for 400 mg once daily was not statistically significant.) There was also evidence to suggest that the adverse effect of dose is more pronounced in patients with higher baseline cardiovascular risk.

In 2005, based on the findings of studies available at the time, EU regulatory authorities[11-13] recommended that:

- selective COX-2 inhibitors should not be used in patients with established ischaemic heart disease or cerebrovascular disease; they are also contra-indicated in those with peripheral arterial disease

- patients with risk factors for heart disease such as hypertension, hyperlipidaemia, diabetes, and smoking should be carefully monitored if given selective COX-2 inhibitors
- all patients should be assessed individually on the risks and benefits of selective COX-2 inhibitor treatment, particularly cardiovascular and gastrointestinal risk factors, and alternative treatments considered

Similar advice has also been issued by the FDA;[14] however, the only absolute contra-indication is in the immediate postoperative period after coronary artery bypass surgery. (In the USA celecoxib is currently the only available selective COX-2 inhibitor.)

COX-2 inhibitors such as celecoxib do not possess the intrinsic antiplatelet activity associated with aspirin and possibly other non-selective NSAIDs and consequently do not provide protection against ischaemic cardiac events.[3,15]

1. Silverstein FE, *et al.* Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS study: a randomized controlled trial. *JAMA* 2000; **284:** 1247–55.
2. White WB, *et al.* Comparison of thromboembolic events in patients treated with celecoxib, a cyclooxygenase-2 specific inhibitor, versus ibuprofen or diclofenac. *Am J Cardiol* 2002; **89:** 425–30.
3. CSM/MCA. COX-2 selective NSAIDs lack antiplatelet activity. *Current Problems* 2001; **27:** 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007458&RevisionSelectionMethod=LatestReleased (accessed 01/11/07)
4. Pathak A, *et al.* Celecoxib-associated torsade de pointes. *Ann Pharmacother* 2002; **36:** 1290–1.
5. Solomon SD, *et al.* Adenoma Prevention with Celecoxib (APC) Study Investigators. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med* 2005; **352:** 1071–80.
6. FDA. Celecoxib (marketed as Celebrex) (issued 7th April, 2005). Available at: http://www.fda.gov/cder/drug/infopage/celebrex/celebrex-hcp.pdf (accessed 01/11/07)
7. Arber N, *et al.* Celecoxib for the prevention of colorectal adenomatous polyps. *N Engl J Med* 2006; **355:** 885–95.
8. ADAPT Research Group. Cardiovascular and cerebrovascular events in the randomized, controlled Alzheimer's disease anti-inflammatory prevention trial (ADAPT). Available at: http://clinicaltrials.plosjournals.org/archive/1555-5887/1/7/pdf/10.1371_journal.pctr.0010033-L.pdf (accessed 01/11/07)
9. Bertagnolli MM, *et al.* Celecoxib for the prevention of sporadic colorectal adenomas. *N Engl J Med* 2006; **355:** 873–84.
10. Solomon SD, *et al.* Cross Trial Safety Assessment Group. Cardiovascular risk of celecoxib in 6 randomized placebo-controlled trials: the cross trial safety analysis. *Circulation* 2008; **117:** 2104–13.
11. MHRA. Updated advice on the safety of selective COX-2 inhibitors. Message from Professor G Duff, Chairman of CSM (issued 17th February, 2005). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON019458&RevisionSelectionMethod=LatestReleased (accessed 01/11/07)
12. EMEA. European Medicines Agency announces regulatory action on COX-2 inhibitors (issued 17th February, 2005). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/6275705en.pdf (accessed 29/08/08)
13. EMEA. European Medicines Agency concludes action on COX-2 inhibitors (issued 27th June, 2005). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/20776605en.pdf (accessed 01/11/07)
14. FDA. FDA issues public health advisory recommending limited use of cox-2 inhibitors: agency requires evaluation of prevention studies involving cox-2 selective agents. (issued 23rd December, 2004). Available at: http://www.fda.gov/bbs/topics/ANSWERS/2004/ANS01336.html (accessed 01/11/07)
15. Bing RJ, Lomnicka M. Why do cyclo-oxygenase-2 inhibitors cause cardiovascular events? *J Am Coll Cardiol* 2002; **39:** 521–2.

Effects on the gastrointestinal tract. It is generally accepted that the inhibition of cyclo-oxygenase-1 (COX-1) plays a role in the adverse gastrointestinal effects of the NSAIDs, and that the selective inhibition of the other isoform, COX-2, by NSAIDs such as celecoxib may cause less gastrotoxicity than the non-selective inhibition of the traditional NSAIDs.

Results from controlled studies suggested that NSAIDs selective for COX-2 were associated with a lower incidence of serious gastrointestinal effects. In a placebo-controlled study[1] the incidence of endoscopically determined gastroduodenal ulcers in patients taking celecoxib for rheumatoid arthritis (dose range 200 to 800 mg daily) was not significantly different to that seen with the placebo group. Another study[2] in patients taking celecoxib at supratherapeutic doses (800 mg daily) concluded that there was a lower combined incidence of symptomatic gastrointestinal ulcers and ulcer complications (bleeding, perforation, and obstruction) after 6 months of treatment when compared with non-selective NSAIDS (ibuprofen 2.4 g daily or diclofenac 150 mg daily). However, the incidence of ulcer complications alone was not significantly different to that seen with other NSAIDs. A re-analysis of the study by the FDA, including both the 6-month and full-term data, also found that there was no significant reduction in the rate of ulcer complications with celecoxib compared with the non-selective NSAIDs although, in subjects not taking aspirin, there was a strong trend in favour of celecoxib compared with ibuprofen.[3] The risk of ulcer complications was also significantly increased in celecoxib users taking concomitant low-dose aspirin.[2] A later systematic review[4] of studies of patients receiving celecoxib or NSAIDs for at least 12 weeks claimed to show improved gastrointestinal safety and tolerability in those receiving celecoxib (including in patients also taking low-dose aspirin) but this has been criticised on grounds of data selection.[5,6]

It has been noted that the use of aspirin appears to nullify any potential protective effect of COX-2 selectivity by celecoxib.[7,8]

There have been individual case reports of gastrotoxicity with celecoxib.[9-11]

1. Simon LS, *et al.* Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis: a randomized controlled trial. *JAMA* 1999; **282:** 1921–8.
2. Silverstein FE, *et al.* Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS study: a randomized controlled trial. *JAMA* 2000; **284:** 1247–55.
3. FDA. Celebrex capsules (celecoxib) NDA 20-998/S009—Medical Officer Review. 2000. Available at: http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b1_03_med.pdf (accessed 01/11/07)
4. Deeks JJ, *et al.* Efficacy, tolerability, and upper gastrointestinal safety of celecoxib for treatment of osteoarthritis and rheumatoid arthritis: systematic review of randomised controlled trials. *BMJ* 2002; **325:** 619–23.
5. Jüni P, *et al.* Systematic review of celecoxib for osteoarthritis and rheumatoid arthritis: problems compromise review's validity. *BMJ* 2003; **326:** 334.
6. Metcalfe S, *et al.* Systematic review of celecoxib for osteoarthritis and rheumatoid arthritis: celecoxib's relative gastrointestinal safety is overstated. *BMJ* 2003; **326:** 334–5.
7. Lichtenstein DR, Wolfe MM. COX-2-selective NSAIDs: new and improved? *JAMA* 2000; **284:** 1297–9.
8. Bates DE, Lennaire JB. Possible celecoxib-induced gastroduodenal ulceration. *Ann Pharmacother* 2001; **35:** 782–3.
9. Mohammed S, Croom DW. Gastropathy due to celecoxib, a cyclooxygenase-2 inhibitor. *N Engl J Med* 1999; **340:** 2005–6.
10. Adverse Drug Reactions Advisory Committee (ADRAC). Celecoxib: early Australian reporting experience. *Aust Adverse Drug React Bull* 2000; **19:** 6–7. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0006.pdf (accessed 29/08/08)
11. Adverse Drug Reactions Advisory Committee (ADRAC). Serious gastrointestinal effects with celecoxib and rofecoxib. *Aust Adverse Drug React Bull* 2003; **22:** 15. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0308.htm (accessed 01/11/07)

Effects on the kidneys. Increasing evidence suggests that selective cyclo-oxygenase-2 (COX-2) inhibitors such as celecoxib appear to have adverse effects on renal function similar to those of the non-selective NSAIDs (see p. 106.2).

Some references to the adverse renal effects of celecoxib.

1. Boyd IW, *et al.* COX-2 inhibitors and renal failure: the triple whammy revisited. *Med J Aust* 2000; **173:** 274.
2. Perazella MA, Tray K. Selective cyclooxygenase-2 inhibitors: a pattern of nephrotoxicity similar to traditional nonsteroidal anti-inflammatory drugs. *Am J Med* 2001; **111:** 64–7.
3. Graham MG. Acute renal failure related to high-dose celecoxib. *Ann Intern Med* 2001; **135:** 69–70.
4. Alkhuja S, *et al.* Celecoxib-induced nonoliguric acute renal failure. *Ann Pharmacother* 2002; **36:** 52–4.
5. Ahmad SR, *et al.* Renal failure associated with the use of celecoxib and rofecoxib. *Drug Safety* 2002; **25:** 537–44.
6. Alper AB, *et al.* Nephrotic syndrome and interstitial nephritis associated with celecoxib. *Am J Kidney Dis* 2002; **40:** 1086–90.
7. Akhund L, *et al.* Celecoxib-related renal papillary necrosis. *Arch Intern Med* 2003; **163:** 114–15.
8. Markowitz GS, *et al.* Membranous glomerulopathy and acute interstitial nephritis following treatment with celecoxib. *Clin Nephrol* 2003; **59:** 137–42.
9. Brewster UC, Perazella MA. Acute tubulointerstitial nephritis associated with celecoxib. *Nephrol Dial Transplant* 2004; **19:** 1017–18.
10. Clifford TM, *et al.* Celecoxib-induced nephrotoxicity in a renal transplant recipient. *Pharmacotherapy* 2005; **25:** 773–7.
11. Tabibian JH, *et al.* Late-onset celecoxib-induced combined hepatonephrotoxicity. *Br J Clin Pharmacol* 2008; **66:** 150–1.

Effects on the liver. Cholestatic hepatitis developed in a 54-year-old woman taking celecoxib;[1] her liver function tests improved and her symptoms resolved after drug withdrawal. Despite the temporal relationship between celecoxib use and the onset of hepatotoxicity, the manufacturers stated that evidence available at that time did not support such a relationship.[2] However, other cases[3,4] have since been reported, including a case report[5] of late-onset hepatorenal toxicity where symptoms developed 10 months after starting therapy. Licensed product information now states that cases of severe hepatic reactions, including fulminant hepatitis (some fatal), liver necrosis, and hepatic failure (some fatal or requiring transplant), have been reported. Of the cases that reported time to onset, most of these reactions had developed within 1 month of starting celecoxib therapy. Patients with signs and/or symptoms suggesting hepatic dysfunction, or in whom an abnormal liver test has occurred, should be monitored closely; celecoxib therapy should be stopped if clinical signs and/or symptoms consistent with liver disease develop, or if systemic manifestations occur.

For a case of acute hepatitis with pancreatitis, see Pancreatitis, below.

1. O'Beirne JP, Cairns SR. Cholestatic hepatitis in association with celecoxib. *BMJ* 2001; **323:** 23.
2. Arellano FM, *et al.* Case of cholestatic hepatitis with celecoxib did not fulfil international criteria. *BMJ* 2002; **324:** 789–90.
3. Grieco A, *et al.* Acute cholestatic hepatitis associated with celecoxib. *Ann Pharmacother* 2002; **36:** 1887–9.
4. Chamouard P, *et al.* Prolonged cholestasis associated with short-term use of celecoxib. *Gastroenterol Clin Biol* 2005; **29:** 1286–8.
5. Tabibian JH, *et al.* Late-onset celecoxib-induced combined hepatonephrotoxicity. *Br J Clin Pharmacol* 2008; **66:** 150–1.

Effects on the lungs. Report of a case of pulmonary oedema and possible pneumonitis in a patient taking celecoxib.[1]

1. Olin JL, *et al.* Pulmonary edema and possible pneumonitis associated with celecoxib. *Ann Pharmacother* 2004; **38:** 1086.

Effects on the nervous system. Acute neuropsychiatric reactions such as confusion, somnolence, and insomnia have occurred after celecoxib use.[1] There has also been a case report of aseptic meningitis.[2]

1. Adverse Drug Reations Advisory Committee (ADRAC). Acute neuropsychiatric events with celecoxib and rofecoxib. *Aust Adverse Drug React Bull* 2003; **22:** 3. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0302.pdf (accessed 01/11/07)
2. Papaioannides DH, *et al.* Aseptic meningitis possibly associated with celecoxib. *Ann Pharmacother* 2004; **38:** 172.

Hypersensitivity. A 52-year-old man developed allergic vasculitis after 8 days of treatment with celecoxib.[1] Despite intensive treatment the patient died from multiple organ failure and diffuse cutaneous necrolysis. The authors noted that potentially fatal skin reactions have occurred with other sulfa-containing drugs, although there is some evidence[2] suggesting that the potential for cross-reactivity in patients sensitive to sulfonamides is relatively low (see also p. 367.3) nonetheless, licensed product information contra-indicates the use of celecoxib in such patients.

1. Schneider F, *et al.* Fatal allergic vasculitis associated with celecoxib. *Lancet* 2002; **359:** 852–3.
2. Shapiro LE, *et al.* Safety of celecoxib in individuals allergic to sulfonamides: a pilot study. *Drug Safety* 2003; **26:** 187–95.

Pancreatitis. Acute hepatitis and pancreatitis developed in an elderly patient with a reported history of hypersensitivity to sulfonamides who was given celecoxib.[1] Symptoms resolved on stopping the drug. Pancreatitis has also been reported in a sulfonamide-tolerant patient.[2]

Celecoxib was one of the more commonly implicated drugs cited in case reports of drug-induced pancreatitis received by the Adverse Drug Reactions Advisory Committee in Australia.[3]

1. Carrillo-Jimenez R, Nurnberger M. Celecoxib-induced acute pancreatitis and hepatitis: a case report. *Arch Intern Med* 2000; **160:** 553–4.
2. Baciewicz AM, *et al.* Acute pancreatitis associated with celecoxib. *Ann Intern Med* 2000; **132:** 680.
3. Australian Adverse Drug Reactions Advisory Committee (ADRAC). Drug induced pancreatitis. *Aust Adverse Drug React Bull* 2006; **25:** 22. Also available at: http://www.tga.gov.au/adr/aadrb-aadr0612.pdf (accessed 01/11/07)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies celecoxib as probably not porphyrinogenic: it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 23/10/11)

Interactions

The metabolism of celecoxib is mediated mainly by the cytochrome P450 isoenzyme CYP2C9. Use with other drugs that inhibit or induce or are metabolised by this isoenzyme may result in changes in plasma concentration of celecoxib; fluconazole has increased plasma concentrations of celecoxib and UK licensed product information recommends that the dose of celecoxib should be halved when given with fluconazole.

Celecoxib is an inhibitor of the isoenzyme CYP2D6 and the potential therefore exists for an effect on drugs metabolised by this enzyme.

For interactions associated with NSAIDs in general, see p. 107.3.

Pharmacokinetics

Celecoxib is absorbed from the gastrointestinal tract and peak plasma concentrations occur after about 3 hours. Protein binding is about 97%. Celecoxib is metabolised in the liver mainly by the cytochrome P450 isoenzyme CYP2C9, which shows genetic polymorphism; the three identified metabolites are inactive as inhibitors of cyclo-oxygenase-1 (COX-1) or COX-2 enzymes. It is eliminated mainly as metabolites in the faeces and urine; less than 3% is recovered as unchanged drug. The effective terminal half-life is about 11 hours. Celecoxib is distributed into breast milk. The pharmacokinetics of celecoxib may vary in different ethnic groups; it has been stated that the area under the concentration-time curve is elevated in patients of Afro-Caribbean origin, although any clinical significance is unclear.

References.

1. Davies NM, *et al.* Clinical pharmacokinetics and pharmacodynamics of celecoxib: a selective cyclo-oxygenase-2 inhibitor. *Clin Pharmacokinet* 2000; **38:** 225–42.
2. Stempak D, *et al.* Single-dose and steady-state pharmacokinetics of celecoxib in children. *Clin Pharmacol Ther* 2002; **72:** 490–7. Correction. *ibid.* 2006; **80:** 667.

3. Kirchheiner J, *et al.* Influence of CYP2C9 genetic polymorphisms on pharmacokinetics of celecoxib and its metabolites. *Pharmacogenetics* 2003; **13:** 473–80.
4. Lundblad MS, *et al.* Accumulation of celecoxib with a 7-fold higher drug exposure in individuals homozygous for CYP2C9*3. *Clin Pharmacol Ther* 2006; **79:** 287–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Algybrex†; Celebrex; Coxtenk; Radicacine; ***Austral.***: Celebrex; ***Austria***: Celebrex; Onsenal†; ***Belg.***: Celebrex; Onsenal†; ***Braz.***: Celebra; ***Canad.***: Celebrex; ***Chile***: Celebra; ***China***: Celebrex (西乐葆); ***Cz.***: Celebrex; Onsenal†; ***Denm.***: Celebra; Celebrex; Onsenal†; ***Fin.***: Celebra; ***Fr.***: Celebrex; Onsenal†; ***Ger.***: Celebrex; Onsenal†; ***Gr.***: Adarex; Celebrex; ***Hong Kong***: Celebrex; ***Hung.***: Celebrex; ***India***: CE; Celact; Celcib; Celcox; Celecap; Celedol; Celemax; Celetop; Celib†; Cobix; Colcibra; Coxib; Eloxib; Icel; Orthocel; Zycel; ***Indon.***: Celebrex; ***Irl.***: Celebrex; Onsenal†; ***Israel***: Celcox; Celebra; ***Ital.***: Artilog; Celebrex; ***Malaysia***: Celebrex; ***Mex.***: Celebrex; ***Neth.***: Celebrex; Onsenal†; ***Norw.***: Celebra; ***NZ***: Celebrex; ***Philipp.***: Aubrex; Celcoxx; Celebrex; Celexib; Coxbitor; Coxoral; Coxzan; Dolcelox; Euroflam; Flamar; Lexib; Lincox; ***Pol.***: Celebrex; ***Port.***: Celebrex; Onsenal†; Solexa; ***Rus.***: Celebrex (Целебрекс); ***S.Afr.***: Celebrex; ***Singapore***: Celebrex; ***Spain***: Artilog; Celebrex; Onsenal†; ***Swed.***: Celebra; Onsenal†; ***Switz.***: Celebrex; ***Thai.***: Celebrex; ***Turk.***: Celebrex; ***UK***: Celebrex; Onsenal†; ***Ukr.***: Celebrex (Целебрекс); Flogoxib (Флогоксиб); Ranselex (Ранселекс); Reumoxib (Ревмоксиб); ***USA***: Celebrex; ***Venez.***: Cexb.

Certolizumab Pegol *(BAN, USAN, rINN)*

CDP-870; Certolizumab Pégol; Certolizumabum Pegolum; PHA-738144; Цертолизумаб Пегол.

CAS — 428863-50-7.
ATC — L04AB05.
ATC Vet — QL04AB05.
UNII — UMD07X179E.

Uses and Administration

Certolizumab pegol is a pegylated TNF antibody fragment that binds specifically to TNFα and neutralises membrane-associated and soluble human TNFα in a dose-dependent manner. It also inhibits the production of lipopolysaccharide-induced TNFα and interleukin-1β (IL-1β). Elevated levels of TNF and IL-1 have been found in the affected tissues and fluids of patients with rheumatoid arthritis (p. 13.2), ankylosing spondylitis including axial spondyloarthritis, and psoriatic arthritis (see Spondyloarthropathies, p. 14.3), and Crohn's disease (see Inflammatory Bowel Disease, p. 1811.3). Certolizumab pegol is described as a biological disease-modifying antirheumatic drug (DMARD).

Certolizumab pegol is used in the treatment of moderate to severe, active **rheumatoid arthritis** and active **psoriatic arthritis**. In the treatment of rheumatoid arthritis, UK licensed product information recommends that certolizumab pegol should be given with methotrexate to patients who have had an inadequate response to DMARDs, although monotherapy may be used in those who have had an inadequate response to, or are intolerant of, methotrexate. Certolizumab pegol is also used in the treatment of active **ankylosing spondylitis**: UK licensed product information recommends that it should only be used in patients with severe disease who have had an inadequate response to, or are intolerant of, NSAIDs. In the UK, it is also licensed for the treatment of severe **axial spondyloarthritis** without radiographic evidence of ankylosing spondylitis in patients who have had an inadequate response to, or are intolerant of, NSAIDs. Certolizumab pegol is used in the treatment of moderate to severe, active **Crohn's disease** unresponsive to conventional treatment. For all the above indications, the initial dose is 400 mg given as two subcutaneous injections of 200 mg, repeated after 2 and 4 weeks. In the treatment of inflammatory joint disorders, this is followed by 200 mg every other week although maintenance with 400 mg every 4 weeks may be considered. Patients with Crohn's disease who have a clinical response may receive a maintenance dose of 400 mg every 4 weeks.

References.
1. Sandborn WJ, *et al.* PRECISE 1 Study Investigators. Certolizumab pegol for the treatment of Crohn's disease. *N Engl J Med* 2007; **357:** 228–38.
2. Schreiber S, *et al.* PRECISE 2 Study Investigators. Maintenance therapy with certolizumab pegol for Crohn's disease. *N Engl J Med* 2007; **357:** 239–50. Correction. *ibid.*: 1357.
3. Keystone E, *et al.* Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis Rheum* 2008; **58:** 3319–29.
4. Fleischmann R, *et al.* Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. *Ann Rheum Dis* 2009; **68:** 805–11.
5. Smolen J, *et al.* Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. *Ann Rheum Dis* 2009; **68:** 797–804.
6. Shao LM, *et al.* Meta-analysis: the efficacy and safety of certolizumab pegol in Crohn's disease. *Aliment Pharmacol Ther* 2009; **29:** 605–14.
7. Smith LS, *et al.* Certolizumab pegol: a TNF-α antagonist for the treatment of moderate-to-severe Crohn's disease. *Ann Pharmacother* 2010; **44:** 333–42.
8. Evans AT, Lee SD. A review and expert opinion of the use of certolizumab for Crohn's disease. *Expert Opin Biol Ther* 2012; **12:** 363–70.
9. Deeks ED. Certolizumab pegol: a review of its use in the management of rheumatoid arthritis. *Drugs* 2013; **73:** 75–97.
10. Keystone E, *et al.* Long-term safety and efficacy of certolizumab pegol in combination with methotrexate in the treatment of rheumatoid arthritis: 5-year results from the RAPID 1 trial and open-label extension. *Ann Rheum Dis* 2013. Available at: doi:10.1136/annrheumdis-2013-203695
11. Song IH, Rudwaleit M. Certolizumab pegol in axial spondyloarthritis. *Expert Rev Clin Immunol* 2013; **9:** 1161–72.
12. Mease PJ, *et al.* Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). *Ann Rheum Dis* 2014; **73:** 48–55.
13. Landewé R, *et al.* Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled Phase 3 study. *Ann Rheum Dis* 2014; **73:** 39–47.

Adverse Effects and Precautions

As for Infliximab, p. 75.3.

References.
1. Bykerk VP, *et al.* Update on the safety profile of certolizumab pegol in rheumatoid arthritis: an integrated analysis from clinical trials. *Ann Rheum Dis* 2013. Available at: doi:10.1136/annrheumdis-2013-203660

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies certolizumab as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/10/11)

Pregnancy. Studies in *animals* have not shown harm to the fetus when certolizumab is given during pregnancy. There are few human data, although one case report in a woman with Crohn's disease who received 2 doses of certolizumab during pregnancy (one during the first, and one during the third trimester) reported normal growth and development of the child up to 1 month of age. Genital bleeding due to retention of part of the placenta occurred 9 weeks after the second dose of certolizumab.[1]

1. Oussalah A, *et al.* Certolizumab use in pregnancy. *Gut* 2009; **58:** 608.

Interactions

As for Infliximab, p. 77.3

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Cimzia; ***Austria***: Cimzia; ***Belg.***: Cimzia; ***Canad.***: Cimzia; ***Cz.***: Cimzia; ***Denm.***: Cimzia; ***Fr.***: Cimzia; ***Ger.***: Cimzia; ***Gr.***: Cimzia; ***Irl.***: Cimzia; ***Jpn***: Cimzia; ***Neth.***: Cimzia; ***Norw.***: Cimzia; ***Pol.***: Cimzia; ***Port.***: Cimzia; ***Spain***: Cimzia; ***Swed.***: Cimzia; ***Switz.***: Cimzia; ***UK***: Cimzia; ***USA***: Cimzia.

Choline Magnesium Trisalicylate

Trisalicilato de colina y magnesio; Холин Магнезиум Трисалицилаты.

$C_{26}H_{29}O_{10}NMg$=539.8
CAS — 64425-90-7.
UNII — DJJ95FJP1H.

Profile

Choline magnesium trisalicylate is a combination of the salicylic acid derivatives choline salicylate (below) and magnesium salicylate (p. 85.2). It has analgesic, anti-inflammatory, and antipyretic actions similar to those of aspirin (p. 22.3). After oral administration, choline magnesium trisalicylate dissociates and the salicylate moiety is rapidly absorbed. Each unit dose of 500 mg of salicylate is provided by about 293 mg of choline salicylate with 362 mg of magnesium salicylate (anhydrous). Choline magnesium trisalicylate has been used in osteoarthritis, rheumatoid arthritis, and other arthritides; it has also been used in the general management of other forms of pain and fever.

Choline Salicylate *(BAN, USAN, rINN)*

Choline, Salicylate de; Cholini Salicylas; Koliinisalisylaatti; Kolinsalicylat; Salicilato de colina; Холина Салицилат.

(2-Hydroxyethyl)trimethylammonium salicylate.
$C_{12}H_{19}NO_4$=241.3
CAS — 2016-36-6.
ATC — N02BA03.
ATC Vet — QN02BA03.
UNII — KD510K1QW.

Pharmacopoeias. ***Br.*** includes a solution.

BP 2014: (Choline Salicylate Solution). An aqueous solution containing 47.5 to 52.5% of choline salicylate. It is a clear colourless liquid. It may contain a suitable antimicrobial preservative.

Profile

Choline salicylate is a salicylic acid derivative (see Aspirin, p. 22.2) used in the treatment of pain and fever, and in the management of rheumatic disorders. In terms of salicylate content, choline salicylate 435 mg is equivalent to about 325 mg of aspirin. Choline salicylate is given orally in doses of 435 to 870 mg every four hours as necessary for pain and fever, and in doses of 4.8 to 7.2 g daily in divided doses for rheumatic disorders.

Choline salicylate is also used as a local analgesic. Solutions containing up to about 20% choline salicylate are used in ear disorders such as the relief of pain in otitis media and externa but are considered to be of doubtful value; they are also used to soften ear wax as an aid to removal (see p. 1839.3). An 8.7% gel is used for lesions of the mouth (p. 1814.2). Choline salicylate has also been applied topically in a rubefacient preparation for the relief of muscular and rheumatic pain.

Choline salicylate is also given in the form of choline magnesium trisalicylate (see above).

Adverse effects and precautions. A 21-month-old boy developed salicylate poisoning after his mother had rubbed the contents of 3 tubes of *Bonjela* teething ointment (containing a total of 2.61 g of choline salicylate) on his gums over 48 hours.[1]

In another case, an 8-year-old boy with G6PD deficiency developed an oral mucosal burn a few hours after application of about half a tube of *Teejel* oral gel.[2] He developed mouth ulcers and displayed signs of apathy, lethargy, and nasal congestion 3 days after exposure. His condition improved after a week. The authors felt that G6PD deficiency may have been a contributing factor in the occurrence of adverse effects.

In the UK, the MHRA contra-indicates the use of topical oral pain relief preparations containing salicylates in children under 16 years of age (for details, see Reye's Syndrome, below).

1. Paynter AS, Alexander FW. Salicylate intoxication caused by teething ointment. *Lancet* 1979; **ii:** 1132.
2. Sapir S, Bimstein E. Cholinsalicylate gel induced oral lesion: report of case. *J Clin Pediatr Dent* 2000; **24:** 103–6.

REYE'S SYNDROME. The link between aspirin use in children and the development of Reye's syndrome is well recognised although a causal relationship remains to be established and the evidence for other salicylates could not be adequately evaluated (see p. 25.3). However, a 20-month-old boy who had received a teething gel containing choline salicylate (applied in doses of 1.31 g daily, equivalent to acetylsalicylate 100 mg/kg daily, which exceeds the recommended dose) developed Reye's syndrome following a viral illness.[1] The authors noted that the MHRA in the UK were aware of two earlier reports suggesting an association between choline salicylate and Reye's syndrome. As of April 2009, the MHRA[2] had received 3 such reports in which all 3 children were hospitalised but Reye's syndrome was not confirmed in any of them; in addition, 4 reports of vomiting or diarrhoea after the use of choline salicylate oral gel had been received. Consequently, the MHRA contra-indicated the use of topical oral pain relief preparations containing salicylates in children under 16 years of age due to the theoretical risk of Reye's syndrome.

1. Oman TK, *et al.* Topical choline salicylates implicated in Reye's syndrome. *BMJ* 2008; **336:** 1376.
2. MHRA. Press release: new advice on oral salicylate gels in under 16s (issued 23rd April, 2009). Available at: http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON044014 (accessed 24/04/09)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dercolina; ***Austral.***: Applicaine†; Herron Baby Teething Gel; Ora-Sed Jel; ***Austria***: Mundisal; ***Cz.***: Mundisal; ***Hong Kong***: Ora-Sed; ***India***: Gelora; Oraflora Gel; Zytee; ***Irl.***: Audax; ***Malaysia***: Ora-Sed; ***NZ***: Ora-Sed; ***Pol.***: Cholinex; Otinum; ***Port.***: Bucagel; ***Rus.***: Mundisal (Мундизал); Otinum (Отинум); ***Singapore***: Ora-Sed; ***Switz.***: Mundisal; ***Turk.***: Dencol; ***Ukr.***: Faringin (Фарингин); Otinum (Отинум).

Multi-ingredient Preparations. ***Arg.***: Pansoral; ***Austral.***: Bonjela; Sedagel; ***Belg.***: Givalex; Teejel; ***Fr.***: Givalex; Pansoral; ***Gr.***: Mundisal; ***Hong Kong***: Bonjela; Dermojela; Oris-gel†; ***Hung.***: Mundisal; ***India***: Bonzela; Clenora; Clenorush; Dentogel; Dentra; Dologel-CT; Dologel; Nitra-Dent; Ora-G; Ora-Sore; Orasia; Orawin; Orex-Lo; Orex; ***Irl.***: Bonjela; Teejel†; ***Israel***: Baby

Gum; Bonjela†; Teejel; ***Malaysia***: Bonjela; Orregel; ***NZ***: Bonjela; ***Pol.***: Sachol zel Stomatologiczny; ***Rus.***: Cholisal (Холисал); Dologel (Дологель); Pansoral (Пансорал); ***S.Afr.***: Bonjela; ***Singapore***: Bonjela; Soragel; ***Switz.***: Pansoral†; Tenderdol; ***Thai.***: Bonjela; ***UK***: Bonjela Cool Mint; Bonjela; Earex Plus†; ***Ukr.***: Angilex (Ангилекс); Cholisal (Холисал); Givalex (Гивалекс); Heppylor (Хепилор).

Pharmacopoeial Preparations
BP 2014: Choline Salicylate Ear Drops; Choline Salicylate Oromucosal Gel.

Clofexamide *(rINN)*

ANP-246; Clofexamida; Clofexamidum; Клофексамид.
2-(4-Chlorophenoxy)-*N*-(2-diethylaminoethyl)acetamide.
$C_{14}H_{21}ClN_2O_2$=284.8
CAS — 1223-36-5.
UNII — 071P4J77HF.

Profile

Clofexamide has been used topically as the hydrochloride in preparations for musculoskeletal, joint, and soft-tissue disorders.

Clofezone *(rINN)*

ANP-3260; Clofezona; Clofézone; Clofezonum; Клофезон.
An equimolar combination of clofexamide and phenylbutazone.
$C_{14}H_{21}ClN_2O_2$,$C_{19}H_{20}N_2O_2$,$2H_2O$=629.2
CAS — 60104-29-2.
ATC — M01AA05; M02AA03.
ATC Vet — QM01AA05; QM02AA03.
UNII — TPT3MH65LD.

Profile

Clofezone, a combination molecule containing clofexamide (above) and phenylbutazone (p. 125.1), has been given orally and by rectal suppository and applied topically in preparations for musculoskeletal, joint, and soft-tissue disorders.

Clonixin *(USAN, rINN)*

CBA-93626; Clonixine; Clonixino; Clonixinum; Sch-10304; Клониксин.
2-(3-Chloro-o-toluidino)nicotinic acid.
$C_{13}H_{11}ClN_2O_2$=262.7
CAS — 17737-65-4.
UNII — V7DXN0M42R.

Clonixin Lysine *(rINNM)*

Clonixin Lysinate; Clonixine Lysine; Clonixino lisina; Clonixinum Lysinum; L-104; Lysine Clonixinate; R-173; Клониксина Лизин.
$C_{13}H_{11}ClN_2O_2$, $C_6H_{14}N_2O_2$=408.9
CAS — 55837-30-4.
UNII — 06PW4M190R.

Profile

Clonixin is an NSAID (p. 102.3). It has been used as the lysine salt in oral doses of up to 250 mg four times daily for the relief of pain. Clonixin lysine has also been given by intramuscular or intravenous injection and as a rectal suppository.

References.
1. Eberhardt R, *et al.* Analgesic efficacy and tolerability of lysine-clonixinate versus ibuprofen in patients with gonarthrosis. *Curr Ther Res* 1995; **56**: 573–80.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Clonixil; Diclen; Dolex; Dorixina; Lazalgena; ***Braz.***: Dolamin; ***Chile***: Adoplan; Blonax; Celex; Clonalgin; Colmax; Dentagesic; Diminon†; Lafigesic; Medigesic; Nefersil; Traumicid†; ***Mex.***: Disinal; Donodol; Dorixina; Firac; Lixitin; Lonixer; Prestodol; Sedepron; ***Port.***: Algimate; Clonix; ***Spain***: Dolalgial; ***Venez.***: Dorixina.

Multi-ingredient Preparations. ***Arg.***: Amplibenzatin Bronquial; Antispasmina Compuesto; Becebuen Compuesto; Dorixina B1 B6 B12; Dorixina Forte; Dorixina Relax; Espasmo Dolex; Migra Dorixina; Mikesan; Nova Paratropina Compositum; Propalgin; Sertal Compuesto; ***Braz.***: Dolamin Flex; ***Chile***: Clonalgin Compuesto; Ergonef; Migra-Nefersil; Nefersil B; Neurocam; ***Mex.***: Doltrix; Donodol Compuesto; Dorixina Relax; Espacil Compuesto; Firac Plus; Klonaza; Optium; Plidan Compuesto; Prestodol Compuesto; Prestoflam; Yuredol; ***Venez.***: Dologinex; Dorixina Flex; Migradorixina; Plidan Compuesto.

Codeine *(BAN)*

Codein; Codeína; Codéine; Codeinum; Codeinum Monohydricum; Kodeiini; Kodein; Kodein monohydrát; Kodeína; Kodeinás; Methylmorphine; Metilmorfina; Morphine Methyl Ether; Кодеин.
7,8-Didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-ol monohydrate.
$C_{18}H_{21}NO_3H_2O$=317.4
CAS — 76-57-3 (anhydrous codeine); 6059-47-8 (codeine monohydrate).
ATC — R05DA04.
ATC Vet — QR05DA04.
UNII — Q830PW7520.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of codeine:

AC/DC; Barr; Captain Cody; Cody; Coties; Cough Syrup; Down; Karo; Lean; Nods; School boy; Schoolboy; T3.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 8: (Codeine). White or almost white, crystalline powder or colourless crystals. Soluble in boiling water; freely soluble in alcohol. Protect from light.

USP 36: (Codeine). Colourless or white crystals or white crystalline powder. It effloresces slowly in dry air. Soluble 1 in 120 of water, 1 in 2 of alcohol, 1 in 0.5 of chloroform, and 1 in 50 of ether. Its saturated solution in water is alkaline to litmus. Store in airtight containers. Protect from light.

Codeine Hydrochloride *(BANM)*

Codeína, hidrocloruro de; Codéine (chlorhydrate de) dihydraté; Codeini Hydrochloridum Dihydricum; Kodeiinihydroklorididihydraatti, Kodein-hidroklorid-dihidrát; Kodeinhydrochlorid dihydrát; Kodeinhydrokloriddihydrat; Kodeino hidrochloridas dihidratas; Кодеина Гидрохлорид.
$C_{18}H_{21}NO_3HCl,2H_2O$=371.9
CAS — 1422-07-7 (anhydrous codeine hydrochloride).
UNII — NTZ53GG7XN.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Codeine Hydrochloride Dihydrate; Codeine Hydrochloride BP 2014). Small colourless crystals or a white or almost white, crystalline powder. Soluble in water; slightly soluble in alcohol; practically insoluble in cyclohexane. Protect from light.

Codeine Phosphate *(BANM)*

Codeína, fosfato de; Codéine, phosphate de; Codeine Phosphate Hemihydrate; Codeini Phosphas; Codeini Phosphas Hemihydricus; Codeinii Phosphas; Codeinphosphat-Hemihydrat; Kodeiinifosfaatti; Kodein-fosfát hemihydrát; Kodeinfosfathemi; Kodein-foszfát-hemihidrát; Kodeino fosfatas hemihidratas; Kodeiny fosforan; Kodeiny fosforan półwodny; Methylmorphine Phosphate; Кодеина Фосфат.
$C_{18}H_{21}NO_3,H_3PO_4,½H_2O$=406.4
CAS — 52-28-8 (anhydrous codeine phosphate); 41444-62-6 (codeine phosphate hemihydrate); 5913-76-8 (codeine phosphate sesquihydrate).
UNII — GSL05Y1MN6 (codeine phosphate hemihydrate); 2X585M1M3T (anhydrous codeine phosphate).

NOTE. Compounded preparations of codeine phosphate may be represented by the following names:
- Co-codamol *x/y* (*BAN*)—where *x* and *y* are the strengths in milligrams of codeine phosphate and paracetamol respectively
- Co-codAPAP (*PEN*)—codeine phosphate and paracetamol
- Co-codaprin (*BAN*)—codeine phosphate 1 part and aspirin 50 parts (w/w)
- Co-codaprin (*PEN*)—codeine phosphate and aspirin.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Pharmacopoeias may specify the hemihydrate, sesquihydrate, or both, either under one monograph or as separate monographs.

Ph. Eur. 8: (Codeine Phosphate Hemihydrate; Codeine Phosphate BP 2014). A white or almost white, crystalline powder or small, colourless crystals. Freely soluble in water; slightly soluble or very slightly soluble in alcohol. A 4% solution in water has a pH of 4.0 to 5.0. Protect from light.

Ph. Eur. 8: (Codeine Phosphate Sesquihydrate; Codeini Phosphas Sesquihydricus). A white or almost white, crystalline powder or small, colourless crystals. Freely soluble in water; slightly soluble in alcohol. A 4% solution in water has a pH of 4.0 to 5.0. Protect from light.

USP 36: (Codeine Phosphate). The hemihydrate occurs as fine, white, needle-shaped crystals or white crystalline powder; odourless. Soluble 1 in 2.5 of water, 1 in 0.5 of water at 80 degrees, 1 in 325 of alcohol, and 1 in 125 of boiling alcohol. Its solutions are acid to litmus. Store in airtight containers at a temperature up to 40 degrees as permitted by the manufacturer. Protect from light.

Incompatibility. Acetylation of codeine phosphate by aspirin has occurred in solid dosage forms containing the two drugs, even at a low moisture level.[1] *Animal* work suggested that the analgesic activity of codeine was not affected by acetylation.[2]

1. Galante RN, *et al.* Solid-state acetylation of codeine phosphate by aspirin. *J Pharm Sci* 1979; **68**: 1494–8.
2. Buckett WR, *et al.* The analgesic properties of some 14-substituted derivatives of codeine and codeinone. *J Pharm Pharmacol* 1964; **16**: 177–82.

Codeine Sulfate *(BANM)*

Codeína, sulfato de; Codeine Sulphate; Кодеина Сульфат.
$(C_{18}H_{21}NO_3)_2,H_2SO_4,3H_2O$=750.9
CAS — 1420-53-7 (anhydrous codeine sulfate); 6854-40-5 (codeine sulfate trihydrate).
UNII — 11QV9BS0CB.

Pharmacopoeias. In *US*.

USP 36: (Codeine Sulfate). White crystals, usually needle-like, or white crystalline powder. Soluble 1 in 30 of water, 1 in 6.5 of water at 80 degrees, and 1 in 1300 of alcohol; insoluble in chloroform and in ether. Store in airtight containers. Protect from light.

Stability. Codeine sulfate solutions appear to be intrinsically more stable than codeine phosphate solutions.[1]

1. Powell MF. Enhanced stability of codeine sulfate: effect of pH, buffer, and temperature on the degradation of codeine in aqueous solution. *J Pharm Sci* 1986; **75**: 901–3.

Uses and Administration

Codeine, a phenanthrene derivative, is an opioid analgesic (p. 108.1) obtained from opium or made by methylating morphine. It is much less potent as an analgesic than morphine and has relatively mild sedative effects.

Codeine or its salts, especially the phosphate, are given orally in the form of linctuses for the relief of cough, and as tablets for the relief of mild to moderate pain, often with a non-opioid analgesic such as aspirin, ibuprofen, or paracetamol. The phosphate is also given by intramuscular injection, in doses similar to those used orally, for the relief of pain; the intravenous, subcutaneous, and rectal routes have also been used.

For the relief of **pain** codeine phosphate may be given in doses of 30 to 60 mg every 4 hours to a usual maximum of 240 mg daily.

To allay non-productive **cough** codeine phosphate may be given in doses of 15 to 30 mg three or four times daily.

Codeine phosphate is also used as tablets or in mixtures for the symptomatic relief of **acute diarrhoea** in doses of 15 to 60 mg given 3 or 4 times daily.

For details of doses in children, see below.

Other codeine salts used include the hydrochloride, sulfate, camsilate, and hydrobromide. Codeine polistirex (a codeine and sulfonated diethenylbenzene-ethenylbenzene copolymer complex) is used in modified-release preparations.

Administration in children. In the UK, the use of codeine is restricted to the short-term treatment of acute, moderate *pain* in children over 12 years of age who do not respond to other analgesics such as paracetamol or ibuprofen (for further details, see Genetic Polymorphism, p. 41.3). The recommended oral dose is 30 to 60 mg (or 0.5 to 1 mg/kg) of codeine phosphate given every 6 hours when necessary, up to the usual adult maximum dose of 240 mg daily; the duration of treatment should not exceed 3 days. The *BNFC* suggests that this dose may also be given by intramuscular injection. Guidelines[1] for analgesia in children in Accident and Emergency departments in the UK recommend the use of oral codeine as an alternative, or in addition, to diclofenac, for moderate pain such as that associated with small burns or scalds, finger tip injuries, forearm, elbow, or ankle fracture, or appendicitis. Case reports of adverse reactions such as vasodilatation, severe hypotension, and apnoea in infants and children after intravenous doses of codeine have precluded its use by this route in children of all ages.[2]

Antimotility drugs such as codeine should not be used in infants and young children with acute *diarrhoea*.[3,4] Those aged over 12 years may be given the usual adult dose of codeine phosphate for this indication (see above).

The MHRA advises that over-the-counter *cough* and *cold* preparations containing codeine should not be used in those aged under 18 years (for details, see Cough, p. 41.1). However, codeine phosphate is licensed to allay

non-productive cough in children over 12 years of age; the usual adult dose for this indication (see p. 40.3) may be given.

1. The College of Emergency Medicine. Best practice guideline: management of pain in children (issued July 2013). Available at: http://secure.collemergencymed.ac.uk/asp/document.asp?ID=4682 (accessed 11/12/13)
2. Marsh DF, *et al.* Opioid systems and the newborn. *Br J Anaesth* 1997; 79: 787–95.
3. Anonymous. Drugs in the management of acute diarrhoea in infants and young children. *Bull WHO* 1989; 67: 94–6.
4. Cimolai N, Carter JE. Antimotility agents for paediatric use. *Lancet* 1990; 336: 874.

Administration in renal impairment. See under Precautions, p. 42.1.

Cough. A systematic review[1] of over-the-counter (OTC) preparations for acute cough (p. 1651.2) concluded that codeine appeared no more effective than placebo in reducing cough symptoms in adults or children, although the number of patients in the studies considered was small. More recently, in October 2010, the MHRA[2] advised that OTC cough and cold preparations containing codeine should not be used in those aged under 18 years. The review they had conducted also found a lack of robust evidence of its efficacy in the symptomatic treatment of cough in children of any age. Safety concerns over its central mode of action, significant variability in its metabolism to morphine, and possible abuse and dependence in adolescents were considered to outweigh the possible benefits of such use.

1. Smith SM, *et al.* Over-the-counter medications for acute cough in children and adults in ambulatory settings. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 26/06/08).
2. MHRA. Oral liquid cough medicines containing codeine: should not be used in children and young people under 18 years (issued 11th October, 2010). Available at: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON096796 (accessed 25/01/11) See also: MHRA. Public Assessment Report. Oral liquid cough medicines containing codeine: should not be used in children and young people under 18 years (issued October 2010). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON096798&RevisionSelectionMethod=Latest (accessed 25/01/11)

Pain. Systematic reviews[1,2] comparing paracetamol-codeine combinations versus paracetamol alone concluded that in single-dose studies addition of codeine to paracetamol produced a comparatively small but statistically significant increase in analgesic effect; however, there was an increased incidence of adverse effects with the combination. Another systematic review[3] of analgesic use in moderate to severe postoperative pain found that single oral doses of codeine alone provided low levels of clinically useful pain relief when compared with placebo; better pain relief was noted with other commonly used analgesics such as NSAIDs and paracetamol, given alone and in combination preparations with codeine.

1. de Craen AJM, *et al.* Analgesic efficacy and safety of paracetamol-codeine combinations versus paracetamol alone: a systematic review. *BMJ* 1996; 313: 321–5.
2. Toms L, *et al.* Single dose oral paracetamol (acetaminophen) with codeine for postoperative pain in adults. Available in The Cochrane Database of Systematic Reviews: Issue 1. Chichester: John Wiley; 2009 (accessed 02/11/09).
3. Derry S, *et al.* Single dose oral codeine, as a single agent, for acute postoperative pain in adults. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley: 2010 (accessed 30/06/10).

Dependence and Withdrawal

As for Opioid Analgesics, p. 109.1.

Codeine is subject to abuse (see under Precautions, below), but produces less euphoria and sedation than morphine.

Neonatal abstinence syndrome. Some of the symptoms characteristic of the neonatal abstinence syndrome were seen in a neonate whose mother had taken about 90 mg of codeine daily during the last 2 months of pregnancy.[1]

1. Khan K, Chang J. Neonatal abstinence syndrome due to codeine. *Arch Dis Child* 1997; 76: F59–F60.

Adverse Effects and Treatment

As for Opioid Analgesics in general, p. 110.1.

In therapeutic doses codeine is much less liable than morphine to produce adverse effects, although constipation may be troublesome with long-term use. After large doses of codeine, excitement and convulsions may occur.

Codeine, like morphine, has a dose-related histamine-releasing effect. Anaphylactic reactions after intravenous use have been reported rarely.

Effects on mental function. Central effects of codeine phosphate appeared to be limited, but dose-related, in subjects given 30, 60, or 90 mg; visuo-motor coordination was altered with doses of 60 and 90 mg and dynamic visual acuity with 90 mg.[1] Drowsiness reported by subjects given 90 mg of codeine phosphate could not be linked with impaired performance whereas nausea could.

1. Bradley CM, Nicholson AN. Effects of a μ -opioid receptor agonist (codeine phosphate) on visuo-motor coordination and dynamic visual acuity in man. *Br J Clin Pharmacol* 1986; 22: 507–12.

Effects on the pancreas. A 26-year-old woman developed acute pancreatitis on 2 separate occasions a few hours after taking a single, 40-mg dose of codeine.[1] There was no history of alcohol consumption and her recovery was uneventful. Other cases have been reported.[2-5]

1. Hastier P, *et al.* Pancreatitis induced by codeine: a case report with positive rechallenge. *Gut* 1997; 41: 705–6.
2. Locher C, *et al.* Pancréatite aiguë après la prise d'une association paracétamol-codéine. *Gastroenterol Clin Biol* 2003; 27: 124–5.
3. Kohlen K, *et al.* Codein-induzierte Pankreatitis. *Dtsch Med Wochenschr* 2005; 130: 878–9.
4. Moreno Escobosa MC, *et al.* Pancreatitis due to codeine. *Allergol Immunopathol (Madr)* 2005; 33: 175–7.
5. Belhassen García M, *et al.* Pancreatitis secundaria a paracetamol-codeína. *An Med Interna* 2006; 23: 400–401.

Effects on the skin. Pruritus and burning erythemato-vesicular plaques that developed in a patient in response to oral codeine were attributed to a fixed drug eruption.[1] A similar reaction occurred in another patient after taking various analgesics including a combined preparation of paracetamol and codeine;[2] patch testing showed a positive response for codeine only. Maculopapular rash has been seen as part of a hypersensitivity syndrome associated with oral codeine phosphate;[3] fever, splenomegaly, and lymphadenopathy also occurred.

1. Gonzalo-Garijo MÁ, Revenga-Arranz F. Fixed drug eruption due to codeine. *Br J Dermatol* 1996; 135: 498–9.
2. Gastaminza G, *et al.* Erythrodermia caused by allergy to codeine. *Contact Dermatitis* 2005; 52: 227–8.
3. Enomoto M, *et al.* Codeine phosphate-induced hypersensitivity syndrome. *Ann Pharmacother* 2004; 38: 799–802.

Hypersensitivity. See Effects on the Skin, above.

Overdosage. Acute codeine intoxication in 430 children, due to accidental ingestion of antitussive preparations, was reviewed.[1] The children were nearly all between 1 and 6 years old. Symptoms in decreasing order of frequency included somnolence, rash, miosis, vomiting, itching, ataxia, and swelling of the skin. Respiratory failure occurred in 8 children and 2 died; all 8 had taken 5 mg/kg or more. Infants are at special risk and there have been fatalities[2-4] and severe adverse effects[4-7] after inappropriate treatment in infants and young children given products containing codeine.

Opioid toxicity, in addition to severe salicylate toxicity, has occurred in adults after overdoses of aspirin and codeine tablets.[8]

1. von Mühlendahl KE, *et al.* Codeine intoxication in childhood. *Lancet* 1976; ii: 303–5.
2. Ivey HH, Kattwinkel J. Danger of Actifed-C. *Pediatrics* 1976; 57: 164–5.
3. Magnani B, Evans R. Codeine intoxication in the neonate. Abstract: *Pediatrics* 1999; 104: 1379. Full version: http://pediatrics.aappublications.org/cgi/content/full/104/6/e75 (accessed 26/06/08)
4. Ferreirós N, *et al.* Fatal and severe codeine intoxication in 3-year-old twins—interpretation of drug and metabolite concentrations. *Int J Legal Med* 2009; 123: 387–94.
5. Wilkes TCR, *et al.* Apnoea in a 3-month-old baby prescribed compound linctus containing codeine. *Lancet* 1981; i: 1166–7.
6. Lee AC, *et al.* A case of probable codeine poisoning in a young infant after the use of a proprietary cough and cold medicine. *Hong Kong Med J* 2004; 10: 285–7.
7. Hermanns-Clausen M, *et al.* Drug dosing error with drops: severe clinical course of codeine intoxication in twins. *Eur J Pediatr* 2009; 168: 819–24.
8. Leslie PJ, *et al.* Opiate toxicity after self poisoning with aspirin and codeine. *BMJ* 1986; 292: 96.

Precautions

As for Opioid Analgesics in general, p. 110.3.

Abuse. Although the risk of dependence on codeine is low with normal use,[1] it is the subject of deliberate abuse. In France[2] and in the UK linctuses containing codeine have been particularly liable to abuse. Reports in the literature include the use in New Zealand of codeine-containing preparations to produce demethylated products known as "Homebake" containing variable amounts of morphine[3] and abuse of co-codaprin tablets for their codeine content.[4-6]

1. Rowden AM, Lopez JR. Codeine addiction. *DICP Ann Pharmacother* 1989; 23: 475–7.
2. Armand C, *et al.* 10 ans de détournement d'usage du Néocodion entre 1992 et 2002: Neocodion misuse: evolution between 1992 and 2002. *Therapie* 2004; 59: 547–53.
3. Shaw JP. Drug misuse in New Zealand. *Pharm J* 1987; 238: 607.
4. Sakol MS, Stark CR. Codeine abuse. *Lancet* 1989; ii: 1282.
5. Paterson JR, *et al.* Codeine abuse from co-codaprin. *Lancet* 1990; 335: 224.
6. Sakol MS, Stark CR. Codeine abuse from co-codaprin. *Lancet* 1990; 335: 224.

Breast feeding. Breast-fed infants of mothers taking codeine may be at an increased risk of toxicity from its metabolite, morphine, if the mother is an ultrarapid metaboliser of codeine. In one report,[1] a 13-day-old infant died from opioid toxicity after being exposed to morphine in his mother's breast milk; the mother had been taking oral codeine 30 mg twice daily as part of a combination preparation with paracetamol for about 2 weeks. Assayed morphine concentrations in the breast milk were found to be 87 nanograms/mL; the usual range is 1.9 to 20.5 nanograms/mL after repeated doses of codeine 60 mg four times daily. Later investigations found that the mother's genotype for the cytochrome P450 isoenzyme CYP2D6 (the enzyme involved in the conversion of codeine to morphine) classified her as an ultrarapid metaboliser of codeine. Others[2] have subsequently reported severe neonatal toxicity in breast-fed infants whose mothers were CYP2D6 ultrarapid metabolisers. Furthermore, a quantitative mechanistic modeling study to simulate opiate uptake in nursing neonates[3] suggested that there would be little difference in the rate and extent of morphine formation from codeine in mothers with the extensive metaboliser genotype when compared with ultratapid metabolisers. The model also suggested that low morphine clearance in either the mother or neonate was a significant factor for reaching potentially toxic morphine concentrations in a breast-fed neonate.

The FDA has advised[4] that nursing mothers taking codeine should be informed of the potential risk of morphine overdose and the need to monitor breast-fed infants for signs of toxicity such as increased sleepiness, difficulty feeding or breathing, or limpness. Nursing mothers, themselves, may also develop overdose symptoms including extreme sleepiness, confusion, shallow breathing, and severe constipation. Similar advice has also been issued by Health Canada.[5] In the UK, the MHRA has advised[6] against the use of codeine in nursing mothers. Nonetheless, codeine appears to have been used safely for many years in breast-feeding mothers and the last available guidance from the American Academy of Pediatrics[7] considered that it is usually compatible with breast feeding. Moreover, some of the findings of the original case report have been questioned; in particular, the amount of paracetamol found in the infant's blood at post-mortem was considered too high to be derived from breast milk.[8]

Oxycodone has been used as an alternative to codeine. However, in a retrospective cohort study the incidence of CNS depression was similar in the breast-fed infants of women given either oxycodone or codeine.[9]

1. Koren G, *et al.* Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. *Lancet* 2006; 368: 704.
2. Madadi P, *et al.* Pharmacogenetics of neonatal opioid toxicity following maternal use of codeine during breastfeeding: a case-control study. *Clin Pharmacol Ther* 2009; 85: 31–5.
3. Willmann S, *et al.* Risk to the breast-fed neonate from codeine treatment to the mother: a quantitative mechanistic modeling study. *Clin Pharmacol Ther* 2009; 86: 634–43.
4. FDA. Information for healthcare professional: use of codeine products in nursing mothers (issued 17th August, 2007). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124889 (accessed 02/08/10)
5. Health Canada/Janssen-Ortho. Important safety information about use of "Tylenol" with codeine NO 2,3,4 and elixir in nursing mothers and ultra-rapid metabolizers of codeine (issued 6th October, 2008). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/tylenol_codeine_hpc-cps-eng.pdf (accessed 01/02/10)
6. MHRA/CHM. Codeine for analgesia: restricted use in children because of reports of morphine toxicity. *Drug Safety Update* 2013; 6 (12): A1. Available at: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON296400 (accessed 13/12/13)
7. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/06/08)
8. Bateman DN, *et al.* Codeine and breastfeeding. *Lancet* 2008; 372: 625.
9. Lam J, *et al.* Central nervous system depression of neonates breastfed by mothers receiving oxycodone for postpartum analgesia. *J Pediatr* 2012; 160: 33–7.

Children. See Overdosage, above, Genetic Polymorphism, below, and Administration in Children, p. 40.3.

Driving. Codeine phosphate 50 mg alone and with alcohol had a deleterious effect on driving skills in a simulated driving test.[1]

1. Linnoila M, Häkkinen S. Effects of diazepam and codeine, alone and in combination with alcohol, on simulated driving. *Clin Pharmacol Ther* 1974; 15: 368–73.

Genetic polymorphism. Life-threatening toxicity in a patient given moderate doses of codeine was thought to be due to a genotype predisposing him to ultrarapid metabolism of the drug into morphine by the cytochrome P450 isoenzyme CYP2D6; this was in addition to drug-induced inhibition of the usual major metabolic pathway mediated by CYP3A4, and transient reduction in renal function.[1]

Genetic polymorphism was also considered to contribute to the death of a 2-year-old child given codeine after an adenotonsillectomy had been performed to resolve sleep apnoea and snoring problems.[2] Other contributory factors include evidence of bronchopneumonia at post-mortem. A third report[3] detailed two fatalities and a case of severe respiratory depression following the use of codeine in 3 young children, aged 3 to 5 years, for pain following

adenotonsillectomy. Two of the children had CYP2D6 polymorphisms for extensive or ultrarapid metabolism phenotypes (which can overlap), and this was suspected in the third child given the high morphine concentrations found relative to codeine.

The FDA subsequently issued advice[4] concerning the risks of life-threatening respiratory depression and death following the use of codeine in children for pain following adenotonsillectomy, and contra-indicated its use in this patient group. For the management of other types of pain in children, they advised that codeine should be prescribed for use only when required, at the lowest effective dose for the shortest period of time. Carers should also be advised of the clinical signs of serious adverse effects of codeine. Similar advice has been issued by the UK MHRA;[5] they further advised that codeine should only be used to relieve acute, moderate pain in children older than 12 years of age and only if the use of other analgesics such as paracetamol or ibuprofen is ineffective. They also recommended against the use of codeine in children whose breathing may be compromised, including those with neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory-tract or lung infections, multiple trauma, or undergoing extensive surgical procedures. Health Canada has also restricted[6] the use of codeine to children who are 12 years of age or older.

The MHRA has recommended that codeine is contra-indicated in patients of **all** ages who are known CYP2D6 ultrarapid metabolisers.[5]

For the effect of this genotype in breast-feeding mothers, see Breast Feeding, p. 41.2.

1. Gasche Y, *et al.* Codeine intoxication associated with ultrarapid CYP2D6 metabolism. *N Engl J Med* 2004; **351**: 2827–31. Correction. *ibid.* 2005; **352**: 638.
2. Ciszkowski C, *et al.* Codeine, ultrarapid-metabolism genotype, and postoperative death. *N Engl J Med* 2009; **361**: 827–8.
3. Kelly LE, *et al.* More codeine fatalities after tonsillectomy in North American children. *Pediatrics* 2012; **129**: e1343–e1347.
4. FDA. Drug Safety Communication: safety review update of codeine use in children; new boxed warning and contraindication on use after tonsillectomy and/or adenoidectomy (issued 20th February, 2013). Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/UCM339116.pdf (accessed 13/12/13)
5. MHRA/CHM. Codeine for analgesia: restricted use in children because of reports of morphine toxicity. *Drug Safety Update* 2013; **6** (12): A1. Available at: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON296400 (accessed 13/12/13)
6. Health Canada. Health Canada's review recommends codeine only be used in patients aged 12 and over (issued 6th June, 2013). Available at: http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/33915a-eng.php (accessed 13/12/13)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies codeine as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/10/11)

Pregnancy. See Neonatal Abstinence Syndrome under Dependence and Withdrawal, p. 41.1.

Renal impairment. The renal clearance of codeine and its metabolites is significantly reduced in patients with end-stage renal disease on regular haemodialysis therapy. One such elderly patient developed tonic-clonic seizures 7 days after starting oral codeine phosphate 30 mg 4 times daily; no further seizures occurred after codeine was stopped and naloxone started.[1] The dosage of codeine should be reduced according to renal function in patients with renal impairment but no specific recommendations appear to be given in the literature.

1. Kuo S-C, *et al.* Probable codeine phosphate-induced seizures. *Ann Pharmacother* 2004; **38**: 1848–51.

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

Quinidine. For reference to a suggestion that quinidine can inhibit the analgesic effect of codeine, see Metabolism under Pharmacokinetics, below.

Pharmacokinetics

Codeine and its salts are absorbed from the gastrointestinal tract. Rectal absorption of codeine phosphate has been reported. Ingestion of codeine phosphate produces peak plasma-codeine concentrations in about one hour. Codeine is metabolised by *O*- and *N*-demethylation in the liver to morphine, norcodeine, and other metabolites including normorphine and hydrocodone. Metabolism to morphine is mediated by the cytochrome P450 isoenzyme CYP2D6, which shows genetic polymorphism (see also p. 41.3). Codeine and its metabolites are excreted almost entirely by the kidney, mainly as conjugates with glucuronic acid.

The plasma half-life has been reported to be between 3 and 4 hours after an oral or intramuscular dose.

Codeine crosses the placenta and is distributed into breast milk.

References.

1. Guay DR, *et al.* Pharmacokinetics of codeine after single- and multiple-oral-dose administration to normal volunteers. *J Clin Pharmacol* 1987; **27**: 983–7.
2. Persson K, *et al.* The postoperative pharmacokinetics of codeine. *Eur J Clin Pharmacol* 1992; **42**: 663–6.
3. Lafolie P, *et al.* Urine and plasma pharmacokinetics of codeine in healthy volunteers: implications for drugs-of-abuse testing. *J Anal Toxicol* 1996; **20**: 541–6.
4. Kim I, *et al.* Plasma and oral fluid pharmacokinetics and pharmacodynamics after oral codeine administration. *Clin Chem* 2002; **48**: 1486–96.

Administration. In a comparative study[1] codeine had an oral/intramuscular analgesic relative potency ratio of 6:10. This was high compared with that of morphine and was attributed to protection from rapid first-pass metabolism rather than more efficient absorption after oral doses. In a comparative study in children[2] the absorption rate of codeine from a suppository was found to be similar to that from an intramuscular injection; however, peak plasma concentrations were not as high when given rectally.

1. Beaver WT, *et al.* Analgesic studies of codeine and oxycodone in patients with cancer I: comparisons of oral with intramuscular codeine and of oral with intramuscular oxycodone. *J Pharmacol Exp Ther* 1978; **207**: 92–100.
2. McEwan A, *et al.* A comparison of rectal and intramuscular codeine phosphate in children following neurosurgery. *Paediatr Anaesth* 2000; **10**: 189–93.

Metabolism. The analgesic effect of codeine may be partly due to its metabolite morphine and it has been suggested that its efficacy may be impaired in patients who are poor metabolisers of codeine[1-4] or in those who are also receiving drugs, such as quinidine, that impair its metabolism.[1] However, patients unable to demethylate codeine to produce detectable plasma concentrations of morphine obtained a similar analgesic effect to patients with detectable plasma morphine concentrations.[5] A study[6] involving infants aged 6 to 10 months has indicated that children were capable of demethylating codeine to morphine at the age of 6 months although glucuronidation of the morphine appeared to be impaired when compared with older children.

For reports of severe toxicity thought to be due to altered metabolism of codeine see Genetic Polymorphism, p. 41.3.

1. Desmeules J, *et al.* Impact of environmental and genetic factors on codeine analgesia. *Eur J Clin Pharmacol* 1991; **41**: 23–6.
2. Chen ZR, *et al.* Disposition and metabolism of codeine after single and chronic doses in one poor and seven extensive metabolisers. *Br J Clin Pharmacol* 1991; **31**: 381–90.
3. Sindrup SH, *et al.* Codeine increases pain thresholds to copper vapor laser stimuli in extensive but not poor metabolizers of sparteine. *Clin Pharmacol Ther* 1991; **49**: 686–93.
4. Williams DG, *et al.* Pharmacogenetics of codeine metabolism in an urban population of children and its implications for analgesic reliability. *Br J Anaesth* 2002; **89**: 839–45.
5. Quiding H, *et al.* Analgesic effect and plasma concentrations of codeine and morphine after two dose levels of codeine following oral surgery. *Eur J Clin Pharmacol* 1993; **44**: 319–23.
6. Quiding H, *et al.* Infants and young children metabolise codeine to morphine: a study after single and repeated rectal administration. *Br J Clin Pharmacol* 1992; **33**: 45–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Actacode; ***Austria***: Codipertussin; Codipront Mono†; Tricodein†; ***Belg.***: Bromophar; Broncho-pectoralis Codeine; Bronchodine; Bronchosedal; Glottyl; Toux-San Codeine; ***Canad.***: Codeine Contin; Procet; ***China***: Nikekang (尼柯康); ***Fr.***: Antarene Codeine; Codedrill; Codenfan; Neo-Codion; Paderyl; ***Ger.***: Bronchicum Mono Codein; codi OPT; Codicaps mono; Codicaps Neo; Codicompren; Codipertussin; Makatussin Codein†; Optipect Kodein; Tussoret; ***Gr.***: Codipront N; ***Hong Kong***: Cough-C†; ***India***: Codifos; Codin; Codine; Lincotuss; Montokuf; ***Irl.***: Codant†; Codinex; ***Israel***: Codical; Rekod; ***Neth.***: Bronchicum Extra Sterk; Melrosum Extra Sterk; ***Philipp.***: Codipront N; ***Port.***: Toseina; ***Rus.***: Neo-Codion (Нео-Кодион)†; ***Singapore***: Colinctus; LTR Cough Linctus; LTR; SP-Codin; ***Spain***: Bisoltus; Codeisan; Fludan Codeina; Histaverin; Notusin; Perduretas Codeina; Toseina; ***Switz.***: Codicalm; Tropect pastilles pour les bronches; Makatussin; Pectocalmine Junior N; ***Thai.***: Para-Co; Zorituss; ***Turk.***: Nurofen Plus; ***UK***: Bepro; Galcodine; ***Venez.***: Codebromil; Codipront Mono.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

BP 2014: Co-codamol Capsules; Co-codamol Tablets; Co-codaprin Tablets; Codeine Linctus; Codeine Phosphate Injection; Codeine Phosphate Oral Solution; Codeine Phosphate Tablets; Dispersible Co-codaprin Tablets; Effervescent Co-codamol Tablets; Paediatric Codeine Linctus; Paracetamol, Codeine Phosphate and Caffeine Capsules; Paracetamol, Codeine Phosphate and Caffeine Tablets;

USP 36: Acetaminophen and Codeine Phosphate Capsules; Acetaminophen and Codeine Phosphate Oral Solution; Acetaminophen and Codeine Phosphate Oral Suspension; Acetaminophen and Codeine Phosphate Tablets; Aspirin and Codeine Phosphate Tablets; Bromodiphenhydramine Hydrochloride and Codeine Phosphate Oral Solution; Butalbital Aspirin, Caffeine, and Codeine Phosphate Capsules; Carisoprodol, Aspirin, and Codeine Phosphate Tablets; Codeine Phosphate Injection; Codeine Phosphate Oral Suspension; Codeine Phosphate Tablets; Codeine Sulfate Tablets; Guaifenesin and Codeine Phosphate Syrup; Terpin Hydrate and Codeine Elixir.

Croton Oil

Aceite de crotón; Aceite de croton; Oleum Crotonis; Oleum Tiglii; Кротоновое Масло.

CAS — 8001-28-3.

UNII — WK97EQG57S.

Pharmacopoeias. *Chin.* includes fruits of *Croton tiglium*.

Profile

Croton oil is an oil expressed from the seeds of *Croton tiglium* (Euphorbiaceae). Externally, it is a powerful counter-irritant and vesicant. Croton oil is also used with phenol in cosmetic chemical peeling of the skin.

Croton oil has such a violent purgative action that it should not be used as a laxative. Croton oil contains phorbol esters, which are carcinogenic.

Homoeopathy

Croton has been used in homoeopathic medicines under the following names: Croton tiglium; Crot. tig.

References.

1. Benstmon RH. Croton oil peels. *Aesthet Surg J* 2008; **28**: 33–45. Correction. *ibid.*; 221.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Canad.*: Homeo-Form CO†.

Devil's Claw Root

Djävulsklorot; Harpagofytový kořen; Harpagonjuuri; Harpagophyti Radix; Harpagophyton; Harpagophyton, racine d'; Harpagophytum; Inkaruočių šaknys; Ördögcsáklya gyökér; Raíz de harpagofito; Teufelskrallenwurzel; Гарпагофитум; Дьявольский Коготь.

CAS — 19210-12-9 (harpagoside).

ATC Herb — HM01AW5009 (Harpagophytum procumbens: root).

UNII — 1OYM338E89.

Pharmacopoeias. In *Eur.* (see p. vii), which also includes the dry extract.

Ph. Eur. 8: (Devil's Claw Root; Devil's Claw BP 2014). The cut and dried tuberous, secondary roots of *Harpagophytum procumbens* and/or *H. zeyheri*. Greyish-brown to dark brown with a bitter taste. Contains not less than 1.2% harpagoside ($C_{24}H_{30}O_{11}$ = 494.5), calculated with reference to the dried drug. Protect from light.

Profile

Devil's claw root is used in herbal remedies for musculoskeletal and joint disorders. Its activity is attributed in part to the plant's content of iridoid glycosides, notably harpagoside.

Reviews.

1. Brendler T, *et al.* Devil's Claw (*Harpagophytum procumbens* DC): an evidence-based systematic review by the Natural Standard Research Collaboration. *J Herb Pharmacother* 2006; **6**: 89–126.
2. Anonymous. *Harpagophytum procumbens* (devil's claw). *Altern Med Rev* 2008; **13**: 248–52.

Pain. Preparations containing devil's claw root have been tried with some success in the treatment of musculoskeletal disorders such as low back pain and osteoarthritis. There is some evidence of efficacy for daily oral doses standardised to 50 to 100 mg harpagoside but the quality of reporting in studies is generally poor and its place in therapy is not established.[1,2] An evidence-based report[3] by the Arthritis Research Campaign in the UK concluded that although devil's claw root may be effective for osteoarthritis, adverse effects remain a concern. Serious, but uncommon, adverse effects such as abnormal heart rhythm and bleeding have been reported.

1. Gagnier JJ, *et al.* Harpgophytum [sic] procumbens for osteoarthritis and low back pain: a systematic review. *BMC Complement Altern Med* 2004; **4**: 13.
2. Gagnier JJ, *et al.* Herbal medicine for low back pain. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 05/10/06).
3. Arthritis Research Campaign. Complementary and alternative medicines for the treatment of rheumatoid arthritis, osteoarthritis and fibromyalgia (issued February 2009). Available at: http://www.arthritisresearchuk.org/pdf/Complementary%20and%20alternative%20medicines_110120101543331.pdf (accessed 28/07/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Arpadol; Garra do Diabo†; Tenitrat†; *Denm.*: AEgte Venustorn; *Fr.*: Artrophytum†; Elusanes Harpagesic†; Harpadol; *Ger.*: Arthrotabs; Bomarthros†; Cefatec†; Dolo-Arthrosetten H; Doloteffin; flexi-loges; Harpagoforte; Jucurba; Pascoe-Agil; Rheuma-Sern; Rivoltan; Sogoon†; Teltonal†; Teufelskralle; *Hung.*: Sanhelios Teufelskralle; *Irl.*: Atrosan; *Mon.*: Dolosoft; *Neth.*: Harpadol; *Pol.*: Reumaphyt; *Spain*: Allynat; Harpagofito Orto†; HarpagoMed; Harpax†; Normoreum; *Swed.*: Helaflex; *Switz.*: HarpagoMed; Pascoe-Agil; Sanaflex; *UK*: Atrosan; DiaBackpain; DiaHarp; Flexiherb; Harpadol; HarpagoCaps; JointEeze; Moveze; *Ukr.*: Reumafit (Ревмафит).

Multi-ingredient Preparations. *Austral.*: Arthri Plus†; Arthriforte†; Arthritic Pain Herbal Formula 1†; Boswellia Compound; Devils Claw Plus†; Extralife Arthri-Care†; *Belg.*: Algi-Cool†; *Canad.*: Restorativ Glucosamine Muscle and Joint; *Cz.*: Antirevmaticky Caj†; *Fr.*: Arkophytum†; Chondrosteo; Fleximax; Geldolor; OM3flex†; *Ger.*: Dr Wiemanns Rheumatonikum†; *Ital.*: Body Guard; Cartago; Flodolor; Lik-Gel†; Nevril; Pik Gel; Proctocella Complex; Reumafort; Reumilase Plus; Reumilase; Valedol; *Mex.*: Rodan; *Pol.*: Reumaherb; *Switz.*: A Vogel Comprimes en cas de rhumatisme.

Homoeopathic Preparations. *Austria*: Globuli gegen Gelenkschmerzen; *Ger.*: Bomarthros Harpagophytum Complex; Pascoe-Agil HOM; Rheuma-Hevert.

Dexibuprofen *(BAN, USAN, rINN)*

Deksibuprofeeni; Dexibuprofène; Dexibuprofeno; Dexibuprofenum; *S*-(+)-Ibuprofen; Дексибупрофен.

CAS — 51146-56-6.
ATC — M01AE14.
ATC Vet — QM01AE14.
UNII — 671DKG7P5S.

Profile

Dexibuprofen is the *S*(+)-enantiomer of ibuprofen (p. 68.2) and is used similarly in the management of mild to moderate pain and inflammation in conditions such as dysmenorrhoea, headache, postoperative pain, dental pain, sprains, and soft-tissue rheumatism. It is also used in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis. It may be used as an antipyretic to reduce fever.

The usual oral dose is 600 to 900 mg daily in up to 3 divided doses, adjusted according to response, to a usual maximum of 1.2 g daily. Elderly patients should be started at the lower end of the dose range; dosage may then be increased according to tolerance. Dose reductions are also recommended in patients with hepatic or renal impairment, see below.

For doses in children, see below.

References.

1. Phleps W. Overview on clinical data of dexibuprofen. *Clin Rheumatol* 2001; **20** (suppl 1): S15–S21.
2. Mayrhofer F. Efficacy and long-term safety of dexibuprofen [S(+)-ibuprofen]: a short-term efficacy study in patients with osteoarthritis of the hip and a 1-year tolerability study in patients with rheumatic disorders. *Clin Rheumatol* 2001; **20** (suppl 1): S22–S29.
3. Hawel R, *et al.* Comparison of the efficacy and tolerability of dexibuprofen and celecoxib in the treatment of osteoarthritis of the hip. *Int J Clin Pharmacol Ther* 2003; **41**: 153–64.
4. Moore RA, *et al.* Single dose oral dexibuprofen [S(+)-ibuprofen] for acute postoperative pain in adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2009 (accessed 08/09/09).

Administration in children. Although dexibuprofen is not licensed for use in children under 18 years of age in the UK, some countries permit such use. For example, in Switzerland, dexibuprofen has been given to children aged 6 years and over; usual oral doses are 10 to 15 mg/kg daily in 2 to 4 divided doses. Licensed product information for one preparation recommends a maximum dose of 300 mg daily for those weighing less than 30 kg.

A multicentre randomised study[1] in children aged 6 months to 14 years found single doses of dexibuprofen 5 or 7 mg/kg to be as effective as ibuprofen 10 mg/kg in reducing fever.

1. Yoon JS, *et al.* The effects and safety of dexibuprofen compared with ibuprofen in febrile children caused by upper respiratory tract infection. *Br J Clin Pharmacol* 2008; **66**: 854–60.

Administration in hepatic and renal impairment. UK licensed product information specifies that the initial dose of dexibuprofen should be reduced in patients with mild to moderate hepatic or renal impairment; it should not be used in those with severe impairment.

Pharmacokinetics. For mention of the metabolism of *R*-(-)-ibuprofen to dexibuprofen, see p. 70.2.

Further references.

1. Eller N, *et al.* Pharmacokinetics of dexibuprofen administered as 200 mg and 400 mg film-coated tablets in healthy volunteers. *Int J Clin Pharmacol Ther* 1998; **36**: 414–17.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dexibuprofen as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 23/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Cefalex VL; *Austria*: Eu-Med Neu; Seractil; *Chile*: Dexelle; *Cz.*: Seractil†; *Denm.*: Seractiv; *Ger.*: Deltaran; Dolomagon; *Gr.*: Seractil; *Hung.*: Seractil; *India*: Brutek; Sibet; *Ital.*: Seractil; *Neth.*: Seractil; *Norw.*: Seractiv; *Pol.*: Dexprofen†; Seractil; *Port.*: Seractil; *Spain*: Atriscal; Seractil; *Swed.*: Tradil; *Switz.*: DexOptifen†; Seractil; *Turk.*: Tradil; *UK*: Seractil.

Multi-ingredient Preparations. *India*: Brutek-P; Dexigesic-P.

Dextromoramide *(BAN, pINN)* ⊗

Dekstromoramidi; Dextrodiphenopyrine; Dextromoramid; Dextromoramida; Dextromoramidum; *d*-Moramid; Pyrrolamidol; Декстроморамид.

(+)-1-(3-Methyl-4-morpholino-2,2-diphenylbutyryl)pyrrolidine.

$C_{25}H_{32}N_2O_2$=392.5

CAS — 357-56-2.
ATC — N02AC01.
ATC Vet — QN02AC01.
UNII — 9S4S6CIY83.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of dextromoramide:

Palf.

Dextromoramide Tartrate *(BANM, pINNM)* ⊗

Bitartrate de Dextromoramide; Dekstromoramiditartraatti; Dekstromoramido tartratas; Dextromoramidá, tartrato de; Dextromoramide Acid Tartrate; Dextromoramide Hydrogen Tartrate; Dextromoramide, Tartrate de; Dextromoramidhydrogentartrat; Dextromoramidi tartras; Dextromoramidtartarát; Dextromoramidtartrat; Tartrato de dextromoramida; Декстроморамида Тартрат.

$C_{25}H_{32}N_2O_2.C_4H_6O_6$=542.6

CAS — 2922-44-3.
UNII — J778U505W5.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Dextromoramide Tartrate). A white or almost white, crystalline or amorphous powder. Soluble in water; sparingly soluble in alcohol. A 1% solution in water has a pH of 3.0 to 4.0.

Profile

Dextromoramide is an opioid analgesic (p. 108.1) structurally related to methadone (p. 88.3). It has been used in the treatment of severe pain although it was not recommended for use in obstetric analgesia because of an increased risk of neonatal depression. Dextromoramide is subject to abuse.

Dextromoramide has been given orally as the tartrate. It has also been given rectally as suppositories and by subcutaneous or intramuscular injection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Irl.*: Palfium†; *Neth.*: Palface†; Palfium.

Pharmacopoeial Preparations
BP 2014: Dextromoramide Tablets.

Dextropropoxyphene *(BAN, pINN)*

Dekstropropoksifeeni; Dextropropoxifen; Dextropropoxifeno; Dextropropoxyphène; Dextropropoxyphenum; Propoxyphene; Декстропропоксифен.

(+)-(1*S*,2*R*)-1-Benzyl-3-dimethylamino-2-methyl-1-phenylpropyl propionate.

$C_{22}H_{29}NO_2$=339.5

CAS — 469-62-5.
ATC — N02AC04.
ATC Vet — QN02AC04.
UNII — S2F83W92TK.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of dextropropoxyphene:

Dummies.

Dextropropoxyphene Hydrochloride

(BANM, pINNM)

Dekstropropoksifeenihydrokloridi; Dekstropropoksifeno hidrochloridas; Dextropropoxifén-hidroklorid; Dextropropoxifenhydroklorid; Dextropropoxifeno, hidrocloruro de; Dextropropoxyfen-hydrochlorid; Dextropropoxyphène, Chlorhydrate de; Dextropropoxyphenhydrochlorid; Dextropropoxypheni Hydrochloridum; Hidrocloruro de dextropropoxifeno; Propoxyphene Hydrochloride (USAN); Декстропропоксифена Гидрохлорид.

$C_{22}H_{29}NO_2$.HCl=375.9

CAS — 1639-60-7.
UNII — CB2TL9PS0T.

NOTE. Compounded preparations of dextropropoxyphene hydrochloride may be represented by the following names:

- Co-proxamol (*BAN*)—dextropropoxyphene hydrochloride 1 part and paracetamol 10 parts (w/w).

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Dextropropoxyphene Hydrochloride). A white or almost white crystalline powder. Very soluble in water; freely soluble in alcohol. Protect from light.

USP 36: (Propoxyphene Hydrochloride). A white odourless crystalline powder. Freely soluble in water; soluble in alcohol, in acetone, and in chloroform; practically insoluble in ether and in benzene. Store in airtight containers.

Dextropropoxyphene Napsilate

(BANM, pINNM)

Dextropropoxifeno, napsilato de; Dextropropoxyphène, Napsilate de; Dextropropoxyphene Napsylate; Dextropropoxypheni Napsilas; Napsilato de dextropropoxifeno; Propoxyphene Napsylate (USAN); Декстропропоксифена Напсилат.

Dextropropoxyphene naphthalene-2-sulphonate monohydrate.

$C_{22}H_{29}NO_2.C_{10}H_8O_3S.H_2O$=565.7

CAS — 17140-78-2 (anhydrous dextropropoxyphene napsilate); 26570-10-5 (dextropropoxyphene napsilate monohydrate).
UNII — 38M219L1OJ.

NOTE. Compounded preparations of dextropropoxyphene napsilate may be represented by the following names:

- Co-proxAPAP (*PEN*)—dextropropoxyphene napsilate and paracetamol.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Dextropropoxyphene Napsilate). An odourless or almost odourless white powder. It exhibits polymorphism. Practically insoluble in water; soluble in alcohol; freely soluble in chloroform.

USP 36: (Propoxyphene Napsylate). A white powder having essentially no odour. Very slightly soluble in water; soluble 1 in 15 of alcohol and 1 in 10 of chloroform; soluble in acetone and in methyl alcohol. Store in airtight containers.

Uses and Administration

Dextropropoxyphene is an opioid analgesic (p. 108.1) structurally related to methadone (p. 88.3). It has mild analgesic activity and is given orally as the hydrochloride or napsilate to alleviate mild to moderate pain. Unlike the laevo-isomer (levopropoxyphene), dextropropoxyphene has little antitussive activity.

Dextropropoxyphene is mainly used with other analgesics that have anti-inflammatory and antipyretic effects, such as aspirin or paracetamol. The usual licensed dose is 65 mg of the hydrochloride or 100 mg of the napsilate given every 4 hours up to a maximum total daily dose of 390 mg or 600 mg, respectively. In the UK similar doses were given three or four times daily.

The EMEA and the FDA have recommended that *all* dextropropoxyphene-containing preparations be no longer available in the EU and USA, respectively (see also Overdosage, p. 44.2) although such preparations remain on the market in other countries.

Pain. A detailed review[1] of the analgesic efficacy of dextropropoxyphene suggested that with respect to single oral doses, recommended doses of dextropropoxyphene were no more (and probably less) effective than usual doses of paracetamol, aspirin, or other NSAIDs. However, the comparative efficacy may vary substantially depending on the cause of the pain.

When it comes to comparative studies involving combinations of dextropropoxyphene with other analgesics, findings are even less clear-cut.[2] The efficacy of co-proxamol has long been a matter of controversy yet despite this a

survey[3] conducted in 30 UK teaching hospitals found that co-proxamol was the most widely used paracetamol-containing analgesic at the time. It was suggested that the popularity of co-proxamol was purely down to prescribing habits passed on to new medical staff, rather than hard evidence regarding efficacy. This view has been refuted by others[4] who say that a large number of studies have shown clear analgesic effects for dextropropoxyphene. However, any assumption that the combination was widely used because it was more effective than paracetamol alone was not supported by a systematic overview of single-dose studies.[5] This concluded that while co-proxamol was indeed an effective analgesic it was no better than paracetamol alone. Although the evidence from this and other systematic reviews indicate that co-proxamol should be replaced by paracetamol alone for acute pain, the position for chronic use is considered to be not so clear (but see below).[6]

Concerns about the safety and efficacy of dextropropoxyphene, in particular its safety in overdose, have led the EMEA and the FDA to recommend that *all* dextropropoxyphene-containing preparations be no longer available in the EU and USA, respectively, although such preparations remain on the market in other countries. For further details see Effects on the Cardiovascular System and Overdosage, below.

1. Beaver WT. Analgesic efficacy of dextropropoxyphene and dextropropoxyphene-containing combinations: a review. *Hum Toxicol* 1984; 3 (suppl): 191S–220S.
2. Moore RA, *et al.* Single dose dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 1999 (accessed 26/06/08).
3. Haigh S. 12 Years on: co-proxamol revisited. *Lancet* 1996; 347: 1840–1. Correction. *ibid.*; 348: 346.
4. Sykes JV, *et al.* Coproxamol revisited. *Lancet* 1996; 348: 408.
5. Li Wan Po A, Zhang WY. Systematic overview of co-proxamol to assess analgesic effects of addition of dextropropoxyphene to paracetamol. *BMJ* 1997; 315: 1565–71. Correction *ibid.* 1998; 316: 116 and 656.
6. Anonymous. Co-proxamol or paracetamol for acute pain? *Drug Ther Bull* 1998; 36: 80.

Dependence and Withdrawal

As for Opioid Analgesics, p. 109.1.

Dextropropoxyphene has been subject to abuse (see under Precautions, p. 45.1).

Reports of dextropropoxyphene dependence and its treatment.

1. Wall R, *et al.* Addiction to Distalgesic (dextropropoxyphene). *BMJ* 1980; 280: 1213–14.
2. D'Abadie NB, Lenton JD. Propoxyphene dependence: problems in management. *South Med J* 1984; 77: 299–301.

Adverse Effects

As for Opioid Analgesics in general, p. 110.1.

In the recommended dosage the adverse effects of dextropropoxyphene are less marked than those of morphine. Gastrointestinal effects, dizziness, and drowsiness are the most common. Liver impairment, manifest as abnormal liver function tests and, more rarely, as reversible jaundice, has been reported.

There have been a large number of fatalities from either accidental or intentional overdosage with dextropropoxyphene. Many reports emphasise the rapidity with which death ensues; death within an hour of overdosage is not uncommon, and it can occur within 15 minutes. Overdosage is often complicated by patients also taking other CNS depressants such as alcohol and using mixed preparations such as dextropropoxyphene with paracetamol or aspirin.

Symptoms of overdosage are similar to those of opioid poisoning in general, but in addition patients may have psychotic reactions. There may be cardiac conduction abnormalities and arrhythmias.

Dextropropoxyphene injections are painful and have a very destructive effect on soft tissues and veins when abused in this way.

Anorectal reactions have followed the prolonged use of suppositories containing dextropropoxyphene; the reactions appear to be dose dependent.

Effects on the blood. A 12-year history of haemolysis and subsequent significant haemolytic anaemia in an elderly woman[1] was associated with chronic, periodic, and occasionally excessive intake of co-proxamol.

1. Fulton JD, McGonigal G. Steroid responsive haemolytic anaemia due to dextropropoxyphene paracetamol combination. *J R Soc Med* 1989; 82: 228.

Effects on the cardiovascular system. In November 2010, the FDA reported on its safety review of dextropropoxyphene.[1] A randomised, double-blind, placebo-controlled study in 18 healthy subjects receiving an oral daily dose of dextropropoxyphene [napsilate] titrated to 600 mg (the maximum licensed dose) or 900 mg for 11 days found significant prolongation of the QT interval in both cohorts; dose-dependent prolongation of the PR and QRS intervals was also noted. Indeed, the study was halted because of safety concerns. Consequently, based on this and other data available at that time, the FDA considered that the risks of dextropropoxyphene outweighed its benefits and requested its withdrawal from the US market (see also Overdosage, below).

1. FDA. FDA drug safety communication: FDA recommends against the continued use of propoxyphene (issued 19th November, 2010). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm234338.htm (accessed 23/11/10)

Effects on the ears. A report of complete nerve deafness associated with chronic abuse of co-proxamol was made to the UK CSM.[1] The CSM had received 2 other reports of permanent hearing loss attributed to co-proxamol abuse; transient hearing loss had also been reported in 2 patients taking usual doses; 7 further reports described tinnitus.

1. Ramsay BC. Complete nerve deafness after abuse of co-proxamol. *Lancet* 1991; 338: 446–7.

Effects on the liver. There have been occasional reports of jaundice in patients taking dextropropoxyphene alone but many of the 49 suspected hepatic reactions with dextropropoxyphene reported to the UK CSM by 1985[1] had involved use with paracetamol; clinical features including malaise, jaundice, raised serum transaminases, and sometimes fever, were however generally characteristic of dextropropoxyphene alone. Relapsing jaundice mimicking biliary disease was attributable to the dextropropoxyphene component of co-proxamol in 3 patients,[2] whereas there was no abnormality of liver function in 11 patients on long-term co-proxamol analgesia.[3] Another report of 9 cases found that the hepatotoxicity of dextropropoxyphene mimicked symptoms of large bile duct obstruction, and suggested that such toxicity might be misdiagnosed.[4] A more recent review[5] also concluded that hepatotoxicity with dextropropoxyphene might mimic a biliary tract disease, sometimes with few or no symptoms.

1. CSM. Hepatotoxicity with dextropropoxyphene. *Current Problems* 17 1986. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024424&RevisionSelectionMethod=LatestReleased (accessed 26/06/08)
2. Bassendine MF, *et al.* Dextropropoxyphene induced hepatotoxicity mimicking biliary tract disease. *Gut* 1986; 27: 444–9.
3. Hutchinson DR, *et al.* Liver function in patients on long-term paracetamol (co-proxamol) analgesia. *J Pharm Pharmacol* 1986; 38: 242–3.
4. Rosenberg WMC, *et al.* Dextropropoxyphene induced hepatotoxicity: a report of nine cases. *J Hepatol* 1993; 19: 470–4.
5. Bergeron L, *et al.* Dextropropoxyphène et atteintes hépatiques: à propos de 4 cas et revue de littérature. *Therapie* 2002; 57: 464–72.

Effects on the lungs. Hypersensitivity pneumonitis and skin rash have been reported in a patient taking co-proxamol.[1] No such reaction occurred when the patient was subsequently given paracetamol alone.

1. Matusiewicz SP, *et al.* Hypersensitivity pneumonitis associated with co-proxamol (paracetamol + dextropropoxyphene) therapy. *Postgrad Med J* 1999; 75: 475–6.

Hypoglycaemia. Hypoglycaemia has occasionally been reported with the use of dextropropoxyphene.[1-6]

1. Wiederholt IC, *et al.* Recurrent episodes of hypoglycemia induced by propoxyphene. *Neurology* 1967; 17: 703–4.
2. Almirall J, *et al.* Propoxyphene-induced hypoglycemia in a patient with chronic renal failure. *Nephron* 1989; 53: 273–5.
3. Laurent M, *et al.* Hypoglycemie sous dextropropoxyphène chez des grands vieillards: 7 cas. *Presse Med* 1991; 20: 1628.
4. Lowenstein W, *et al.* Hypoglycémie au dextropropoxyphène: une urgence chez le toxicomane. *Presse Med* 1993; 22: 133.
5. Santos Gil I, *et al.* Hipoglucemia secundaria a ingestión de dextropropoxifeno en un paciente adicto a drogas. *Med Clin (Barc)* 1998; 110: 475–6.
6. Shah P, *et al.* Propoxyphene-induced hypoglycemia in renal failure. *Endocr Pract* 2006; 12: 170–3.

Overdosage. There have been several reviews or retrospective studies of acute self-poisoning with dextropropoxyphene.[1-4] At a symposium on the safety and efficacy of dextropropoxyphene[5] many of the participants dealt with the problems of dextropropoxyphene overdosage, often in conjunction with paracetamol and sometimes with alcohol. Profound and even fatal CNS depression can develop rapidly as a result of the dextropropoxyphene content and in many cases death has occurred within an hour;[6] it was suggested that as few as 15 to 20 tablets of co-proxamol may be fatal.[7,8] Analysis of suicides involving drugs in England and Wales between 1997 and 1999 revealed that the odds of dying after overdose with co-proxamol were 2.3 times that for tricyclic antidepressant overdose, and 28.1 times greater than for paracetamol.[9] Another analysis of suicides due to poisoning in 3 areas of the UK between 2000 and 2001 identified 123 cases of fatal overdose with co-proxamol;[10] those who also consumed alcohol had generally taken fewer co-proxamol tablets than those who had not, emphasising the increased toxicity of the combination.

An analysis of overdosage involving combination analgesic preparations prescribed in Scotland between 2000 and 2002 also found that overdoses with co-proxamol were 10 times more likely to be fatal when compared with co-dydramol or co-codamol.[11] In the USA[12] the incidence of dextropropoxyphene-associated deaths reached a peak in 1977 and then fell at a rate that was not matched by a decline in prescribing.

It is not clear whether the metabolite, nordextropropoxyphene, plays an important role in fatalities.[12] However, nordextropropoxyphene, like dextropropoxyphene, is considered to have local anaesthetic activity and the membrane stabilising activity of dextropropoxyphene has been implicated as a major factor responsible for its severe cardiac depressant effect.[13]

In January 2005, the UK CSM found the risk of toxicity of co-proxamol in overdose to be unacceptable;[11] consequently, co-proxamol has been gradually withdrawn from the UK market. Around that time, fixed-dose combinations of dextropropoxyphene and paracetamol were also withdrawn in several other countries including Sweden and Switzerland. Subsequently, in June 2009, the EMEA[15] recommended that *all* dextropropoxyphene containing preparations, both single- and multi-constituent, be withdrawn throughout the EU; it was considered that the benefits of dextropropoxyphene did not outweigh its risks, particularly the risk of fatal overdose. In October 2009 a re analysis requested by the product licence holders upheld the EMEA's original recommendation for non-parenteral preparations of dextropropoxyphene.[16] For parenteral preparations, it was considered that, although their safety in overdosage may be less of a concern given their supervised use in hospitals, data on efficacy were lacking. Consequently, the EMEA recommended that product licences for parenteral preparations be suspended until further data on their efficacy are provided. At that time dextropropoxyphene-containing preparations remained available in the USA although steps such as improving prescriber awareness were taken to reduce the risk of overdose.[17] However, in November 2010, the FDA requested that all dextropropoxyphene-containing preparations be withdrawn from the US market after a safety review had shown evidence of significant cardiotoxicity (see Effects on the Cardiovascular System, above, for further details).

An analysis[18] of prescription data in England and Wales from 1998 to 2007 found that although the withdrawal of co-proxamol resulted in a significant increase of prescriptions for analgesics such as co-codamol, co-dydramol, codeine, and paracetamol, there was no statistical evidence for an increase in deaths by poisoning due to substitution with these analgesics or other drugs.

1. Young RJ. Dextropropoxyphene overdosage: pharmacological considerations and clinical management. *Drugs* 1983; 26: 70–9.
2. Madsen PS, *et al.* Acute propoxyphene self-poisoning in 222 consecutive patients. *Acta Anaesthesiol Scand* 1984; 28: 661–5.
3. Segest E. Poisoning with dextropropoxyphene in Denmark. *Hum Toxicol* 1987; 6: 203–7.
4. Jonasson U, *et al.* Correlation between prescription of various dextropropoxyphene preparations and their involvement in fatal poisonings. *Forensic Sci Int* 1999; 103: 125–32.
5. Bowen D, *et al.* (ed). Distalgesic; safety and efficacy. *Hum Toxicol* 1984; 3 (suppl): 1S–238S.
6. Proudfoot AT. Clinical features and management of Distalgesic overdose. *Hum Toxicol* 1984; 3 (suppl): 85S–94S.
7. Whittington RM. Dextropropoxyphene deaths: coroner's report. *Hum Toxicol* 1984; 3 (suppl): 175S–185S.
8. Young RJ, Lawson AAH. Distalgesic poisoning—cause for concern. *BMJ* 1980; 280: 1045–7.
9. Hawton K, *et al.* Co-proxamol and suicide: a study of national mortality statistics and local non-fatal self-poisonings. *BMJ* 2003; 326: 1006–8.
10. Hawton K, *et al.* A multicentre study of coproxamol poisoning suicides based on coroners' records in England. *Br J Clin Pharmacol* 2005; 59: 207–12.
11. Afshari R, *et al.* Co-proxamol overdose is associated with a 10-fold excess mortality compared with other paracetamol combination analgesics. *Br J Clin Pharmacol* 2005; 60: 444–7.
12. Finkle BS. Self-poisoning with dextropropoxyphene and dextropropoxyphene compounds: the USA experience. *Hum Toxicol* 1984; 3 (suppl): 115S–34S.
13. Henry JA, Cassidy SL. Membrane stabilising activity: a major cause of fatal poisoning. *Lancet* 1986; i: 1414–17.
14. MHRA. Withdrawal of co-proxamol products and interim updated prescribing information. Message from Professor G Duff, Chairman of CSM (issued 31st January, 2005). Available at: http://www.mhra.gov.uk/home/groups/pl-a/documents/websiteresources/con019461.pdf (accessed 28/08/08)
15. EMEA. Press release: European Medicines Agency recommends withdrawal of dextropropoxyphene-containing medicines (issued 25th June, 2009). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500010365.pdf (accessed 02/08/10)
16. EMEA. Questions and answers on the withdrawal of the marketing authorisations for medicines containing dextropropoxyphene (issued 22nd October, 2009). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/dextropropoxyphene_31/WC500014076.pdf (accessed 02/08/10)
17. FDA. News release: FDA takes actions on Darvon, other pain medications containing propoxyphene (issued 7th July, 2009) Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2009/ucm170769.htm (accessed 01/02/10)
18. Hawton K, *et al.* Effect of withdrawal of co-proxamol on prescribing and deaths from drug poisoning in England and Wales: time series analysis Abridged version: *BMJ* 2009; 339: 435–8. Full version: http://www.bmj.com/cgi/reprint/338/jun18_2/b2270 (accessed 03/11/09)

Treatment of Adverse Effects

As for Opioid Analgesics in general, p. 110.3.

Rapid treatment of overdosage with naloxone and assisted respiration is essential. Cardiac effects may not be reversed by naloxone. Although the benefit of gastric decontamination is uncertain, activated charcoal may be of value within 1 hour of ingesting a potentially toxic amount; dialysis is of little use.

Convulsions may require control with an anticonvulsant, bearing in mind that the CNS depressant effects of dextropropoxyphene can be exacerbated (see also Interactions, below). Stimulants should not be used because of the risk of inducing convulsions.

Patients taking overdoses of dextropropoxyphene with paracetamol will also require treatment for paracetamol poisoning (p. 116.2). Mixtures of dextropropoxyphene and aspirin may be involved; the treatment of aspirin poisoning is described on p. 24.2.

Precautions

As for Opioid Analgesics in general, p. 110.3.

Abuse. There have been reports[1] of the abuse of dextropropoxyphene, and some[2] considered that the ready availability of dextropropoxyphene made it liable to abuse although it was a relatively weak opioid analgesic. However, others[3] thought there was no evidence that dextropropoxyphene was frequently associated with abuse, or concluded that, although there was abuse potential, it was of relatively low importance in terms of the community as a whole.[4]

A severe withdrawal syndrome has been reported[5] in an elderly patient who covertly consumed a daily dose of dextropropoxyphene of 1 to 3 g for at least 12 months. The patient was treated by a gradually decreasing dosage schedule of dextropropoxyphene over 9 weeks.

1. Tennant FS. Complications of propoxyphene abuse. *Arch Intern Med* 1973; 132: 191–4.
2. Lader M. Abuse of weak opioid analgesics. *Hum Toxicol* 1984; 3 (suppl): 229S–36S.
3. Finkle BS. Self-poisoning with dextropropoxyphene and dextropropoxyphene compounds: the USA experience. *Hum Toxicol* 1984; 3 (suppl): 115S–34S.
4. Turner P. Final remarks. *Hum Toxicol* 1984; 3 (suppl): 237S–8S.
5. Hedenmalm K. A case of severe withdrawal syndrome due to dextropropoxyphene. *Ann Intern Med* 1995; 123: 473.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving dextropropoxyphene, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/06/08)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dextropropoxyphene as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/10/11)

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

Plasma concentrations of dextropropoxyphene are increased by ritonavir, with a resultant risk of toxicity; they should not be given together.

CNS depressants, including alcohol, may contribute to the hazards of dextropropoxyphene, see also Overdosage, p. 44.2. The convulsant action of high doses of dextropropoxyphene may be enhanced by CNS stimulants.

Dextropropoxyphene interacts with several other drugs through inhibition of liver metabolism. Drugs reported to be affected include antidepressants (see p. 408.2), benzodiazepines (see p. 1068.1), beta blockers (see p. 1322.2), carbamazepine (see p. 516.2), phenobarbital (see p. 537.2), phenytoin (see p. 542.2), and warfarin (see p. 1530.2).

Antimuscarinics. A suggested interaction between *orphenadrine* and dextropropoxyphene has been questioned (see p. 911.1).

Pharmacokinetics

Dextropropoxyphene is readily absorbed from the gastrointestinal tract, the napsilate tending to be more slowly absorbed than the hydrochloride, but both are subject to considerable first-pass metabolism. Peak plasma concentrations occur about 2 to 2.5 hours after ingestion. It is rapidly distributed and concentrated in the liver, lungs, and brain. About 80% of dextropropoxyphene and its metabolites are reported to be bound to plasma proteins. Dextropropoxyphene crosses the placenta. It has been detected in breast milk.

Dextropropoxyphene is *N*-demethylated to nordextropropoxyphene (norpropoxyphene) in the liver. It is excreted in the urine mainly as metabolites. It is now recognised that dextropropoxyphene and nordextropropoxyphene have prolonged elimination half-lives; values of 6 to 12 hours and 30 to 36 hours, respectively, have been reported. Accumulation of dextropropoxyphene and its metabolites may occur with repeated doses and nordextropropoxyphene may contribute to the toxicity seen with overdosage.

Reviews.

1. Pearson RM. Pharmacokinetics of propoxyphene. *Hum Toxicol* 1984; 3 (suppl): 37S–40S.

The elderly. The elimination half-lives of dextropropoxyphene and its metabolite nordextropropoxyphene were prolonged in healthy elderly subjects when compared with young controls.[1] After multiple dosing median half-lives of dextropropoxyphene and nordextropropoxyphene were 36.8 and 41.8 hours, respectively in the elderly compared with 22.0 and 22.1 hours in the young subjects. In this study[1] there was a strong correlation between half-life of nordextropropoxyphene and estimated creatinine clearance.

1. Flanagan RJ, *et al.* Pharmacokinetics of dextropropoxyphene and nordextropropoxyphene in young and elderly volunteers after single and multiple dextropropoxyphene dosage. *Br J Clin Pharmacol* 1989; 28: 463–9.

Hepatic impairment. Plasma concentrations of dextropropoxyphene were higher in patients with cirrhosis given the drug than in healthy subjects whereas concentrations of nordextropropoxyphene were lower.[1]

1. Giacomini KM, *et al.* Propoxyphene and norpropoxyphene plasma concentrations after oral propoxyphene in cirrhotic patients with and without surgically constructed portacaval shunt. *Clin Pharmacol Ther* 1980; 28: 417–24.

Renal impairment. Higher and more persistent plasma concentrations of dextropropoxyphene and nordextropropoxyphene in anephric patients when compared with healthy subjects[1] were attributed to decreased first-pass metabolism of dextropropoxyphene and decreased renal excretion of nordextropropoxyphene in the anephric patients.

1. Gibson TP, *et al.* Propoxyphene and norpropoxyphene plasma concentrations in the anephric patient. *Clin Pharmacol Ther* 1980; 27: 665–70.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Doloxene; ***Belg.***: Depronal†; ***Canad.***: 642†; Darvon-N†; ***Denm.***: Abalgin; Doloxene†; ***Fin.***: Abalgin†; ***Gr.***: Romidon; Zideron; ***Hong Kong***: Dolpoxene†; Dopoxy†; ***India***: Parvodex; ***Mex.***: Darvon Simple†; Saludex; ***Neth.***: Depronal†; ***S.Afr.***: Doloxene; ***Singapore***: Dolpoxene; ***Spain***: Deprancol†; ***Swed.***: Dexofen†; Doloxene†; ***Thai.***: Pardex; ***USA***: Darvon-N†; Darvon†.

Multi-ingredient Preparations. ***Arg.***: Artifene; Calmopirin; Dexprofeno†; Dextro + Dipirona†; Dextrodip†; Dorixina Forte; Dorixina Forte; Gobbicalm; Gobbigesic†; Klosidol B1 B6 B12; Klosidol; Profium Plus; Supragesic D; Supragesic; Vicefeno; ***Austral.***: Capadex; Di-Gesic; Paradex; ***Austria***: APA†; ***Belg.***: Algophene†; ***Braz.***: Doloxene-A; ***China***: Da Ning (达宁); Tong Li Tuo (阿立妥); ***Fr.***: Dextroref†; Di Dolko†; Di-Antalvic†; Dialgirex†; Dioalgo†; Propofan†; ***Hong Kong***: Cosalgesic†; Dolocin; Dolpocetmol; Medonol; Procetalette†; Procetamol†; Propoxymol†; Uni-Proxamol†; ***Hung.***: Novopyrin†; ***India***: Butaproxyvon; Centrivon; Colidex; Corbutyl; Cyclo-P; Darvocet; Dexovon; Hyvon-Spas; Ibruvon Forte; Ibu-Proxyvon; Lobain; Lupivon-D; Lupivon; Neurovon; Nimodex; Novodex; Orthodex Plus; Orthodex; Oxymark; Parvon Forte; Parvon Spas; Parvon-N; Parvon; Proxytab; Proxyvon; Spasmo-Proxyvon; Spasmocip Plus; Spasmocip; Sudhinol; Walagesic; Wygesic; ***Israel***: Algolysin†; Proxol; Rogaan†; ***Mex.***: Neo-Percodan; Qual; ***Norw.***: Aporex†; ***NZ***: Capadex†; Paradex†; ***Port.***: Algifene; ***S.Afr.***: Distalgesic; Doloxene Co; Doxyfene; Lentogesic; Synap; ***Singapore***: Dolpocetmol; ***Thai.***: Davol; ***USA***: Balacet†; Darvocet-N†; Darvocet†; PC-Cap†; Propacet†; Trycet†.

Pharmacopoeial Preparations

BP 2014: Co-proxamol Tablets; Dextropropoxyphene Capsules; USP 36: Propoxyphene Hydrochloride and Acetaminophen Tablets; Propoxyphene Hydrochloride Capsules; Propoxyphene Hydrochloride, Aspirin, and Caffeine Capsules; Propoxyphene Napsylate and Acetaminophen Tablets; Propoxyphene Napsylate and Aspirin Tablets; Propoxyphene Napsylate Oral Suspension; Propoxyphene Napsylate Tablets.

Dezocine *(USAN, rINN)*

Dezocina; Dézocine; Dezocinum; Wy-16225; Дезоцин.

(-)-13β-Amino-5,6,7,8,9,10,11α,12-octahydro-5α-methyl-5,11-methanobenzocyclodecen-3-ol.

$C_{16}H_{23}NO$=245.4

CAS — 53648-55-8.
ATC — N02AX03.
ATC Vet — QN02AX03.
UNII — VHX8K55V4X.

Profile

Dezocine is an opioid analgesic structurally related to pentazocine (p. 120.3), with opioid agonist and antagonist activity. It is used for the relief of moderate to severe pain.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Jialuoning (加罗宁).

Diacerein *(rINN)*

Diacereína; Diacéréine; Diacereinum; Diacerhein; Diacetylrhein; 2,4-Dichlorobenzylique, Alcool; Rhein Diacetate; SF-277; Диацереин.

9,10-Dihydro-4,5-dihydroxy-9,10-dioxo-2-anthroic acid diacetate.

$C_{19}H_{12}O_8$=368.3

CAS — 13739-02-1.
ATC — M01AX21.
ATC Vet — QM01AX21.
UNII — 4HU6J11EL5.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Diacerein). A yellow, crystalline powder. Practically insoluble in water and in anhydrous alcohol; soluble in dimethylacetamide; slightly soluble in tetrahydrofuran. Store in airtight containers. Protect from light.

Profile

Diacerein is an anthraquinone derivative that is used in osteoarthritis (p. 12.3) in oral doses of 50 mg twice daily. Doses should be halved in patients with creatinine clearance less than 30 mL/minute. Diarrhoea is a common adverse effect with diacerein. Its active metabolite, rhein, a constituent of rhubarb (p. 1887.2), is reported to act as an interleukin-1 inhibitor.

Administration in renal impairment. See above and Pharmacokinetics, below.

Musculoskeletal and joint disorders. Diacerein is thought to act via inhibition of interleukin-1β,[1] which plays a role in inflammatory processes. Systematic reviews[2–4] on the use of diacerein in the treatment of osteoarthritis have indicated that diacerein produces a small, but consistent, improvement in pain. Further research is necessary to confirm its short- and long-term efficacy and safety but there is some evidence of residual benefit on stopping treatment,[3] which has been postulated to represent an improvement in the disease process. The increased risk of diarrhoea was a noted effect with diacerein.[4]

1. Van den Berg WB. Les mécanismes d'action de la diacerhéine, premier inhibiteur de l'interleukine 1 dans l'arthrose. *Presse Med* 2004; 33: 10–12.
2. Fidelix TSA, *et al.* Diacerein for osteoarthritis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 06/10/06).
3. Rintelen B, *et al.* A meta-analysis of controlled clinical studies with diacerein in the treatment of osteoarthritis. *Arch Intern Med* 2006; 166: 1899–1906.
4. Bartels EM, *et al.* Symptomatic efficacy and safety of diacerein in the treatment of osteoarthritis: a meta-analysis of randomized placebo-controlled trials. *Osteoarthritis Cartilage* 2010; 18: 289–96.

Pharmacokinetics. References.

1. Debord P, *et al.* Influence of renal function on the pharmacokinetics of diacerein after a single oral dose. *Eur J Drug Metab Pharmacokinet* 1994; 19: 13–19.
2. Nicolas P, *et al.* Clinical pharmacokinetics of diacerein. *Clin Pharmacokinet* 1998; 35: 347–59.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Artrodar; Cominar; Nulartrin; ***Austria***: Artrolyt; Verboril; ***Braz.***: Artrodar; ***Chile***: Artrizona; ***China***: Artrodar (安必丁); ***Cz.***: Artrodar; ***Fr.***: Art; Zondar; ***Gr.***: Arthrofar; Arthrorein; Deserein; Diacer; Diaceril; Idealite; Inflabion; Myobloc; Ostirein; Pentacrin; Reumanisal; Verbodon; Verboril; ***Hong Kong***: Artrodar; ***India***: Acer; Alnamax; Altocerin; Ance; Arthocerin; Arthromuv; Artifit; Artrodar; Biojoint; Cartidin; Cartiel D; Cartifact; Cartiz; Cartrodar; Cedia; Cerdia; Cerin; Daicart; Dencerin; Diacer; Diacure; Dialeed; Diasim; Diasol; Dici; Dicimax; Diez; Diosteo; Diskare; Durajoint; Dycerin; Eljoint; Ferine; Flexibel-D; Glocerin; Gudcerin; Hilin; Icerin; Jaizzy; Joincerin; Lecerein; Lelax; Mycer; Nucerin; Orcerin; Ordi; Orthobact; Ortocer; Osticer; Ostogard; Ostokind; Ostorin; ***Indon.***: Artrodar; Bondi; ***Israel***: Art; Diatrim; ***Ital.***: Fisiodar; ***Malaysia***: Artrodar; ***Port.***: Artrolyt; Cartivix; ***Rus.***: Arthrocare (Артрокер); Artodarin (Артродарин); ***Spain***: Artrizan; Galaxdar;

Glizolan; *Thai.*: Artrodar; *Turk.*: Artrodar; Rexena; *Venez.*: Artrodar.

Multi-ingredient Preparations. *India*: Alnamax-G; Altocerin-GM; Artheal; Arthocerin-A; Arthocerin-G; Arthodia-G; Arthrovit Plus; Cartimost GM; Cartiz-GM; Cedia-AC; Compensate; Cosa-G; Curejoint-AC; Dicimax-G; Difirin Plus; Dims-GM; DN Plus; Durajoint-GM; Dycerin-A; Dycerin-GM; Flexibel-AD; Flextra-D; Icerin-GM; Jaizzy-GM; Lecerein-GM; Lecerein-P; Lefax-G; Mycer G; OA Plus; Ordi-G; Orthocerin-G; Ostakair-D; Ostawin; Osteojoin-D; Ostifin-G; Ostodia-G; Paclo-GMD; *Mex.*: Dolocartigen.

Diamorphine Hydrochloride

(BANM) ⊗

Diacetilmorfina, hidrocloruro de; Diacetylmorphine Hydrochloride; Heroin Hydrochloride; Hidrocloruro de diamorfina; Hidrocloruro de heroína; Героина Гидрохлорид; Диаморфина Гидрохлорид.

4,5-Epoxy-17-methylmorphinan-3,6-diyl diacetate hydrochloride monohydrate.

$C_{21}H_{23}NO_5HCl,H_2O$=423.9

CAS — 561-27-3 (diamorphine); 1502-95-0 (diamorphine hydrochloride).

ATC — N07BC06.

ATC Vet — QN07BC06.

UNII — 8H672SHT8E.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of diamorphine:

57 Chevy; A Sidani; AIP; Al Capone; Amelia; Antifreeze; Aries; Aunt Hazel; Auntie Hazel; Aunty Hazel; Bacalhau; Bad bundle; Bad seed; Ball; Ballot; Bart Simpson; Batman; Beast; Big Bad Boy; Big bag; Big doodig; Big H; Big Harry; Bin laden; Bindle; Birdie powder; Black; Black Dragon; Black eagle; Black Girl; Black pearl; Black stuff; Black tar; Black tootsie roll; Blanche; Blanco; Blast; Bleue; Block busters; Blow; Blows; Blue bag; Blue hero; Blue star; Bobby Brown; Bomb; Bomba; Bombe; Bombido; Bombita; Bombitas; Bombs away; Bone; Bonita; Boy; Bozo; Brad; Brain damage; Brea; Brick gum; Broja; Brother; Brown; Brown crystal; Brown rhine; Brown sugar; Brown tape; Bugger; Bull dog; Bundle; Burra; Butu; Caballo; Caca; Calbo; Capital H; Caps; Captain Jack; Carga; Carne; Cavalo; Chang; Chapopote; Charley; Chatarra; Cheese; Cheevah; Cheva; Cheval; Chi; Chiba; Chick; Chicken; Chicle; Chieva; China cat; China white; Chinche; Chinese H; Chinese red; Chinese Rocks; Chinoise; Chip; Chiva; Chocofan; Chocofan; Chueva; Chunks; Climax; Cocofan; Coffee; Cotics; Cotton Candy; Courage pills; Crank; Crap; Crop; Crown crap; Cura; Dead on arrival; Dead president; Deuce; Diesel; Diggidy; Dirt; DOA; Dog food; Dogee; Dogie; Doogie; Doojee; Dookey Rocks; Dooley; Doosey; Dope; Downtown; Dr. Feelgood; Dragon; Dreck; DT; Dugee; Dugie; Duji; Dujra; Dujre; Dust; Dyno; Dyno-pure; Eggs; Eight; Eighth; Elephant; Estuffa; Fachiva; Ferry dust; Fix; Flea powder; Foil; Foo foo stuff; Foolish powder; Furra; Galloping horse; Gallup; Gamot; Garbage; Gato; Gear; George; George smack; Ghost; Girl; Glacines; Glass; Goat; Gold; Golden Brown; Golden girl; Golpe; Goma; Good; Good H; Good Horse; Good and plenty; Goods; Goop; Grape Jolly Rancher; Gravy; Grey shields; H; H22; H-bomb; H Caps; Hache; Hair; Hairpiece; Hairy; Hammer; Hard candy; Hard stuff; Harriet Tubman; Harry; Harry Jones; Hayron; Hazel; Heaven; Heaven dust; Heavy stuff; Helen; Hell dust; Henry; Hera; Hero; Hero of the underworld; Heroa; Heroina; Heron; Herone; Hessle; Him; Holy terror; Hombre; Homebake; Homicide; Hong-yen; Hood; Hop; Horning; Horse; Horsebite; Hot dope; Hot heroin; HRN; Isda; Jack; Jee gee; Jerry Springer; Jesus; Jive; Jive doo jee; Joharito; Jojee; Jones; Joy; Joy dust; Joy flakes; Joy powder; Judas; Junco; Junk; Kabayo; Kaka Water; Karachi; Kermit the Frog; La Buena; La Chiva; Lady H; Layne; LBJ; Lemonade; Life saver; Little bomb; Man; Manteca; Matsakow; Mayo; Mexican Black Tar; Mexican brown; Mexican Dirt; Mexican horse; Mexican mud; Mister Brownstone; Mojo; Money talks; Monkey; Montego; Morse Code Features; Morotgara; Mortal combat; Mother pearl; Mr. Brownstone; Mud; Murotugora; Muzzle; Nanoo; Nice and easy; Nickel bag; Nickel deck; Nixon; Noddy Brown; Noise; Nose; Nose drops; Number 3; Number 4; Number 8; Nurse; Oddy Noddy; Of course my horse; Ogoy; Oil; Old garbage; Old navy; Old Steve; One way; Orange line; Outfit; Pack; Pakistanaise; Pako; Pangonadalot; Parachute; P-dope; Peg; Pepper; Perfect high; P-funk; Pluto; Po; Poeira; Poison; Polvo; Poppy; Poudre; Powder; Predator; Primo; Produto; Pulborn; Pure; Quill; Race horse Charlie; Racehorse Charlie; Ragweed; Rain; Rambo; Rane; Raw; Raw fusion; Raw hide; Raw Opportunities; Ready rock; Red chicken; Red devil; Red eagle; Red rock; Red rum; Reindeer dust; Rhine; Ring of Turd; Rob Flaherty; Rock; Rocks; Rush hour; Sack; Salt; Scag; Scat; Scate; Schmack; Schmeck; Schmeek; Scott; Scramble; Second to none; Shit; Shmeck; Shmeek; Shmek; Shoot; Silk; Skag; Skid; Skunk; Slack-dad-eat-your-heart-out; Slam; Sleeper; Sleepers; Slime; Slow; Sludge; Smack; Snotty; Snow; Spider; Spider blue; Stuff; Stunna; Sugar; Suicide; Sweet dreams; Sweet Jesus; Sweet stuff; Synthe; Tang; Tar; Taste; Tecata; Tecate; Thailandaise; Thanie; The beast; The fake throwdown; The Jack Bauer; The Loud-House Permadillo; The Nax; The witch; Thing; Thunder; Tiger; Tigre; Tigre Blanco; Tigre del Norte; Tits; TNT; T.N.T.; Tongs; Tootsie roll; Top drool; Train; Trash; Twin towers; Twists; Vidrio; Whack; Whicked; White; White Bitch; White boy; White dragon; White dynamite; White girl; White horse; White junk; White lady; White nurse; White Pony; White stuff; White Tiger; Wicked; Wings; Witch; Witch hazel; WTC; Zoquete.

Pharmacopoeias. In *Br.* and *Swiss*. *Swiss* also includes the anhydrous form.

BP 2014: (Diamorphine Hydrochloride). A white or almost white crystalline powder, odourless when freshly prepared but develops an odour characteristic of acetic acid on storage. Freely soluble in water and in chloroform; soluble in alcohol; practically insoluble in ether. Protect from light.

Incompatibility. Diamorphine hydrochloride is incompatible with mineral acids and alkalis and with chlorocresol.[1]

The *BNF* notes that cyclizine may precipitate from mixtures with diamorphine hydrochloride at concentrations of cyclizine greater than 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 liable to precipitate after 24 hours.

It also considers that mixtures of diamorphine and haloperidol are liable to precipitate after 24 hours if the haloperidol concentration is above 2 mg/mL. Under some conditions mixtures of metoclopramide and diamorphine may become discoloured and should be discarded.

1. McEwan JS, Macmorran GH. The compatibility of some bactericides. *Pharm J* 1947; 158: 260–2.

Stability. Diamorphine is relatively unstable in aqueous solution and is hydrolysed to 6-*O*-monoacetylmorphine and then morphine to a significant extent at room temperature; 3-*O*-monoacetylmorphine is only occasionally detected. The rate of decomposition is at a minimum at about pH 4.[1,2]

In a study of the stability of aqueous solutions of diamorphine in chloroform water it was concluded that such solutions should be used within 3 weeks of preparation when stored at room temperature.[3] Another study[4] noted that the degradation products of diamorphine were not devoid of analgesic activity. Using a more sensitive analytical method it was reported that although the pH range of maximum stability of diamorphine in aqueous solution was 3.8 to 4.4, the addition of buffers reduced stability.[5] Simple unbuffered chloroform water gave maximum stability, the shelf-life of such a solution being 4 weeks at room temperature.

The BP 2014 recommends that solutions for injection be prepared immediately before use by dissolving Diamorphine Hydrochloride for Injection in Water for Injections. This may pose a problem with solutions for subcutaneous infusion when concentrated solutions may remain in infusion pump reservoirs for some time.[6] Investigation of 9 concentrations of diamorphine stored at 4 different temperatures for 8 weeks[7] revealed instability under conditions of concentration, time, and temperature prevalent during subcutaneous infusion. Degradation of diamorphine occurred at all concentrations (0.98 to 250 mg/mL) at temperatures of 4 degrees and above; the effect of temperature was significant at 21 degrees and 37 degrees. The percentage fall in diamorphine concentration was directly related to initial concentration and was accompanied by a corresponding increase in 6-*O*-monoacetylmorphine and, to a lesser extent, morphine; other possible breakdown products such as 3-*O*-monoacetylmorphine were not present in detectable quantities. Diamorphine degradation was associated with a fall in pH and the development of a strong acetic acid-like odour. Precipitation and a white turbidity was seen in solutions of 15.6 mg/mL and above after incubation for 2 weeks at 21 degrees and 37 degrees. It has been noted that solutions for infusion are generally freshly prepared and used within 24 hours, but that signs of precipitation should be watched for, especially when using longer-term infusions and high concentrations of diamorphine.[7]

In another stability study[8] diamorphine hydrochloride in concentrations of both 1 and 20 mg/mL in sodium chloride 0.9% was stable for a minimum of 15 days at room temperature (23 degrees to 25 degrees) and 4 degrees when stored in a PVC container. In one type of disposable infusion device (Infusor) similar solutions were stable for 15 days even at 31 degrees. In another infusion device (Intermate 200) diamorphine was stable for a minimum of 15 days at both concentrations and all temperatures except for the 1 mg/mL solution kept at 31 degrees when stability was only maintained for a minimum of 2 days. When stored in glass syringes both strengths of diamorphine hydrochloride were stable for 15 days at 4 degrees and at room temperature the 1 mg/mL solution was stable for a minimum of 7 days and the 20 mg/mL solution was stable for a minimum of 12 days. There were no substantial changes in physical appearance or pH.

1. Davey EA, Murray JB. Hydrolysis of diamorphine in aqueous solution. *Pharm J* 1969; 203: 737.
2. Davey EA, Murray JB. Determination of diamorphine in the presence of its degradation products using gas liquid chromatography. *Pharm J* 197 ; 207: 167.
3. Cooper H, *et al.* Stability of diamorphine in chloroform water mixtur. *Pharm J* 1981; 226: 682–3.
4. Twycross RG. Stability of diamorphine in chloroform water. *Pharm J* 1981; 227: 218.
5. Beaumont IM. Stability of diamorphine in chloroform water. *Pharm J* 1981; 227: 41.
6. Jones VA, *et al.* Diamorphine stability in aqueous solution for subcutaneous infusion. *Br J Clin Pharmacol* 1987; 23: 651P.
7. Omar OA, *et al.* Diamorphine stability in aqueous solution for subcutaneous infusion. *J Pharm Pharmacol* 1989; 41: 275–7.
8. Kleinberg ML, *et al.* Stability of heroin hydrochloride in infusion devices and containers for intravenous administration. *Am J Hosp Pharm* 199 ; 47: 377–81.

Uses and Administration

Diamorphine hydrochloride is an acetylated morphine derivative and is a more potent opioid analgesic (p. 108.1) than morphine (p. 93.2). Diamorphine is used for the relief of severe pain especially in palliative care. It is also used similarly to morphine for the relief of dyspnoea due to pulmonary oedema resulting from left ventricular failure. Diamorphine has a powerful cough suppressant effect and has been given as Diamorphine Linctus (BPC 1973) to control cough associated with terminal lung cancer although morphine is now preferred.

In the treatment of **acute pain** usual doses of diamorphine hydrochloride by subcutaneous or intramuscular injection are 5 to 10 mg every 4 hours. Doses equivalent to one-quarter to one-half of the corresponding intramuscular dose may be given by slow intravenous injection.

For the pain of myocardial infarction doses of 5 mg are given by slow intravenous injection at a rate of 1 to 2 mg/minute with a further dose of 2.5 to 5 mg if required; doses may be reduced by one-half for elderly or frail patients. Doses of 2.5 to 5 mg may be given intravenously at the same rate for acute **pulmonary oedema**.

For **chronic pain** 5 to 10 mg may be given by subcutaneous or intramuscular injection every 4 hours; the dose may be increased according to needs. Similar doses may be given orally, although it is converted to morphine by first-pass metabolism (see Pharmacokinetics, p. 48.2). Diamorphine hydrochloride may also be given by continuous subcutaneous or intravenous infusion or intraspinally.

For details of doses in children, see below.

Action. Because of its abuse potential, supply of diamorphine is carefully controlled and in many countries it is not available for clinical use; morphine can provide equivalent analgesia by dose adjustment. There has been much debate regarding the relative merits of analgesia with diamorphine or morphine. Many now regard oral morphine to be the opioid analgesic of choice although diamorphine hydrochloride may be preferred for injection because it is more soluble in water thus allowing the use of smaller dose volumes. Diamorphine hydrochloride may also be preferred to morphine salts for intraspinal use because it is more lipid-soluble.

As a guide to relative potency:

- diamorphine hydrochloride 5 mg given intramuscularly is equivalent to about 10 mg given orally, which in turn is equivalent to about 15 mg of oral morphine sulfate
- when either drug is given by subcutaneous infusion diamorphine hydrochloride 10 mg every 24 hours is equivalent to about 15 mg every 24 hours of morphine sulfate

Administration in children. In the treatment of acute or chronic pain in children, the *BNFC* suggests the following doses of diamorphine hydrochloride according to age or body-weight, and adjusted according to response:

by continuous intravenous infusion:

- neonates with spontaneous respiration may be given 2.5 to 7 micrograms/kg per hour
- ventilated neonates may be given 50 micrograms/kg initially by intravenous injection over 30 minutes followed by 15 micrograms/kg per hour by continuous intravenous infusion
- 1 month to 12 years: 12.5 to 25 micrograms/kg per hour

by intravenous injection:

- 1 to 3 months: 20 micrograms/kg every 6 hours
- 3 to 6 months: 25 to 50 micrograms/kg every 6 hour
- 6 to 12 months: 75 micrograms/kg every 4 hours

- 1 to 12 years: 75 to 100 micrograms/kg (maximum of 5 mg) every 4 hours

orally:

- 1 month to 12 years: 100 to 200 micrograms/kg (maximum of 10 mg) every 4 hours

In a study[1] of the effects of diamorphine in 34 premature infants (gestational age 26 to 40 weeks), a loading dose of 50 micrograms/kg given as an *intravenous* infusion over 30 minutes followed by a continuous infusion at a rate of 15 micrograms/kg per hour was considered to be safe and resulted in plasma concentrations of morphine comparable with those that usually produce adequate analgesia in children and adults; the duration of the infusion ranged from 14 to 149 hours. Small but significant reductions in heart rate and mean blood pressure were noted but these were not associated with any clinical deterioration. The fall in respiration rate reflected the desired intention to encourage synchronisation of the infants' breathing with the ventilator. The authors concluded that intravenous diamorphine could be given safely to neonates and would provide adequate analgesia. A later study[2] indicated that the use of a 200 micrograms/kg loading dose conferred no benefit over a 50 micrograms/kg dose and might produce undesirable physiological effects. In a comparative study[3] with morphine (200 micrograms/kg loading dose over 2 hours, followed by maintenance infusion of 25 micrograms/kg per hour) in ventilated preterm neonates requiring sedation, diamorphine (120 micrograms/kg over 2 hours and then 15 micrograms/kg per hour) was as effective as morphine in producing sedation and also had a faster onset of action. The small but significant drop in blood pressure noted during morphine infusions was not seen with diamorphine infusions.

The *subcutaneous* route appeared to be as effective and safe as the intravenous route for infusions in children for postoperative pain relief after elective abdominal surgery.[4] The dose of diamorphine used in both groups of children was 1 mg/kg given at a rate of 20 micrograms/kg per hour.

Intranasal diamorphine has been investigated in adults and children, and appears to be effective and well tolerated; because it does not require a needle it may offer particular advantages in children.[5] Guidelines[6] for analgesia in children in Accident and Emergency departments in the UK recommend the use of intranasal diamorphine as an alternative to, or before treatment with, intravenous morphine for severe pain such as that associated with large burns, long bone fracture or dislocation, appendicitis, or sickle-cell crisis. In the UK, an intranasal spray containing the equivalent of 720 or 1600 micrograms of diamorphine per actuation is licensed for the treatment of acute severe nociceptive pain in children and adolescents aged 2 to 15 years in a hospital setting. The preparation and dose given are dependent on the child's body-weight; children weighing under 30 kg should receive the *nasal spray delivering 720 micrograms per actuation* in the following doses:

- 12 to < 18 kg: 2 sprays (1.44 mg)
- 18 to < 24 kg: 3 sprays (2.16 mg)
- 24 to < 30 kg: 4 sprays (2.88 mg)

Heavier children should receive the *nasal spray delivering 1600 micrograms per actuation* as follows:

- 30 to < 40 kg: 2 sprays (3.2 mg)
- 40 to 50 kg: 3 sprays (4.8 mg)

1. Elias-Jones AC, *et al.* Diamorphine infusion in the preterm neonate. *Arch Dis Child* 1991; **66**: 1155–7.
2. Barker DP, *et al.* Randomised, double blind trial of two loading dose regimens of diamorphine in ventilated newborn infants. *Arch Dis Child* 1995; **73**: F22–F26.
3. Wood CM, *et al.* Randomised double blind trial of morphine versus diamorphine for sedation of preterm neonates. *Arch Dis Child Fetal Neonatal Ed* 1998; **79**: F34–F39.
4. Semple D, *et al.* Comparison of iv and sc diamorphine infusions for the treatment of acute pain in children. *Br J Anaesth* 1996; **76**: 310–12.
5. Kendall JM, Latter VS. Intranasal diamorphine as an alternative to intramuscular morphine: pharmacokinetic and pharmacodynamic aspects. *Clin Pharmacokinet* 2003; **42**: 501–13.
6. The College of Emergency Medicine. Best practice guideline: management of pain in children (July 2013). Available at: http://secure.collemergencymed.ac.uk/asp/document.asp?ID=4682 (accessed 11/12/13)

Opioid dependence. The treatment of opioid dependence is discussed on p. 109.2. Many opiate misusers have expressed a preference for withdrawal using diamorphine rather than methadone. In a comparative study stabilisation was achieved using either diamorphine or methadone 1 mg/mL oral solutions;[1] patients could not identify which they had been given. Whenever signs of physical withdrawal were seen 10 mL of either solution was given and the total amount over the first 24 hours taken as the patient's daily requirement. The mean dose of diamorphine required for stabilisation was 55 mg compared with 36 mg for methadone. Some centres have given diamorphine in the form of reefers. Diamorphine has also been prescribed with methadone in the management of addicts.[2] A systematic review[3] that included this study failed to produce conclusive results about the efficacy of diamorphine (alone or with methadone) in maintenance treatment; however, since the studies were not directly comparable, continued evaluation in clinical studies is required. Oral tablets[4] and intravenous injection[5,6] of diamorphine have also been tried in severely dependent, treatment-resistant patients.

Breast feeding has been used to treat diamorphine dependence in the offspring of dependent mothers but this is no longer considered to be the best method and some authorities recommend that breast feeding should be stopped.

1. Ghodse AH, *et al.* Comparison of oral preparations of heroin and methadone to stabilise opiate misusers as inpatients. *BMJ* 1990; **300**: 719–20.
2. van den Brink W, *et al.* Medical prescription of heroin to treatment resistant heroin addicts: two randomised controlled trials. Abridged version: *BMJ* 2003; **327**: 310–12. Correction. *ibid.*; 724. Full version: http://www.bmj.com/cgi/reprint/327/7410/310 (accessed 26/06/08)
3. Ferri M, *et al.* Heroin maintenance for chronic heroin dependents. Available in The Cochrane Database of Systematic Reviews: Issue 2. Chichester: John Wiley; 2005 (accessed 26/06/08).
4. Frick U, *et al.* A prospective cohort study on orally administered heroin substitution for severely addicted opioid users. *Addiction* 2006; **101**: 1631–9.
5. March JC, *et al.* Controlled trial of prescribed heroin in the treatment of opioid addiction. *J Subst Abuse Treat* 2006; **31**: 203–11.
6. Oviedo-Joekes E, *et al.* Diacetylmorphine versus methadone for the treatment of opioid addiction. *N Engl J Med* 2009; **361**: 777–86.

Pain. *ACUTE PAIN.* Rapid pain relief may be obtained with the intravenous injection of diamorphine. Other routes include the intraspinal route for which diamorphine is well suited because of its lipid solubility and pharmacokinetics. Epidural doses of diamorphine have ranged from 0.5 to 10 mg.[1] Analgesia was significantly more prolonged and more intense after epidural rather than intramuscular injection of diamorphine 5 mg in women who had had caesarean section;[2] itching was reported by 50% of patients undergoing epidural analgesia. Epidural diamorphine alone[3] or with bupivacaine[4] has been used for analgesia during labour; addition of adrenaline appeared to improve the quality and duration of analgesia with diamorphine.[3] In another study addition of diamorphine to bupivacaine produced a high incidence of pruritus and drowsiness.[3] A study[6] of patient-controlled analgesia for postoperative pain found that although epidural diamorphine, used alone or with bupivacaine, reduced the analgesic dose requirement, there was little clinical advantage over the subcutaneous route.

Continuous epidural infusion of diamorphine 500 micrograms/hour in 0.125% bupivacaine provided postoperative analgesia superior to that with either drug alone in patients undergoing major abdominal gynaecological surgery.[7] A similar infusion produced analgesia superior to that with either epidural bolus injection or patient-controlled intravenous diamorphine in patients undergoing total abdominal hysterectomy.[8] However, more patients receiving the continuous epidural infusion were hypoxaemic than in the other 2 groups.

Diamorphine has also been given intrathecally for postoperative analgesia and should be effective at lower doses than with the epidural route because of greater CSF concentrations. Diamorphine 250 or 500 micrograms given intrathecally with bupivacaine spinal anaesthesia both provided greater postoperative analgesia than bupivacaine alone,[9] but the incidence of adverse effects, especially nausea, vomiting, and urinary retention, was still high with either dose and routine use of this technique was not recommended. Intrathecal diamorphine with bupivacaine has also been used for analgesia during labour[10,11] and caesarean section.[12-16] In a study[12] in patients undergoing caesarean section, intrathecal diamorphine 250 micrograms showed comparable postoperative analgesia with a 5-mg epidural dose and was associated with less postoperative nausea and vomiting. Other studies[13,15] found that intrathecal diamorphine reduced supplemental analgesic requirements during and after caesarean section when compared with intrathecal fentanyl. Intrathecal diamorphine 400 micrograms was considered by some[14] to be the lowest dose required to reduce intraoperative analgesic supplementation to below 5%; however, lower doses of 300 micrograms have been used in practice.[16]

Diamorphine has been extensively used by cardiologists in the UK for the management of pain in acute left ventricular failure, unstable angina, and myocardial infarction. It has been theorised that diamorphine may offer benefits over morphine because its stimulatory effects at opioid δ receptors on the myocardium may reduce the extent of myocardial damage.[17] Evidence to support this theory is, however, lacking.

1. Morgan M. The rational use of intrathecal and extradural opioids. *Br J Anaesth* 1989; **63**: 165–88.
2. Macrae DJ, *et al.* Double-blind comparison of the efficacy of extradural diamorphine, extradural phenoperidine and im diamorphine following caesarean section. *Br J Anaesth* 1987; **59**: 354–9.
3. Keenan GMA, *et al.* Extradural diamorphine with adrenaline in labour: comparison with diamorphine and bupivacaine. *Br J Anaesth* 1991; **66**: 242–6.
4. McGrady EM, *et al.* Epidural diamorphine and bupivacaine in labour. *Anaesthesia* 1989; **44**: 400–3.
5. Bailey CR, *et al.* Diamorphine-bupivacaine mixture compared with plain bupivacaine for analgesia. *Br J Anaesth* 1994; **72**: 58–61.
6. Gopinathan C, *et al.* A comparative study of patient-controlled epidural diamorphine, subcutaneous diamorphine and an epidural diamorphine/bupivacaine combination for postoperative pain. *Eur J Anaesthesiol* 2000; **17**: 189–96.
7. Lee A, *et al.* Postoperative analgesia by continuous extradural infusion of bupivacaine and diamorphine. *Br J Anaesth* 1988; **60**: 845–50.
8. Madej TH, *et al.* Hypoxaemia and pain relief after lower abdominal surgery: comparison of extradural and patient-controlled analgesia. *Br J Anaesth* 1992; **69**: 554–7.
9. Reay BA, *et al.* Low-dose intrathecal diamorphine analgesia following major orthopaedic surgery. *Br J Anaesth* 1989; **62**: 248–52.
10. Kestin IG, *et al.* Analgesia for labour and delivery using incremental diamorphine and bupivacaine via a 32-gauge intrathecal catheter. *Br J Anaesth* 1992; **68**: 244–7.
11. Vaughan DJA, *et al.* Choice of opioid for initiation of combined spinal epidural analgesia in labour—fentanyl or diamorphine. *Br J Anaesth* 2001; **86**: 567–9.
12. Hallworth SP, *et al.* Comparison of intrathecal and epidural diamorphine for elective Caesarean section using a combined spinal-epidural technique. *Br J Anaesth* 1999; **82**: 228–32.
13. Cowan CM, *et al.* Comparison of intrathecal fentanyl and diamorphine in addition to bupivacaine for Caesarean section under spinal anaesthesia. *Br J Anaesth* 2002; **89**: 452–8.
14. Saravanan S, *et al.* Minimum dose of intrathecal diamorphine required to prevent intraoperative supplementation of spinal anaesthesia for Caesarean section. *Br J Anaesth* 2003; **91**: 368–72.
15. Lane S, *et al.* A comparison of intrathecal fentanyl and diamorphine as adjuncts in spinal anaesthesia for Caesarean section. *Anaesthesia* 2005; **60**: 453–7.
16. Wrench IJ, *et al.* Dose response to intrathecal diamorphine for elective caesarean section and compliance with a national audit standard. *Int J Obstet Anesth* 2007; **16**: 17–21.
17. Poullis M. Diamorphine and British cardiology: so we are right! *Heart* 1999; **82**: 645–6.

CHRONIC PAIN. Patients with chronic opioid-sensitive pain are often treated with diamorphine given by continuous subcutaneous infusion using a small battery-operated syringe driver. The following technique has been described.[1] Diamorphine hydrochloride 1 g could be dissolved in 1.6 mL of water to give a solution with a volume of 2.4 mL (415 mg/mL), but the maximum suggested concentration was 250 mg/mL. If the analgesic requirement was unknown the following protocol was recommended:

- Start injections every 4 hours of 2.5 or 5 mg diamorphine, or, if the patient has already been taking opioids, a dose that is equivalent to the last dose
- If this is unsatisfactory increase this dose in 50% increments until the patient reports even a little pain relief
- Calculate the 24-hour requirement by multiplying by six, and start the infusion at this level
- Increase the 24-hour dosage in the pump by 50% increments until the pain is controlled. Note that requirements may vary from less than 20 mg to more than 5 g per 24 hours

When starting an infusion it is important not to allow any breakthrough pain. This may be achieved either by starting the infusion more than 2 hours before the previous oral dose wears off or by giving a loading dose injection of the 4-hourly requirement.

Although generally free from complications, sterile abscess formation was reported in 2 patients with advanced cancer receiving diamorphine by continuous subcutaneous infusions.[2]

The intraspinal[3] and intraventricular[4] routes have also been used successfully in patients with intractable pain. Topical application of diamorphine has also been tried[5,6] for the control of pressure ulcer pain in a small number of palliative care patients.

1. Dover SB. Syringe driver in terminal care. *BMJ* 1987; **294**: 553–5.
2. Hoskin PJ, *et al.* Sterile abscess formation by continuous subcutaneous infusion of diamorphine. *BMJ* 1988; **296**: 1605.
3. Baker L, *et al.* Evolving spinal analgesia practice in palliative care. *Palliat Med* 2004; **18**: 507–15.
4. Reeve WG, Todd JG. Intraventricular diamorphine via an Ommaya shunt for intractable cancer pain. *Br J Anaesth* 1990; **65**: 544–7.
5. Flock P. Pilot study to determine the effectiveness of diamorphine gel to control pressure ulcer pain. *J Pain Symptom Manage* 2003; **25**: 547–54.
6. Abbas SQ. Diamorphine-Intrasite dressings for painful pressure ulcers. *J Pain Symptom Manage* 2004; **28**: 532–4.

Dependence and Withdrawal

As for Opioid Analgesics, p. 109.1.

Diamorphine is subject to abuse (see under Adverse Effects, Treatment, and Precautions, below).

Diamorphine is used for substitution therapy in the management of opioid dependence (see under Uses and Administration, above).

Adverse Effects, Treatment, and Precautions

As for Opioid Analgesics in general, p. 110.1.

Pulmonary oedema after overdosage is a common cause of fatalities among diamorphine addicts. Nausea and hypotension are claimed to be less common than with morphine.

There are many reports of adverse effects associated with the abuse of diamorphine, usually obtained illicitly in an adulterated form.

Abuse. Most of the reports of adverse effects with diamorphine involve its abuse. In addition to the central effects, there are effects caused by the administration methods

and by the adulterants.[1,2] Thus in many instances it is difficult to identify the factor causing the toxicity. Most body systems are involved including the immune system,[3] kidneys,[4,5] liver,[6] respiratory system,[7-11] and the nervous system.[12-17]

Other aspects of the illicit use of diamorphine include fatal overdose[18] and smuggling by swallowing packages of drug[19,20] or other methods of internal bodily concealment.

1. Hendrickse RG, *et al.* Aflatoxins and heroin. *BMJ* 1989; 299: 492–3.
2. CDC. Atypical reactions associated with heroin use: five states, January–April 2005. *MMWR* 2005; 54: 793–6. Correction. *ibid.*; 852.
3. Husby G, *et al.* Smooth muscle antibody in heroin addicts. *Ann Intern Med* 1975; 83: 801–5.
4. Cunningham EE, *et al.* Heroin-associated nephropathy. *JAMA* 1983; 250: 2935–6.
5. do Sameiro Faria M, *et al.* Nephropathy associated with heroin abuse in Caucasian patients. *Nephrol Dial Transplant* 2003; 18: 2308–13.
6. Weller IVD, *et al.* Clinical, biochemical, serological, histological and ultrastructural features of liver disease in drug abusers. *Gut* 1984; 25: 417–23.
7. Anderson K. Bronchospasm and intravenous street heroin. *Lancet* 1986; i: 1208.
8. Cygan J, *et al.* Inhaled heroin-induced status asthmaticus: five cases and a review of the literature. *Chest* 2000; 117: 272–5.
9. Boto de los Bueis A, *et al.* Bronchial hyperreactivity in patients who inhale heroin mixed with cocaine vaporized on aluminium foil. *Chest* 2002; 121: 1223–30.
10. Sporer KA, Dorn E. Heroin-related noncardiogenic pulmonary edema: a case series. *Chest* 2001; 120: 1628–32.
11. Whale CI, *et al.* Inhaled heroin causing a life-threatening asthma exacerbation and marked peripheral eosinophilia. *Br J Hosp Med* 2007; 68: 332–3.
12. Sempere AP, *et al.* Spongiform leucoencephalopathy after inhaling heroin. *Lancet* 1991; 338: 320.
13. Roulet Perez E, *et al.* Toxic leucoencephalopathy after heroin ingestion in a 2½-year-old child. *Lancet* 1992; 340: 729.
14. Zuckerman GB. Neurologic complications following intranasal administration of heroin in an adolescent. *Ann Pharmacother* 1996; 30: 778–81.
15. Kriegstein AR, *et al.* Heroin inhalation and progressive spongiform leukoencephalopathy. *N Engl J Med* 1997; 336: 589–90.
16. Long H, *et al.* A fatal case of spongiform leukoencephalopathy linked to "chasing the dragon". *J Toxicol Clin Toxicol* 2003; 41: 887–91.
17. Dabby R, *et al.* Acute heroin-related neuropathy. *J Peripher Nerv Syst* 2006; 11: 304–9.
18. Kintz P, *et al.* Toxicological data after heroin overdose. *Hum Toxicol* 1989; 8: 487–9.
19. Stewart A, *et al.* Body packing—a case report and review of the literature. *Postgrad Med J* 1990; 66: 659–61.
20. Traub SJ, *et al.* Pediatric "body packing". *Arch Pediatr Adolesc Med* 2003; 157: 174–7.

Administration. Although generally free from complications, sterile abscess formation was reported in 2 patients with advanced cancer receiving diamorphine by continuous *subcutaneous* infusions.[1] Acute dysphoric reactions have been reported after the use of *epidural* diamorphine.[2]

1. Hoskin PJ, *et al.* Sterile abscess formation by continuous subcutaneous infusion of diamorphine. *BMJ* 1988; 296: 1605.
2. Holder KJ, Morgan BM. Dysphoria after extradural diamorphine. *Br J Anaesth* 1994; 72: 728.

Breast feeding. The American Academy of Pediatrics has stated[1] that, when used as a drug of abuse by breast-feeding mothers, diamorphine has caused adverse effects in the infant, notably tremors, restlessness, vomiting, and poor feeding. However, the *BNF* considers that diamorphine when given in therapeutic doses to a breast-feeding mother is unlikely to affect the breast-fed infant.

See also Opioid Dependence under Uses and Administration, p. 47.1.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/06/08)

Hypersensitivity. Anaphylaxis occurred in a patient given *intrathecal* diamorphine and bupivacaine for surgical anaesthesia;[1] the authors noted that the patient received patient-controlled analgesia with morphine shortly after the reaction without problem. Subsequent skin prick tests identified diamorphine as the likely causative agent.

1. Gooch J, Gwinnutt C. Anaphylaxis to intrathecal diamorphine. *Resuscitation* 2006; 70: 470–3.

Phaeochromocytoma. Diamorphine can liberate endogenous histamine which may in turn stimulate release of catecholamines. Its use provoked hypertension and tachycardia in a patient with phaeochromocytoma.[1]

1. Chaturvedi NC, *et al.* Diamorphine-induced attack of paroxysmal hypertension in phaeochromocytoma. *BMJ* 1974; 2: 538.

Pregnancy and the neonate. Some references[1-7] to diamorphine dependence in pregnant women and the effects on the fetus and neonate.

1. Pricker HS, Segal S. Narcotic addiction, pregnancy, and the newborn. *Am J Dis Child* 1978; 132: 360–6.
2. Ostrea EM, Chavez CJ. Perinatal problems (excluding neonatal withdrawal) in maternal drug addiction: a study of 830 cases. *J Pediatr* 1979; 94: 292–5.
3. Lifschitz MH, *et al.* Fetal and postnatal growth of children born to narcotic-dependent women. *J Pediatr* 1983; 102: 686–91.
4. Klenka EM. Babies born in a district general hospital to mothers taking heroin. *BMJ* 1986; 293: 745–6.
5. Gregg JEM, *et al.* Inhaling heroin during pregnancy: effects on the baby. *BMJ* 1988; 296: 754.
6. Little BB, *et al.* Maternal and fetal effects of heroin addiction during pregnancy. *J Reprod Med* 1990; 35: 159–62.
7. Mur Sierra A, *et al.* Asociación entre el consumo de heroína durante la gestación y anomalías estructurales de los cilios respiratorios en el período neonatal. *An Esp Pediatr* 2001; 55: 335–8.

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

Pharmacokinetics

Diamorphine hydrochloride is well absorbed from the gastrointestinal tract, although this may be erratic, and after subcutaneous or intramuscular injection. On injection it is rapidly hydrolysed to the active metabolite 6-*O*-monoacetylmorphine (6-acetylmorphine) in the blood and then to morphine (p. 95.3). Oral doses are subject to extensive first-pass metabolism to morphine; neither diamorphine nor 6-acetylmorphine has been detected in the blood after giving diamorphine by this route. Both diamorphine and 6-acetylmorphine readily cross the blood-brain barrier. Morphine glucuronides are the main excretion products in the urine. A small amount is excreted in the faeces.

References.

1. Boerner U, *et al.* The metabolism of morphine and heroin in man. *Drug Metab Rev* 1975; 4: 39–73.
2. Inturrisi CE, *et al.* The pharmacokinetics of heroin in patients with chronic pain. *N Engl J Med* 1984; 310: 1213–17.
3. Moore RA, *et al.* Opiate metabolism and excretion. *Baillieres Clin Anaesthesiol* 1987; 1: 829–58.
4. Barrett DA, *et al.* Morphine kinetics after diamorphine infusion in premature neonates. *Br J Clin Pharmacol* 1991; 32: 31–7.
5. Girardin F, *et al.* Pharmacokinetics of high doses of intramuscular and oral heroin in narcotic addicts. *Clin Pharmacol Ther* 2003; 74: 341–52.
6. Halbsguth U, *et al.* Oral diacetylmorphine (heroin) yields greater morphine bioavailability than oral morphine: bioavailability related to dosage and prior opioid exposure. *Br J Clin Pharmacol* 2008; 66: 781–91.

Administration. *INHALATIONAL ROUTE.* A literature review[1] found that intranasal diamorphine had a similar pharmacokinetic profile to that of intramuscular diamorphine. It is rapidly absorbed, as a dry powder, via the nasal mucosa although this is not as complete as by intramuscular injection; intranasal absorption appeared to be dose dependent.

The pharmacokinetics of inhaled diamorphine fumes ("chasing the dragon") have been studied[2] in diamorphine addicts receiving substitution therapy with diamorphine and methadone. Absorption through the lungs occurred very rapidly and was virtually complete immediately after inhalation; bioavailability was estimated to be about 53%.

1. Kendall JM, Latter VS. Intranasal diamorphine as an alternative to intramuscular morphine: pharmacokinetic and pharmacodynamic aspects. *Clin Pharmacokinet* 2003; 42: 501–13.
2. Rook EJ, *et al.* Population pharmacokinetics of heroin and its major metabolites. *Clin Pharmacokinet* 2006; 45: 401–17.

INTRASPINAL ROUTE. Diamorphine is much more lipid-soluble and has a more rapid onset and shorter duration of action than morphine. Although deacetylation to morphine occurs rapidly in the blood it occurs only slowly in the CSF after intraspinal injection of diamorphine.[1] After intrathecal injection diamorphine was removed from the CSF much more rapidly than morphine.[2] Peak plasma concentrations of morphine after epidural diamorphine injection were significantly higher and were achieved significantly faster than after epidural injection of morphine.[3]

1. Morgan M. The rational use of intrathecal and extradural opioids. *Br J Anaesth* 1989; 63: 165–88.
2. Moore A, *et al.* Spinal fluid kinetics of morphine and heroin. *Clin Pharmacol Ther* 1984; 35: 40–5.
3. Watson J, *et al.* Plasma morphine concentrations and analgesic effects of lumbar extradural morphine and heroin. *Anesth Analg* 1984; 63: 629–34.

Children. Loading doses of either 50 micrograms/kg or 200 micrograms/kg of diamorphine were given as an intravenous infusion over 30 minutes to 19 ventilated neonates followed by a continuous infusion of 15 micrograms/kg per hour, and the pharmacokinetics of the products of diamorphine metabolism (morphine, morphine-6-glucuronide, and morphine-3-glucuronide) studied.[1] Although the overall elimination of morphine was reduced compared with adults, the relative contributions of the various metabolic routes of morphine remained similar between neonates and adults. Data from this study did not indicate any advantage for the higher loading dose (see also under Uses and Administration, p. 46.3).

1. Barrett DA, *et al.* Morphine, morphine-6-glucuronide and morphine-3-glucuronide pharmacokinetics in newborn infants receiving diamorphine infusions. *Br J Clin Pharmacol* 1996; 41: 531–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Switz.*: Diaphin; *UK*: Ayendi.

Pharmacopoeial Preparations

BP 2014: Bupivacaine and Diamorphine Injection; Diamorphine Injection;

BPC 1973: Diamorphine Linctus.

Diclofenac *(BAN, rINN)*

Diclofénac; Diclofenaco; Diclofenacum; Diklofenaakki; Diklofenak; Диклофенак.

[2-(2,6-Dichloroanilino)phenyl]acetic acid.

$C_{14}H_{11}Cl_2NO_2$=296.1

CAS — 15307-86-5.

ATC — D11AX18; M01AB05; M02AA15; S01BC03.

ATC Vet — QD11AX18; QM01AB05; QM02AA15; QS01BC03.

UNII — 144O8QL0L1.

Diclofenac Diethylamine *(BANM)*

Diclofenac Diethylammonium; Diclofenaco dietilamina; Diklofenak Dietilamonyum; Диклофенак Диэтиламин.

$C_{18}H_{22}Cl_2N_2O_2$=369.3

CAS — 78213-16-8.

ATC — D11AX18.

ATC Vet — QD11AX18.

UNII — 6TGQ35Z71K.

Pharmacopoeias. In *Br.*

BP 2014: (Diclofenac Diethylamine). A white to light beige, crystalline powder. Sparingly soluble in water and in acetone; freely soluble in alcohol and in methyl alcohol; practically insoluble in 1M sodium hydroxide. The pH of a 1% solution in alcohol (10%) is between 6.4 and 8.4. Store in airtight containers. Protect from light.

Diclofenac Epolamine

DHEP; Diclofenac Hydroxyethylpyrrolidine; Диклофенак Эполамин.

$C_{14}H_{11}Cl_2NO_2$, $C_6H_{13}NO$=411.3

CAS — 119623-66-4.

ATC — D11AX18.

ATC Vet — QD11AX18.

UNII — X5F8EKL9ZG.

Diclofenac Potassium *(BANM, USAN, rINNM)*

CGP-45840B; Diclofenac-Kalium; Diclofénac Potassique; Diclofenaco potásico; Diclofenacum kalicum; Diklofenaakki-kalium; Diklofenak draselná sůl; Diklofenak Potasyum; Diklofenakkalium; Diklofenák-kálium; Diklofenako kalio druska; Kalii Diclofenacum; Калия Диклофенак.

Potassium [*o*-(2,6-dichloroanilino)phenyl]acetate.

$C_{14}H_{10}Cl_2KNO_2$=334.2

CAS — 15307-81-0.

ATC — D11AX18.

ATC Vet — QD11AX18.

UNII — L4D5UA6CB4.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Diclofenac Potassium). A white or slightly yellowish, slightly hygroscopic, crystalline powder. Sparingly soluble in water; soluble in alcohol; slightly soluble in acetone; freely soluble in methyl alcohol. Store in airtight containers. Protect from light.

USP 36: (Diclofenac Potassium). pH of a 1% solution in water is between 7.0 and 8.5. Store at a temperature of 20 degrees to 25 degrees. Protect from light.

Diclofenac Sodium *(BANM, USAN, rINNM)*

Diclofenac-Natrium; Diclofénac sodique; Diclofenaco sódico; Diclofenacum natricum; Diclophenac Sodium; Diklofenaak-kinatrium; Diklofenak sodná sůl; Diklofenak Sodyum; Diklofenaknatrium; Diklofenák-nátrium; Diklofenako natrio druska; GP-45840; Natrii Diclofenacum; Натрий Диклофенак.

Sodium [2-(2,6-dichloroanilino)phenyl]acetate.

$C_{14}H_{10}Cl_2NNaO_2$=318.1

CAS — 15307-79-6.

ATC — D11AX18.

ATC Vet — QD11AX18.

UNII — QTG126297Q.

NOTE. DICL is a code approved by the BP 2014 for use on single unit doses of eye drops containing diclofenac sodium where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Diclofenac Sodium). A white to slightly yellowish, slightly hygroscopic, crystalline powder. Sparingly soluble in water; soluble in alcohol; slightly soluble in acetone; freely soluble in methyl alcohol. Store in airtight containers. Protect from light.

USP 36: (Diclofenac Sodium). A white to off-white, hygroscopic, crystalline powder. Sparingly soluble in water; soluble in alcohol; practically insoluble in chloroform and in ether; freely soluble in methyl alcohol. pH of a 1% solution in water is between 7.0 and 8.5. Store in airtight containers. Protect from light.

Uses and Administration

Diclofenac, a phenylacetic acid derivative, is an NSAID (p. 102.3). It is used mainly as the sodium salt for the relief of pain and inflammation in various conditions: musculoskeletal and joint disorders such as rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis; peri-articular disorders such as bursitis and tendinitis; soft-tissue disorders such as sprains and strains; and other painful conditions such as renal colic, acute gout, dysmenorrhoea, migraine, and after some surgical procedures. It has also been used in some countries for the management of actinic keratoses and fever. Eye drops of diclofenac sodium are used for the prevention of intra-operative miosis during cataract extraction, for the treatment of inflammation after surgery or laser treatment of the eye, for pain in corneal epithelial defects after surgery or accidental trauma, and for the relief of ocular signs and symptoms of seasonal allergic conjunctivitis.

The usual **oral** or **rectal** dose of diclofenac sodium is 75 to 150 mg daily in divided doses. In the UK the maximum dose regardless of route or indication is 150 mg daily; however, in the USA a maximum oral dose of 200 mg daily is allowed in the treatment of rheumatoid arthritis. Modified-release preparations of diclofenac sodium are available for oral use. Diclofenac has also been given in equivalent oral doses as the free acid in dispersible preparations for short-term treatment up to 3 months long. Diclofenac is also given orally as the potassium salt. Doses of the potassium salt are similar to those for diclofenac sodium. Diclofenac potassium is also used in the treatment of migraine in an initial dose of 50 mg taken at the first signs of an attack; an additional dose of 50 mg may be taken after 2 hours if symptoms persist. If necessary further doses of 50 mg may be taken every 4 to 6 hours to a maximum daily dose of 200 mg.

Diclofenac sodium may also be given by deep intramuscular **injection** into the gluteal muscle in a dose of 75 mg once daily or, if required in severe conditions, 75 mg twice daily. Diclofenac sodium may also be given as a continuous or intermittent intravenous infusion in glucose 5% or sodium chloride 0.9% (both previously buffered with sodium bicarbonate) or as a bolus intravenous injection. For the treatment of postoperative pain a dose of 75 mg may be given over 30 to 120 minutes or as a bolus injection. The dose may be repeated once after 4 to 6 hours if necessary. To prevent postoperative pain, an initial dose of 25 to 50 mg diclofenac sodium may be given after surgery over 15 to 60 minutes followed by 5 mg/hour to a maximum of 150 mg daily. Alternatively, the initial dose may be given as a bolus injection over 5 to 60 seconds followed by additional injections up to the maximum daily dosage; this may be repeated after 4 to 6 hours if necessary although the *total* dose should not exceed the maximum daily dose of 150 mg. The maximum period recommended for parenteral use is 2 days. Diclofenac sodium is also used intramuscularly in renal colic in a dose of 75 mg repeated once after 30 minutes if necessary.

For dosage details in children, see below.

Diclofenac sodium is used as a 0.1% **ophthalmic solution** in various situations:

- for the prevention of intra-operative miosis during cataract surgery, it is instilled in the appropriate eye 4 times during the 2 hours before surgery
- for the treatment of postoperative inflammation after cataract surgery, it is instilled 4 times daily for up to 28 days starting 24 hours after surgery
- for the control of post-photorefractive keratectomy pain, it is instilled twice in the hour before surgery, then one drop twice at 5-minute intervals immediately after the procedure, and then every 2 to 5 hours while awake for up to 24 hours
- for pain control after accidental trauma, one drop is instilled 4 times daily for up to 2 days
- in the treatment of inflammation and discomfort after strabismus surgery, one drop is instilled 4 times daily for the first week; this is reduced to 3 times daily in the second week, twice daily in the third week, and as required for the fourth week
- for the control of inflammation after argon laser trabeculoplasty, one drop is instilled 4 times during the 2 hours before the procedure followed by one drop 4 times daily for up to 7 days after the procedure
- for the treatment of pain and discomfort after radial keratotomy, one drop is instilled before surgery followed by one drop immediately after surgery and then one drop 4 times daily for up to 2 days
- to relieve symptoms of seasonal allergic conjunctivitis, one drop is instilled 4 times daily as necessary

Diclofenac diethylamine is used **topically** as a gel containing the equivalent of 1% of diclofenac sodium for the local symptomatic relief of pain and inflammation; it is applied to the affected site 3 or 4 times daily; treatment should be reviewed after 14 days or after 28 days if used for osteoarthritis. A topical spray containing diclofenac sodium 4% is also available; 4 or 5 sprays (32 or 40 mg of diclofenac sodium) may be applied 3 times daily, up to a maximum of 15 sprays (120 mg of diclofenac sodium) daily; treatment should be reviewed after 7 or 8 days. A topical solution of diclofenac sodium 1.6% is available for the treatment of osteoarthritis in superficial joints such as the wrist or knee; it is applied in small aliquots to achieve a total of 20 or 40 drops, depending on the size of the joint, and repeated four times daily. Diclofenac is also used in the management of actinic keratoses; it is applied twice daily as diclofenac sodium gel 3% for 60 to 90 days but the optimum therapeutic effect may not be seen until 30 days after the end of treatment. Diclofenac epolamine is also used topically as a plaster containing the equivalent of 1% of diclofenac sodium for local symptomatic pain relief in ankle sprain and epicondylitis. In the treatment of ankle sprain, 1 plaster is applied once daily for a maximum of 3 days and for epicondylitis, 1 plaster is applied twice daily for a maximum of 14 days.

Diclofenac is available as a combination preparation with misoprostol (p. 2140.3) for patients at risk of NSAID-induced peptic ulceration.

Administration. *IN CHILDREN.* In children aged 1 to 12 years the licensed UK *oral* or *rectal* dose of diclofenac sodium for juvenile idiopathic arthritis is 1 to 3 mg/kg daily in divided doses. In children aged 6 to 12 years diclofenac sodium may also be given rectally for the treatment of acute post-operative pain, either alone or as an adjunct to opiate therapy; a usual dose is 1 to 2 mg/kg daily in divided doses for a maximum of 4 days. The *parenteral route* is not licensed for use in children although it has been used (see below).

The *BNFC* suggests slightly different doses of diclofenac sodium: in the management of rheumatic disease, including juvenile idiopathic arthritis, in children from 6 months to 18 years of age, it recommends an oral dose of 3 to 5 mg/kg daily, in 2 or 3 divided doses. For relief of mild to moderate pain and inflammation in, for example, soft-tissue disorders, the recommended oral or rectal dose in children from 6 months to 18 years of age is 0.3 to 1 mg/kg given three times daily; children 2 to 18 years of age may be given a similar dose once or twice daily *by intravenous infusion* or *deep intramuscular (gluteal) injection* for up to 2 days for postoperative pain. Rectal doses may also be given for postoperative pain to children from 6 months to 18 years of age, according to body-weight, for a maximum of 4 days: those weighing 8 to 12 kg may be given 12.5 mg twice daily and heavier children 1 mg/kg three times daily.

Regardless of route or indication, a maximum daily dose of 150 mg should not be exceeded.

Diclofenac potassium has also been used in children aged over 14 years for the treatment of rheumatic disease, musculoskeletal disorders, and postoperative pain; it is given in an *oral* dose of 75 to 100 mg daily in 2 or 3 divided doses.

TOPICAL References to the use of plasters providing sustained topical release of diclofenac epolamine,[1-6] and reviews of the use of a topical solution of diclofenac with dimethyl sulfoxide to treat osteoarthritis.[7,8] The latter was found to be effective and better tolerated than oral use.

1. Galeazzi M, Marcolongo R. A placebo-controlled study of the efficacy and tolerability of a nonsteroidal anti-inflammatory drug, DHEP plaster, in inflammatory peri-and extra-articular rheumatological diseases. *Drugs Exp Clin Res* 1993; **19**: 107–15.
2. Dreiser RL, Tisne-Camus M. DHEP plasters as a topical treatment of knee osteoarthritis—a double-blind placebo-controlled study. *Drugs Exp Clin Res* 1993; **19**: 117–23.
3. Affaitati G, *et al.* Effects of topical diclofenac (DHEP plaster) on skin, subcutis and muscle pain thresholds in subjects without spontaneous pain. *Drugs Exp Clin Res* 2001; **27**: 69–76.
4. Jenoure P-J. Évaluation d'un anti-inflammatoire non stéroïdien topique dans le traitement de la douleur et de l'inflammation: exemple de Flector Tissugel 1% dispositif local bioadhésif de diclofénac épolamine. *Presse Med* 2004; **33**: 10–13.
5. Brühlmann P, *et al.* Short-term treatment with topical diclofenac epolamine plaster in patients with symptomatic knee osteoarthritis: pooled analysis of two randomised clinical studies. *Curr Med Res Opin* 2006; **22**: 2429–38.
6. Alessandri F, *et al.* Topical diclofenac patch for postoperative wound pain in laparoscopic gynecologic surgery: a randomized study. *J Minim Invasive Gynecol* 2006; **13**: 195–200.
7. Towheed TE. Pennsaid therapy for osteoarthritis of the knee: a systematic review and metaanalysis of randomized controlled trials. *J Rheumatol* 2006; **33**: 567–73.
8. Moen MD. Topical diclofenac solution. *Drugs* 2009; **69**: 2621–32.

Actinic keratoses. Diclofenac sodium 3% in hyaluronic acid gel is used[1-3] in the treatment of actinic keratoses (see Basal Cell and Squamous Cell Carcinoma, p. 714.2), and a meta-analysis[4] found it to be of benefit, despite previous concerns that the preparation may not be significantly more effective than hyaluronic acid gel alone.[5] An open-label comparison involving 30 patients with multiple actinic keratoses suggested that 90 days of treatment with diclofenac sodium 3% gel (to lesions on one side of the face and scalp) was better tolerated, but slightly less effective, than 28 days of treatment with fluorouracil 5% cream (to lesions on the other side).[6]

1. Rivers JK, McLean DI. An open study to assess the efficacy and safety of topical 3% diclofenac in a 2.5% hyaluronic acid gel for the treatment of actinic keratoses. *Arch Dermatol* 1997; **133**: 1239–42.
2. Rivers JK, *et al.* Topical treatment of actinic keratoses with 3.0% diclofenac in 2.5% hyaluronan gel. *Br J Dermatol* 2002; **146**: 94–100.
3. Ulrich C, *et al.* Treatment of multiple actinic keratoses with topical diclofenac 3% gel in organ transplant recipients: a series of six cases. *Br J Dermatol* 2007; **156** (suppl 3): 40–2.
4. Pirard D, *et al.* Three percent diclofenac in 2.5% hyaluronan gel in the treatment of actinic keratoses: a meta-analysis of the recent studies. *Arch Dermatol Res* 2005; **297**: 185–9.
5. McEwan LE, Smith JG. Topical diclofenac/hyaluronic acid gel in the treatment of solar keratoses. *Australas J Dermatol* 1997; **38**: 187–9.
6. Smith SR, *et al.* Bilateral comparison of the efficacy and tolerability of 3% diclofenac sodium gel and 5% 5-fluorouracil cream in the treatment of actinic keratoses of the face and scalp. *J Drugs Dermatol* 2006; **5**: 156–9.

Pain. Reviews.

1. McCormack PL, Scott LJ. Diclofenac sodium injection (Dyloject): in postoperative pain. *Drugs* 2008; **68**: 123–30. Correction. *ibid.*; 801.
2. Derry P, *et al.* Single dose oral diclofenac for acute postoperative pain in adults. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 09/09/09).
3. Standing JF, *et al.* Diclofenac for acute pain in children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 18/03/10).

Adverse Effects and Treatment

As for NSAIDs in general, p. 104.3.

There may be pain and, occasionally, tissue damage at the site of injection when diclofenac is given intramuscularly. Diclofenac suppositories can cause local irritation. Transient burning and stinging may occur with diclofenac ophthalmic solution; more serious corneal adverse effects have also occurred (see Effects on the Eyes, p. 50.1). Topical preparations of diclofenac, such as plasters and gel, may cause application site reactions.

Incidence of adverse effects. A review of worldwide clinical studies with diclofenac[1] has reported the incidence of drug-associated adverse effects to be about 12%; about 16% of patients who had adverse effects stopped treatment (a figure corresponding to about 2% of the entire patient sample). The most frequently reported adverse effects were gastrointestinal and were reported in 7.6% of patients. CNS-related adverse effects were reported in 0.7% of patients and allergy or local reactions in 0.4%. This and other reviews[2] have shown that adverse effects associated with diclofenac are usually mild and transient and appear to be unrelated to the dose given.

The incidence of adverse effects in children is similar to that in adults.[3]

1. Willkens RF. Worldwide clinical safety experience with diclofenac. *Semin Arthritis Rheum* 1985; **15** (suppl 1): 105–10.
2. Small RE. Diclofenac sodium. *Clin Pharm* 1989; **8**: 545–8.
3. Standing JF, *et al.* Prospective observational study of adverse drug reactions to diclofenac in children. *Br J Clin Pharmacol* 2009; **68**: 243–51.

Effects on the blood. Results of a large survey undertaken to assess the relation between agranulocytosis, aplastic anaemia, and drug exposure indicated that diclofenac was significantly associated with aplastic anaemia, providing an estimated tenfold increase in risk.[1] There are reports of other haematological abnormalities including haemolytic anaemia,[2,3] thrombocytopenia,[4,5] neutropenia,[5] and agranulocytosis[6] occurring in patients given diclofenac.

Localised spontaneous bleeding,[7] bruising,[8] inhibition of platelet aggregation,[7] and prolonged bleeding time[8] have been reported.

1. The International Agranulocytosis and Aplastic Anemia Study. Risks of agranulocytosis and aplastic anemia: a first report of their relation to drug use with special reference to analgesics. *JAMA* 1986; **256**: 1749–57.
2. López A, *et al.* Autoimmune hemolytic anemia induced by diclofenac. *Ann Pharmacother* 1995; **29**: 787.
3. Ahrens N, *et al.* Misdiagnosis in patients with diclofenac-induced hemolysis: new cases and a concise review. *Am J Hematol* 2006; **81**: 128–31.
4. George S, Rahi AHS. Thrombocytopenia associated with diclofenac therapy. *Am J Health-Syst Pharm* 1995; **52**: 420–1.
5. Kim HL, Kovacs MJ. Diclofenac-associated thrombocytopenia and neutropenia. *Ann Pharmacother* 1995; **29**: 713–15.
6. Colomina P, Garcia S. Agranulocytosis caused by diclofenac. *DICP Ann Pharmacother* 1989; **23**: 507.
7. Price AJ, Obeid D. Spontaneous non-gastrointestinal bleeding associated with diclofenac. *Lancet* 1989; **ii**: 1520.
8. Khazan U, *et al.* Diclofenac sodium and bruising. *Ann Intern Med* 1990; **112**: 472–3.

Effects on the cardiovascular system. For a discussion of the cardiovascular effects of NSAIDs, including diclofenac, see p. 105.1.

Effects on electrolytes. A syndrome resembling the syndrome of inappropriate antidiuretic hormone secretion has been reported in elderly women given diclofenac.[1,2] Also the UK CSM had received a report of fatal hyponatraemia in another elderly woman.[2]

1. Petersson I, *et al.* Water intoxication associated with non-steroidal anti-inflammatory drug therapy. *Acta Med Scand* 1987; **221**: 221–3.
2. Cheung NT, *et al.* Syndrome of inappropriate secretion of antidiuretic hormone induced by diclofenac. *BMJ* 1993; **306**: 186.

Effects on the eyes. A patient who had been taking oral diclofenac for several years and had increasingly complained of dry, gritty eyes noticed that eye irritation disappeared within 3 days when diclofenac had to be stopped because of gastrointestinal effects.[1]

Ocular diclofenac and related drugs have been implicated in reports of corneal toxicity. Ulceration of the conjunctiva or cornea, corneal or scleral melts, and perforations have been reported in patients using diclofenac eye drops, particularly after cataract surgery.[2-5] Keratitis and perforations were also reported with ketorolac eye drops,[4] although less frequently. For mention of corneal melting with bromfenac, see p. 30.1.

1. Reid ALA, Henderson R. Diclofenac and dry, irritable eyes. *Med J Aust* 1994; **160**: 308.
2. Lin JC, *et al.* Corneal melting associated with use of topical nonsteroidal anti-inflammatory drugs after ocular surgery. *Arch Ophthalmol* 2000; **118**: 1129–32.
3. Congdon NG, *et al.* Corneal complications associated with topical ophthalmic use of nonsteroidal antiinflammatory drugs. *J Cataract Refract Surg* 2001; **27**: 622–31.
4. Guidera AC, *et al.* Keratitis, ulceration, and perforation associated with topical nonsteroidal anti-inflammatory drugs. *Ophthalmology* 2001; **108**: 936–44.
5. Flach AJ. Corneal melts associated with topically applied nonsteroidal anti-inflammatory drugs. *Trans Am Ophthalmol Soc* 2001; **99**: 205–10.

Effects on the gastrointestinal tract. The most frequent adverse effects reported in patients given diclofenac systemically are gastrointestinal in nature. Typical reactions include epigastric pain, nausea, vomiting, and diarrhoea. Rarely peptic ulcer and gastrointestinal bleeding have occurred. Diclofenac has also been implicated as the causative agent in colonic ulceration,[1] small bowel perforation,[2] and pseudomembranous colitis.[3] Diclofenac suppositories may cause local reactions such as itching, burning, or exacerbation of haemorrhoids.

1. Carson J, *et al.* Colonic ulceration and bleeding during diclofenac therapy. *N Engl J Med* 1990; **323**: 135.
2. Deakin M, *et al.* Small bowel perforation associated with an excessive dose of slow release diclofenac sodium. *BMJ* 1988; **297**: 488–9.
3. Gentric A, Pennec YL. Diclofenac-induced pseudomembranous colitis. *Lancet* 1992; **340**: 126–7.

Effects on the kidneys. Renal papillary necrosis[1] and nephrotic syndrome[2-4] have been reported in patients taking diclofenac. See also Effects on Electrolytes, p. 49.3.

1. Scott SJ, *et al.* Renal papillary necrosis associated with diclofenac sodium. *BMJ* 1986; **292**: 1050.
2. Beun GDM, *et al.* Isolated minimal change nephropathy associated with diclofenac. *BMJ* 1987; **295**: 182–3.
3. Yinnon AM, *et al.* Nephrotic syndrome associated with diclofenac sodium. *BMJ* 1987; **295**: 556.
4. Tattersall J, *et al.* Membranous nephropathy associated with diclofenac. *Postgrad Med J* 1992; **68**: 392–3.

Effects on the liver. Elevations of serum aminotransferase activity and clinical hepatitis,[1-8] including fatal fulminant hepatitis[2,5] have occurred in patients taking diclofenac. There has also been a case report of hepatorenal damage attributed to diclofenac.[9] Analysis[10] of 180 of the cases of diclofenac-associated hepatic injury received by the FDA between November 1988 and June 1991 suggested an increased risk of hepatotoxicity in female patients and those taking diclofenac for osteoarthritis. Hepatotoxicity had been detected within 6 months of starting diclofenac in 85% of the patients. The biochemical pattern of injury was hepatocellular or mixed hepatocellular in 66%, of patients and cholestatic injury was found in 8% of patients. Signs of hypersensitivity were uncommon and it was considered that the mechanism of hepatic injury was likely to be a metabolic idiosyncratic reaction rather than due to intrinsic toxicity of diclofenac.

1. Dunk AA, *et al.* Diclofenac hepatitis. *BMJ* 1982; **284**: 1605–6.
2. Breen EG, *et al.* Fatal hepatitis associated with diclofenac. *Gut* 1986; **27**: 1390–3.
3. Schapira D, *et al.* Diclofenac-induced hepatotoxicity. *Postgrad Med J* 1986; **62**: 63–5.
4. Ryley NG, *et al.* Diclofenac associated hepatitis. *Gut* 1989; **30**: A708.
5. Helfgott SM, *et al.* Diclofenac-associated hepatotoxicity. *JAMA* 1990; **264**: 2660–2.
6. Purcell P, *et al.* Diclofenac hepatitis. *Gut* 1991; **32**: 1381–5.
7. Bhogaraju A, *et al.* Diclofenac-associated hepatitis. *South Med J* 1999; **92**: 711–13.
8. Greaves RRSH, *et al.* Inadvertent diclofenac rechallenge from generic and non-generic prescribing, leading to liver transplantation for fulminant liver failure. *Eur J Gastroenterol Hepatol* 2001; **13**: 71–3.
9. Diggory P, *et al.* Renal and hepatic impairment in association with diclofenac administration. *Postgrad Med J* 1989; **64**: 507–8.
10. Banks AT, *et al.* Diclofenac-associated hepatotoxicity: analysis of 180 cases reported to the Food and Drug Administration as adverse reactions. *Hepatology* 1995; **22**: 820–7.

Effects on the skin. Self-limiting skin reactions such as rash or pruritus may occur in patients given diclofenac. More serious skin reactions attributed to diclofenac include bullous dermatitis[1] and erythema multiforme.[2,3] Local irritation and necrosis have occurred on intramuscular injection of diclofenac.[4-7]

1. Gabrielsen TØ, *et al.* Drug-induced bullous dermatosis with linear IgA deposits along the basement membrane. *Acta Derm Venereol (Stockh)* 1981; **61**: 439–41.
2. Morris BAP, Remtulla SS. Erythema multiforme major following use of diclofenac. *Can Med Assoc J* 1985; **133**: 665.
3. Young J. Erythema multiforme-like eruption as a result of 'Solaraze' treatment. *J Dermatol Treat* 2003; **14**: 189.
4. Stricker BHC, van Kasteren BJ. Diclofenac-induced isolated myonecrosis and the Nicolau syndrome. *Ann Intern Med* 1992; **117**: 1058.
5. Pillans PI, O'Connor N. Tissue necrosis and necrotising fasciitis after intramuscular administration of diclofenac. *Ann Pharmacother* 1995; **29**: 264–6.
6. Ezzedine K, *et al.* Nicolau syndrome following diclofenac administration. *Br J Dermatol* 2004; **150**: 385–7.
7. Mutalik S, Belgaumkar V. Nicolau syndrome: a report of 2 cases. *J Drugs Dermatol* 2006; **5**: 377–8.

Hypersensitivity. Aspirin-sensitive asthmatic patients have developed reactions (rhinorrhoea, tightness of chest, wheezing, dyspnoea) when challenged with diclofenac in doses of 10 to 25 mg[1] and the UK CSM has received a report of an aspirin-sensitive patient who died from acute asthma 4 hours after a single 25-mg dose of diclofenac.[2]

Anaphylactic shock has been reported.[3]

1. Szczeklik A, *et al.* Asthmatic attacks induced in aspirin-sensitive patients by diclofenac and naproxen. *BMJ* 1977; **2**: 231–2.
2. CSM/MCA. Avoid all NSAIDs in aspirin-sensitive patients. *Current Problems* 1993; **19**: 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024455&RevisionSelectionMethod=LatestReleased (accessed 01/11/07)
3. Dux S, *et al.* Anaphylactic shock induced by diclofenac. *BMJ* 1983; **286**: 1861.

Precautions

As for NSAIDs in general, p. 107.1.

Systemic diclofenac is contra-indicated in patients with moderate to severe heart failure (NYHA class II to IV), ischaemic heart disease, peripheral arterial disease, or cerebrovascular disease. It should be used with caution in patients with significant risk factors for cardiovascular events such as hypertension, hyperlipidaemia, diabetes mellitus, and smoking. Systemic diclofenac is also contra-indicated in patients with severe hepatic or renal impairment.

In addition, use of intravenous diclofenac is contra-indicated in patients with moderate or severe renal impairment, hypovolaemia, or dehydration; it should also not be given intravenously to patients with a history of haemorrhagic diathesis, cerebrovascular bleeding (including suspected), or asthma nor in patients undergoing surgery with a high risk of haemorrhage.

Ophthalmic preparations containing diclofenac should not be used by patients who wear soft contact lenses.

Breast feeding. Diclofenac is distributed into breast milk although the *BNF* considers the amount to be too small to be harmful to breast-fed infants.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies diclofenac as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 23/10/11)

Veterinary use. Veterinary use of diclofenac in cattle in South Asia has been associated with severe decline in the numbers of vultures, to whom the residues are highly toxic if they consume the carcasses.[1,2] Meloxicam (p. 86.3) has been suggested as an alternative.

1. Shultz S, *et al.* Diclofenac poisoning is widespread in declining vulture populations across the Indian subcontinent. *Proc Biol Sci* 2004; **271** (suppl 6): S458–S460.
2. Sharp D. Meloxicam to prevent rabies? *Lancet* 2006; **367**: 887–8.

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Diclofenac should not be given intravenously to patients already receiving other NSAIDs or anticoagulants including low-dose heparin.

Ciclosporin. Deterioration in renal function has been attributed to the use of diclofenac with ciclosporin.[1] Increased concentrations of diclofenac were also noted with ciclosporin;[2] licensed product information for ciclosporin recommends that the dosage of diclofenac should be reduced by about one-half when the two are given together.

1. Branthwaite JP, Nicholls A. Cyclosporin and diclofenac interaction in rheumatoid arthritis. *Lancet* 1991; **337**: 252.
2. Kovarik JM, *et al.* Cyclosporine and nonsteroidal antiinflammatory drugs: exploring potential drug interactions and their implications for the treatment of rheumatoid arthritis. *J Clin Pharmacol* 1997; **37**: 336–43.

Corticosteroids. Concomitant use of ophthalmic preparations containing diclofenac with those containing corticosteroids in patients with significant pre-existing corneal inflammation may increase the risk of developing corneal complications.

Diuretics. Deterioration in renal function has been attributed to the use of diclofenac with *triamterene*.[1]

1. Härkönen M, Ekblom-Kullberg S. Reversible deterioration of renal function after diclofenac in patient receiving triamterene. *BMJ* 1986; **293**: 698–9.

Gastrointestinal drugs. A decrease in the plasma concentration of diclofenac has been reported[1] when given after *sucralfate*.

1. Pedrazzoli J, *et al.* Short-term sucralfate administration alters potassium diclofenac absorption in healthy male volunteers. *Br J Clin Pharmacol* 1997; **43**: 104–8.

Lipid regulating drugs. *Colestyramine* appears substantially to reduce the bioavailability of diclofenac when the two drugs are given together;[1] *colestipol* produces a similar but smaller effect.

1. al-Balla SR, *et al.* The effects of cholestyramine and colestipol on the absorption of diclofenac in man. *Int J Clin Pharmacol Ther* 1994; **32**: 441–5.

Misoprostol. The plasma concentration of diclofenac was reduced when it was given as a 100-mg dose daily in the form of a modified-release preparation to subjects receiving misoprostol 800 micrograms daily.[1] Use together was also associated with an increase in the incidence and severity of gastrointestinal effects. Studies by the manufacturer[2] had failed to find any significant pharmacokinetic interactions between diclofenac and misoprostol when given in a formulation containing diclofenac 50 mg and misoprostol 200 micrograms.

1. Dammann HG, *et al.* Differential effects of misoprostol and ranitidine on the pharmacokinetics of diclofenac and gastrointestinal symptoms. *Br J Clin Pharmacol* 1993; **36**: 345–9.
2. Karim A. Pharmacokinetics of diclofenac and misoprostol when administered alone or as a combination product. *Drugs* 1993; **45** (suppl 1): 7–14.

Parasympathomimetics. Licensed product information for acetylcholine chloride ophthalmic preparations has stated that there have been reports that *acetylcholine* and *carbachol* have been ineffective when used in patients treated with topical (ophthalmic) NSAIDs.

Pharmacokinetics

Diclofenac is rapidly absorbed when given as an oral solution, sugar-coated tablets, rectal suppository, or by intramuscular injection. It is absorbed more slowly when given as enteric-coated tablets, especially when this dosage form is given with food. Although diclofenac given orally is almost completely absorbed, it is subject to first-pass metabolism so that about 50% of the drug reaches the systemic circulation in the unchanged form. Diclofenac is also absorbed percutaneously. At therapeutic concentrations it is more than 99% bound to plasma proteins. Diclofenac penetrates synovial fluid where concentrations may persist even when plasma concentrations fall; small amounts are distributed into breast milk. The terminal plasma half-life is about 1 to 2 hours. Diclofenac is metabolised to 4′-hydroxydiclofenac, 5-hydroxydiclofenac, 3′-hydroxydiclofenac, and 4′,5-dihydroxydiclofenac. It is then excreted in the form of glucuronide and sulfate conjugates, mainly in the urine (about 60%) but also in the bile (about 35%); less than 1% is excreted as unchanged diclofenac.

References.

1. Fowler PD, *et al.* Plasma and synovial fluid concentrations of diclofenac sodium and its major hydroxylated metabolites during long-term treatment of rheumatoid arthritis. *Eur J Clin Pharmacol* 1983; **25**: 389–94.
2. Maggi CA, *et al.* Comparative bioavailability of diclofenac hydroxyethylpyrrolidine vs diclofenac sodium in man. *Eur J Clin Pharmacol* 1990; **38**: 207–8.
3. Davies NM, Anderson KE. Clinical pharmacokinetics of diclofenac. therapeutic insights and pitfalls. *Clin Pharmacokinet* 1997; **33**: 184–213.
4. Brenner SS, *et al.* Influence of age and cytochrome P450 2C9 genotype on the steady-state disposition of diclofenac and celecoxib. *Clin Pharmacokinet* 2003; **42**: 283–92.
5. Hinz B, *et al.* Bioavailability of diclofenac potassium at low doses. *Br J Clin Pharmacol* 2005; **59**: 80–4.
6. Standing JF, *et al.* Population pharmacokinetics of oral diclofenac for acute pain in children. *Br J Clin Pharmacol* 2008; **66**: 846–53.
7. Miyatake S, *et al.* Randomized clinical comparisons of diclofenac concentration in the soft tissues and blood plasma between topical and oral applications. *Br J Clin Pharmacol* 2009; **67**: 125–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Ainedif; Aldoron NF; Algicler; Algioxib; Anaflex; ATM 101; Atomo Desinflamante Geldic; Banoclus; Befol; Blokium Prost†; Blokium; Calmoflex; Curinflam VL; Curinflam; DFN; Diastone; Diclac; Diclofilab; Diclogesic; Diclogrand; Diclolabsa; Diclolam; Diclomar; Diclonex; Dicloreumol; Difenac Forte; Difenac; Dilam†; Dioxaflex Protect; Dioxaflex; Disipan; Distec; Dolo Tomanil; Dolofenac; Doloneitor; Dolvan; Doxtran; Excelentia Analgesico; Faboflem†; Flexin; Flexiplen; Flogolisin; Fluxpiren; Gel Antiinflamatorio; Gentisalyl; Iglodine; Imanol; Ingecloft; Kamox†; Kinalgin; Klonafenac; Levedad; Lorbifenac; Metaflex NF; Miocalm†; Nalgiflex; Natura Fenac; Norviken; Oxa; Oxaprost; Pronix; Quer-Out; Rati Salil D; Reumosan; Rodinac; Salicrem Forte; Silfox; Tomanil; Vesa-

lion; Viartril NF; Vimultisa; Virobron Gel; Virobron NF; Volforte; Voltaren Colirio; Voltaren Migra†; Voltaren; Xedenol; ***Austral.***: Arthrotec; Clonact†; Dencorub Anti-Inflammatory; Diclact†; Diclohexal†; Dinact†; Fenac; Imflac; Solaraze; Viclofen; Voltaren Ophtha; Voltaren; Voltfast; ***Austria***: Algefit; Arthrotec; Dedolor; Deflamat; DiclacHexal; Diclobene; Diclomelan; Diclostad; Diclosyl; Dolostrip; Dolpasse; Flector; Solaraze; Tratul; Voltadol; Voltaren; ***Belg.***: Arthrotec; Cataflam; Dicloabak; Diclofast†; Diclofemed†; Diclotop†; Docdiclofe†; Flector; Kinespir; Motifene; Polyflam; Voltapatch; Voltaren; ***Braz.***: Artren; Belfaren; Benevran; Biofenac; Cataflam; Cataflex; Cataflexym; Cinaflan; Cinatil; Clofenak; Clofenid; Deltaflogin; Deltaren; Diclac; Diclo P; Dicloflogil; Diclogenom; Diclonaco; Diclonax; Diclonil; Diclosodico†; Diclostir; Dicloton; Dioxaflex; Dnaren; Dorflan; Dorgen; Dryltac; Fenaflan; Fenaren; Fenburil†; Fisioren; Fladon†; Flamatrat P; Flanakin†; Flanaren; Flodin Duo; Flogan; Flogiren; Flotac; Infladex; Inflamax; Kindaren†; Maxilerg; Neocoflan; Neotaflan; Neotaren; Olfen†; Ortoflan†; Poltax; Probenxil; Prodofenaco†; Sodix; Still; Tekaflex; Vendrex; Volflanil; Voltaflan; Voltaflex; Voltaren Colirio; Voltaren; Voltrix; Zotac; ***Canad.***: Apo-Diclo; Arthrotec; Novo-Difenac†; Nu-Diclo; Pennsaid; Pro-Diclo; Voltaren Ophtha; Voltaren; ***Chile***: 3A Ofteno; Amofen; Artren; Autdol; Cataflam; Deflamat; Diclac; Diclotaren; Dicogel; Elitiran; Exflam†; Flamesan; Flector; Flotac; Klafenac; Lertus; Merpal; Oftic; Pirexyl; Piroflam; Pro Lertus; Sipirac; Turbogesic; Voltaren; ***China***: Aofen (澳芬); Apo-Diclo (奥贝); Arthrotec (奥斯克); Bi Si Fu (毕斯福); Chen Jing (辰录); De Fu Ka (得富卡); Di Fu Xin (迪扶欣); Di Pu (迪普); Diclac (迪克乐克); Difene (戴芬); Difnal (迪弗纳); Digen (迪根); Fei Ya Ning (菲亚宁); Fei Yan (非言)†; Fen Di Ning (芬迪宁); Fen Na Ke (芬那克); Fendi (芬迪); Gede (格得); Ji Song (吉松); Jiu Ning (久宁); Kaflan (抗他搓); Kang Tai (康泰); Lai Bi Xin (来比新); Li Shu (立舒); Lu Lin (路林); Luck (乐可); Luo Pu Jia (洛普佳); Novolten (诺福丁); Olfen (奥尔芬); Pu Ta Ning (普他宁); Rui Pei En (瑞培恩); Shi Xiang (仕享); Si Fu Xin (思孚欣); Tian Jun Li (天君利); Tian Xin Li Do (天新利博); Tong Du Ding (同杜叮); Voltaren (扶他林); Voren (非言); Xi Shu (普舒); Xin Pu Fen (欣普芬); Yi Er Song (依尔松); Yi Ke (依柯); Yi Ke Lin (宜克林); Yi Lin (依林); Yingtaiqing (英太青); Zhi Qing (至清); ***Cz.***: Almiral; Apo-Diclo; Dicloabak; Diclofen†; Dicloreum; DIKY; Dolmina; Dorosan†; Flector; Monoflam; Myogit; Naklofen; Olfen; Rewodina†; Uniclophen; Uno; Veral; Voltaren; ***Denm.***: Alterflex; Arthrotec; Diclodan; Diclon; Diclopax; Dicuno; Difenet; Eeze; Fenacop†; Fenacta; Flector†; Instantin; Modifenac†; Solaraze; Voltaren; ***Fin.***: Arthrotec; Diclomex; Dicuno; Eeze; Flector†; Motifene; Solaraze; Voltaren; ***Fr.***: Artotec; Compralfene; Dicloced; Dispadol; Flector; Solaraze; Tendol; Tevalgiespray†; VoltarenActigo; Voltarendolo; Voltarene; Voltarenophta; Voltarenplast; Xenid; ***Ger.***: Allvoran†; Arthotec; Diclabeta; Diclact†; Diclo-Divido†; Diclo-Puren†; Diclo-saar†; Diclo; Diclodoc†; Diclofenbeta; Difen; Dolgit-Diclo†; Effekton; Flector; Jutafenac†; Monoflam; Optalidon Zahnschmerz mit Diclofenac†; Rewodina†; Sandoz Schmerzgel†; Solaraze; Voltaren Ophtha; Voltaren; ***Gr.***: Actisuny; Anthraxiton; Arthrotec; Batafil; Cataflam; Clonac; Contralg; Counterflame; Declofon; Delimon; Denaclof; DicloDuo; Diclofast; Diclojet; Diclophlogont; Dicloplast; Dicloral; Difend; Dinaclon; Evinopon; Eyeclof; Fenoclof; Figrel; Flefarmin; Inflaforte; Javipren; Linobol; Miniflam; Optobet; Pengon; Pennsaid; Relipain; Rheumavek; Ruvominox; Sfinac; Topalgon; Urigon; Vilacril; Vilonit; Voltaren; Vurdon; ***Hong Kong***: Almiral; Apo-Diclo; Artharen†; Arthrotec; Aston†; Cataflam; Clofec; Clofenac; Curinflam; Diclo-Denk; Diclofen; Diclogesic†; Dicofen; Difenac; Difenol†; Doroxan; Erdon; Eurofenac; Fenac; Fenadium; Flector; Flogofenac†; Grofenac†; Inflanac; Lesflam; Olfen; Painoff†; Panaflex; Remafen; Remethan; Ren; Rhemofenax†; Ruvominox; Synfenac†; Takst†; Tapain; Uniren; Vartelon; Viclofenac†; Voltaren Ophtha; Voltaren; Voltont†; Votalen†; Zolterol; ***Hung.***: Cataflam; Diclac; Diclomel; Flameril†; Flector; Fortedol; Voltaren Ophta; Voltaren; ***India***: Aclomax; Adgel; Adiflam; Agile-K; Agile; Alefen; Antiflam; Argesic; Ark; Armdic; Artilov; B-Nac; Beconac; Bestodek; Bidnac; Bionac; Bioran; Cadmax; Cannact; Capsigyl-D; Caredec; Clopar; Cofenac; Combinac; D-Nova; Dacron; Deedo; Defcin; Delbitol; Delta-K; Demo; Dersy; Devona; Diclam; Diclasia; Diclo-DT; Diclo-K; Dicloact; Dicloat; Diclobit; Diclodol; Diclodyne; Diclofam; Diclofast; Diclofen; Dicloflam; Dicloflame; Diclolab; Dicloma; Diclomax; Diclomol; Diclomol; Diclomove; Diclonac; Diclonet; Diclonij; Diclonip; Diclonova; Dicloran; Diclostar; Diclotal; Diclovar; Diclowin; Diclozed; Dicnac; Dicnacx; Dico; Dicol; Dicoliv; Dicos; Dicron; Dicven; Difenac; Difenic; Difin; Difisal; Diklofen; Dikonb; Dikpa; Dikul; Dilofen; Dilona; Dion; Disoral; Divexx; Divon; DLF; Dofec; Doflex; Dolact; Dolocide K; Dolocide Plus; Dolzy; DS-15; Dynapar; E-Nac; E-Par; Emflam; Emflam; Esgipyrin DS; Exflam; Fenac; Fenbest; Fendase; Fengel; Fensaid; Fensaide; Fento; Fineact; Flamese; Flexigesic-K; Flexigesic; Gic; Haloran; I-Gesic; Imflamol; Inac; Indofen; Intragesic; Jonac; Justin; K-Fenac; Knac; Lafen; Leemax; Lipcy; Lofen; Lofy; Lysoflam; Mifenac; Mindol; Mishanac; Misonac; Mobiaid; Mobyle; Nac Gel; Nac; Naclo; Nal-M; Neodol; Nifdec; Noctel; Novofen; Novoflam; NSAID Eye; Nudiclo; Nufenac; Nupatch; Odonac; Onafen; Ontac; Oronac; Osteoflam; Oxalgin-D; Oxalgin-SR; Oxalgin; Oxynal; Painkair; Panama; Parafortan; Profenac; Reactine; Relaxyl; Relaxyl; Solunact†; Tromagesic; Tromax; Voveran; ***Indon.***: Abdiflam†; Aclonac; Alflam; Araclof; Atranac; Berifen†; Cataflam; Catanac; Deflamat; Dicloflam; Diclomec†; Diflam; Divoltar; Eflagen; Elithris; Exaflam; Fenaren†; Fenavel; Flamar; Flamenact†; Flamic; Inflam; Kadiflam; Kaditic; Kaflam; Kamaflam; Klotaren; Laflanac; Linac; Matsunaflam; Merflam; Nacoflar; Nadifen; Neurofenac; Nichoflam; Nilaren; Potazen†; Prostanact†; Provoltar; Reclofen; Renadinac; Renvol; Scanaflam; Scantaren; Tirmaclo; Troflam; Valto; Volmatik; Voltadex; Voltaren Ophtha; Voltaren; Voren; X-Flam; Xepathritis; Yariflam; Zegren; ***Irl.***: Arthrotec; Cataflam; Diclac; Diclo; Diclomax†; Diclomel†; Difene; Flector; Kyflam; Solaraze; Voltarol Ophtha; Voltarol; Voltfast; ***Israel***: Abitren; Arthrotec; Betaren; Cataflam; Demofenac; Dicloftil; Dicloplast; Diclorengel; Olfen; Physicare Gel; Swiss Relief; Voltaren Ophtha; Voltaren; ***Ital.***: Algosenac; Artrotec; Dealgic; Deflamat; Diclocular; Diclofan; Dicloftil; Dicloral; Dicloreum; Diclotears; Diep Grat; Dolaut; Doroxan; Dropflam; Fenadol; Fender; Flector; Flogofenac; Itami; Leviogel; Misofenac; Nadiclopht; Novapirina; Pennsaid; Solaraze; Topfans†; Traulen; Voltadol; Voltadvance; Voltaren; Voltfast; Zeroflog; ***Jpn***: Anavan; ***Malaysia***: Almiral; Analpan; Cataflam; Clofec; Clofenac†; Difnal; Doroxan; Fenac; Inflanac; Lesflam; Neo-Pyrazon†; Olfen; Panaflex Extra; Remafen†; Remethan; Rhemofenax; Uniren; Vokam; Voltaren; Voren; Zolterol; ***Mex.***: 3A Ofteno; Alsidexten†; Ariflam; Artrenac Pro; Artrenac; Artrene; Artrotec; Atalak; Calaffler; Catafast; Cataflam; Clo-Far; Clofenix; Clonodifen†; Coral; Deflox; Dicfafena; Diclac; Diclopisa; Dicloran; Diclosol; Dioxaflex; Diqfanol; Dirret; Docril; Dofen†; Doflatem; Dolaren; Dolflam; Dolofenac; Doltarac; Evadol; Fenagel; Fenalgin; Fervex; Flamydol; Flamygel; Flankol; Flogoken; Flotac; Fortical; Fustaren†; Galedol; Hipo Sport; Lertus; Lifenac; Liroken; Lodyfen; Lonatec; Lufac-Z; Mafena; Manacon; Merxil; Metracin†; Musol; Nediclon; Neo-Dolaren; Pharmaflam; Practiser; Precifenac; Selectofen; Solof; Still; Vicmafen†; Volfenac; Voltaren; ***Neth.***: Arthrotec; Cataflam; Dicloabak; Eminocs; Itami†; Misofenac†; Naclof; Normulen†; Otriflu; Voltaren Emulgel; Voltaren; ***Norw.***: Arthrotec; Cataflam; Modifenac; Otriflu†; Solaraze; Voltaren Ophtha; Voltaren; Voltarol; ***NZ***: Apo-Diclo; Cataflam; Diclax; Diclohexal†; Flameril; Voltaren Ophtha; Voltaren; Voltfast; ***Philipp.***: Acuflam; Canefol; Cataflam; Cataflin; Clofenix; Clofil; Clonaren†; Curafen; Dafenac; Diclogen; Difenamin; Difenax; Diflapane; Doloflam; Dycon; Dynapar; Eslofen†; Fenaspec; Fendil; Klaxon; Lobafen; Lofenax; Maxi; Medclof; Neo-Pyrazon; Nepenthe†; Parafortan; Rheuflam; Uniclonax†; Vifenac; Vodefen; Volfenn; Voltaren; Voren; Votan; Zobid; ***Pol.***: Apo-Diclo†; Arthrotec; Cataflam; Diclac; Dicloabak; Diclober‖; Diclobion†; DicloDuo; Dicloratio; Dicloreum; Diclozjaja; Difadol; Diklonat P; Diklozjaja†; Diky; Felogel; Glimbax; Majamil; Naclof; Naklofen; Olfen; Ratiogel†; Rewodina†; Veral; Voltaren; Voltenac; ***Port.***: Arthrotec; Cataflam; Clofen: Dagesil; Dicloabak; Diclodent; Diclofar; Dicloftal†; Diclospray; Dicloteq†; Dofene; Dolacen; Dorcalor; Fenac; Fenil-V; Flameril; Flector; Frenalgil; Olfen; Otriflu; Painex; Pennsaid; Solaraze; Voltadol; Voltaren; ***Rus.***: Almiral (Альмирал)†; Apo-Diclo (Апо-дикло)†; Arthrotec (Артротек); Bioran (Биоран); Diclac (Диклак); Diclo-F (Дикло-ф); Diclobene (Диклобене); Dicloberl (Диклоберл)†; Diclogen (Диклоген); Diclonat (Диклонат); Dicloran (Диклоран); Diclovit (Дикловит); Etyfenac (Этифенак); Flameril (Фламерил); Naclof (Наклоф)†; Naklofen (Наклофен); Naklofen Duo (Наклофен Дуо); Neodol (Неодол); Ortofen (Ортофен); Ortofer (Ортофер); Ortoflex (Ортофлекс); Ortophen (Ортофен); Rapten Duo (Раптен дуо); Rapten Rapid (Раптен Рапид); Rheumavek (Ревмавек); Uniclophen (Униклофен); Voltaren (Вольтарен); ***S.Afr.***: Adco-Clofelam; Arcanafenac†; Arthrotec; Arthru-Derm; Catafast; Cataflam; Dicloflam; Diclohexal; Difen; Difenject; Dynak; Fenisun; Flexagen†; Fortfen; Infla-Ban†; K-Fenak; Panamor; Veltex; Voltaren Ophtha; Voltaren; ***Singapore***: Almiral; Analpan; Apo-Diclo; Cataflam; Clofec; Clofenac; Diclo-Denk; Diclo; Dicloran; Difenac; Difnal; Fenac; Fenadium; Flector; Inac; Inflanac; Lesflam; Neodol; Olfen; Panaflex Extra†; Panamax; Pritaren; Remafen; Remethan; Rhewlin; SP-Nadofen; Ultrafen; Uniren; Voltaren Ophtha; Voltaren; Voltfast; Voren; Zolterol: ***Spain***: Artrotec; Di Retard; Dicloabak; Dolo Nervobion†; Dolo-Voltaren; Dolotren; Luaset†; Normulen†; Ratioparch†; Solaraze; Voltadol; Voltaren; Xibol; ***Swed.***: Arthrotec; Dicuno; Eeze; Eezeneo; Flector†; Solaraze; Voltaren Ophtha; Voltaren T; Voltaren; ***Switz.***: Arthrotec; Diclac; Dicloabak; Diclosifar†; Difen-Stulln; Ecofenac; Effigel; Fenisole†; Fenisun; Flam-X; Flector; Fortenac; Grofenac; Inflamac; Olfen; Primofenac; Relova; Solaraze; Tonopan; Vifenac; Voltaren Dolo; Voltaren Emulgel; Voltaren Ophta; Voltarene; Voltfast; ***Thai.***: Ammi-Votara; Ammmac; Antenac; Arclonac; Cataflam; Catanac; Cencenac; Chinclona; Chinclonac; Clofec; Clofon; Covonac; D-Fiam; Demac; Diclo; Diclogel; Diclogesic; Diclolan; Diclomol†; Diclosian; Difaren; Difelene; Difen†; Difenac; Difengesic; Difeno; Difensic; Dinac; Dinefec; Dolonil; Dosnac; Fema; Fenac; Fenacaine; Fenacil; Fenagel; Flexy; Infenac; Inflamma; Inflanac; Klyzen; Lesflam; Lofenac; Manfenac; Masaren; Myfenax; Myonac; N-Zen; Naclof†; Ostaren; Pai-Noren; Painelief; Posnac†; Remethan; Rhumanol; Sefnac; Sinclonac; Subsyde; Takst†; Tarjen; Tarjena; Uniren; V-Therlen; Vasalen†; Veenac; Ventarone; Vesconac; Volfen†; Volfenac; Volnac; Volta; Voltanac; Voltaren; Voltex Kool; Volverac; Voren; Votamed; ***Turk.***: Actinoma; Arthrotec; Cataflam; Deflamat; Dicloflam; Diclomec; Dicol; Difenak; Diklo-S; Diklopain; Dikloron; Dikloron; Dikloteva; Dolorex: Flector; Inflased; Kalidren; Miyadren; Romatim; Volfenaks; Voltaflam; Voltaren Ophta; Voltaren; ***UAE***: Clofen; ***UK***: Arthrotec; Defanac; Defenac; Dexomon; Dicloflex; Diclomax; Diclovol; Diclozip; Dyloject; Econac; Fenactol; Flamatak; Flamrase; Misofen; Mobigel†; Motifene; Pennsaid; Rheumatac; Rhumalgan; Slofenac; Solaraze; Volraman; Volsaid; Voltarol Ophtha; Voltarol; ***Ukr.***: Catafast (Катафаст); Clodifen (Клодифен); Diclac (Диклак); Diclo-F (Дикло-Ф); Diclobene (Диклобене); Dicloberl (Диклоберл); Diclobru (Диклобрю); Diclocain (Диклокаин); Diclopherol (Диклоферол)†; Diftal (Дифталь); Megafen Plus (Мегафен Плюс)†; Naclof (Наклоф); Naklofen (Наклофен); Olfen (Олфен); Rapten (Раптен); Voltaren (Вольтарен); ***USA***: Arthrotec; Cambia; Cataflam; Flector; Pennsaid; Solaraze; Voltaren; Voltaren; Zipsor; Zorvolex; ***Venez.***: 3A Ofteno; Arthrotec; Artren; Campal; Cataflam; Clofen; Clofenac; Diagesic; Diclofen P; Diclosal; Difenac; Diklason; Diralon; Dival; Flogaren; Flotac; Klafenac; Viavox; Voltaren; Volten; Votaxil.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

BP 2014: Diclofenac Gel; Gastro-resistant Diclofenac Tablets; Prolonged-release Diclofenac Capsules; Prolonged-release Diclofenac Tablets;

USP 36: Diclofenac Potassium Tablets; Diclofenac Sodium Delayed-release Tablets; Diclofenac Sodium Extended-Release Tablets.

Diethylamine Salicylate

Diaethylamini Salicylas; Dietylaminsalicylat; Dietyyliamiinisalisylaatti; Salicilato de dietilamina; Salisilat Dietilamin; Диэтиламин Салицилат; Салицилат Диэтиламина.

$C_{11}H_{17}NO_3$=211.3

CAS — 4419-92-5.

UNII — 5V7PT38BJU.

Pharmacopoeias. In *Br.* and *Chin.*

BP 2014: (Diethylamine Salicylate). White or almost white, odourless or almost odourless crystals. Very soluble in water; freely soluble in alcohol and in chloroform. Protect from light. Avoid contact with iron or iron salts.

Profile

Diethylamine salicylate is a salicylic acid derivative used topically in rubefacient preparations similarly to methyl salicylate (p. 92.1) for rheumatic and muscular pain.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Algesal†; ***Canad.***: Chirogesic; Physiogesic; ***China***: Duo Rui (多瑞); ***Fin.***: Algesal†; ***Fr.***: Algesal; ***Gr.***: Algesal; ***Hung.***: Aciphen; ***India***: Multigesic; ***Neth.***: Algesal†; ***Norw.***: Algesal; ***Pol.***: Saldiam; ***Port.***: Algicum†; Algiderma†; Massagim; ***Swed.***: Algesal; ***Turk.***: Algesal; Reparil; ***UK***: Algesal; Lloyd's Cream; ***Venez.***: Alesal.

Multi-ingredient Preparations. ***Arg.***: Algesal; Cartiflex; Crema Antiinflamatoria; Rati Salil Flex; Salicrem; ***Austral.***: Rubesal; ***Austria***: Algesal; Derivon; Dolo-Menthoneurin; Latesyl; Reparil; Rheugesal†; Rilfit-Rheumasalbe; Traumasal; ***Belg.***: Reparil; ***Braz.***: Reparil; Reparil; ***Chile***: Repariven; ***China***: Ou Lai (欧莱); Reparil-Gel N (利百莱凝胶); ***Cz.***: Algesal; Reparil-Gel N; ***Fr.***: Algesal Suractive; Reparil; Traumalgyl†; ***Ger.***: Algesal†; Reparil-Gel N; ***Gr.***: Algesal Suractive; Ponostop; ***Hong Kong***: Reparil; Rubesal†; ***Hung.***: Algesal; Reparil N; ***India***: Neurophen; ***Indon.***: Algesal Superactive; ***Ital.***: Edeven; Liotontrauma; Reparil CM; Sedalpan; Viamal Trauma; ***Malaysia***: Reparil-Gel N; ***Neth.***: Algesal Forte†; ***Philipp.***: Reparil N; ***Pol.***: Reparil N; ***Port.***: Algesal; Latesil; Medalginan; Venoparil; ***Rus.***: Reparil-Gel N (Репарил-Гель Н); ***S.Afr.***: Reparil; ***Singapore***: Reparil-Gel N; ***Spain***: Algesal; Contusin; Dolmitin†; Feparil; Radio Salil; ***Switz.***: Mavena Proctal-Gen†; Reparil N; ***Thai.***: Reparil; Veno-Gel†; ***Turk.***: Algesal Suractive; Prepagel; ***UAE***: Rubicalm; ***UK***: Fiery Jack; Transvasin Heat Spray; ***Ukr.***: Reparil-Gel N (Репарил-Гель Н); ***Venez.***: Lemazol.

Pharmacopoeial Preparations

BP 2014: Diethylamine Salicylate Cream.

Diflunisal *(BAN, USAN, rINN)*

Diflunisaali; Diflunisalis; Diflunisalum; Difluniszal; MK-647; Дифлунисал.

5-(2,4-Difluorophenyl)salicylic acid.

$C_{13}H_8F_2O_3$=250.2

CAS — 22494-42-4.

ATC — N02BA11.

ATC Vet — QN02BA11.

UNII — 7C546U4DEN.

Pharmacopoeias. In *Br.*, *Chin.*, and *US.*

BP 2014: (Diflunisal). A white or almost white, crystalline powder. Practically insoluble in water; soluble in alcohol. Dissolves in dilute solutions of alkali hydroxides. It exhibits polymorphism. Protect from light.

USP 36: (Diflunisal). A white to off-white, practically odourless, powder. Insoluble in water and in hexane; freely soluble in alcohol and in methyl alcohol; soluble in acetone and in ethyl acetate; slightly soluble in carbon tetrachloride, in chloroform, and in dichloromethane.

Uses and Administration

Diflunisal is a salicylic acid derivative (see Aspirin, p. 22.3) but it is not hydrolysed to salicylate and its clinical effects resemble more closely those of propionic acid derivative NSAIDs such as ibuprofen (p. 68.3). Diflunisal is given in the

acute or long-term management of mild to moderate pain, and pain and inflammation associated with osteoarthritis and rheumatoid arthritis. The usual initial oral dose for pain relief is 1 g followed by a maintenance dose of 500 mg every 12 hours although some patients may require 500 mg every 8 hours. In others, a lower initial dose of 500 mg followed by 250 mg every 8 to 12 hours may be sufficient. The usual oral dose for arthritis is 500 mg to 1 g daily in 2 divided doses, adjusted according to response. Maintenance doses greater than 1.5 g daily are not recommended regardless of indication. Doses may need to be reduced in patients with renal impairment, see below.

Diflunisal arginine has been used similarly given orally or by intramuscular or intravenous injection.

Administration in renal impairment. Diflunisal may need to be given in reduced dosage in patients with significant renal impairment and should not be given when renal impairment is severe.

Adverse Effects and Treatment

As for NSAIDs in general, p. 104.3. The commonest adverse effects occurring with diflunisal are gastrointestinal disturbances, headache, and rash. Peptic ulceration and gastrointestinal bleeding have been reported. Dizziness, drowsiness, insomnia, and tinnitus may also occur.

Effects on the blood. Haematological adverse effects associated with diflunisal appear to be infrequent. Thrombocytopenia associated with diflunisal-induced peripheral platelet destruction has been reported in a patient with rheumatoid arthritis.[1] Heinz-body haemolytic anaemia has also been reported, see Hypersensitivity, below.

1. Bobrove AM. Diflunisal-associated thrombocytopenia in a patient with rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 148–9.

Effects on the kidneys. Acute interstitial nephritis, presenting as acute oliguric renal failure, erythroderma, and eosinophilia has followed the use of diflunisal.[1]

1. Chan LK, *et al.* Acute interstitial nephritis and erythroderma associated with diflunisal. *BMJ* 1980; 280: 84–5.

Effects on the lungs. For reference to pneumonitis associated with diflunisal therapy, see Hypersensitivity, below.

Effects on the skin. Reports of Stevens-Johnson syndrome associated with diflunisal.[1,2] See also Hypersensitivity, below.

1. Hunter JA, *et al.* Diflunisal and Stevens-Johnson syndrome. *BMJ* 1978; 2: 1088.
2. Grom JA, *et al.* Diflunisal-induced erythema multiforme major. *Hosp Formul* 1986; 21: 353–4.

Hypersensitivity. Three cases of hypersensitivity to diflunisal in which the main clinical features were fever, elevated liver enzyme values, erythroderma, and eosinophilia, have been reported.[1] Heinz-body haemolytic anaemia occurred in one of the patients. Other hypersensitivity reactions associated with diflunisal therapy have included pneumonitis[2] and fulminant necrotising fasciitis.[3]

1. Cook DJ, *et al.* Three cases of diflunisal hypersensitivity. *Can Med Assoc J* 1988; 138: 1029–30.
2. Rich MW, Thomas RA. A case of eosinophilic pneumonia and vasculitis induced by diflunisal. *Chest* 1997; 111: 1767–9.
3. Krige JEJ, *et al.* Necrotising fasciitis after diflunisal for minor injury. *Lancet* 1985; ii: 1432–3.

Overdosage. Diflunisal poisoning has sometimes been fatal.[1,2] A dose of 15 g has been reported to have caused death when no other drugs were involved but a dose of 7.5 g has also been fatal when taken with other drugs.

1. Court H, Volans GN. Poisoning after overdose with non-steroidal anti-inflammatory drugs. *Adverse Drug React Acute Poisoning Rev* 1984; 3: 1–21.
2. Levine B, *et al.* Diflunisal related fatality: a case report. *Forensic Sci Int* 1987; 35: 45–50.

Precautions

As for NSAIDs in general, p. 107.1. Diflunisal may need to be given in reduced dosage in patients with significant renal impairment and should not be given when renal impairment is severe. Aspirin and other acetylated salicylates are not recommended for use in children unless specifically indicated, because of the risk of Reye's syndrome. Although this precaution has not been specifically extended to diflunisal it is not generally licensed for use in children.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies diflunisal as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Aspirin may produce a small decrease in the plasma concentration of diflunisal. Diflunisal has been reported to increase the plasma concentrations of indometacin and paracetamol; diflunisal with indometacin has been associated with fatal gastrointestinal haemorrhage and therefore the combination should not be used. Regular use of antacids may reduce the absorption of diflunisal.

Benzodiazepines. For the effect of diflunisal on plasma concentrations of *oxazepam*, see p. 1068.1.

Probenecid. Average steady-state plasma concentrations of diflunisal were increased by 65% when it was given with probenecid.[1] This was due mainly to reduced formation of the phenolic and acyl glucuronides. However, plasma concentrations of these glucuronides and the sulfate conjugate were also increased even more because probenecid also reduced their renal clearance.

1. Macdonald JI, *et al.* Effect of probenecid on the formation and elimination kinetics of the sulphate and glucuronide conjugates of diflunisal. *Eur J Clin Pharmacol* 1995; 47: 519–23.

Pharmacokinetics

Diflunisal is well absorbed from the gastrointestinal tract and peak plasma concentrations occur about 2 to 3 hours after ingestion of a single dose. It is more than 99% bound to plasma protein and has a plasma half-life of about 8 to 12 hours. Diflunisal exhibits non-linear pharmacokinetics so that doubling the dose more than doubles drug accumulation. Due to the long half-life and non-linear kinetics, several days are required to reach steady-state plasma concentrations after multiple dosing. The time to steady-state concentrations can be reduced by giving an initial loading dose. Concentrations of diflunisal in synovial fluid reach about 70% of those in plasma. Diflunisal is excreted in the urine mainly as glucuronide conjugates. Some biliary recycling may also occur. Diflunisal is distributed into breast milk with concentrations reported to be about 2 to 7% of those in plasma.

References.
1. Loewen GR, *et al.* Effect of dose on the glucuronidation and sulphation kinetics of diflunisal in man: single dose studies. *Br J Clin Pharmacol* 1988; 26: 31–9.
2. Eriksson L-O, *et al.* Influence of renal failure, rheumatoid arthritis and old age on the pharmacokinetics of diflunisal. *Eur J Clin Pharmacol* 1989; 36: 165–74.
3. Verbeeck RK, *et al.* The effect of multiple dosage on the kinetics of glucuronidation and sulphation of diflunisal in man. *Br J Clin Pharmacol* 1990; 29: 381–9.
4. Macdonald JI, *et al.* Sex-difference and the effects of smoking and oral contraceptive steroids on the kinetics of diflunisal. *Eur J Clin Pharmacol* 1990; 38: 175–9.
5. Nuernberg B, *et al.* Pharmacokinetics of diflunisal in patients. *Clin Pharmacokinet* 1991; 20: 61–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Cleating (巨力新); Ning Hu Shu Xin (宁湖舒欣); ***Gr.***: Analeric; Di-Flu; ***Thai.***: Dolobid; ***Turk.***: Dolphin.

Pharmacopoeial Preparations
BP 2014: Diflunisal Tablets;
USP 36: Diflunisal Tablets.

Dihydrocodeine *(BAN, rINN)*

Dihidrocodeína; Dihydrocodéine; Dihydrocodeinum; Дигидрокодеин.

4,5-Epoxy-3-methoxy-17-methylmorphinan-6-ol.

$C_{18}H_{23}NO_3$=301.4

CAS — 125-28-0.

ATC — N02AA08.

ATC Vet — QN02AA08.

UNII — N9I9HDB855.

Dihydrocodeine Phosphate *(BANM, rINNM)*

Dihidrocodeína, fosfato de; Dihydrocodéine, Phosphate de; Dihydrocodeini Phosphas; Fosfato de dihidrocodeína; Hydrocodeine Phosphate; Дигидрокодеина Фосфат.

$C_{18}H_{23}NO_3.H_3PO_4$=399.4

CAS — 24204-13-5.

ATC — N02AA08.

ATC Vet — QN02AA08.

UNII — 5D9XI60ASE.

Pharmacopoeias. In *Jpn*.

Dihydrocodeine Tartrate *(BANM, rINNM)*

Dihidrocodeína, tartrato de; Dihidrokodein-hidrogén-tartrát; Dihidrokodeino-vandenilio tartratas; Dihydrocodeine Acid Tartrate; Dihydrocodeine Bitartrate; Dihydrocodeine Hydrogen Tartrate; Dihydrocodéine, hydrogénotartrate de; Dihydrocodéine, Tartrate de; Dihydrocodeini Bitartras; Dihydrocodeini Hydrogenotartras; Dihydrocodeini Tartras; Dihydrocodein[(R,R)-tartrat]; Dihydrokodeiinivetytartratti; Dihydrokodein-tartarát; Dihydrokodeinvätetartrat; Dihydrokodeiny wodorowinian; Drocode Bitartrate; Hydrocodeine Bitartrate; Tartrato de dihidrocodeína; Дигидрокодеина Тартрат.

$C_{18}H_{23}NO_3.C_4H_6O_6$=451.5

CAS — 5965-13-9.

UNII — 8LXS95B5A9.

NOTE. Compounded preparations of dihydrocodeine tartrate may be represented by the following names:

- Co-dydramol (*BAN*)—dihydrocodeine tartrate 1 part and paracetamol 50 parts (w/w).

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of dihydrocodeine tartrate:

DFs; Diffs; Duncan Flockharts.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Dihydrocodeine Hydrogen Tartrate; Dihydrocodeine Tartrate BP 2014). A white or almost white crystalline powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in cyclohexane. A 10% solution in water has a pH of 3.2 to 4.2. Protect from light.

USP 36: (Dihydrocodeine Bitartrate). pH of a 10% solution in water is between 3.2 and 4.2. Store in airtight containers.

Uses and Administration

Dihydrocodeine is an opioid analgesic (p. 108.1). It is related to codeine (p. 40.3) and has similar analgesic activity. Dihydrocodeine is used for the relief of moderate to severe pain, often in combination preparations with paracetamol. It has also been used as a cough suppressant.

For **analgesia** the usual oral dose of dihydrocodeine tartrate is 30 mg after food every 4 to 6 hours; up to 240 mg daily may be given for severe pain. Modified-release preparations are available for twice daily dosage in patients with chronic severe pain.

Dihydrocodeine tartrate may also be given by deep subcutaneous or intramuscular injection in doses of up to 50 mg every 4 to 6 hours.

For details of doses in children, see below.

As a **cough suppressant** dihydrocodeine tartrate may be given in oral doses of 10 to 30 mg up to three times daily.

Dihydrocodeine phosphate has also been used. Other salts of dihydrocodeine used, mainly for their antitussive effects, include the hydrochloride, the polistirex, and the thiocyanate. Dihydrocodeine polistirex has also been used in modified-release preparations.

Administration in children. In the UK, dihydrocodeine tartrate may be given orally, or by deep subcutaneous or intramuscular injection, for analgesia in children aged from 4 to 12 years in usual doses of 0.5 to 1 mg/kg (to a maximum of 30 mg) every 4 to 6 hours; older children may be given the usual adult dose (see above). Although unlicensed in children aged under 4 years, the *BNFC* suggests giving those aged 1 to 4 years 500 micrograms/kg every 4 to 6 hours.

Dyspnoea. Dihydrocodeine has been reported[1] to have produced benefit in normocapnic patients severely disabled by breathlessness due to chronic airflow obstruction. A dose of 15 mg was taken 30 minutes before exercise up to three times daily.

1. Johnson MA, *et al.* Dihydrocodeine for breathlessness in 'pink puffers'. *BMJ* 1983; 286: 675–7.

Pain. Dihydrocodeine is used in the management of moderate to severe pain. However, dose-related increase in postoperative pain has been seen[1] in patients given 25 or 50 mg dihydrocodeine tartrate intravenously after dental surgery, and it has been proposed that dihydrocodeine might act as an antagonist in situations where acute pain was accompanied by high opioid activity.[2] Systematic review of the use of single oral doses of dihydrocodeine has indicated that these are insufficient to provide adequate relief of postoperative pain, and that dihydrocodeine is less effective than ibuprofen.[3]

1. Seymour RA, *et al.* Dihydrocodeine-induced hyperalgesia in postoperative dental pain. *Lancet* 1982; i: 1425–6.
2. Henry JA. Dihydrocodeine increases dental pain. *Lancet* 1982; ii: 223.
3. Moore RA, *et al.* Single dose dihydrocodeine for acute postoperative pain. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2000 (accessed 26/06/08).

Dependence and Withdrawal

As for Opioid Analgesics, p. 109.1.

Dihydrocodeine has been subject to abuse (see under Precautions, below).

Adverse Effects and Treatment

As for Opioid Analgesics in general, p. 110.1; adverse effects of dihydrocodeine are less pronounced than those of morphine.

Overdosage. A 29-year-old man who had taken 2.1 g of dihydrocodeine had biochemical evidence of acute renal and hepatic impairment when admitted 13 hours after the overdose.[1] Severe life-threatening respiratory depression subsequently developed 36 hours after the overdose and only responded to treatment with naloxone after large doses (a total of 46.6 mg of naloxone) over a long period (106 hours). Commenting on this report some questioned the evidence for hepatic impairment and considered that the raised liver enzyme values were of muscular origin as a result of rhabdomyolysis.[2-4] Rhabdomyolysis may also have contributed to renal failure.

An anaphylactoid reaction after an overdose with an unspecified number of dihydrocodeine tablets[5] appeared to respond to intravenous naloxone.

1. Redfern N. Dihydrocodeine overdose treated with naloxone infusion. *BMJ* 1983; **287:** 751–2.
2. Buckley BM, Vale JA. Dihydrocodeine overdose treated with naloxone infusion. *BMJ* 1983; **287:** 1547.
3. Blain PG, Lane RJM. Dihydrocodeine overdose treated with naloxone infusion. *BMJ* 1983; **287:** 1547.
4. Wen P. Dihydrocodeine overdose treated with naloxone infusion. *BMJ 1983*; **287:** 1548.
5. Panos MZ, *et al.* Use of naloxone in opioid-induced anaphylactoid reaction. *Br J Anaesth* 1988; **61:** 371.

Pain. For reference to increased postoperative pain associated with the use of dihydrocodeine, see under Uses and Administration, p. 52.3.

Precautions

As for Opioid Analgesics in general, p. 110.3.

Abuse. Dihydrocodeine has been reported to be widely abused by opiate addicts.[1-4]

1. Swadi H, *et al.* Misuse of dihydrocodeine tartrate (DF 118) among opiate addicts. *BMJ* 1990; **300:** 1313.
2. Robertson JR, *et al.* Misuse of dihydrocodeine tartrate (DF 118) among opiate addicts. *BMJ* 1990; **301:** 119.
3. Sirang J, *et al.* Misuse of dihydrocodeine tartrate (DF 118) among opiate addicts. *BMJ* 1990; **301:** 119.
4. Seymour A, *et al.* The role of dihydrocodeine in causing death among drug users in the west of Scotland. *Scott Med J* 2001; **46:** 143–6.

The elderly. Despite some renal impairment an elderly group of patients[1] appeared to handle dihydrocodeine similarly to healthy young subjects. There was marked variability in all measurements and on the basis of this study no clear conclusions on guidelines for dosage in elderly patients could be drawn. However, the recommendation that small doses be given initially with subsequent doses according to response was endorsed.

1. Davies KN, *et al.* The effect of ageing on the pharmacokinetics of dihydrocodeine. *Eur J Clin Pharmacol* 1989; **37:** 375–9.

Renal impairment. Caution is necessary when giving dihydrocodeine to patients with severe renal impairment. Severe narcosis occurred in a patient with anuria and on maintenance haemodialysis after she had received dihydrocodeine orally for 4 days.[1] She responded to treatment with naloxone.

See also under Pharmacokinetics, below.

1. Barnes JN, Goodwin FJ. Dihydrocodeine narcosis in renal failure. *BMJ* 1983; **286:** 438–9.

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

Quinidine. Dihydrocodeine is metabolised via the cytochrome P450 isoenzyme CYP2D6 to active metabolites, which may perhaps play a role in its analgesic activity in extensive metabolisers; quinidine impairs this metabolism, but a study in 11 healthy subjects did not find any reduced analgesic activity when dihydrocodeine was given with quinidine, despite a three- to fourfold reduction in plasma concentrations of the metabolite dihydromorphine.[1]

1. Wilder-Smith CH, *et al.* The visceral and somatic antinociceptive effects of dihydrocodeine and its metabolite, dihydromorphine: a cross-over study with extensive and quinidine-induced poor metabolizers. *Br J Clin Pharmacol* 1998; **45:** 575–81.

Pharmacokinetics

Peak concentrations of dihydrocodeine occur about 1.2 to 1.8 hours after oral doses; oral bioavailability is only about 20%, probably because of substantial first-pass metabolism in the gut wall or liver. Dihydrocodeine is metabolised in the liver via the cytochrome P450 isoenzyme CYP2D6, to dihydromorphine, which has potent analgesic activity, although the analgesic effect of dihydrocodeine appears to be mainly due to the parent compound; some is also converted via CYP3A4 to nordihydrocodeine. Dihydrocodeine is excreted in urine as unchanged drug and metabolites, including glucuronide conjugates. Elimination half-life is reported to range from about 3.5 to 5 hours.

References.

1. Rowell FJ, *et al.* Pharmacokinetics of intravenous and oral dihydrocodeine and its acid metabolites. *Eur J Clin Pharmacol* 1983; **25:** 419–24.
2. Fromm MF, *et al.* Dihydrocodeine: a new opioid substrate for the polymorphic CYP2D6 in humans. *Clin Pharmacol Ther* 1995; **58:** 374–82.
3. Ammon S, *et al.* Pharmacokinetics of dihydrocodeine and its active metabolite after single and multiple dosing. *Br J Clin Pharmacol* 1999; **48:** 317–22.
4. Webb JA, *et al.* Contribution of dihydrocodeine and dihydromorphine to analgesia following dihydrocodeine administration in man: a PK-PD modelling analysis. *Br J Clin Pharmacol* 2001; **52:** 35–43.

Renal impairment. The pharmacokinetics of dihydrocodeine tartrate, given as a single oral 60-mg dose, were affected in 9 patients with chronic renal failure treated with haemodialysis when compared with 9 healthy subjects.[1] Time to peak plasma concentration in those with renal failure was 3 hours compared with 1 hour in healthy subjects; the area under the plasma concentration-time curve was greater in those with renal failure; and after 24 hours dihydrocodeine was still detectable in the plasma of all renal failure patients, but in only 3 of the healthy subjects.

1. Barnes JN, *et al.* Dihydrocodeine in renal failure: further evidence for an important role of the kidney in the handling of opioid drugs. *BMJ* 1985; **290:** 740–2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Paracodin†; Rikodeine; ***Austria***: Codidol; Dehace; Paracodin; Paracodin; ***Belg.***: Codicontin†; Paracodine; ***China***: Xi Gai Ke (西盖克); ***Cz.***: DHC Continus; ***Fr.***: Dicodin; ***Ger.***: DHC; Paracodin N; Paracodin; Tiamon Mono; ***Gr.***: Dolcontin; ***Hong Kong***: DF 118; ***Hung.***: DHC; Hydrocodin; ***Irl.***: DF 118; DHC Continus†; Paracodin; ***Ital.***: Paracodina; ***Malaysia***: DF 118; Dicogesic; Suncodin; ***NZ***: DHC Continus; ***Pol.***: DHC Continus; ***S.Afr.***: DF 118; Paracodin; ***Spain***: Paracodina; Tosidrin; ***Switz.***: Codicontin; Paracodin; ***UK***: DF 118; DHC Continus.

Multi-ingredient Preparations. ***Arg.***: Lentusin; ***Austral.***: Codox†; ***China***: Gugaike (路盖克); ***Hong Kong***: Codaewon; ***Irl.***: Paramol; ***Ital.***: Cardiazol-Paracodina; Paracodina; ***Jpn***: Colgen Kowa IB; Lightgen; ***Malaysia***: Dihydrocodeine P; ***Switz.***: Escotussin; Makatussin Comp; ***UK***: Dypracet; Paramol: Remedeine; ***USA***: Alahist DHC; Despec PDC; Despec-EXP†; DHC Plus; DiHydro-CP†; DiHydro-GP†; DiHydro-PE†; Donatuss DC; Duohist DH; EndaCof-DH†; J-COF DHC; J-Max DHC; Novahistine DH; Pancof PD†; Pancof-EXP†; Pancof†; Panlor†; Poly Hist DHC; Poly-Tussin DHC; Poly-Tussin EX; Synalgos-DC; Trezix.

Pharmacopoeial Preparations

BP 2014: Co-dydramol Tablets; Dihydrocodeine Injection; Dihydrocodeine Oral Solution; Dihydrocodeine Tablets.

Dipipanone Hydrochloride *(BANM, rINNM)*

Dipipanona, hidrocloruro de; Dipipanone, Chlorhydrate de; Dipipanoni Hydrochloridum; Hidrocloruro de dipipanona; Phenylpiperone Hydrochloride; Piperidyl Methadone Hydrochloride; Piperidylamidone Hydrochloride; Дипипанона Гидрохлорид.

(±)-4,4-Diphenyl-6-piperidinoheptan-3-one hydrochloride monohydrate.

$C_{24}H_{31}NO,HCl,H_2O$=404.0

CAS — 467-83-4 (dipipanone); 856-87-1 (dipipanone hydrochloride).

UNII — 8VY0OAJ0RL

Pharmacopoeias. In *Br.*

BP 2014: (Dipipanone Hydrochloride). An odourless or almost odourless, white, crystalline powder. Sparingly soluble in water; freely soluble in alcohol and in acetone; practically insoluble in ether. A 2.5% solution in water has a pH of 4.0 to 6.0.

Profile

Dipipanone hydrochloride is an opioid analgesic (p. 108.1) structurally related to methadone (p. 88.3). Used alone it is reported to be less sedating than morphine. It is used in the treatment of moderate to severe pain.

Dipipanone hydrochloride is usually given in combination preparations with the antiemetic cyclizine hydrochloride to reduce the incidence of nausea and vomiting, but the use of such preparations is not recommended for the management of chronic pain, as the antiemetic is usually only required for the first few days of treatment. The usual oral dose of dipipanone hydrochloride is 10 mg, repeated every 6 hours. The dose may be increased if necessary in increments of 5 mg; it is seldom necessary to exceed a dose of 30 mg. After an oral dose the analgesic effect begins within an hour and lasts about 4 to 6 hours.

Preparations of dipipanone hydrochloride with cyclizine hydrochloride are subject to abuse.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***S.Afr.***: Wellconal; ***UK***: Diconal†.

Pharmacopoeial Preparations

BP 2014: Dipipanone and Cyclizine Tablets.

Dipyrone *(BAN, USAN)*

Aminopyrine-sulphonate Sodium; Analginum; Dipiron; Dipirona; Dipyron; Dipyroni; Dipyronum; Metamitsolinatrium; Metamizol; Metamizol-Natrium; Metamizol sódico; Metamizol sodná sůl monohydrát; Metamizol sodowy; Metamizol Sodyum; Métamizole sodique; Metamizole Sodium (pINN); Metamizolnatrium; Metamizol-nátrium; Metamizolo natrio druska; Metamizolum Natricum; Metamizolum Natricum Monohydricum; Methampyrone; Methylmelubrin; Natrium Novaminsulfonicum; Noramidazophenum; Novamidazofen; Novaminsulfone Sodium; NSC-73205; Sodium Noramidopyrine Methanesulphonate; Sulpyrine; Метамизол Натрий.

Sodium *N*-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)-*N*-methylaminomethanesulphonate monohydrate.

$C_{13}H_{16}N_3NaO_4S,H_2O$=351.4

CAS — 68-89-3 (anhydrous dipyrone); 5907-38-0 (dipyrone monohydrate).

ATC — N02BB02.

ATC Vet — QN02BB02.

UNII — 6429L0L52Y (dipyrone); VSU62Z74ON (anhydrous dipyrone).

NOTE. Confusingly the term dipyrone sodium also appears to be used synonymously for dipyrone itself. Dipyrone is referred to in some countries by the colloquial name 'Mexican aspirin'. The names noraminophenazonum and novaminsulfon have apparently been applied to dipyrone, but it is not clear whether these are the sodium salt.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn*.

Ph. Eur. 8: (Metamizole Sodium Monohydrate; Dipyrone BP 2014). A white or almost white crystalline powder. Very soluble in water; soluble in alcohol; practically insoluble in dichloromethane. Protect from light.

Uses and Administration

Dipyrone is the sodium sulfonate of aminophenazone (p. 21.1) and has similar properties. Because of the risk of serious adverse effects, in many countries its use is considered justified only in severe pain or fever where no alternative is available or suitable. Dipyrone has been given orally in doses of 0.5 to 4 g daily in divided doses. It has also been given by intramuscular or intravenous injection and rectally as a suppository.

A magnesium congener of dipyrone, metamizole magnesium has been used similarly to dipyrone as has the calcium congener metamizole calcium.

Adverse Effects and Precautions

Use of dipyrone is associated with an increased risk of agranulocytosis and with shock.

References.

1. Levy M. Hypersensitivity to pyrazolones. *Thorax* 2000; **55** (suppl 2): S72–S74.

Effects on the blood. Data collected from 8 population groups in Europe and Israel by the International Agranulocytosis and Aplastic Anemia Study[1] revealed that there was a significant regional variability in the rate-ratio estimate for agranulocytosis and dipyrone (0.9 in Budapest to 33.3 in Barcelona). Although a large relative increase in risk between agranulocytosis and use of dipyrone was found, the incidence was less than some previous reports had suggested.

Blood dyscrasias such as agranulocytosis and granulocytopenia have continued to be reported where dipyrone remains available.[2-7]

1. The International Agranulocytosis and Aplastic Anemia Study. Risks of agranulocytosis and aplastic anemia: a first report of their relation to drug use with special reference to analgesics. *JAMA* 1986; **256:** 1749–57.
2. Hedenmalm K, Spigset O. Agranulocytosis and other blood dyscrasias associated with dipyrone (metamizole). *Eur J Clin Pharmacol* 2002; **58:** 265–74.
3. Maj S, Lis Y. The incidence of metamizole sodium-induced agranulocytosis in Poland. *J Int Med Res* 2002; **30:** 488–95.
4. Maj S, Centkowski P. A prospective study of the incidence of agranulocytosis and aplastic anemia associated with the oral use of metamizole sodium in Poland. *Med Sci Monit* 2004; **10:** PI93–PI95.

5. Ibanez L, *et al.* Agranulocytosis associated with dipyrone (metamizol). *Eur J Clin Pharmacol* 2005; 60: 821–9.
6. Hamerschlak N, Cavalcanti AB. Neutropenia, agranulocytosis and dipyrone. *Sao Paulo Med J* 2005; 123: 247–9.
7. Garcia S, *et al.* Dipyrone-induced granulocytopenia: a case for awareness. *Pharmacotherapy* 2006; 26: 440–2.

Effects on the skin. Dipyrone has been considered responsible for a case of drug-induced toxic epidermal necrolysis.[1]

1. Roujeau J-C, *et al.* Sjögren-like syndrome after drug-induced toxic epidermal necrolysis. *Lancet* 1985; i: 609–11.

Hypersensitivity. Cross-sensitivity between aspirin and dipyrone occurred in a patient.[1] Dipyrone produced an exacerbation of dyspnoea, cyanosis, and respiratory arrest.

1. Bartoli E, *et al.* Drug-induced asthma. *Lancet* 1976; i: 1357.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dipyrone (metamizole sodium) as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 10/11/11)

Pharmacokinetics

After oral doses dipyrone is rapidly hydrolysed in the gastrointestinal tract to the active metabolite 4-methylamino-antipyrine, which after absorption undergoes metabolism to 4-formyl-amino-antipyrine and other metabolites. Dipyrone is also rapidly undetectable in plasma after intravenous doses. None of the metabolites of dipyrone are extensively bound to plasma proteins. Most of a dose is excreted in the urine as metabolites. Dipyrone metabolites are also distributed into breast milk.

References.

1. Heinemeyer G, *et al.* The kinetics of metamizol and its metabolites in critical-care patients with acute renal dysfunction. *Eur J Clin Pharmacol* 1993; 45: 445–50.
2. Levy M, *et al.* Clinical pharmacokinetics of dipyrone and its metabolites. *Clin Pharmacokinet* 1995; 28: 216–34.
3. Zylber-Katz E, *et al.* Dipyrone metabolism in liver disease. *Clin Pharmacol Ther* 1995; 58: 198–209.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Analgina; Dioxadol; Dipigrand; Ditral; Fiebrol; Integrobe; Lisalgil; Novacler; Novalgina; Novemina; Taxenil; Unibios Simple; *Austria*: Novalgin; *Belg.*: Analgine; Novalgine; *Braz.*: Algirona; Anador; Analgesil†; Apiron; Baralgin; Conmel; Difebril; Dipigina; Dipimax; Dipiron†; Dipix; Diprin; Domal†; Dorona; Dorpinon†; Magnopyrol; Maxiliv; Mirador; Nofebrin; Novagreen; Novalgina; Pirogina; Prodopirona†; Santidor; Termonal; Termopirona; Termoprins†; *Chile*: Baralgina M; Conmel; *China*: Di Shuang (迪双); *Cz.*: Novalgin; *Ger.*: Analgin; Berlosin; Nopain†; Novalgin; Novaminsulfon; *Gr.*: Natralgin; Telalgin; *Hung.*: Algopyrin; Algozone; Novalgin†; Panalgorin; *India*: Analgin; Baralgan-M; Novalgin; *Indon.*: Antalgin; Antrain; Cornalgin; Foragin; Lexagin; Licogin; Norages; Novalgin; Panstop; Pragesol; Pyronal; Ronalgin; Scanalgin; Unagen; *Israel*: Optalgin; Phanalgin†; V-Dalgin; V-Talgin†; *Ital.*: Novalgina; Piralgin; *Mex.*: Alnex; Anaprol†; Anapyrol†; Avafontan; Conmel; Dalmasin; Dalsin; Defin; Dimetirol; Dipydol; Dofisan; Dolgan; Dolizol; Dolofur†; Domenal†; Exodalina; Fandall; Fardolpin; Farlin; Gelcom; Indigon; Infatem; Lozima; Mach-2; Macodin; Magnidol; Magnil; Magnol; Magnolonas; Magnopyrol; Magsons; Mayoprina; Medipirol†; Mermid†; Messelfenil; Metapirona; Midelin; Minoral; Mizoltec; Modimet†; Neo-Melubrina; Neomelin†; Neosedal; Paleodina†; Pirol†; Pirandall; Pirasod; Pirinovag; Piromebrina; Precidona; Prodolina; Prolubrin; Pyranol; Pyron; Suprin; Termonil†; Utidol; Vegal†; *Neth.*: Novalgin; *Pol.*: Pyrahexal; Pyralgin; Pyralgina; Pyralginum†; *Port.*: Dolocalma; Nolotil; *Rus.*: Analgin (Анальгин); Baralgin M (Баралгин М); *Spain*: Algi; Dolemicin; Lasain†; Metalgial; Neo Melubrina†; Nolotil; *Switz.*: Minalgin; Novalgin; *Thai.*: Centagin†; Deparon†; Genergin†; Invoigin†; Kno-Paine†; Mezabox†; Nivagin†; Novalgin†; Olan-Gin†; Pyronpac; V Day Pyrin; *Turk.*: Adepiron; Andolor; Baralgin M; Devaljin; Feninox†; Geralgine-M; Kafalgin; Nogesic; Novakom-S; Novalgin; Novo-Plan; Novopyrine; Sebon; Sedalmine; Seskaljin; Veraljin; *Urug.*: Dolanet; *Venez.*: Bral; Conmel; Delsal; Dipamona; Dipidol; Novalcina; Promel.

Multi-ingredient Preparations. *Arg.*: Antispasmina; Apasmo Compuesto; Apasmo; Artifene; Bellatotal; Buscapina Compositum; Calmopirin; Cifespasmo Compuesto; Colobolina D; Cronopen Balsamico; Dentolina Plus†; Dexiro + Dipirona†; Dextrodip†; Dioxadol; Dorixina Forte; Espasmo Biotenk; Espasmo Dioxadol; Fadagrip; Flexicamin A; Gastrolina Compuesta; Gobbicalm; Hioscina Compuesta; Integrobe Plus; Klosidol B1 B6 B12; Klosidol; Lisalgil Compuesto; Luar-G Compositum; Migra Dioxadol; Migral Compositum; Migral; Multin; Novopasmil Compuesto; Paratropina Compuesta; Pasmodina Compuesta; Profium Plus; Rupe-N Compuesto; Solacil; Sumal; Supragesic D; Tetralgin Novo; Tetralgin; Vicefeno; *Austria*: Buscopan Compositum; *Belg.*: Buscopan Compositum; *Braz.*: Algexin; Algice; Ana-Flex; Analgin C-R; Belspan; Besodin; Bicavine; Binospan; Bioflex; Buscopan Composto; Buscoveran Composto; Butilamin†; Cafilisador; Cefaldina†; Cefaliv; Dalgex†; Dexalgen; Disbuspan†; Doralgex; Doralgina; Dorciflex†; Dorflex; Dorgil; Doricin; Doridina; Dorilen; Doriless; Dorsedin; Dorspan Composto; Dorzone; Drenogrip; Enxak; Espasmocron†; Espasmodid Composto; Flexalgex; Flexdor; Gripsay; Hioariston; Hiospan Composto; Kindpasm†; Lisador; Lisantil; Migraliv; Migraranette; Mionevrix; Miorrelax; Neocopan; Neosaldina; Neuralgina; Nevralgex; Nogripe; Novralflex; Par; Reflex; Relaflex; Rielex; Royflex; Sedador; Sedalene; Sedalex; Sedalgina; Sedalin†; Sedamed; Sedol; Spasmotropin; Tensaldin; Tetrapulmo†; Tropinal; Veratropan Composto†; *Chile*: Bramedil Compuesto; Buscapina Compositum; Cefadol; Cefalmin; Cinabel; Crotalgina; Dolcopin; Dolnix; Dolonase; Esamigran; Fredol; Migragesic; Migranol; Migratam; Neo Butartrol; Nospasmin Compuesto; Piretanyl; Piretanyl; Precenid; Scopanil; Ultrimin; Viadil Compuesto; Viplan Compuesto; Viproxil Compuesto; *Cz.*: Algifen Neo; Algifen; Analgin; *Fin.*: Litalgin; *Gr.*: Dispalgine; *Hung.*: Algopyrin Complex; Quarelin; *India*: Ketonal-D; *Indon.*: Analsik; Arsinal; Biomega†; Cetalgin-T; Cetalgin; Corsanural; Dactron†; Danalgin; Deparon†; Dolo Scanneuron; Dolo-Licobion; Dormi Comp; Foraneural; Goralgin; Hedix; Hexalgin; Ikaneuron Plus; Metaneuron; Neuralgin RX; Neurindo; Neuro Panstop; Neurobat A; Neurodial; Neurogen†; Neurosanbe Plus; Neurotropic Plus; Neuroval; Opineuron; Penagon; Potensik; Pritagesic; Procolic; Proneuron; Spaslic; Spasmal; Spasminal†; Stileran; Supranal; Tropineuron; Unthecol†; Viron; *Mex.*: Algosfar; Alivin Plus; Anadil; Benfol†; Biomesina Compuesta; Bipasmin Compuesto; Buscapina Compositum; Busconet; Busepan; Busprina; Colepren; Dolo-Tiaminal; Espasmogress; Hiosultrina-F; Korifen†; Mebuxina; Neo-Brontyl†; Neo-Pasmonal; Pasmodil†; Pirobutil; Respicil; Retodol Compositum; Selpiran; Serralpina Compuesta; Singril; Viladol-Met†; *Pol.*: Gardan P†; Scopolan Compositum; Spasmalgon; Tolargin†; *Rus.*: Analgin-Chinin (Анальгин-Хинин); Andipal (Андипал); Antigrippin-ANVI (Антигриппин-АНВИ); Benalgin (Бенальгин); Bioralgin (Биоралгин); Bral (Брал); Bralangine (Бралангин); Maxigan (Максиган); Nebalgan (Небалган); Pentabufen (Пентабуфен); Pentalgin-N (Пенталгин-Н); Plenalgin (Пленалгин); Pyralgin (Пиралгин); Quintalgine (Квинталгин); Renalgan (Реналган); Revalgin (Реваллгин); Santoperalgin (Сантопералгин); Santotiralgin (Сантотиралгин); Sedal-M (Седал-М); Sedalgin-Neo (Седальгин-Нео); Spasgan (Спазган); Spasmalgon (Спазмалгон); Spasmalin (Спазмалин); Tempalgin (Темпалгин); Tempanginol (Темпангинол); Tetralgin (Тетралгин); *S.Afr.*: Buscopan Compositum; Scopex Co; *Spain*: Buscapina Compositum; *Thai.*: Butarion†; Nalgin-P; Novapam†; *Turk.*: Buscopan Compositum†; Penikin†; Peraljin†; Skopolin†; *Ukr.*: Baralginus (Баралгинус)†; Bellalgin (Беллалгин); Sedal-M (Седал-М); Spasgan (Спазган); Spasmadol (Спазмадол)†; Spasmalgon (Спазмалгон); Spasmil-M (Спазмил-М); Tempalgin (Темпалгин); Tempanal (Темпанал); Tetralgin (Тетралгин); *Venez.*: Buscapina Compositum; Butilamina Compuesta; Flemibar; Praxona; Sistalcin Compositum.

Eltenac *(rINN)*

Elténac; Eltenaco; Eltenacum; Эльтенак.
4-(2,6-Dichloroanilino)-3-thiopheneacetic acid.
$C_{12}H_9Cl_2NO_2S$=302.2
CAS — 72895-88-6.
UNII — A153L3JA99.

Profile

Eltenac is an NSAID (p. 102.3) used in veterinary medicine.

Embutramide *(BAN, USAN, rINN)*

Embutramida; Embutramidum; Hoe-18-680; Эмбутрамид.
N-(β,β-Diethyl-*m*-methoxyphenethyl)-4-hydroxybutyramide.
$C_{17}H_{27}NO_3$=293.4
CAS — 15687-14-6.
UNII — 3P4TQG94T1.

Profile

Embutramide is an opioid analgesic used in veterinary medicine for euthanasia.

Enoxolone *(BAN, rINN)*

Ácido glicirrético; Ácido glicirretínico; Enoksolonas; Enoksoloni; Enoxolon; Enoxolona; Ênoxolone; Enoxolonum; Glycyrrhetic Acid; Glycyrrhetinic Acid; Kwas glicyryzynowy; Эноксолон.
3β-Hydroxy-11-oxo-olean-12-en-30-oic acid.
$C_{30}H_{46}O_4$=470.7
CAS — 471-53-4.
ATC — D03AX10.
ATC Vet — QD03AX10.
UNII — P540XA09DR.

NOTE. Do not confuse with glycyrrhizic acid (p. 2520.2).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Enoxolone). A white or almost white, crystalline powder. It exhibits polymorphism. Practically insoluble in water; soluble in dehydrated alcohol; sparingly soluble in dichloromethane. Protect from light.

Profile

Enoxolone is a complex triterpene prepared from glycyrrhizic acid (p. 2520.2), a constituent of liquorice (p. 1856.2). Enoxolone is used locally in preparations for the treatment of non-infective inflammatory disorders of the skin, mouth, throat, and rectum. Enoxolone potassium (potassium glycyrrhetinate) has been used similarly.

Derivatives of enoxolone, including its aluminium salt (p. 1843.3) and carbenoxolone (p. 1828.3) have been used in the treatment of benign peptic ulcer disease and other gastrointestinal disorders.

Enoxolone is a potent inhibitor of the enzyme 11β hydroxysteroid dehydrogenase, which inactivates cortisol and use with hydrocortisone has been shown in *anima* studies to potentiate the activity of hydrocortisone in skin. Whether this also increased the systemic absorption and toxicity of hydrocortisone was unclear.[2] However, fo reference to adverse effects attributed to systemic inhibition of cortisol when enoxolone (glycyrrhetinic acid) is produced during metabolism of ingested liquorice, see Mineralocorticoid Effects, p. 1856.3.

A cream containing enoxolone with hyaluronic acid telmesteine, and a grape extract, has been investigated with apparent benefit in the management of mild to moderate eczema[3,4] and is available for such use in some countries However, topical application of enoxolone has been associated with contact dermatitis.[5]

1. Teelucksingh S, *et al.* Potentiation of hydrocortisone activity in skin by glycyrrhetinic acid. *Lancet* 1990; 335: 1060–3.
2. Greaves MW. Potentiation of hydrocortisone activity in skin by glycerrhetinic acid. *Lancet* 1990; 336: 876.
3. Belloni G, *et al.* A randomised, double-blind, vehicle-controlled study to evaluate the efficacy and safety of MAS063D (Atopiclair) in the treatment of mild to moderate atopic dermatitis. *Eur J Dermatol* 2005; 15 31–6.
4. Abramovits W, Boguniewicz M. Adult Atopiclair Study Group. A multicenter, randomized, vehicle-controlled clinical study to examine the efficacy and safety of MAS063DP (Atopiclair) in the management of mild to moderate atopic dermatitis in adults. *J Drugs Dermatol* 2006; 5 236–44.
5. Tanaka S, *et al.* Allergic contact dermatitis from enoxolone. *Contact Dermatitis* 2001; 44: 192.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Dermanox; *Fr.*: Arthrodont; PO 12; *Hung.*: Arthrodont; *S.Afr.*: Arthrodont†; *Singapore*: Arthrodont; *USA*: PruClair.

Multi-ingredient Preparations. *Arg.*: Anastim; Empecid Pie; *Austral.*: Atopiclair†; *Braz.*: Capilos; *Chile*: Gelclair; Ruboril; Sebium AKN†; Suavigel; *Fr.*: Dermeol; Eryginе†; Hexalyse; Humex Gorge Irritee†; Hyseke Solaire; Hyseke; Kelual DS; Kelual DS; Night Peel†; Novophane DS; Novophane K; Phlebocreme; Phlebosup; Pyreflor†; Sebium AKN; Sedorrhoide; Vocadys; *Ger.*: Gelclair; *Hong Kong*: Alox†; Hexalyse; *Indon.*: Aloclair; Atopiclair; Polikf†; *Israel*: Aphtagone†; Aptha-X†; Atopiclair; Xclair; *Ital.*: Acnesan; Bactilene†; Biolastic T5; Biothymus DS; Biogofort†; Brunex; Flogofort Cremagel; Fluocaril; Lenipasta; Lenirose; Lisomucil Gola; Neo-Stomygen; Perfluxi Cremagel; Prurex; Resvelife Sole; Resvelife; Skab 2†; Vaginol; *Mex.*: Angenovag; Periodentyl; *Mon.*: Phytospray; *Port.*: Despigmentante†; *Rus.*: Hexalyse (Гексализ); *Singapore*: Atopiclair; Vetic; *Spain*: Angileptol; Anginovag; Roberfarin; *UK*: Atopiclair; Gelclair; Xclair; *Ukr.*: Anginovag (Ангиновaг); Anzibel (Анзибел); Hexalyse (Гексализ); *USA*: Atopiclair; Gelclair; *Venez.*: Sebium AKN; Sensibio DS.

Epirizole *(USAN, pINN)*

DA-398; Epirizol; Épirizole; Epirizolum; Mepirizole; Эпиризол.
4-Methoxy-2-(5-methoxy-3-methylpyrazol-1-yl)-6-methylpyrimidine.
$C_{11}H_{14}N_4O_2$=234.3
CAS — 18694-40-1.
UNII — 3B46O2FH8I.

Pharmacopoeias. In *Jpn.*

Profile

Epirizole is an NSAID (p. 102.3) that has been given in a usual oral dose of 150 to 450 mg daily in divided doses; larger doses of up to 600 mg daily have been used in patients with rheumatoid arthritis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Mebron; *Venez.*: Dalex.

Eptazocine Hydrobromide *(HNNM)*

Eptazocine, Bromhydrate d'; Eptazocini Hydrobromidum; Hidrobromuro de eptazocina; ST-2121; Эптазоцина гидробромид.

(-)-(1*S*,6*S*)-2,3,4,5,6,7-Hexahydro-1,4-dimethyl-1,6-methano-1*H*-4-benzazonin-10-ol hydrobromide.

$C_{15}H_{21}NO,HBr$=312.3

CAS — 72522-13-5 (eptazocine); 72150-17-5 (eptazocine hydrobromide).

UNII — 865626Y4ON.

Profile

Eptazocine hydrobromide is an opioid analgesic with mixed opioid agonist and antagonist actions. It has been given by subcutaneous or intramuscular injection for the relief of pain.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Sedapain.

Etanercept *(BAN, USAN, rINN)*

Etanercept; Etanerceptum; Etanersept; Etanersepti; rhu-TNFR:Fc; TNR-001; Этанерцепт.

A dimer of 1-235 tumour necrosis factor receptor (human) fusion protein with 236-467-immunoglobulin G1 (human γ1-chain Fc fragment).

CAS — 185243-69-0.

ATC — L04AB01.

ATC Vet — QL04AB01.

UNII — OP401G7OJC.

Uses and Administration

Etanercept is a recombinant version of soluble human TNF receptor that binds specifically to tumour necrosis factor (p. 878.2) and blocks its interaction with endogenous cell-surface TNF receptors. This interaction prevents the important effect of TNF in the inflammatory processes of rheumatoid arthritis; elevated TNF levels are also found in psoriatic plaques, in the synovium of patients with psoriatic arthritis, and in the serum and synovium of patients with ankylosing spondylitis. Etanercept is described as a biological disease-modifying antirheumatic drug (DMARD).

Etanercept is used in the treatment of moderately to severely active **rheumatoid arthritis** (below) and active and progressive **psoriatic arthritis** (see Spondyloarthropathies, below). In the UK, it is licensed for use in patients who have had an inadequate response to standard DMARDs although in severe rheumatoid arthritis it may be used in patients not previously treated with methotrexate. In the USA, it is licensed to treat early rheumatoid arthritis or psoriatic arthritis. Etanercept is also indicated in the treatment of severely active **ankylosing spondylitis** (see Spondyloarthropathies, below); in the UK, its use is again limited to those who have had an inadequate response to conventional therapy. For all the above indications, it is given as a subcutaneous injection in a dose of 25 mg twice weekly at intervals of 3 or 4 days; the equivalent weekly dose of 50 mg may also be given as a single 50-mg injection. In the UK, NICE recommends that etanercept be stopped if there is no adequate response after 6 months for the treatment of rheumatoid arthritis, and after 12 weeks for psoriatic arthritis or ankylosing spondylitis.

Etanercept is also used in the treatment of chronic, moderate to severe **plaque psoriasis** (below). In the UK, its use is usually limited to patients unresponsive to, or intolerant of, conventional systemic therapy including photochemotherapy. The recommended initial dose is 25 mg twice weekly. Alternatively, an initial dose of 50 mg twice weekly at intervals of 3 or 4 days may be given for 12 weeks; the dose should then be reduced to 25 mg twice weekly or 50 mg once weekly. Initial doses of 25 or 50 mg once weekly have also been shown to be effective. Treatment should continue until remission is achieved, for up to 24 weeks. Etanercept should be stopped after 12 weeks in patients who show no response.

For details of uses and dosage in children, see below.

Administration in children. Etanercept is used in the treatment of moderately to severely active polyarticular **juvenile idiopathic arthritis** in children aged 2 years and older. In the UK, it is licensed for the treatment of polyarthritis or extended oligoarthritis in those who have had an inadequate response to, or who are intolerant of, the disease-modifying antirheumatic drug (DMARD) methotrexate. Etanercept is given subcutaneously in a dose of 400 micrograms/kg (up to a maximum dose of 25 mg) twice weekly at intervals of 3 or 4 days; alternatively, 800 micrograms/kg (up to a maximum dose of 50 mg) may be given once weekly. In the USA, etanercept is licensed for use in children aged 2 years and older to reduce the signs and symptoms of moderately to severely active polyarticular disease. Similar doses are used although doses to be given as 2 separate injections may either be given on the same day or 3 to 4 days apart. In the UK, NICE recommends that treatment be stopped in children if there is no response after 6 months, or an initial response is not maintained.

In the UK, etanercept is also licensed for the treatment of enthesitis-related arthritis and **psoriatic arthritis** in those aged 12 years and older who have had an inadequate response to, or who are intolerant of, conventional therapy; doses are similar to those given for polyarticular juvenile idiopathic arthritis above.

Etanercept is also used in the treatment of chronic severe plaque **psoriasis** in children aged 6 years and older; its use is limited to those in whom other systemic treatments are not suitable. The UK licensed dose is 800 micrograms/kg (up to a maximum dose of 50 mg) subcutaneously once weekly for up to 24 weeks; treatment should be stopped after 12 weeks in those who show no response.

Asthma. TNF inhibitors such as etanercept have been investigated in the treatment of refractory asthma (p. 1195.2).[1-3] There is some evidence that only a minority of patients will respond to such therapy, and that the benefits and risks must therefore be carefully assessed.[4]

1. Howarth PH, *et al.* Tumour necrosis factor (TNFα) as a novel therapeutic target in symptomatic corticosteroid dependent asthma. *Thorax* 2005; **60**: 1012–18.
2. Berry MA, *et al.* Evidence of a role of tumor necrosis factor α in refractory asthma. *N Engl J Med* 2006; **354**: 697–708.
3. Morjaria JB, *et al.* The role of a soluble TNFα receptor fusion protein (etanercept) in corticosteroid refractory asthma: a double blind, randomised, placebo controlled trial. *Thorax* 2008; **63**: 584–91.
4. Brightling C, *et al.* Targeting TNF-α: a novel therapeutic approach for asthma. *J Allergy Clin Immunol* 2008; **121**: 5–10.

Dementia. A small pilot study[1] and individual case reports[2] have suggested that perispinal injection of etanercept, in doses of 25 to 50 mg weekly, may improve signs of dementia in patients with Alzheimer's disease. However, randomised controlled studies are required to confirm any benefit.

1. Tobinick E, *et al.* TNF-alpha modulation for treatment of Alzheimer's disease: a 6-month pilot study. *MedGenMed* 2006; **8**: 25. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1785182/?tool=pubmed (accessed 28/07/10)
2. Tobinick EL, Gross H. Rapid cognitive improvement in Alzheimer's disease following perispinal etanercept administration. *J Neuroinflammation* 2008; **5**: 2. Available at: http://www.jneuroinflammation.com/content/pdf/1742-2094-5-2.pdf (accessed 13/06/08)

Psoriasis. Etanercept is effective in patients with moderate to severe plaque psoriasis (p. 1688.1).[1-12] It has also been successfully tried in the treatment of erythrodermic psoriasis,[13] and of plaque psoriasis in children and adolescents.[14]

Efficacy may be dose-related; in one study,[1] 25% of patients in the low-dose (25 mg once weekly) group showed at least a 75% improvement compared with 44% in the medium-dose group (25 mg twice weekly) and 59% in the high-dose group (50 mg twice weekly) after 24 weeks of etanercept treatment. However, a later multicentre study[2] in patients with chronic plaque psoriasis found that the therapeutic effect of etanercept was maintained when the dose was reduced after 12 weeks from 50 mg twice weekly to 25 mg twice weekly. An open-label extension[8] of these 2 studies found that efficacy was also sustained when patients who had received etanercept 25 mg twice weekly for at least 24 weeks had their dose altered to 50 mg once weekly.

1. Leonardi CL, *et al.* Etanercept as monotherapy in patients with psoriasis. *N Engl J Med* 2003; **349**: 2014–22.
2. Papp KA, *et al.* A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. *Br J Dermatol* 2005; **152**: 1304–12.
3. NICE. Etanercept and efalizumab for the treatment of adults with psoriasis: Technology Appraisal Guidance 103 (issued July 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/TA103guidance.pdf (accessed 13/06/08)
4. Boehncke W-H, *et al.* European Dermatology Expert Group. Recommendations for the use of etanercept in psoriasis: a European dermatology expert group consensus. *J Eur Acad Dermatol Venereol* 2006; **20**: 988–98.
5. Woolacott N, *et al.* NHS Health Technology Assessment Programme. Etanercept and efalizumab for the treatment of psoriasis: a systematic review (issued November 2006). Available at: http://www.hta.ac.uk/fullmono/mon1046.pdf (accessed 13/06/08)
6. Tyring S, *et al.* Long-term safety and efficacy of 50 mg of etanercept twice weekly in patients with psoriasis. *Arch Dermatol* 2007; **143**: 719–26.
7. Romero-Maté A, *et al.* Efficacy and safety of etanercept in psoriasis/psoriatic arthritis: an updated review. *Am J Clin Dermatol* 2007; **8**: 143–55.
8. Elewski B, *et al.* Comparison of clinical and pharmacokinetic profiles of etanercept 25 mg twice weekly and 50 mg once weekly in patients with psoriasis. *Br J Dermatol* 2007; **156**: 138–42.
9. Ahmad K, Rogers S. Two years of experience with etanercept in recalcitrant psoriasis. *Br J Dermatol* 2007; **156**: 1010–14.
10. van de Kerkhof PCM, *et al.* Once weekly administration of etanercept 50 mg is efficacious and well tolerated in patients with moderate-to-severe plaque psoriasis: a randomized controlled trial with open-label extension. *Br J Dermatol* 2008; **159**: 1177–85.
11. Ortonne J-P, *et al.* Patients with moderate-to-severe psoriasis recapture clinical response during re-treatment with etanercept. *Br J Dermatol* 2009; **161**: 1190–5.
12. Sterry W, *et al.* Comparison of two etanercept regimens for treatment of psoriasis and psoriatic arthritis: PRESTA randomised double blind multicentre trial. Abridged version: *BMJ* 2010; **340**: 300. Full version: http://www.bmj.com/cgi/reprint/340/feb02_2/c147 (accessed 06/05/10)
13. Esposito M, *et al.* Treatment of erythrodermic psoriasis with etanercept. *Br J Dermatol* 2006; **155**: 156–9.
14. Paller AS, *et al.* Etanercept Pediatric Psoriasis Study Group. Etanercept treatment for children and adolescents with plaque psoriasis. *N Engl J Med* 2008; **358**: 241–51.

Rheumatoid arthritis. Some references[1-22] to the use of etanercept in rheumatoid arthritis (p. 13.2) and juvenile idiopathic arthritis (p. 12.1).

1. NICE. Guidance on the use of etanercept for the treatment of juvenile idiopathic arthritis: Technology Appraisal Guidance 35 (issued March 2002). Available at: http://www.nice.org.uk/nicemedia/pdf/JIA-PDF.pdf (accessed 13/06/08)
2. Klareskog L, *et al.* TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) Study Investigators. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet* 2004; **363**: 675–81.
3. Genovese MC, *et al.* Longterm safety, efficacy, and radiographic outcome with etanercept treatment in patients with early rheumatoid arthritis. *J Rheumatol* 2005; **32**: 1232–42.
4. Bathon JM, *et al.* Safety and efficacy of etanercept treatment in elderly subjects with rheumatoid arthritis. *J Rheumatol* 2006; **33**: 234–43.
5. van Riel PLCM, *et al.* ADORE (Add Enbrel or Replace Methotrexate) Study Investigators. Efficacy and safety of combination etanercept and methotrexate versus etanercept alone in patients with rheumatoid arthritis with an inadequate response to methotrexate: the ADORE study. *Ann Rheum Dis* 2006; **65**: 1478–83.
6. Moreland LW, *et al.* Etanercept treatment in adults with established rheumatoid arthritis: 7 years of clinical experience. *J Rheumatol* 2006; **33**: 854–61.
7. van der Heijde D, *et al.* Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. *Arthritis Rheum* 2006; **54**: 1063–74.
8. Chen Y-P, *et al.* NHS Health Technology Assessment Programme. A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness (issued November 2006). Available at: http://www.hta.ac.uk/fullmono/mon1042.pdf (accessed 13/06/08)
9. Weisman MH, *et al.* A placebo-controlled, randomized, double-blinded study evaluating the safety of etanercept in patients with rheumatoid arthritis and concomitant comorbid diseases. *Rheumatology (Oxford)* 2007; **46**: 1122–5.
10. Dhillon S, *et al.* Etanercept: a review of its use in the management of rheumatoid arthritis. *Drugs* 2007; **67**: 1211–41. Correction. *ibid.*: 1849.
11. van der Heijde D, *et al.* Etanercept Study 400 Investigators. The safety and efficacy of adding etanercept to methotrexate or methotrexate to etanercept in moderately active rheumatoid arthritis patients previously treated with monotherapy. *Ann Rheum Dis* 2008; **67**: 182–8.
12. van der Heijde D, *et al.* Disease remission and sustained halting of radiographic progression with combination etanercept and methotrexate in patients with rheumatoid arthritis. *Arthritis Rheum* 2007; **56**: 3928–39.
13. NICE. Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis (includes a review of technology appraisal guidance 36): Technology Appraisal Guidance 130 (issued October 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/TA130guidance.pdf (accessed 13/06/08)
14. Gartlehner G, *et al.* Biologics for the treatment of juvenile idiopathic arthritis: a systematic review and critical analysis of the evidence. *Clin Rheumatol* 2008; **27**: 67–76.
15. Lovell DJ, *et al.* Pediatric Rheumatology Collaborative Study Group. Safety and efficacy of up to eight years of continuous etanercept therapy in patients with juvenile rheumatoid arthritis. *Arthritis Rheum* 2008; **58**: 1496–1504.
16. Emery P, *et al.* Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. *Lancet* 2008; **372**: 375–82.
17. NICE. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (part review of NICE technology appraisal guidance 36 and review of NICE technology appraisal guidance 126 and 141): Technology Appraisal Guidance 195 (issued August 2010). Available at: http://www.nice.org.uk/nicemedia/live/13108/50413/50413.pdf (accessed 04/11/10)
18. Emery P, *et al.* COMET (Combination of Methotrexate and Etanercept in Early Rheumatoid Arthritis) Trial Group. Two-year clinical and radiographic results with combination etanercept-methotrexate therapy versus monotherapy in early rheumatoid arthritis: a two-year, double-blind, randomized study. *Arthritis Rheum* 2010; **62**: 674–82. Correction. *ibid.*: 3005.
19. Wiens A, *et al.* Meta-analysis of the efficacy and safety of adalimumab, etanercept, and infliximab for the treatment of rheumatoid arthritis. *Pharmacotherapy* 2010; **30**: 339–53.
20. Klareskog L, *et al.* Etanercept Study 301 Investigators. Assessment of long-term safety and efficacy of etanercept in a 5-year extension study in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2011; **29**: 238–47.
21. Otten MH, *et al.* Factors associated with treatment response to etanercept in juvenile idiopathic arthritis. *JAMA* 2011; **306**: 2340–7.
22. Atzeni F, Sarzi-Puttini P. Twelve years' experience with etanercept in the treatment of rheumatoid arthritis: how it has changed clinical practice. *Expert Rev Clin Immunol* 2012; **8**: 213–22.

Spondyloarthropathies. References[1-16] to the use of etanercept in the treatment of ankylosing spondylitis and psoriatic arthritis (p. 14.3).

1. Davis JC, *et al.* Enbrel Ankylosing Spondylitis Study Group. Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. *Arthritis Rheum* 2003; **48**: 3230–6.
2. Mease PJ, *et al.* Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. *Arthritis Rheum* 2004; **50**: 2264–72.

3. Baraliakos X, *et al.* Outcome of patients with active ankylosing spondylitis after two years of therapy with etanercept: clinical and magnetic resonance imaging data. *Arthritis Rheum* 2005; 53: 856–63.
4. Mease PJ, *et al.* Continued inhibition of radiographic progression in patients with psoriatic arthritis following 2 years of treatment with etanercept. *J Rheumatol* 2006; 33: 712–21.
5. van der Heijde D, *et al.* Etanercept Study 314 Investigators. Etanercept 50 mg once weekly is as effective as 25 mg twice weekly in patients with ankylosing spondylitis. *Ann Rheum Dis* 2006; 65: 1572–7.
6. Cantini F, *et al.* Switching from infliximab to once-weekly administration of 50 mg etanercept in resistant or intolerant patients with ankylosing spondylitis: results of a fifty-four-week study. *Arthritis Rheum* 2006; 55: 812–6.
7. Woolacott NF, *et al.* Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review. *Clin Exp Rheumatol* 2006; 24: 587–93.
8. Gottlieb AB, *et al.* Use of etanercept for psoriatic arthritis in the dermatology clinic: the Experience Diagnosing, Understanding Care, and Treatment with Etanercept (EDUCATE) study. *J Dermatolog Treat* 2006; 17: 343–52.
9. Braun J, *et al.* Improvement in patient-reported outcomes for patients with ankylosing spondylitis treated with etanercept 50 mg once-weekly and 25 mg twice-weekly. *Rheumatology (Oxford)* 2007; 46: 999–1004.
10. Romero-Maté A, *et al.* Efficacy and safety of etanercept in psoriasis/psoriatic arthritis: an updated review. *Am J Clin Dermatol* 2007; 8: 143–55.
11. Frankel EH, *et al.* Etanercept improves psoriatic arthritis patient-reported outcomes: results from EDUCATE. *Cutis* 2007; 79: 322–6.
12. McLeod C, *et al.* NHS Health Technology Assessment Programme. Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation (issued August 2007). Available at: http://www.hta.ac.uk/fullmono/mon1128.pdf (accessed 31/10/08)
13. Hoy SM, Scott LJ. Etanercept: a review of its use in the management of ankylosing spondylitis and psoriatic arthritis. *Drugs* 2007; 67: 2609–33.
14. NICE. Adalimumab, etanercept and infliximab for ankylosing spondylitis: Technology Appraisal Guidance 143 (issued May 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA143Guidance.pdf (accessed 31/10/08)
15. Sterry W, *et al.* Comparison of two etanercept regimens for treatment of psoriasis and psoriatic arthritis: PRESTA randomised double blind multicentre trial. Abridged version: *BMJ* 2010; 340: 300. Full version: http://www.bmj.com/cgi/reprint/340/feb02_2/c147 (accessed 06/05/10)
16. NICE. Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (review of technology appraisal guidance 104 and 125): Technology Appraisal Guidance 199 (issued August 2010). Available at: http://www.nice.org.uk/nicemedia/live/13110/50422/50422.pdf (accessed 19/10/10)

Vasculitic syndromes. For a preliminary report on the use of etanercept in Takayasu's arteritis, see p. 1614.3.

Adverse Effects, Treatment, and Precautions

As for Infliximab, p. 75.3.

Mild to moderate injection site reactions with symptoms of erythema, itching, pain, or swelling are common with etanercept. Other common reactions include headache, dizziness, asthenia, nausea and vomiting, abdominal pain, dyspepsia, and allergic reactions. Antibodies to etanercept may develop.

Etanercept should be used with caution in patients with heart failure.

References.
1. Sánchez Carazo JL, *et al.* Safety of etanercept in psoriasis: a critical review. *Drug Safety* 2006; 29: 675–85.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies etanercept as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 15/11/11)

Wegener's granulomatosis. The addition of etanercept to standard therapy (including cyclophosphamide or methotrexate and corticosteroids) was not shown to be effective in patients with Wegener's granulomatosis and was associated with an increased incidence of various non-cutaneous malignancies.[1] Licensed product information recommends that etanercept should not be added to therapy in patients with Wegener's granulomatosis.

1. Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus standard therapy for Wegener's granulomatosis. *N Engl J Med* 2005; 352: 351–61.

Interactions

As for Infliximab, p. 77.3. The use of etanercept with sulfasalazine has resulted in decreased white blood cell counts; however, the clinical significance of this is unknown. For an increased incidence of malignancy when etanercept was added to standard immunosuppressive therapy in patients with Wegener's granulomatosis, see above.

Pharmacokinetics

After a single subcutaneous dose of etanercept, UK licensed product information states that the mean half-life is about 70 hours, and the time to peak serum concentration 48 hours. In contrast, US information gives the half-life as 102 hours and the time to peak concentration as about 70 hours, although with a considerable range. Repeated dosing was noted to result in a two- to sevenfold increase in serum levels of etanercept in some patients.

References.
1. Korth-Bradley JM, *et al.* The pharmacokinetics of etanercept in healthy volunteers. *Ann Pharmacother* 2000; 34: 161–4.
2. Zhou H. Clinical pharmacokinetics of etanercept: a fully humanized soluble recombinant tumor necrosis factor receptor fusion protein. *J Clin Pharmacol* 2005; 45: 490–7.
3. Yim D-S, *et al.* Population pharmacokinetic analysis and simulation of the time-concentration profile of etanercept in pediatric patients with juvenile rheumatoid arthritis. *J Clin Pharmacol* 2005; 45: 246–56.
4. Don BR, *et al.* The pharmacokinetics of etanercept in patients with end-stage renal disease on haemodialysis. *J Pharm Pharmacol* 2005; 57: 1407–13.
5. Nestorov I. Clinical pharmacokinetics of tumor necrosis factor antagonists. *J Rheumatol* 2005; 74 (suppl): 13–18.
6. Sullivan JT, *et al.* Bioequivalence of liquid and reconstituted lyophilized etanercept subcutaneous injections. *J Clin Pharmacol* 2006; 46: 654–61.
7. Nestorov I, *et al.* Pharmacokinetics of subcutaneously administered etanercept in subjects with psoriasis. *Br J Clin Pharmacol* 2006; 62: 435–45.
8. Elewski B, *et al.* Comparison of clinical and pharmacokinetic profiles of etanercept 25 mg twice weekly and 50 mg once weekly in patients with psoriasis. *Br J Dermatol* 2007; 156: 138–42.
9. Zhou SY, *et al.* Integrated population pharmacokinetics of etanercept in healthy subjects and in patients with rheumatoid arthritis and ankylosing spondylitis. *J Clin Pharmacol* 2011; 51: 864–75.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Enbrel; *Austral.*: Enbrel; *Austria*: Enbrel; *Belg.*: Enbrel; *Braz.*: Enbrel; *Canad.*: Enbrel; *Chile*: Enbrel; *China*: Enbrel (恩利); Yisaipu (益赛普); *Cz.*: Enbrel; *Denm.*: Enbrel; *Fin.*: Enbrel; *Fr.*: Enbrel; *Ger.*: Enbrel; *Gr.*: Enbrel; *Hong Kong*: Enbrel; *Hung.*: Enbrel; *India*: Enbrel; Enbrol; *Indon.*: Enbrel; *Irl.*: Enbrel; *Israel*: Enbrel; *Ital.*: Enbrel; *Malaysia*: Enbrel; *Mex.*: Enbrel; *Neth.*: Enbrel; *Norw.*: Enbrel; *NZ*: Enbrel; *Philipp.*: Enbrel; *Pol.*: Enbrel; *Port.*: Enbrel; *Rus.*: Enbrel (Энбрел); *S.Afr.*: Enbrel; *Singapore*: Enbrel; *Spain*: Enbrel; *Swed.*: Enbrel; *Switz.*: Enbrel; *Thai.*: Enbrel; *Turk.*: Enbrel; *UK*: Enbrel; *USA*: Enbrel; *Venez.*: Enbrel.

Ethenzamide *(BAN, rINN)*

Aethoxybenzamidum; Etentsamidi; Etenzamid; Etenzamida; Etenzamide; Éthenzamide; Ethenzamidum; Ethoxybenzamide; Ethylsalicylamide; HP-209; Этензамид.

2-Ethoxybenzamide.

$C_9H_{11}NO_2$=165.2

CAS — 938-73-8.

ATC — N02BA07.

ATC Vet — QN02BA07.

UNII — L929ZCK4BF.

Pharmacopoeias. In *Jpn*.

Profile

Ethenzamide is a salicylic acid derivative (see Aspirin, p. 22.2) given orally in painful and inflammatory conditions and to reduce fever.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Helopyrin; Seltoc†; *Indon.*: Farapon; Neo Novapon Plus; *Jpn*: Sin Colgen Kowa Kaze†; *Pol.*: Erka; Etomar; Etopiryna; *Port.*: Cephyl†; *Rus.*: Nextrim Aktiv (Некстрим Актив).

Ethoheptazine Citrate *(BANM, rINNM)*

Citrato de etoheptacina; Éthoheptazine, Citrate d'; Ethoheptazini Citras; Etoheptacina, citrato de; Wy-401; Этогептазина Цитрат.

Ethyl 1-methyl-4-phenylperhydroazepine-4-carboxylate dihydrogen citrate.

$C_{16}H_{23}NO_2.C_6H_8O_7$=453.5

CAS — 77-15-6 (ethoheptazine); 6700-56-7 (ethoheptazine citrate); 2085-42-9 ((±)-ethoheptazine citrate).

UNII — LXK8EE245D.

Profile

Ethoheptazine citrate is an opioid analgesic (p. 108.1) structurally related to pethidine (p. 121.3). It has been used as an analgesic in the short-term treatment of mild to moderate pain, usually with other drugs such as aspirin and meprobamate.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *India*: Equagesic; *S.Afr.*: Equagesic†.

Ethyl Nicotinate

Nicotinato de etilo; Этилникотинат.

$C_8H_9NO_2$=151.2

CAS — 614-18-6.

UNII — NIJ3H353YH.

Profile

Ethyl nicotinate is used in concentrations of up to 2% in topical rubefacient preparations for the relief of pain in musculoskeletal, joint, and soft-tissue disorders. It has also been used as suppositories in anorectal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Mucotherm.

Multi-ingredient Preparations. *Belg.*: Transvane; *Hung.*: Nicoflex; *Irl.*: Transvasin†; *Rus.*: Nicoflex (Никофлекс); *Switz.*: Baume Esco Forte†; Knobel Huile N†; Ziegella†; *UK*: Boots Pain Relief Heat Rub; Boots Pain Relief Heat Spray; Pain Relief Balm†; Pain Heat Spray†; Transvasin Heat Rub.

Ethyl Salicylate

Salicilato de etilo; Этилсалицилат.

Ethyl 2-hydroxybenzoate.

$C_9H_{10}O_3$=166.2

CAS — 118-61-6.

UNII — 555U6TZ2MV.

Profile

Ethyl salicylate is a salicylic acid derivative that is used similarly to methyl salicylate (p. 92.1) in concentrations of up to 5% in topical rubefacient preparations for the relief of pain in musculoskeletal, joint, and soft-tissue disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Deep Heat; *Belg.*: Rado-Salil; *Chile*: Calorub Sport; *Hung.*: Deep Heat Spray; *Irl.*: Deep Heat; Ralgex; *Israel*: Deep Heat Spray; *Ital.*: Remystick; *Pol.*: Deep Heat; *S.Afr.*: Deep Heat Spray†; *UK*: Deep Heat Spray; Dubam; Numark Muscle Spray†; *Ukr.*: Deep Heat (Дип Хит).

Ethylmorphine Hydrochloride *(BANM)*

Aethylmorphinae Hydrochloridum; Aethylmorphini Hydrochloridum; Chlorhydrate de Codéthyline; Ethylmorfin-hydrochlorid dihydrát; Éthylmorphine, chlorhydrate d'; Ethylmorphinhydrochlorid; Ethylmorphini Hydrochloridum; Ethylmorphini Hydrochloridum Dihydricum; Ethylmorphinium Chloride; Etilmorfina, hidrocloruro de; Etilmorfin-hidroklorid; Etilmorfino hidrocloridas; Etylmorfinhydroklorid; Etylomorfiny chlorowodorek; Etyylimorfiinihydrokloridi; Этилморфина Гидрохлорид.

3-O-Ethylmorphine hydrochloride dihydrate; 7,8-Didehydro-4,5-epoxy-3-ethoxy-17-methylmorphinan-6-ol hydrochloride dihydrate.

$C_{19}H_{23}NO_3.HCl.2H_2O$=385.9

CAS — 76-58-4 (ethylmorphine); 125-30-4 (ethylmorphine hydrochloride).

ATC — R05DA01; S01XA06.

ATC Vet — QR05DA01; QS01XA06.

UNII — MFM5450P3T (ethylmorphine hydrochloride); 407X3NQV4N (ethylmorphine hydrochloride dihydrate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn*.

Ph. Eur. 8: (Ethylmorphine Hydrochloride). A white or almost white crystalline powder. Soluble in water and in alcohol. A 2% solution in water has a pH of 4.3 to 5.7. Protect from light.

Profile

Ethylmorphine hydrochloride is an opioid analgesic (p. 108.1) and has properties similar to those of codeine (p. 40.2). It is used mainly as a cough suppressant. It has also been used for its analgesic and antidiarrhoeal properties. It was formerly given in eye drops as a lymphagogue.

Ethylmorphine free base and the camphorate and camsilate have also been used.

References.
1. Aasmundstad TA, *et al.* Biotransformation and pharmacokinetics of ethylmorphine after a single oral dose. *Br J Clin Pharmacol* 1995; 39: 611–20.
2. Jonasson B, *et al.* Fatal poisonings where ethylmorphine from antitussive medications contributed to death. *Int J Legal Med* 1999; 112: 299–302.
3. Helland A, *et al.* Death of a 10-month-old boy after exposure to ethylmorphine. *J Forensic Sci* 2010; 55: 551–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dionina; ***Belg.***: Codethyline; ***Cz.***: Diolan†; ***Fin.***: Cocillana; ***Fr.***: Clarix Toux Seche Codethyline; Pectosan Toux Seche†; Peter's Sirop; ***India***: Dionindon; ***UK***: Collins Elixir.

Multi-ingredient Preparations. ***Belg.***: Baume Pulmonaire; Longbalsem†; Saintbois; ***Chile***: Codelasa; ***Fin.***: Indalgin; ***Fr.***: Ephydion†; Tussipax; Tussipax; Vegetoserum†; Vegetoserum; ***Hong Kong***: Fritussin†; ***Hung.***: Dolor†; ***India***: Bell Diono Resolvent†; Bell Resolvent†; ***Norw.***: Cosylan; Solvipect comp; ***Spain***: Demusin†; ***Swed.***: Cocillana-Etyfin; Lepheton; ***Switz.***: Phol-Tux; Sano Tuss; ***Turk.***: Fenokodin†; Neocodin; ***Venez.***: Novacodin.

Etodolac *(BAN, USAN, rINN)*

AY-24236; Etodolaakki; Étodolac; Etodolaco; Etodolacum; Etodolak; Etodolák; Etodolakas; Etodolic Acid; Этодолак.

1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-ylacetic acid.

$C_{17}H_{21}NO_3$=287.4

CAS — 41340-25-4.

ATC — M01AB08.

ATC Vet — QM01AB08.

UNII — 2M36281008.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Etodolac). A white or almost white crystalline powder. Practically insoluble in water; freely soluble in dehydrated alcohol and in acetone.

USP 36: (Etodolac). Store in airtight containers.

Uses and Administration

Etodolac, a pyrano-indoleacetic acid derivative, is an NSAID (p. 102.3) reported to be a preferential inhibitor of cyclo-oxygenase-2 (COX-2). It is used for rheumatoid arthritis, including juvenile idiopathic arthritis, and osteoarthritis and for the treatment of acute pain.

For the treatment of rheumatoid arthritis and osteoarthritis, the recommended oral dose is initially 0.6 to 1 g daily in divided doses adjusted according to response to a usual dose of 300 to 600 mg daily. Modified-release preparations are available for once-daily use in these conditions. For doses in children, see below.

For the treatment of acute pain, the recommended dose is 200 to 400 mg every 6 to 8 hours to a maximum of 1 g daily.

Reviews.

1. Tirunagari SK, *et al.* Single dose oral etodolac for acute postoperative pain in adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2009 (accessed 09/09/09).

Administration in children. In the USA modified-release preparations of etodolac may be given for the oral treatment of juvenile idiopathic arthritis in children aged 6 to 16 years. Doses are given once daily according to bodyweight as follows:

- 20 to 30 kg: 400 mg
- 31 to 45 kg: 600 mg
- 46 to 60 kg: 800 mg
- over 60 kg: 1 g

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3.

The presence of phenolic metabolites of etodolac in the urine may give rise to a false-positive reaction for bilirubin.

Effects on the blood. Agranulocytosis has been reported in a patient receiving etodolac.[1] Coombs-positive haemolytic anaemia due to sensitivity to etodolac metabolites has also been reported.[2]

1. Cramer RL, *et al.* Agranulocytosis associated with etodolac. *Ann Pharmacother* 1994; **28:** 458–60.
2. Cunha PD, *et al.* Immune hemolytic anemia caused by sensitivity to a metabolite of etodolac, a nonsteroidal anti-inflammatory drug. *Transfusion* 2000; **40:** 663–8.

Effects on the gastrointestinal tract. Etodolac is reported to be a preferential inhibitor of cyclo-oxygenase-2 (COX-2) and consequently it may produce less gastric toxicity than the non-selective NSAIDs such as naproxen.[1-3]

1. Taha AS, *et al.* Effect of repeated therapeutic doses of naproxen and etodolac on gastric and duodenal mucosal prostaglandins (PGs) in rheumatoid arthritis (RA). *Gut* 1989; **30:** A751.
2. Bianchi Porro G, *et al.* A double-blind gastroscopic evaluation of the effects of etodolac and naproxen on the gastrointestinal mucosa of rheumatic patients. *J Intern Med* 1991; **229:** 5–8.
3. Weideman RA, *et al.* Risks of clinically significant upper gastrointestinal events with etodolac and naproxen: a historical cohort analysis. *Gastroenterology* 2004; **127:** 1322–8.

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Pharmacokinetics

Etodolac is a chiral compound given as the racemate. Peak plasma concentrations of the active *S*-enantiomer and of the inactive *R*-enantiomer usually occur within about 2 hours of an oral dose but plasma concentrations of the *R*-enantiomer have been reported to greatly exceed those of the *S*-enantiomer. Both enantiomers are highly bound to plasma proteins. Both are also distributed to the synovial fluid, although the difference in their concentrations may not be as large as the difference in plasma concentrations. The plasma half-life of total etodolac has been reported to be about 7 hours; excretion is mainly in the urine as hydroxylated metabolites and glucuronide conjugates; some may be excreted in the bile.

References.

1. Brocks DR, *et al.* Stereoselective disposition of etodolac enantiomers in synovial fluid. *J Clin Pharmacol* 1991; **31:** 741–6.
2. Brocks DR, *et al.* The stereoselective pharmacokinetics of etodolac in young and elderly subjects, and after cholecystectomy. *J Clin Pharmacol* 1992; **32:** 982–9.
3. Brocks DR, Jamali F. Etodolac clinical pharmacokinetics. *Clin Pharmacokinet* 1994; **26:** 259–74.
4. Boni J, *et al.* Pharmacokinetic and pharmacodynamic action of etodolac in patients after oral surgery. *J Clin Pharmacol* 1999; **39:** 729–37.
5. Boni JP, *et al.* Pharmacokinetics of etodolac in patients with stable juvenile rheumatoid arthritis. *Clin Ther* 1999; **21:** 1715–24.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Flancox; ***China***: Etolac (依特); Lodine (罗丁); Na Zhi (那止); Shu Ya Ke (舒雅柯); Yi Fen (依芬); ***Denm.***: Todolac; ***Fin.***: Lodine; ***Fr.***: Lodine; ***Gr.***: Ecridoxan; Etolac; Impovituss; Lonine; Luberyl; Ofniskel; Silgonitran; ***Hong Kong***: Etonox†; Lodine†; ***India***: Etofact; Etolor; Etomax; Etova; ***Indon.***: Lonene†; ***Israel***: Etopan; ***Jpn***: Hypen; ***Philipp.***: Etoflam; ***Port.***: Acudor†; Articulan†; Dualgan; Exodolan; Sodolac; ***Switz.***: Lodine; ***Thai.***: Etonox; ***Turk.***: Dolarit; Edolar; Esodax; Etodin; Etol; Etopan; Etoteva; Etoxa; Lodine; Tadolak; Tilac; ***UK***: Eccoxolac; Etopan; Lodine; ***Ukr.***: Etol (Этол Форт).

Multi-ingredient Preparations. ***India***: Etolex-P; Etolor-P; Etomax-P; Etova-P.

Pharmacopoeial Preparations

BP 2014: Etodolac Capsules; Etodolac Tablets;

USP 36: Etodolac Capsules; Etodolac Extended-Release Tablets; Etodolac Tablets.

Etofenamate *(BAN, USAN, rINN)*

B-577; Bay-d-1107; Etofenamaatti; Etofenamat; Etofenamát; Etofenamatas; Étofénamate; Etofenamato; Etofenamatum; TV-485; TVX-485; WHR-5020; Этофенамат.

2-(2-Hydroxyethoxy)ethyl *N*-(α,α,α-trifluoro-*m*-tolyl)anthranilate.

$C_{18}H_{18}F_3NO_4$=369.3

CAS — 30544-47-9.

ATC — M02AA06.

ATC Vet — QM02AA06.

UNII — KZF0XM66JC.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Etofenamate). A yellowish viscous liquid. Practically insoluble in water; miscible with alcohol and with ethyl acetate.

Profile

Etofenamate is an NSAID (p. 102.3) that has been applied topically in a concentration of 5 or 10% for the relief of pain and inflammation associated with musculoskeletal, joint, and soft-tissue disorders. It has also been given by deep intramuscular injection in single doses of 1 g.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Flogol; ***Austria***: Rheumon; Traumon; ***Belg.***: Flexium; ***Braz.***: Aspisport; Bayro; ***Chile***: Bayagel†; Flogojet; Valorel; ***China***: Rheumon (优迈); ***Cz.***: Rheumon†; Traumon; ***Ger.***: Rheuma-Gel†; Rheumon; Traumon†; ***Gr.***: Celanat; Cimal; Etofenol; Etogel; Fenam; Ferepat; Herponil; Irifone; Kovotherm; Melferut; Pazergicel; Radermin; Reumina; Roiplon; Vellodrying; ***Hong Kong***: Flogoprofen; Rheuma-Denk†; ***Hung.***: Activon; Rheumon; ***Irl.***: Etoflam; ***Ital.***: Gemadol; ***Mex.***: Bayro; ***Pol.***: Rheumon; Traumon; ***Port.***: Fenogel†; Inalgex; Reumon; Traumon†; ***Spain***: Aspitopic; Flogoprofen; Zenavan; ***Switz.***: Rheumon; Traumalix; ***Turk.***: Doline; Flexo; Painex; Rheumon; ***Venez.***: Traflan.

Multi-ingredient Preparations. ***Arg.***: Bayagel; ***Austria***: Thermo-Rheumon; ***Gr.***: Thermo-Roiplon; ***Mex.***: Bayro Termo; ***Pol.***: Thermo-Rheumon; ***Turk.***: Thermo-Doline; Thermo-Rheumon; Thermoflex; Thermove; ***Venez.***: Reugel.

Etoricoxib *(BAN, USAN, rINN)*

Etoricoxib; Etoricoxibum; Etorikoksib; Etorikoksibi; Etorikoxib; L-791456; MK-0663; MK-663; Эторикоксиб.

5-Chloro-6′-methyl-3-[*p*-(methylsulfonyl)phenyl]-2,3′-bipyridine.

$C_{18}H_{15}ClN_2O_2S$=358.8

CAS — 202409-33-4.

ATC — M01AH05.

ATC Vet — QM01AH05.

UNII — WRX4NFY03R.

Uses and Administration

Etoricoxib is an NSAID (p. 102.3) reported to be a selective inhibitor of cyclo-oxygenase-2 (COX-2). It is used in the symptomatic relief of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and acute gouty arthritis.

In osteoarthritis, etoricoxib is given orally in a usual dose of 30 mg once daily, increased to 60 mg once daily if necessary. The recommended dose in rheumatoid arthritis and in ankylosing spondylitis is 90 mg once daily; higher doses of 120 mg once daily are used in gouty arthritis although such doses should only be used for the acute symptomatic period and for a maximum of 8 days. For dosage recommendations in patients with hepatic impairment, see below.

References.

1. Patrignani P, *et al.* Clinical pharmacology of etoricoxib: a novel selective COX2 inhibitor. *Expert Opin Pharmacother* 2003; **4:** 265–84.
2. Dallob A, *et al.* Characterization of etoricoxib, a novel, selective COX-2 inhibitor. *J Clin Pharmacol* 2003; **43:** 573–85.
3. Martina SD, *et al.* Etoricoxib: a highly selective COX-2 inhibitor. *Ann Pharmacother* 2005; **39:** 854–62.

Administration in hepatic impairment. The maximum oral dose of etoricoxib in patients with mild hepatic impairment (Child-Pugh score of 5 to 6), regardless of indication, is 60 mg once daily; those with moderate impairment (Child-Pugh 7 to 9) should be given a maximum of 60 mg every other day or 30 mg once daily. Etoricoxib should not be given to patients with severe hepatic impairment (Child-Pugh 10 or more).

Musculoskeletal and joint disorders. The selective cyclo-oxygenase-2 (COX-2) inhibitor etoricoxib is used in the treatment of ankylosing spondylitis (see Spondyloarthropathies, p. 14.3), osteoarthritis (p. 12.3), and rheumatoid arthritis (p. 13.2); it is also used in gouty arthritis (p. 600.1). However, in the UK, it is recommended that the use of selective COX-2 inhibitors is limited to patients with good cardiovascular health and at high risk of developing serious gastrointestinal problems if given a non-selective NSAID (see p. 105.3).

References.

1. Cochrane DJ, *et al.* Etoricoxib. *Drugs* 2002; **62:** 2637–51.
2. Schumacher HR, *et al.* Randomised double blind trial of etoricoxib and indometacin in treatment of acute gouty arthritis. *BMJ* 2002; **324:** 1488–92.
3. Gottesdiener K, *et al.* Results of a randomized, dose-ranging trial of etoricoxib in patients with osteoarthritis. *Rheumatology (Oxford)* 2002; **41:** 1052–61.
4. Wiesenhutter CW, *et al.* Evaluation of the comparative efficacy of etoricoxib and ibuprofen for treatment of patients with osteoarthritis: a randomized, double-blind, placebo-controlled trial. *Mayo Clin Proc* 2005; **80:** 470–9.
5. van der Heijde D, *et al.* Evaluation of the efficacy of etoricoxib in ankylosing spondylitis: results of a fifty-two-week, randomized, controlled study. *Arthritis Rheum* 2005; **52:** 1205–15.
6. Curtis SP, *et al.* Etoricoxib in the treatment of osteoarthritis over 52 weeks: a double-blind, active-comparator controlled trial [NCT00242489]. *BMC Musculoskelet Disord* 2005; **6:** 58. Available at: http://www.biomedcentral.com/content/pdf/1471-2474-6-58.pdf (accessed 01/11/07)
7. Bingham CO, *et al.* Efficacy and safety of etoricoxib 30 mg and celecoxib 200 mg in the treatment of osteoarthritis in two identically designed, randomized, placebo-controlled, non-inferiority studies. *Rheumatology (Oxford)* 2007; **46:** 496–507.
8. Croom KF, Siddiqui MAA. Etoricoxib: a review of its use in the symptomatic treatment of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis and acute gouty arthritis. *Drugs* 2009; **69:** 1513–32.

Pain. A systematic review[1] found that a single 120-mg dose of etoricoxib, given orally, provided effective pain relief after surgery. When compared indirectly, etoricoxib was considered to be at least as effective as other commonly used analgesics.

1. Clarke R, *et al.* Single dose oral etoricoxib for acute postoperative pain in adults. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 09/09/09).

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3.

Hypersensitivity reactions including anaphylaxis and angioedema have occurred in patients receiving etoricoxib; it should be stopped at the first signs of hypersensitivity.

Etoricoxib should not be used in patients with ischaemic heart disease, peripheral arterial disease, or cerebrovascular disease. It should be used with caution in patients with significant risk factors for cardiovascular disease such as hypertension, hyperlipidaemia, and diabetes mellitus. Etoricoxib, particularly at high doses, may be associated with more frequent and severe hypertension compared with other NSAIDs and selective cyclo-oxygenase-2 (COX-2) inhibitors; blood pressure monitoring during etoricoxib treatment is recommended. Etoricoxib should not be used in patients with hypertension whose blood pressure is not controlled (see also Effects on the Cardiovascular System, below).

Etoricoxib is also contra-indicated in patients with inflammatory bowel disease, moderate to severe heart failure (NYHA class II to IV), and renal impairment associated with a creatinine clearance of less than 30 mL/minute. It should be avoided in patients with severe hepatic impairment (Child-Pugh score of 10 or more). Therapy should be stopped if persistently abnormal liver enzyme values are seen. Caution is recommended when using etoricoxib in dehydrated patients; it may be advisable to rehydrate patients before giving etoricoxib.

Effects on the cardiovascular system. There have been concerns about the adverse cardiovascular effects of selective cyclo-oxygenase-2 (COX-2) inhibitors after the worldwide withdrawal of rofecoxib (see p. 128.3). The cardiovascular safety of etoricoxib has been assessed in the MEDAL programme,[1] which pooled data from 3 studies involving over 30 000 patients with either osteoarthritis or rheumatoid arthritis. Patients with osteoarthritis were given etoricoxib 60 or 90 mg daily; those with rheumatoid arthritis received 90 mg daily. In all studies, diclofenac 150 mg daily was given as the comparator; low-dose aspirin (100 mg daily or less) was also allowed where indicated. After an average treatment duration of 18 months, the rates of thrombotic events such as myocardial infarction, stroke, and sudden or unexplained death with etoricoxib were similar to those for diclofenac. (It has been suggested that diclofenac itself may increase the risk of some thrombotic events; for further details, see p. 105.1.) The programme also found that the rate of some other non-thrombotic cardiovascular events was increased with etoricoxib: one of the 3 studies showed that there was a non-significant increase in the rate of heart failure with etoricoxib 90 mg daily compared with diclofenac; withdrawals due to oedema were also more frequent with high-dose etoricoxib than with diclofenac or etoricoxib 60 mg daily. In addition, the number of patients stopping treatment because of hypertension was higher with both doses of etoricoxib than with diclofenac. Similar results were seen in the other 2 studies.

In another study[2] that pooled pre-licensing data, the risk of thrombotic events with etoricoxib, given at a dose of at least 60 mg daily, was also found to be similar to that for placebo treatment, ibuprofen (2.4 g daily), diclofenac (150 mg daily), and naproxen (1 g daily), although there was a trend towards more events with etoricoxib than with naproxen. For details on the relative risk of thrombotic events associated with non-selective NSAIDs, see p. 105.1.

After a recommendation from the EMEA's Committee for Medicinal Products for Human Use (CHMP),[3] licensed product information for etoricoxib states that it must not be given to patients whose blood pressure is persistently above 140/90 mmHg and inadequately controlled; in addition, high blood pressure should be controlled before starting treatment and monitored for 2 weeks afterwards then regularly thereafter.

For discussion and advice on the use of selective COX-2 inhibitors in patients with cardiovascular or cerebrovascular disease, see under Celecoxib, p. 37.3.

1. Cannon CP, *et al.* Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. *Lancet* 2006; **368**: 1771–81.
2. Curtis SP, *et al.* Pooled analysis of thrombotic cardiovascular events in clinical trials of the COX-2 selective inhibitor etoricoxib. *Curr Med Res Opin* 2006; **22**: 2365–74.
3. EMEA. EMEA recommends strengthening warnings and contra-indications for etoricoxib-containing medicines used in the treatment of rheumatoid arthritis and ankylosing spondylitis (issued 26th June, 2008). Available at: http://www.emea.europa.eu/pdfs/human/press/pt/33363608en.pdf (accessed 16/07/08)

Effects on the gastrointestinal tract. It is generally accepted that the inhibition of cyclo-oxygenase-1 (COX-1) plays a role in the adverse gastrointestinal effects of the NSAIDs, and that the selective inhibition of the other isoform, COX-2, by NSAIDs such as etoricoxib may cause less gastrotoxicity than that seen with the non-selective inhibition of the traditional NSAIDs. However, licensed product information states that upper gastrointestinal perforation, ulceration, and bleeds, in some cases fatal, have occurred with etoricoxib treatment; consequently, it should be used with caution in patients with a history of, or at risk of developing, such events. In addition, etoricoxib should not be used in patients with active gastrointestinal ulceration or bleeding.

Results from controlled studies have suggested that NSAIDs selective for COX-2 were associated with a lower incidence of serious gastrointestinal effects. In a study[1] of the pooled data from 3 randomised clinical studies, etoricoxib (in doses of 60 or 90 mg daily) was associated with significantly less frequent upper gastrointestinal clinical events than diclofenac (150 mg daily). The result was attributed to the lower rate of uncomplicated ulcers with etoricoxib compared with diclofenac; there was no difference in the rate of complicated gastrointestinal events between the 2 drugs. The lower rate of uncomplicated events with etoricoxib compared with diclofenac was not affected by treatment with low-dose aspirin or proton pump inhibitors. An analysis[2] by the manufacturer, of pooled data from 10 randomised clinical studies, found that etoricoxib (in daily doses of 60, 90, or 120 mg) was associated with a lower combined risk of upper gastrointestinal perforations and bleeding, and symptomatic gastroduodenal ulcers when compared with non-selective NSAIDs (diclofenac 150 mg daily, ibuprofen 2.4 g daily, or naproxen 1 g daily) as a group. This reduced risk was seen even in patients with known risk factors for such complications such as the elderly and those with a history of gastrointestinal reactions.

1. Laine L, *et al.* Assessment of upper gastrointestinal safety of etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. *Lancet* 2007; **369**: 465–73.
2. Ramey DR, *et al.* The incidence of upper gastrointestinal adverse events in clinical trials of etoricoxib vs. non-selective NSAIDs: an updated combined analysis. *Curr Med Res Opin* 2005; **21**: 715–22.

Effects on the kidneys. Limited evidence of the renal toxicity of the selective cyclo-oxygenase-2 (COX-2) inhibitors such as etoricoxib suggests that such NSAIDs appear to have effects on renal function similar to those of the non-selective NSAIDs (see p. 106.2).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies etoricoxib as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 23/10/11)

Interactions

The metabolism of etoricoxib is mediated by the cytochrome P450 isoenzyme CYP3A4. Use with other drugs that inhibit or induce this isoenzyme may result in changes in plasma concentration of etoricoxib. In addition, *in vitro* studies suggest that several other isoenzymes may also mediate the main metabolic pathway of etoricoxib. Rifampicin, a potent inducer of CYP isoenzymes, has produced decreased plasma concentrations of etoricoxib.

Etoricoxib is an inhibitor of human sulfotransferase activity and has been shown to increase the plasma concentration of ethinylestradiol. Interactions with other drugs, such as oral salbutamol and minoxidil, also metabolised by this enzyme may be a possibility and licensed product information advises care with such combinations.

For interactions associated with NSAIDs in general, see p. 107.3.

Pharmacokinetics

Etoricoxib is well absorbed from the gastrointestinal tract after oral doses. Peak plasma concentrations occur in about 1 hour in fasted adults; food delays absorption by about 2 hours, although it has no effect on the extent of absorption. Plasma protein binding is about 92%. At steady state the half-life of etoricoxib is about 22 hours. Etoricoxib is extensively metabolised with less than 2% of a dose recovered in the urine as the parent drug. The major route of metabolism is via cytochrome P450 isoenzymes including CYP3A4 to form the 6'-hydroxymethyl derivative of etoricoxib, which is then oxidised to the 6'-carboxylic acid derivative, the major metabolite. Both are inactive or only weak cyclo-oxygenase-2 (COX-2) inhibitors. Excretion is mainly via the urine (70%) with only 20% of a dose appearing in the faeces. Studies in *animals* suggest that etoricoxib may cross the placenta and that some is distributed into breast milk.

References.

1. Agrawal NGB, *et al.* Single- and multiple-dose pharmacokinetics of etoricoxib, a selective inhibitor of cyclooxygenase-2, in man. *J Clin Pharmacol* 2003; **43**: 268–76.
2. Agrawal NGB, *et al.* Pharmacokinetics of etoricoxib in patients with hepatic impairment. *J Clin Pharmacol* 2003; **43**: 1136–48.
3. Agrawal NGB, *et al.* Pharmacokinetics of etoricoxib in patients with renal impairment. *J Clin Pharmacol* 2004; **44**: 48–58.
4. Takemoto JK, *et al.* Clinical pharmacokinetic and pharmacodynamic profile of etoricoxib. *Clin Pharmacokinet* 2008; **47**: 703–20.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Arcoxia; ***Austral.***: Arcoxia; ***Austria***: Arcoxia; Auxib†; ***Belg.***: Arcoxia; Ranacox; ***Braz.***: Arcoxia; ***Chile***: Arcoxia; ***China***: Arcoxia (安康信); ***Cz.***: Arcoxia; ***Denm.***: Arcoxia; ***Fin.***: Arcoxia; Turox†; ***Fr.***: Arcoxia; ***Ger.***: Arcoxia; ***Gr.***: Arcoxia; Turox; ***Hong Kong***: Arcoxia; ***Hung.***: Arcoxia; ***India***: Alcoxib; Coxet; Coxifact; Doricox; E-Tocom; Ebov; Eleton; Erofica; Eteron; Eticox; Etobus; Etocos; Etody; Etofan; Etolex; Etom; Etorl; Etorica; Etosaid; Etoshine; Etoxym; Etoxib; Etozox; Etrik; Etro; Etrobax; Ezact; Hicox; Hireto; Hydrox; Intacoxia; Ixidol; Kingcox; Kretos; L-Kon; M-Con; Nucoxia; O-Cox; ***Indon.***: Arcoxia; ***Irl.***: Acoxxel; Arcoxia; ***Israel***: Arcoxia; ***Ital.***: Algix; Arcoxia; Exinef; Tauxib; ***Malaysia***: Arcoxia; ***Mex.***: Arcoxia; ***Neth.***: Arcoxia; Auxib; ***Norw.***: Arcoxia; ***NZ***: Arcoxia; ***Philipp.***: Arcoxia; ***Port.***: Arcoxia; Exxiv; Turox; ***Rus.***: Arcoxia (Аркоксиа); ***S.Afr.***: Arcoxia; ***Singapore***: Arcoxia; ***Spain***: Acoxxel; Arcoxia; Exxiv; ***Swed.***: Arcoxia; Turox; ***Switz.***: Arcoxia; ***Thai.***: Arcoxia; ***UK***: Arcoxia; ***Ukr.***: Arcoxia (Аркоксія); ***Venez.***: Arcoxia.

Multi-ingredient Preparations. ***India***: Etro-P; Nucoxia-MR; Nucoxia-P; Nucoxia-SP.

Etorphine Hydrochloride *(BANM, rINNM)*

Etorfina, hidrocloruro de; Étorphine, Chlorhydrate d'; Etorphini Hydrochloridum; Hidrocloruro de etorfina; M-99; 19-Propylorvinol Hydrochloride; Эторфина Гидрохлорид

(6*R*,7*R*,14*R*)-7,8-Dihydro-7-[(1*R*)-1-hydroxy-1-methylbutyl]-5-*O*-methyl-6,14α-ethenomorphine hydrochloride; (2*R*)-2-[(5*R*,6*R*,7*R*,14*R*)-4,5-Epoxy-3-hydroxy-6-methoxy-9a-methyl-6,14-ethenomorphinan-7-yl]pentan-2-ol hydrochloride.

$C_{25}H_{33}NO_4HCl$=448.0

CAS — 14521-96-1 (etorphine); 13764-49-3 (etorphine hydrochloride).

UNII — BCBE01N748.

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2014: (Etorphine Hydrochloride). A white or almost white microcrystalline powder. Sparingly soluble in water and in alcohol; very slightly soluble in chloroform; practically insoluble in ether. A 2% solution in water has a pH of 4.0 to 5.5. Protect from light.

Uses and Administration

Etorphine hydrochloride is a highly potent opioid analgesic (p. 108.1) used for reversible neuroleptanalgesia (see Anaesthetic Techniques, p. 1899.3) in veterinary medicine. It is given with acepromazine maleate or levomepromazine (*Immobilon*) to restrain animals and before minor veterinary surgery. The duration of action of etorphine is up to about 45 to 90 minutes depending on the species but it may be longer in man, especially if the large animal preparation is involved.

Dependence and Withdrawal

As for Opioid Analgesics, p. 109.1.

Adverse Effects and Treatment

As for Opioid Analgesics in general, p. 110.1. Etorphine is not used therapeutically in humans.

Etorphine hydrochloride is highly potent and rapid acting; minute amounts can exert serious effects leading to coma. It may be absorbed through skin and mucous membranes. It is thus advisable to inject an antagonist *immediately* after contamination of skin or mucous membranes with preparations containing etorphine hydrochloride and to wash the affected areas copiously. Accidental injection or needle scratch injuries should also be treated immediately by injecting an antagonist. Naloxone is preferred as the antagonist in medical treatment. However, veterinary preparations of etorphine are supplied with a preparation (*Revivon*) containing diprenorphine hydrochloride (p. 1550.2) and this should be used for immediate first-aid antagonism if naloxone is not available.

Felbinac *(BAN, USAN, rINN)*

CL-83544; Felbinaakki; Felbinaco; Felbinacum; Felbinak; LJC-10141; Фелбинак.

Biphenyl-4-ylacetic acid.

$C_{14}H_{12}O_2$=212.2

CAS — 5728-52-9.

ATC — M02AA08.

ATC Vet — QM02AA08.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*.

Ph. Eur. 8: (Felbinac). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; soluble in methyl alcohol.

Uses and Administration

Felbinac, an active metabolite of fenbufen (below), is an NSAID (p. 102.3). It is used topically in the symptomatic treatment of musculoskeletal pain including that due to soft-tissue injuries. It is applied as a 3% gel or a 3.17% foam to unbroken skin over affected areas 2 to 4 times daily. The total daily dose of gel or foam should not exceed 25 g regardless of the size or number of affected areas. Therapy should be reviewed after 14 days.

Diisopropanolamine felbinac has been used similarly.

References.
1. Hosie GAC. The topical NSAID, felbinac, versus oral ibuprofen: a comparison of efficacy in the treatment of acute lower back injury. *Br J Clin Res* 1993; 4: 5–17.

Adverse Effects and Precautions

Mild local reactions such as erythema, dermatitis, and pruritus have occurred in patients using felbinac topically. More serious adverse effects including bullous dermatoses such as epidermal necrolysis and erythema multiforme, photosensitivity, anaphylaxis, and bronchospasm or wheeziness have also been reported. Gastrointestinal disturbances may occur.

Felbinac preparations should be avoided in patients with a history of hypersensitivity reactions to aspirin or other NSAIDs.

Incidence of adverse effects. The UK CSM had received 49 reports of adverse reactions associated with felbinac by October 1989, about 11 months after it was released on the UK market.[1] Bronchospasm or wheeziness was reported in 8 patients using felbinac gel. Four of these patients had a history of asthma of whom 3 were reported to have had a similar reaction to aspirin or other NSAIDs. Other reported reactions included rashes (17 cases), local application site reactions (7 cases), and dyspepsia (6 cases).

1. CSM. Felbinac (Traxam) and bronchospasm. *Current Problems 27* 1989. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024444&RevisionSelectionMethod=LatestReleased (accessed 01/11/07)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Flexfree; *China*: Tong Er Qi (通尔其); *Gr.*: Dolinac; *Irl.*: Traxam; *Ital.*: Dolinac; *Jpn*: Napageln; Seltouch; *UK*: Traxam.

Pharmacopoeial Preparations
BP 2014: Felbinac Cutaneous Foam; Felbinac Gel.

Fenbufen *(BAN, USAN, rINN)*

CL-82204; Fenbufeeni; Fenbufén; Fenbufenas; Fenbufène; Fenbufenum; Фенбуфен.
4-(Biphenyl-4-yl)-4-oxobutyric acid.
$C_{16}H_{14}O_3$=254.3
CAS — 36330-85-5.
ATC — M01AE05.
ATC Vet — QM01AE05.
UNII — 9815R1WR9B.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn*.

Ph. Eur. 8: (Fenbufen). A white or almost white, fine crystalline powder. Very slightly soluble in water; slightly soluble in alcohol, in acetone, and in dichloromethane.

Uses and Administration

Fenbufen, a propionic acid derivative, is an NSAID (p. 102.3). It is given for the relief of pain and inflammation associated with musculoskeletal and joint disorders such as rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis in oral doses of 900 mg daily; the dose may be either 450 mg in the morning and evening or 300 mg in the morning with 600 mg in the evening.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3, although the commonest adverse effects of fenbufen are rashes, usually occurring within the first 2 weeks of therapy, and particularly in women and in patients with seronegative rheumatoid arthritis or psoriatic arthritis. Disorders such as epidermal necrolysis, erythema multiforme, and Stevens-Johnson syndrome have also been reported. A small number of patients who develop rash may go on to develop a severe illness characterised by pulmonary eosinophilia or allergic alveolitis. Treatment with fenbufen should be stopped immediately if a rash appears.

Breast feeding. UK licensed product information advises that fenbufen should be avoided in breast-feeding mothers, because of the presence of its metabolites in breast milk.

Effects on the blood. Haemolytic anaemia[1] and aplastic anaemia[2] have been reported in patients receiving fenbufen.

1. Martland T, Stone WD. Haemolytic anaemia associated with fenbufen. *BMJ* 1988; 297: 921.
2. Andrews R, Russell N. Aplastic anaemia associated with a non-steroidal anti-inflammatory drug: relapse after exposure to another such drug. *BMJ* 1990; 301: 38.

Effects on the lungs. In January 1989 the UK CSM reported that it had received 7 reports of a suspected association between rash and an allergic interstitial lung disorder in patients receiving fenbufen.[1] In 5 patients, the lung disorder was diagnosed as pulmonary eosinophilia; in the 2 other patients the pulmonary component of the reaction was described as allergic alveolitis. Several of these reactions have been reported in the literature.[2,3]

1. CSM. Fenbufen, rash and pulmonary eosinophilia. *Current Problems 24* 1989. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024431&RevisionSelectionMethod=LatestReleased (accessed 01/11/07)
2. Swinburn CR. Alveolitis and haemolytic anaemia induced by azapropazone. *BMJ* 1987; 294: 375.
3. Burton GH. Rash and pulmonary eosinophilia associated with fenbufen. *BMJ* 1990; 300: 82–3.

Effects on the skin. In September 1988 the UK CSM reported[1] that it was still receiving large numbers of reports of adverse reactions to fenbufen when such reports were expected to have declined. Fenbufen was the most commonly reported suspect drug in 1986 and 1987. At the time of the report more than 6000 such reports had been received, 80% concerning mucocutaneous reactions and most involving a generalised florid erythematous rash, often with pruritus. There were 178 reports of erythema multiforme, 30 of Stevens-Johnson syndrome, and 2 fatalities.

1. CSM. Fenbufen and mucocutaneous reactions. *Current Problems 23* 1988. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024430&RevisionSelectionMethod=LatestReleased (accessed 01/11/07)

Hypersensitivity. See under Effects on the Lungs (above).

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Use of fenbufen with aspirin may result in decreased serum concentrations of fenbufen and its metabolites.

Pharmacokinetics

Fenbufen is absorbed from the gastrointestinal tract after oral use and peak plasma concentrations occur in about 70 minutes. Fenbufen is over 99% bound to plasma proteins. It is metabolised in the liver to the active metabolites, biphenylacetic acid and 4-hydroxy-biphenylbutyric acid. Fenbufen and its metabolites are reported to have plasma half-lives of about 10 to 17 hours and are mainly eliminated as conjugates in the urine. Metabolites of fenbufen have been detected in breast milk in small amounts.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Indon.*: Cybufen†; *Irl.*: Lederfen†; *Port.*: Basifen; *Thai.*: Cepal; Cinopal; Forbufen; *Turk.*: Cinopal†; *UK*: Lederfen†.

Pharmacopoeial Preparations
BP 2014: Fenbufen Capsules; Fenbufen Tablets.

Fenoprofen Calcium *(BANM, USAN, rINNM)*

Calcii Fenoprofenum; Fénoprofène Calcique; Fenoprofeno cálcico; Lilly-53858 (fenoprofen); Lilly-61169 (fenoprofen sodium); Lilly-69323; Кальций Фенопрофен.
Calcium (±)-2-(3-phenoxyphenyl)propionate dihydrate.
$(C_{15}H_{13}O_3)_2Ca,2H_2O$=558.6
CAS — 31879-05-7 (fenoprofen); 34597-40-5 (anhydrous fenoprofen calcium); 53746-45-5 (fenoprofen calcium dihydrate).
ATC — M01AE04.
ATC Vet — QM01AE04.
UNII — 0X2CW1QABJ.

Pharmacopoeias. In *Br.*, *Chin.*, and *US*.

BP 2014: (Fenoprofen Calcium). A white or almost white odourless or almost odourless crystalline powder. Slightly soluble in water and in chloroform; soluble in alcohol.

USP 36: (Fenoprofen Calcium). A white crystalline powder. Slightly soluble in water, in methyl alcohol, and in n-hexanol; practically insoluble in chloroform. Store in airtight containers.

Uses and Administration

Fenoprofen, a propionic acid derivative, is an NSAID (p. 102.3) used in the management of mild to moderate pain and for the relief of pain and inflammation associated with disorders such as osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. It is given as the calcium salt although doses are expressed in terms of the base; fenoprofen calcium (dihydrate) 1.2 g is equivalent to about 1 g of fenoprofen. A usual oral dose is the equivalent of 300 to 600 mg of fenoprofen three or four times daily, adjusted thereafter according to response. In the USA, lower doses of 200 mg every 4 to 6 hours are recommended for mild to moderate pain. It has been recommended that the total daily dose should not exceed 3 g (UK) or 3.2 g (USA).

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3.

Dysuria, cystitis, haematuria, interstitial nephritis, and acute renal insufficiency have been reported with fenoprofen. Nephrotic syndrome, which may be preceded by fever, rash, arthralgia, oliguria, azotaemia, and anuria, has also occurred. Upper respiratory-tract infection and nasopharyngitis have been reported. There have been reports of severe hepatic reactions, including jaundice and fatal hepatitis.

Breast feeding. Fenoprofen is distributed into breast milk although the amount is considered by the *BNF* to be too small to be harmful to a breast-fed infant. In contrast, licensed product information does not recommend its use since safety has not been established.

Effects on the blood. Haematological adverse effects including agranulocytosis,[1] aplastic anaemia,[2] and thrombocytopenia[3,4] have been reported in patients taking fenoprofen; licensed product information also reports haemolytic anaemia.

1. Simon SD, Kosmin M. Fenoprofen and agranulocytosis. *N Engl J Med* 1978; 299: 490.
2. Ashraf M, *et al.* Aplastic anaemia associated with fenoprofen. *BMJ* 1982; 284: 1301–2.
3. Simpson RE, *et al.* Acute thrombocytopenia associated with fenoprofen. *N Engl J Med* 1978; 298: 629–30.
4. Katz ME, Wang P. Fenoprofen-associated thrombocytopenia. *Ann Intern Med* 1980; 92: 262.

Effects on the liver. Cholestatic jaundice and hepatitis developed in a 68-year-old woman after receiving fenoprofen 600 mg four times daily for 7 weeks. Subsequent use of naproxen and indometacin did not result in hepatotoxicity.[1] However, there has been a report of cross-hepatotoxicity between fenoprofen and naproxen.[2]

1. Stennett DJ, *et al.* Fenoprofen-induced hepatotoxicity. *Am J Hosp Pharm* 1978; 35: 901.
2. Andrejak M, *et al.* Cross hepatotoxicity between non-steroidal anti-inflammatory drugs. *BMJ* 1987; 295: 180–1.

Effects on the skin. Toxic epidermal necrolysis was associated with fenoprofen in 2 patients.[1]

1. Stotts JS, *et al.* Fenoprofen-induced toxic epidermal necrolysis. *J Am Acad Dermatol* 1988; 18: 755–7.

Overdosage. Coma, respiratory depression, hypotension, and metabolic acidosis occurred in a patient who had ingested between 24 and 36 g of fenoprofen.[1] The patient responded to gastric lavage and activated charcoal and intensive supportive care.

1. Kolodzik JM, *et al.* Nonsteroidal anti-inflammatory drugs and coma: a case report of fenoprofen overdose. *Ann Emerg Med* 1990; 19: 378–81.

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Aspirin is reported to reduce plasma concentrations of fenoprofen.

Antiepileptics. *Phenobarbital* might increase the rate of metabolism of fenoprofen.[1] US licensed product information suggests that dosage adjustment of fenoprofen may be required when given with phenobarbital.

1. Helleberg L, *et al.* A pharmacokinetic interaction in man between phenobarbitone and fenoprofen, a new anti-inflammatory agent. *Br J Clin Pharmacol* 1974; 1: 371–4.

Pharmacokinetics

Fenoprofen is readily absorbed from the gastrointestinal tract; bioavailability is about 85% but food and milk may reduce the rate and extent of absorption. Peak plasma concentrations occur 1 to 2 hours after a dose. The plasma half-life is about 3 hours. Fenoprofen is 99% bound to plasma proteins. About 90% of a dose is excreted in the urine in 24 hours, chiefly as the glucuronide and the glucuronide of hydroxylated fenoprofen. Fenoprofen is distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: FeiLin (飞林); *Fr.*: Nalgesic; *Gr.*: Expron; Nazipons; *UK*: Fenopron; *USA*: Nalfon.

Pharmacopoeial Preparations
BP 2014: Fenoprofen Tablets;
USP 36: Fenoprofen Calcium Capsules; Fenoprofen Calcium Tablets.

Fentanyl *(BAN, rINN)* ⊗

Fentanil; Fentanilis; Fentanilo; Fentanylum; Fentanyyli; Фентанил.

N-(1-Phenethyl-4-piperidyl) propionanilide.

$C_{22}H_{28}N_2O$=336.5

CAS — 437-38-7.

ATC — N01AH01; N02AB03.

ATC Vet — QN01AH01; QN02AB03.

UNII — UF599785JZ.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of fentanyl:

Apache; China girl; China town; China white; Dance fever; Fentanest; Friend; Goodfellas; Great bear; He-man; Jackpot; King ivory; Murder 8; Poison; Tango & Cash; TNT; T.N.T.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Fentanyl). A white or almost white polymorphic powder. Practically insoluble in water; freely soluble in alcohol and in methyl alcohol. Protect from light.

USP 36: (Fentanyl). Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Fentanyl Citrate *(BANM, USAN, rINNM)* ⊗

Citrato de fentanilo; Fentanil-citrát; Fentanilio citratas; Fentanilo, citrato de; Fentanyl, citrate de; Fentanylcitrat; Fentanyl-citrát; Fentanyli Citras; Fentanylu cytrynian; Fentanyylisitraatti; McN-JR-4263-49; Phentanyl Citrate; R-4263; Фентанила Цитрат.

N-(1-Phenethyl-4-piperidyl)propionanilide dihydrogen citrate.

$C_{22}H_{28}N_2O.C_6H_8O_7$=528.6

CAS — 990-73-8.

UNII — MUN5LYG46H.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Fentanyl Citrate). White or almost white powder. Soluble in water; sparingly soluble in alcohol; freely soluble in methyl alcohol. Protect from light.

USP 36: (Fentanyl Citrate). A white crystalline powder or white glistening crystals. Sparingly soluble in water; slightly soluble in chloroform; soluble in methyl alcohol. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Fentanyl Hydrochloride *(BANM, rINNM)* ⊗

Fentanyl, Chlorhydrate de; Fentanyli Hydrochloridum; Hidrocloruro de fentanilo; Фентанила Гидрохлорид.

$C_{22}H_{28}N_2O.HCl$=372.9

CAS — 1443-54-5.

UNII — 59H156XY46.

Incompatibility. Fentanyl citrate is incompatible with thiopental sodium and methohexital sodium.

A thick white precipitate formed in the intravenous tubing when fentanyl citrate with droperidol was given shortly after nafcillin sodium. There was no precipitate when fentanyl citrate alone was mixed with nafcillin sodium.[1]

Fentanyl citrate underwent rapid and extensive loss when admixed with fluorouracil in PVC containers.[2] The loss was due to sorption of fentanyl to the PVC as a result of the alkaline pH of the admixture, and presumably could occur from admixture of fentanyl citrate with any sufficiently alkaline drug.

See also Stability, below.

1. Jeglum EL, *et al.* Nafcillin sodium incompatibility with acidic solutions. *Am J Hosp Pharm* 1981; 38: 462, 464.
2. Xu QA, *et al.* Rapid loss of fentanyl citrate admixed with fluorouracil in polyvinyl chloride containers. *Ann Pharmacother* 1997; 31: 297–302.

Stability. In a 48-hour study fentanyl citrate in glucose 5% or sodium chloride 0.9% was stable when stored at room temperature under usual light conditions in glass or PVC containers;[1] the concentration of fentanyl delivered by a patient-controlled system was relatively constant throughout a 30-hour study period. Fentanyl citrate injection diluted to 20 micrograms/mL with sodium chloride 0.9% was stable for 30 days at 3 degrees or 23 degrees in PVC reservoirs for portable infusion pumps.[2] In another study[3] fentanyl citrate diluted to 50 micrograms/mL with sodium chloride 0.9% remained stable for at least 14 days when stored at room temperature in PVC reservoirs for portable patient-controlled systems.

An admixture of fentanyl citrate and bupivacaine in sodium chloride 0.9% appeared[4] compatible and stable when stored for up to 30 days at 3 degrees or 23 degrees in a portable infusion pump. In another study[5] the stability of solutions containing fentanyl, bupivacaine, and adrenaline, alone and in combination was studied over a period of 56 days when stored at various temperatures in the light or in the dark in PVC bags. Both fentanyl and bupivacaine were adsorbed from solution onto the PVC for the first 3 days but thereafter concentrations of these drugs remained relatively stable; freezing appeared to slow the concentration change for bupivacaine but not for fentanyl. Solutions containing adrenaline became more acidic during the study as the adrenaline progressively deteriorated but this was greatly reduced by freezing. Autoclaving produced a further reduction in the concentration of all drugs. There was no sign of precipitation from any of the solutions studied.

An admixture of fentanyl citrate, ketamine hydrochloride, and droperidol in sodium chloride 0.9% was stable[6] for at least 30 days when stored in glass bottles at 25 degrees; the minor decrease in the concentrations of all 3 drugs was attributed to either hydrolytic degradation or adsorption. This admixture also appeared compatible when stored in PVC bags at 4 degrees and 25 degrees; the small increase in drug concentrations over 30 days may be a result of water permeation and evaporation through the bags.

Fentanyl is potentially unstable in PVC containers when mixed with alkaline drugs (see Incompatibility, above).

1. Kowalski SR, Gourlay GK. Stability of fentanyl citrate in glass and plastic containers and in a patient-controlled delivery system. *Am J Hosp Pharm* 1990; 47: 1584–7.
2. Allen LV, *et al.* Stability of fentanyl citrate in 0.9% sodium chloride solution in portable infusion pumps. *Am J Hosp Pharm* 1990; 47: 1572–4.
3. Chapalain-Pargade S, *et al.* Microbiological and physicochemical stability of fentanyl and sufentanil solutions for patient-controlled delivery systems. *J Pain Symptom Manage* 2006; 32: 90–7.
4. Tu Y-H, *et al.* Stability of fentanyl citrate and bupivacaine hydrochloride in portable pump reservoirs. *Am J Hosp Pharm* 1990; 47: 2037–40.
5. Dawson PJ, *et al.* Stability of fentanyl, bupivacaine and adrenaline solutions for extradural infusion. *Br J Anaesth* 1992; 68: 414–17.
6. Lee DKT, *et al.* Compatibility of fentanyl citrate, ketamine hydrochloride, and droperidol in 0.9% sodium chloride injection stored in polyvinyl chloride bags. *Am J Health-Syst Pharm* 2005; 62: 1190–2.

Uses and Administration

Fentanyl, a phenylpiperidine derivative, is a potent opioid analgesic (p. 108.1) chemically related to pethidine (p. 121.3) and is mainly a μ-opioid agonist.

Fentanyl is used as an analgesic, as an adjunct to general anaesthetics, and as an anaesthetic for induction and maintenance. It is also used as a respiratory depressant in the management of mechanically ventilated patients under intensive care. When used with an antipsychotic such as droperidol it can induce a state of neuroleptanalgesia in which the patient is calm and indifferent to his surroundings and is able to cooperate with the surgeon.

Fentanyl is usually given parenterally, intranasally, or by the transmucosal route as the citrate, or in transdermal patches as the base. The hydrochloride was available as an iontophoretic transdermal delivery preparation but this was withdrawn from the market because of a defective delivery system. Fentanyl citrate 157 micrograms and fentanyl hydrochloride 111 micrograms are each equivalent to about 100 micrograms of fentanyl. Doses are expressed in terms of the base.

It is more lipid soluble than morphine and after an intravenous injection of 100 micrograms the effects of fentanyl begin almost immediately, although maximum analgesia and respiratory depression may not occur for several minutes; the duration of action of fentanyl depends on the dose and the intensity of the pain involved, and may vary from 10 minutes to several hours.

For **premedication** the equivalent of 50 to 100 micrograms of fentanyl may be given *intramuscularly* 30 to 60 minutes before the induction of anaesthesia.

As an **adjunct** to general anaesthesia, fentanyl is usually given by *intravenous* injection. Dosage recommendations show a wide range depending on the technique.

- *Patients with spontaneous respiration* may be given 50 to 200 micrograms as an initial dose with supplements of 50 micrograms. In the USA it is recommended that doses above 2 micrograms/kg be accompanied by assisted ventilation. Significant respiratory depression follows doses of more than 200 micrograms
- *Patients whose ventilation is assisted* may be given 300 micrograms to 3.5 mg (up to 50 micrograms/kg) as an initial dose, with supplements of 100 to 200 micrograms depending on the patient's response. High doses have been reported to moderate or attenuate the response to surgical stress (see Anaesthesia, p. 61.2)

Fentanyl may also be given by intravenous infusion. In ventilated patients a loading dose of about 1 microgram/kg per minute is given for the first 10 minutes followed by an infusion of about 100 nanograms/kg per minute; alternatively, the loading dose may be given as a bolus. The infusion rate should be titrated according to response and rates of up to 3 micrograms/kg per minute have been used in cardiac surgery. Infusions should be stopped about 40 minutes before the end of surgery unless artificial ventilation is to be continued postoperatively. In patients with spontaneous respiration, lower infusion rates of 50 to 80 nanograms/kg per minute are used.

Reduced doses are used in *the elderly* or debilitated patients.

Similar doses to those used for premedication may also be given by *intramuscular* injection **postoperatively**, and by *intramuscular* or *slow intravenous injection* as an adjunct to **regional anaesthesia**.

For the treatment of **intractable chronic pain** in adults when opioid analgesia is indicated *transdermal* patches delivering amounts of fentanyl ranging from 12 to 100 micrograms/hour are available. In the UK, fentanyl patches may be used in strong opioid-naive patients; however, in the USA, use is restricted to patients who are already tolerant to opioid therapy of comparable potency.

- Doses should be individually titrated for each patient according to previous opioid usage. Initial dosages should not exceed 25 micrograms/hour in *opioid-naive* patients; in addition, it is recommended that these patients are initially titrated with low doses of short-acting opioids before transferring to fentanyl patches
- For *patients who have been receiving a strong opioid analgesic* the initial dose of the fentanyl patch should be based on the previous 24-hour opioid requirement. Use of a patch providing 25 micrograms of fentanyl per hour is equivalent to about 60 to 90 mg daily of oral morphine sulfate. During transfer to treatment with fentanyl patches previous opioid analgesic therapy should be phased out gradually in order to allow for the gradual increase in plasma-fentanyl concentrations
- More than one patch may be applied if doses greater than 100 micrograms/hour are required (applied at the same time to avoid confusion); additional or alternative analgesic therapy should be considered if doses greater than 300 micrograms/hour are required. Patches should be replaced every 72 hours; however, replacement after 48 hours is permitted in patients who have a marked decrease in analgesia before the 72-hour period ends. The new patch should be applied to a different site; use of the same area of the skin should be avoided for several days
- *Elderly* or debilitated patients should be observed carefully for signs of toxicity and the dose reduced if necessary

Fentanyl patches are not appropriate for acute or postoperative pain. The bioavailability of different brands of fentanyl transdermal patches may not be equivalent and patients should not switch brands without further advice.

A lozenge-on-a-stick dosage form of fentanyl citrate for *transmucosal* delivery is used as an analgesic in the management of **breakthrough cancer pain** in those already receiving and tolerant to opioid treatment. Lozenges containing the equivalent of 200 micrograms to up to 1.6 mg of fentanyl are available. An initial unit dose of 200 micrograms may be taken over 15 minutes for an episode of breakthrough pain and repeated once if necessary after a further 15 minutes. Doses are subsequently titrated according to response, up to a unit dose of 1.6 mg if necessary. Once the patient has been stabilised on an effective dose, no more than 4 unit doses should be taken daily.

Buccal and sublingual tablets containing fentanyl citrate for transmucosal delivery are also available and licensed for the same indication as the lozenge. Tablets containing the equivalent of 100 to 800 micrograms of fentanyl are available. An initial dose of 100 micrograms may be taken for an episode of breakthrough pain and repeated once if necessary after 30 minutes; thereafter, depending on the brand used, patients must wait at least 2 or 4 hours before treating another episode. A buccal film containing fentanyl citrate for transmucosal delivery is also available; the films contain the equivalent of 200 micrograms to 1.2 mg of fentanyl. An initial dose of 200 micrograms may be taken for an episode of breakthrough pain; thereafter, patients must wait at least 4 hours before treating another episode. Doses are subsequently titrated according to response. The dose of the maintenance opioid used for persistent pain should be re-evaluated if the patient has more than 4 episodes of breakthrough pain daily.

Caution must be exercised when switching between the different transmucosal preparations as the extent of absorption may be substantially different.

Intranasal preparations containing fentanyl citrate, equivalent to 50 to 400 micrograms of fentanyl per spray, are available for the same indication as the transmucosal

preparations. Depending on the brand used, an initial dose of 50 or 100 micrograms is sprayed into one nostril for an episode of breakthrough pain and repeated once if necessary after 10 minutes; thereafter, depending on the brand used, patients must wait at least 2 or 4 hours before treating another episode. Doses are subsequently titrated according to response; up to a maximum of 4 episodes may be treated daily. The dose of the maintenance opioid used for persistent pain should be re-evaluated if the patient has more than 4 episodes of breakthrough pain daily.

For details of doses in *children*, see below.

Administration. *INHALATION ROUTE.* In a study[1] inhaled fentanyl provided plasma concentrations similar to those after intravenous doses; use as patient-controlled analgesia was suggested. Inhaled formulations of fentanyl are under investigation for the treatment of breakthrough cancer pain and acute pain.

1. Mather LE, *et al.* Pulmonary administration of aerosolised fentanyl: pharmacokinetic analysis of systemic delivery. *Br J Clin Pharmacol* 1998; 46: 37–43.

INTRANASAL ROUTE. Studies[1-3] have shown that intranasal fentanyl is as effective as the intravenous route for post-operative pain management and that it can be used in a patient-controlled analgesia system. Intranasal fentanyl has also been studied[4-6] for the management of acute pain in children.

An intranasal spray formulation of fentanyl is available for the treatment of breakthrough cancer pain.[7-9]

1. Striebel HW, *et al.* Intranasal fentanyl titration for postoperative pain management in an unselected population. *Anaesthesia* 1993; 48: 753–7.
2. Striebel HW, *et al.* Patient-controlled intranasal analgesia: a method for noninvasive postoperative pain management. *Anesth Analg* 1996; 83: 548–51.
3. Toussaint S, *et al.* Patient-controlled intranasal analgesia: effective alternative to intravenous PCA for postoperative pain relief. *Can J Anesth* 2000; 47: 299–302.
4. Manjushree R, *et al.* Intranasal fentanyl provides adequate postoperative analgesia in pediatric patients. *Can J Anesth* 2002; 49: 190–3.
5. Borland ML, *et al.* Intranasal fentanyl is an equivalent analgesic to oral morphine in paediatric burns patients for dressing changes: a randomised double blind crossover study. *Burns* 2005; 31: 831–7.
6. Borland M, *et al.* A randomized controlled trial comparing intranasal fentanyl to intravenous morphine for managing acute pain in children in the emergency department. *Ann Emerg Med* 2007; 49: 335–40.
7. Kress HG, *et al.* Efficacy and tolerability of transdermal fentanyl spray 50 to 200 microg for breakthrough pain in patients with cancer: a phase III, multinational, randomized, double-blind, placebo-controlled, crossover trial with a 10-month, open-label extension treatment period. *Clin Ther* 2009; 31: 1177–91.
8. Portenoy RK, *et al.* A multicenter, placebo-controlled, double-blind, multiple-crossover study of Fentanyl Pectin Nasal Spray (FPNS) in the treatment of breakthrough cancer pain. *Pain* 2010; 151: 617–24.
9. Mystakidou K, *et al.* Fentanyl nasal spray for the treatment of cancer pain. *Expert Opin Pharmacother* 2011; 12: 1653–9.

INTRASPINAL ROUTE. For a discussion on the intraspinal use of fentanyl, see Postoperative Pain, below.

TRANSDERMAL ROUTE. Transdermal fentanyl is used for chronic intractable cancer pain in adults and children.[1-7] It is also used in the treatment of chronic non-cancer pain;[4,5,8] however, such use is contra-indicated in the management of acute or postoperative pain because the problems of dose titration in the short term increase the possibility of development of significant respiratory depression[4] (see also Effects on the Respiratory System, p. 62.2 and Transdermal Route, under Precautions, p. 63.1).

Although the usual interval for transdermal patches of fentanyl is 72 hours studies have suggested that up to about 25% of cancer patients may require more frequent application with some patients requiring fresh patches every 48 hours.[9,10] Equally, in an attempt to supply lower doses than are allowed for by existing transdermal dosage forms, patches have sometimes been cut, folded, or partially masked with non-porous dressings; the manufacturers do not recommend such practices as they consider the dose supplied will be unreliable, and there is potential for overdosage.

An iontophoretic drug delivery preparation containing fentanyl hydrochloride was also available for the management of acute moderate to severe postoperative pain in a hospital setting (see Postoperative Pain, below for some references) but was withdrawn from the market because of a defective delivery system.

1. Jeal W, Benfield P. Transdermal fentanyl: a review of its pharmacological properties and therapeutic efficacy in pain control. *Drugs* 1997; 53: 109–38.
2. Muijsers RBR, Wagstaff AJ. Transdermal fentanyl: an updated review of its pharmacological properties and therapeutic efficacy in chronic cancer pain control. *Drugs* 2001; 61: 2289–2307.
3. Gourlay GK. Treatment of cancer pain with transdermal fentanyl. *Lancet Oncol* 2001; 2: 165–72.
4. Kornick CA, *et al.* Benefit-risk assessment of transdermal fentanyl for the treatment of chronic pain. *Drug Safety* 2003; 26: 951–73.
5. Zernikow B, *et al.* Transdermal fentanyl in childhood and adolescence: a comprehensive literature review. *J Pain* 2007; 8: 187–207.
6. Hoy SM, Keating GM. Fentanyl transdermal matrix patch (Durotep MT patch; Durogesic DTrans; Durogesic SMAT): in adults with cancer-related pain. *Drugs* 2008; 68: 1711–21.
7. Hair PI, *et al.* Transdermal matrix fentanyl membrane patch (Matrifen): in severe cancer-related chronic pain. *Drugs* 2008; 68: 2001–9.
8. Allan L, *et al.* Randomised crossover trial of transdermal fentanyl and sustained release oral morphine for treating chronic non-cancer pain. *BMJ* 2001; 322: 1154–8.
9. Donner B, *et al.* Long-term treatment of cancer pain with transdermal fentanyl. *J Pain Symptom Manage* 1998; 15: 168–75.
10. Radbruch L, *et al.* Transdermal fentanyl for the management of cancer pain: a survey of 1005 patients. *Palliat Med* 2001; 15: 309–21.

TRANSMUCOSAL ROUTE. Transmucosal fentanyl has been tried for sedation and analgesia before anaesthesia or painful procedures in adults[1] and children[2,3] and is used for breakthrough cancer pain in opioid-tolerant patients.[4-7] It has been noted[8] that this dosage method can cause all the adverse effects of parenteral opioids; nausea and vomiting are common and potentially lethal respiratory depression can occur (see also under Precautions, p. 63.1). Dosage guidelines have been suggested.[9]

1. Macaluso AD, *et al.* Oral transmucosal fentanyl citrate for premedication in adults. *Anesth Analg* 1996; 82: 158–61.
2. Nelson PS, *et al.* Comparison of oral transmucosal fentanyl citrate and an oral solution of meperidine, diazepam, and atropine for premedication in children. *Anesthesiology* 1989; 70: 616–21.
3. Schechter NL, *et al.* The use of oral transmucosal fentanyl citrate for painful procedures in children. *Pediatrics* 1995; 95: 335–9.
4. Blick SKA, Wagstaff AJ. Fentanyl buccal tablet: in breakthrough pain in opioid-tolerant patients with cancer. *Drugs* 2006; 66: 2387–93.
5. Zeppetella G, Ribeiro MDC. Opioids for the management of breakthrough (episodic) pain in cancer patients. Available in the Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 26/06/08).
6. Rauck R, *et al.* Fentanyl buccal soluble film (FBSF) for breakthrough pain in patients with cancer: a randomized, double-blind, placebo-controlled study. *Ann Oncol* 2010; 21: 1308–14.
7. Chwieduk CM, McKeage K. Fentanyl sublingual: in breakthrough pain in opioid-tolerant adults with cancer. *Drugs* 2010; 70: 2281–8.
8. Anonymous. Oral transmucosal fentanyl citrate. *Med Lett Drugs Ther* 1994; 36: 24–5.
9. Aronoff GM, *et al.* Evidence-based oral transmucosal fentanyl citrate (OTFC) dosing guidelines. *Pain Med* 2005; 6: 305–14.

Administration in children. Indications for fentanyl therapy in children are similar to those in adults (see Uses and Administration, p. 60.2).

Fentanyl is usually given by *intravenous* injection as an **adjunct** to general anaesthesia. In the UK recommended initial doses range from 1 to 3 micrograms/kg in children aged 2 to 12 years with *spontaneous respiration*; supplements of 1 to 1.25 micrograms/kg may be given. (The *BNFC* suggests initial doses of 1 to 3 micrograms/kg for those aged from 1 month to 12 years, with supplements of 1 microgram/kg.) When *ventilation* is *assisted*, the initial recommended dose is also 1 to 3 micrograms/kg, with supplements of 1 to 1.25 micrograms/kg. (The *BNFC* suggests an initial dose of 1 to 5 micrograms/kg for neonates and children up to 12 years of age, with supplements of 1 to 3 micrograms/kg.) In the USA, doses are similar to those licensed in the UK.

The *BNFC* suggests that fentanyl may be given by intravenous infusion to provide **analgesia and respiratory depression** in ventilated children under intensive care. A loading dose of 1 to 5 micrograms/kg is given by intravenous injection, followed by an infusion of 1.5 micrograms/kg per hour in neonates, or 1 to 6 micrograms/kg per hour in those aged 1 month to 18 years, adjusted according to response.

Transdermal patches delivering amounts of fentanyl ranging from 12 to 100 micrograms/hour may be used for the treatment of **intractable chronic pain** in children aged 2 to 16 years who are already tolerant to opioid therapy of comparable potency. The initial dose should be based on the previous 24-hour opioid requirement. Use of a patch providing 12 micrograms of fentanyl per hour is equivalent to about 30 to 44 mg daily of oral morphine sulfate. See Uses and Administration, p. 60.2 for further details. Patches should be applied to the upper backs of young children to minimise the potential for removal.

The *transmucosal* lozenge-on-a-stick formulation is licensed for use in adolescents aged 16 years and older for the management of **breakthrough pain** in those already receiving and tolerant to opioid treatment; the usual adult dose may be given (see p. 60.2).

Anaesthesia. Fentanyl and its congeners alfentanil, remifentanil, and sufentanil are shorter-acting than morphine and appear to produce fewer circulatory changes; they are preferred for use as supplements during anaesthesia with inhalational or intravenous drugs. Fentanyl is widely used as the analgesic component of balanced anaesthesia. It has been used to attenuate cardiovascular stress responses to intubation (see Anaesthesia, p. 2028.1), and may be used in higher doses in an attempt to reduce the cardiovascular, endocrine, and metabolic changes that may accompany surgery. When attenuation of surgical stress is especially important, for example in cardiac surgery, intravenous fentanyl 50 to 100 micrograms/kg with oxygen and a neuromuscular blocker, and sometimes up to 150 micrograms/kg, may be used for general anaesthesia. Total intravenous anaesthesia with fentanyl and propofol has been successful.[1]

Satisfactory anaesthesia has been reported[2] with high-dose fentanyl citrate (30 to 50 micrograms/kg) in *premature infants* when used as sole anaesthetic, with pancuronium, for ligation of patent ductus arteriosus; cardiovascular stability was maintained throughout the procedure. However, others[3] found significant hypotension in preterm infants given either fentanyl 20 micrograms/kg, isoflurane, halothane, or ketamine; systolic arterial pressure was best maintained with the ketamine technique. The surgical stress response in preterm babies was abolished by the addition of fentanyl 10 micrograms/kg intravenously to an anaesthetic regimen of nitrous oxide and tubocurarine.[4] Dose responses of fentanyl in *neonatal* anaesthesia have been discussed.[5]

For details of doses in neonates and children, see above.

Neuroleptanalgesia. An injection of short-acting fentanyl 50 micrograms/mL with the longer-acting antipsychotic droperidol 2.5 mg/mL has been used for neuroleptanalgesia, premedication, and as an adjunct to anaesthesia. However, the use of such a fixed-ratio combination cannot be recommended.

1. Jenstrup M, *et al.* Total iv anaesthesia with propofol-alfentanil or propofol-fentanyl. *Br J Anaesth* 1990; 64: 717–22.
2. Robinson S, Gregory GA. Fentanyl-air-oxygen anesthesia for ligation of patent ductus arteriosus in preterm infants. *Anesth Analg* 1981; 60: 331–4.
3. Friesen RH, Henry DB. Cardiovascular changes in preterm neonates receiving isoflurane, halothane, fentanyl, and ketamine. *Anesthesiology* 1986; 64: 238–42.
4. Anand KJS, *et al.* Randomised trial of fentanyl anaesthesia in preterm babies undergoing surgery: effects on the stress response. *Lancet* 1987; i: 243–8.
5. Yaster M. The dose response of fentanyl in neonatal anesthesia. *Anesthesiology* 1987; 66: 433–5.

PHAEOCHROMOCYTOMA. Unlike morphine and some other opioids, fentanyl and alfentanil do not release histamine and may be used safely in the anaesthetic management of patients with phaeochromocytoma.[1]

1. Hull CJ. Phaeochromocytoma: diagnosis, preoperative preparation and anaesthetic management. *Br J Anaesth* 1986; 58: 1453–68.

POSTOPERATIVE SHIVERING. As pethidine appears to be effective in the treatment of postoperative shivering, other opioids including fentanyl have also been tried. Not all opioids are necessarily effective but fentanyl has been reported to be so,[1] although information is scanty.[2]

1. Alfonsi P, *et al.* Fentanyl, as pethidine, inhibits post anaesthesia shivering. *Br J Anaesth* 1993; 70 (suppl 1): 38.
2. Kranke P, *et al.* Pharmacological treatment of postoperative shivering: a quantitative systematic review of randomized controlled trials. *Anesth Analg* 2002; 94: 453–60.

Intensive care. Despite the short duration of action of fentanyl after single doses, rapid redistribution in the body results in an elimination half-life longer than that of morphine. Consequently fentanyl is not a short-acting drug when used for analgesia in intensive care, and may offer little advantage over morphine.[1]

1. Aitkenhead AR. Analgesia and sedation in intensive care. *Br J Anaesth* 1989; 63: 196–206.

Pain. *CANCER PAIN.* Transdermal fentanyl is used in the management of chronic intractable cancer pain; for references see Administration, Transdermal Route, above. For references to the use of intranasal and transmucosal fentanyl in the management of breakthrough cancer pain, see Administration, Intranasal Route and Transmucosal Route, above.

LABOUR PAIN. Fentanyl has been reported to be an effective intravenous analgesic during active labour. Epidural fentanyl is unreliable when used alone,[1,2] although it does enhance the epidural analgesia achieved with the local anaesthetic bupivacaine. The reduction in the minimum local analgesic concentration of epidural bupivacaine for labour pain increased with increasing dose of fentanyl added to bupivacaine.[3] However, the incidence of pruritus increased significantly with fentanyl in a dose of 4 micrograms/mL and therefore the optimum dose of fentanyl may be 3 micrograms/mL for bupivacaine-sparing epidural analgesia during labour. Respiratory depression has also been reported with the combination.[4]

1. Reynolds F. Extradural opioids in labour. *Br J Anaesth* 1989; 63: 251–3.
2. Lindow SW, *et al.* A randomised double-blind comparison of epidural fentanyl versus fentanyl and bupivicaine [sic] for pain relief in the second stage of labour. *Br J Obstet Gynaecol* 2004; 111: 1075–80.
3. Lyons G, *et al.* Extradural pain relief in labour: bupivacaine sparing by extradural fentanyl is dose dependent. *Br J Anaesth* 1997; 78: 493–7.
4. McClure JH, Jones G. Comparison of bupivacaine and bupivacaine with fentanyl in continuous extradural analgesia during labour. *Br J Anaesth* 1989; 63: 637–40.

POSTOPERATIVE PAIN. Small intravenous bolus doses of an opioid analgesic may be injected immediately after surgery for postoperative analgesia and faster acting opioids such as fentanyl may be preferable to morphine.[1] Fentanyl has also been given by epidural injection in doses of 100 or 200 micrograms or by continuous epidural infusion in doses of 20 to 80 micrograms/hour; patient-controlled systems have been used.[2]

Epidural fentanyl or sufentanil provided effective postoperative analgesia after caesarean section with comparable adverse effect profiles.[3] The suggested optimal dose of fentanyl was 100 micrograms. For references comparing epidural fentanyl with alfentanil, see Postoperative Analgesia under Uses and Administration of Alfentanil, p. 19.1. In a review[4] of perioperative pain management epidural opioids were considered to provide effective

analgesia at lower doses than systemic opioids. Fentanyl may be given through a lumbar epidural catheter that is often inserted immediately postoperatively. After an initial loading dose of 1 to 1.5 micrograms/kg of fentanyl, infusion at the rate of 0.7 to 2 micrograms/kg per hour is begun and continued for about 48 hours on average. Some prefer to use intermittent injection. A small study[5] comparing 2 patient-controlled routes of administration found that cervical epidural fentanyl provided better postoperative pain relief at rest than intravenous fentanyl; however, there was no decrease in the total dose required and the authors considered that the benefits of epidural fentanyl did not outweigh its potential complications.

Combined opioid and local anaesthetic epidural infusions have also proved effective, for example fentanyl 1 microgram/mL with bupivacaine 0.1%; both could be infused at lower rates than either drug alone. Although a study[6] comparing bupivacaine-fentanyl combinations with each drug alone for epidural analgesia after caesarean section confirmed an additive analgesic effect for the combination, there was no demonstrable clinical benefit compared with fentanyl alone in this patient group who expect early mobilisation. However, the combination may be of greater benefit in patients for whom early ambulation is not routine.

Fentanyl has also been given by epidural injection to children for postoperative analgesia.[7]

Fentanyl has been tried by intrathecal injection for postoperative pain.[8]

As mentioned in Administration, Transdermal Route, p. 61.1, an iontophoretic transdermal system for postoperative pain was also available.[9-11]

1. Mitchell RWD, Smith G. The control of acute postoperative pain. *Br J Anaesth* 1989; 63: 147–58.
2. Morgan M. The rational use of intrathecal and extradural opioids. *Br J Anaesth* 1989; 63: 165–88.
3. Grass JA, *et al.* A randomized, double-blind, dose-response comparison of epidural fentanyl versus sufentanil analgesia after cesarean section. *Anesth Analg* 1997; 85: 365–71.
4. Swarm RA, *et al.* Pain treatment in the perioperative period. *Curr Probl Surg* 2001; 38: 835–920.
5. Roussier M, *et al.* Patient-controlled cervical epidural fentanyl compared with patient-controlled i.v. fentanyl for pain after pharyngolaryngeal surgery. *Br J Anaesth* 2006; 96: 492–6.
6. Cooper DW, *et al.* Patient-controlled extradural analgesia with bupivacaine, fentanyl, or a mixture of both, after caesarean section. *Br J Anaesth* 1996; 76: 611–15.
7. Lejus C, *et al.* Postoperative extradural analgesia in children: comparison of morphine with fentanyl. *Br J Anaesth* 1994; 72: 156–9.
8. Sudarshan G, *et al.* Intrathecal fentanyl for post-thoracotomy pain. *Br J Anaesth* 1995; 75: 19–22.
9. Chelly JE. An iontophoretic, fentanyl HCl patient-controlled transdermal system for acute postoperative pain management. *Expert Opin Pharmacother* 2005; 6: 1205–14.
10. Koo PJ. Postoperative pain management with a patient-controlled transdermal delivery system for fentanyl. *Am J Health-Syst Pharm* 2005; 62: 1171–6.
11. Mayes S, Perrone M. Fentanyl HCl patient-controlled iontophoretic transdermal system for the management of acute postoperative pain. *Ann Pharmacother* 2006; 40: 2178–86.

Dependence and Withdrawal

As for Opioid Analgesics, p. 109.1.

Fentanyl and illicitly manufactured analogues are subject to abuse (see under Precautions, below).

Plasma concentrations required to produce satisfactory sedation have been reported to increase steadily in neonates receiving continuous infusions, suggesting the development of *tolerance* to the sedating effects of fentanyl.[1]

Movement disorders, extreme irritability, and symptoms characteristic of *opioid abstinence syndrome* have been reported in children after withdrawal of prolonged fentanyl infusions.[2,3] Similarly, withdrawal symptoms and, in one case, myoclonus have occurred in adults when fentanyl transdermal patches have been stopped.[4,5] Acute opioid withdrawal syndrome has also been seen in cancer patients switched from modified-release oral morphine to transdermal fentanyl despite adequate analgesia being maintained.[6]

1. Arnold JH, *et al.* Changes in the pharmacodynamic response to fentanyl in neonates during continuous infusion. *J Pediatr* 1991; 119: 639–43.
2. Lane JC, *et al.* Movement disorder after withdrawal of fentanyl infusion. *J Pediatr* 1991; 119: 649–51.
3. Dominguez KD, *et al.* Opioid withdrawal in critically ill neonates. *Ann Pharmacother* 2003 37: 473–7.
4. Han PKJ, *et al.* Myoclonus secondary to withdrawal from transdermal fentanyl: case report and literature review. *J Pain Symptom Manage* 2002; 23: 66–72.
5. Ishihara C, *et al.* Withdrawal symptom after discontinuation of transdermal fentanyl at a daily dose of 0.6 mg. *Pharm World Sci* 2005; 27: 13–15.
6. Anonymous. Opiate withdrawal with transdermal fentanyl. *Pharm J* 1995; 255: 680.

Adverse Effects and Treatment

As for Opioid Analgesics in general, p. 110.1.

Respiratory depression, which occurs especially with high doses of fentanyl, responds to naloxone (see also Effects on the Respiratory System, below). Atropine may be used to block the vagal effects of fentanyl such as bradycardia. Unlike morphine, fentanyl is reported not to cause significant histamine release. Transient hypotension may follow intravenous dosage. Muscle rigidity can occur and may require neuromuscular blockers.

Local reactions such as rash, erythema, and itching have been reported with transdermal use. Gum bleeding and irritation, and taste perversion have been reported with transmucosal use. Intranasal use may cause throat irritation, epistaxis, nasal ulcers, and rhinorrhoea.

Effects on the cardiovascular system. For a reference to the effects of fentanyl on histamine release compared with some other opioids, see under Pethidine, p. 122.3.

Effects on mental function. Fentanyl had some dose-related effects on mental function and motor activity in healthy subjects,[1] but immediate and delayed recall were not affected. See also under Alfentanil (p. 19.2).

Acute toxic delirium has been reported after treatment with transdermal fentanyl.[2]

1. Scamman FL, *et al.* Ventilatory and mental effects of alfentanil and fentanyl. *Acta Anaesthesiol Scand* 1984; 28: 63–7.
2. Kuzma PJ, *et al.* Acute toxic delirium: a uncommon reaction to transdermal fentanyl. *Anesthesiology* 1995; 83: 869–71.

Effects on the nervous system. There have been reports of seizures with low and high doses of fentanyl or sufentanil.[1] There was, however, no EEG evidence of cortical seizure activity in a patient who had seizure-like muscle movements during a fentanyl infusion;[2] the muscle movements might have been due to myoclonus produced by depression of higher CNS inhibitory centres or to a pronounced form of opioid-induced muscle rigidity.

For a report of encephalopathy associated with prolonged use of fentanyl and midazolam in infants in intensive care, see Encephalopathy under Adverse Effects of Diazepam, p. 1066.2.

1. Zaccara G, *et al.* Clinical features, pathogenesis and management of drug-induced seizures. *Drug Safety* 1990; 5: 109–51.
2. Scott JC, Samquist FH. Seizure-like movements during a fentanyl infusion with absence of seizure activity in a simultaneous EEG recording. *Anesthesiology* 1985; 62: 812–14.

Effects on the respiratory system. Fentanyl, like other opioid agonists, causes dose-related respiratory depression; it is significant with *intravenous* fentanyl doses of more than 200 micrograms and may be more prolonged than analgesia. Anaesthesia with fentanyl may result in either prolonged or delayed respiratory depression postoperatively.[1] Consequently, patients should continue to be monitored postoperatively until spontaneous breathing has been re-established. Severe respiratory depression in a 14-month-old child after intravenous sedation with fentanyl and midazolam has also highlighted the necessity for careful monitoring when giving with other respiratory depressants.[2] If present at the end of operation respiratory depression may be reversed by an opioid antagonist such as naloxone; alternatively, a respiratory stimulant such as doxapram that does not reverse analgesia has been given.

Rigidity of the respiratory muscles (chest wall rigidity) may occur during fentanyl anaesthesia. The effects can be minimised by using a slow intravenous injection but a neuromuscular blocker may be required to allow artificial ventilation; rigidity has been reversed postoperatively by naloxone. Similar muscle rigidity induced by alfentanil could be attenuated by pretreatment with a benzodiazepine whereas small doses of neuromuscular blockers appeared to be ineffective.[3]

Coughing has been associated[4] with intravenous fentanyl; incidence was decreased with a longer injection time,[5] in light cigarette smokers,[5,6] and in older patients.[6] For the use of beclometasone and lidocaine to prevent cough associated with intravenous fentanyl in anaesthesia, see p. 1622.1 and p. 1980.3, respectively.

The risk of respiratory depression associated with *epidural* doses of fentanyl, a highly lipid-soluble opioid, has been considered relatively small and only slight ventilatory depression was noted[7] after a dose of 50 micrograms. However, profound delayed respiratory depression has been reported in 2 women 100 minutes[8] and 80 minutes,[9] respectively after fentanyl 100 micrograms had been given epidurally for caesarean section. No adverse effects on neonatal respiration or neurobehaviour were detected in a study[10] of neonates of mothers given epidural infusions of bupivacaine and fentanyl during labour. However, a later report[11] described 2 neonates who developed respiratory depression after their mothers were given epidural fentanyl during labour; the effect was reversed by intramuscular naloxone 400 micrograms. The authors noted that the doses of fentanyl used were higher than those in the previous study.

Respiratory depression is also a risk with *topically* applied fentanyl preparations. Severe hypoventilation with some fatalities has occurred in patients given fentanyl as a transdermal patch for minor painful conditions.[12] More recently, Health Canada had received 2 reports of fatal respiratory depression associated with the use of transdermal fentanyl patches in adolescents for relatively minor conditions (chronic headache and throat pain);[13] in both cases the respiratory depression developed within 24 hours of applying the first and only patch. See also Administration, Transdermal Route, under Precautions, p. 63.1.

1. Bennett MRD, Adams AP. Postoperative respiratory complications of opiates. *Clin Anaesthesiol* 1983; 1: 41–56.
2. Yaster M, *et al.* Midazolam-fentanyl intravenous sedation in children: case report of respiratory arrest. *Pediatrics* 1990; 86: 463–7.
3. Sanford TJ, *et al.* Pretreatment with sedative-hypnotics, but not with nondepolarizing muscle relaxants, attenuates alfentanil-induced muscle rigidity. *J Clin Anesth* 1994; 6: 473–80.
4. Tweed WA, Dakin D. Explosive coughing after bolus fentanyl injection. *Anesth Analg* 2001; 92: 1442–3.
5. Lin J-A, *et al.* Prolonged injection time and light smoking decrease the incidence of fentanyl-induced cough. *Anesth Analg* 2005; 101: 670–4.
6. Oshima T, *et al.* Identification of independent risk factors for fentanyl-induced cough. *Can J Anesth* 2006; 53: 753–8.
7. Morisot P, *et al.* Ventilatory response to carbon dioxide during extradural anaesthesia with lignocaine and fentanyl. *Br J Anaesth* 1989; 63: 97–10 .
8. Brockway MS, *et al.* Profound respiratory depression after extradural fentanyl. *Br J Anaesth* 1990; 64: 243–5.
9. Wang CY. Respiratory depression after extradural fentanyl. *Br J Anaesth* 1992; 69: 544.
10. Porter J, *et al.* Effect of epidural fentanyl on neonatal respiration. *Anesthesiology* 1998; 89: 79–85.
11. Kumar M, Paes B. Epidural opioid analgesia and neonatal respiratory depression. *J Perinatol* 2003; 23: 425–7.
12. *FDC Reports Pink Sheet* 1994; January 24: 12.
13. Health Canada. Transdermal fentanyl (Duragesic): respiratory arrest in adolescents. *Can Adverse React News* 2004; 14 (4): 1–2. Also available at http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/can-bcei_v14n4-eng.pdf (accessed 26/06/08)

Effects on the skin. A patient developed a macular rash covering the whole body, except for the face and scalp while using transdermal fentanyl patches.[1]

1. Stoukides CA, Stegman M. Diffuse rash associated with transdermal fentanyl. *Clin Pharm* 1992; 11: 222.

Effects on the urinary tract. Urinary retention developed in 2 premature infants after sedation with fentanyl infusion at a dose of 3 micrograms/kg per hour.[1] In both cases catheterisation relieved symptoms.

1. Das UG, Sasidharan P. Bladder retention of urine as a result of continuous intravenous infusion of fentanyl: 2 case reports. *Pediatrics* 2001; 108: 1012–1015.

Precautions

As for Opioid Analgesics in general, p. 110.3.

Caution is advised in patients with myasthenia gravis; the effects of muscular rigidity on respiration may be particularly pronounced in these patients.

US licensed product information contra-indicates the use of standard transdermal fentanyl patches in opioid-naive patients because of the risk of fatal respiratory depression (see Effects on the Respiratory System, above and Administration, Transdermal Route, p. 63.1). Similar contra-indications apply to transmucosal formulations of fentanyl (see also Administration, Transmucosal Route, p. 63.1). The use of fentanyl intranasal spray is contra-indicated in opioid-naive patients, and in those with previous facial radiotherapy or recurrent episodes of epistaxis.

Absorption of fentanyl from standard transdermal patches may be increased as the temperature rises and patients should therefore avoid exposing the patch to external heat; similarly, patients with fever may require monitoring because of increased absorption. It may take 17 hours or longer for plasma concentrations of fentanyl to decrease by 50% after removal of a transdermal patch; patients who have had adverse effects should be monitored for up to 24 hours and those requiring replacement opioid therapy should initially receive low doses increased gradually thereafter. Similar advice has also been given for patients receiving fentanyl via an iontophoretic drug delivery system; the mean half-life of fentanyl in this system is 11 hours.

The bioavailability of different transmucosal fentanyl preparations is not equivalent and consequently they should not be substituted on a dose-per-dose basis.

Abuse. Several synthetic analogues of fentanyl, so-called 'designer drugs', have been manufactured illicitly for recreational use, particularly in the USA. They are highly potent, and respiratory depression and death may occur very rapidly.[1] The 'fentanyls' have been smoked or snorted as well as injected intravenously.

Fentanyl analogues identified by WHO[2,3] as being subject to street abuse or likely to be abused include: α-methylfentanyl (also known as 'China white' or 'synthetic heroin'), 3-methylfentanyl, acetyl-α-methylfentanyl, α-methylthiofentanyl, *p*-fluorofentanyl, β-hydroxyfentanyl, β-hydroxy-3-methylfentanyl, thiofentanyl, and 3-methylthiofentanyl.

Fentanyl itself is also subject to illicit use. It is chemically unrelated to morphine and does not react in screening tests for morphine-related opioids. It has therefore been recommended[4] that fentanyl should be tested for specifically in cases with suspected opioid misuse.

Used fentanyl transdermal systems may contain significant amounts of fentanyl and have been subject to abuse. In some cases the contents of the patches have been injected intravenously; such abuse has resulted in death.[5,6] Licensed product information advises that used patches should be folded firmly in half, adhesive side inwards to conceal the release membrane, and disposed of safely.

1. Buchanan JF, Brown CR. Designer drugs': a problem in clinical toxicology. *Med Toxicol* 1988; 3: 1–17.
2. WHO. WHO expert committee on drug dependence: twenty-fourth report. *WHO Tech Rep Ser 761* 1988.
3. WHO. WHO expert committee on drug dependence: twenty-sixth report. *WHO Tech Rep Ser 787* 1989.
4. Berens AJL, *et al.* Illicit fentanyl in Europe. *Lancet* 1996; 347: 1334–5.
5. Reeves MD, Ginifer CJ. Fatal intravenous misuse of transdermal fentanyl. *Med J Aust* 2002; 177: 552–3.
6. Tharp AM, *et al.* Fatal intravenous fentanyl abuse: four cases involving extraction of fentanyl from transdermal patches. *Am J Forensic Med Pathol* 2004; 25: 178–81.

Administration. *INTRAVENOUS ROUTE.* Fentanyl is much more lipid-soluble than morphine and after standard single intravenous doses has a rapid onset and short duration of action. However, fentanyl is rapidly redistributed in the body and its half-life (see under Pharmacokinetics, below) is longer than that of morphine. Hence, with high or repeated doses, fentanyl becomes a relatively long-acting drug; to avoid accumulation patients should be monitored and doses adjusted accordingly.

Repeated intra-operative doses of fentanyl should be given with care, since not only may the respiratory depression persist into the postoperative period but it may become apparent for the first time postoperatively when the patient is away from immediate nursing attention.

TRANSDERMAL ROUTE. Fatalities have been associated with the use of standard fentanyl transdermal patches (see Effects on the Respiratory System, p. 62.2). Incorrect or inappropriate use resulting in serious adverse effects and fatalities had prompted regulatory authorities to issue warnings and recommendations for changes to product labelling; in particular transdermal fentanyl patches are not appropriate for the treatment of acute or postoperative pain. Nonetheless, reports of fatalities and life-threatening adverse reactions have continued to be received[1-4] and, in December 2007, the FDA[1] reiterated that:

- fentanyl patches are indicated for the management of persistent, moderate to severe chronic pain in opioid-tolerant patients
- licensed product information must be consulted when determining the initial dose as overestimating when converting patients from another opioid analgesic can result in fatal overdose with the first dose
- use with any inhibitors of the cytochrome P450 isoenzyme CYP3A4 may result in an increase in plasma-fentanyl concentrations, which may cause potentially fatal respiratory depression; patients who are taking CYP3A4 inhibitors and using fentanyl patches for an extended period of time should be monitored and the dose of fentanyl adjusted if necessary

1. FDA. Information for healthcare professionals: fentanyl transdermal system (marketed as Duragesic and generics) (issued 21st December, 2007). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm084307 (accessed 02/08/10)
2. Health Canada. Fentanyl transdermal patch and fatal adverse reactions. *Can Adverse React News* 2008; 18 (3): 1–2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v18n3-eng.pdf (accessed 23/07/08)
3. MHRA/CHM. Fentanyl patches: serious and fatal overdose from dosing errors, accidental exposure, and inappropriate use. *Drug Safety Update* 2008; 2 (2): 2–3. Available at: http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON025631 (accessed 03/11/09)
4. Health Canada. Fentanyl transdermal patches and accidental child exposure. *Can Adverse React News* 2009; 19 (3): 3. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v19n3-eng.pdf (accessed 03/11/09)

TRANSMUCOSAL ROUTE. The FDA[1] has received reports of serious adverse effects, including fatalities, in patients who have taken the fentanyl buccal tablets, *Fentora* (*Cephalon, USA*), resulting from inappropriate use in patients who were not opioid tolerant, misunderstanding of dosing instructions, or inappropriate substitution for other fentanyl-containing formulations. The FDA reiterated that *Fentora*:

- should only be used for breakthrough pain in opioid-tolerant cancer patients
- should not be used in those who only need an opioid on an intermittent, or as required, basis and who are not on around-the-clock opioids
- should not be used for the management of acute or postoperative pain including headaches, migraines, and pain due to injury
- should not be directly substituted for other fentanyl-containing formulations

Similar restrictions are also mentioned in the licensed product information for other transmucosal preparations of fentanyl.

1. FDA. Information for healthcare professionals: fentanyl buccal tablets (marketed as Fentora) (issued 26th September, 2007). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm126082 (accessed 02/08/10)

Breast feeding. The American Academy of Pediatrics[1] states that there have been no reports of any clinical effect in infants of breast-feeding mothers given fentanyl, and that therefore it may be considered to be usually compatible with breast feeding. However, licensed product information states that, since fentanyl is distributed into breast milk, it should be avoided in nursing mothers because of the possibility of sedation or respiratory depression in breast-fed infants. The *BNF* recommends that breast-fed infants should be monitored for opioid-induced adverse effects.

A study[2] using fentanyl 100 micrograms intravenously for induction of anaesthesia in 5 mothers concluded that the amount of fentanyl excreted into breast milk within 24 hours of induction was less than 0.1% of the maternal dose, and hence unlikely to affect a healthy full-term breast-feeding infant.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/06/08)
2. Nitsun M, *et al.* Pharmacokinetics of midazolam, propofol, and fentanyl transfer to human breast milk. *Clin Pharmacol Ther* 2006; 79: 549–57.

Children. The half-life of fentanyl is prolonged in neonates and accumulation is likely with prolonged use; muscle rigidity may occur and the use of muscle relaxants may be required. See also under Pharmacokinetics, p. 64.1.

Exercise. Opioid toxicity requiring naloxone treatment occurred in a patient who wore a fentanyl patch while engaging in vigorous outdoor exercise.[1] Physicians should be aware that along with fever and external heat sources, physical activity may cause increased absorption of transdermal fentanyl.

1. Carter KA. Heat-associated increase in transdermal fentanyl absorption. *Am J Health-Syst Pharm* 2003; 60: 191–2.

Handling. Avoid contact with skin and the inhalation of fentanyl citrate particles.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fentanyl as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/10/11)

Interactions

For interactions associated with opioid analgesics, see p. 111.2. Use of fentanyl with non-vagolytic neuromuscular blockers may produce bradycardia and possibly asystole.

Fentanyl is metabolised via the cytochrome P450 isoenzyme CYP3A4; use with potent inhibitors of this isoenzyme, such as ritonavir and other HIV-protease inhibitors, may increase fentanyl plasma concentrations.

Antidepressants. For reference to a possible case of serotonin syndrome associated with use of fentanyl and *SSRIs*, see Opioid Analgesics under Interactions of Fluoxetine, p. 427.1.

Antivirals. *Ritonavir*, an inhibitor of the cytochrome P450 isoenzyme CYP3A4, might prolong fentanyl-induced respiratory depression. The plasma clearance of fentanyl was decreased, and the elimination half-life and area under the plasma concentration-time curve increased, when given with ritonavir in a study in healthy subjects.[1]

1. Olkkola KT, *et al.* Ritonavir's role in reducing fentanyl clearance and prolonging its half-life. *Anesthesiology* 1999; 91: 681–5.

Benzodiazepines. For the effects of opioids such as fentanyl with benzodiazepines, see Analgesics under Interactions of Diazepam, p. 1068.1 and Effects on the Respiratory System, p. 62.2.

Propofol. For reference to the effect that fentanyl has on blood concentrations of propofol, see p. 1915.2.

Pharmacokinetics

After parenteral doses fentanyl citrate has a rapid onset and short duration of action. After transmucosal delivery, up to 50% of the dose is rapidly absorbed from the buccal mucosa; the remainder is swallowed and slowly absorbed from the gastrointestinal tract. Some first-pass metabolism occurs via this route. The absolute bioavailability of transmucosal delivery is about half that for intravenous fentanyl but varies between formulations. The absolute bioavailability of intranasal delivery is about 89% and fentanyl is absorbed very rapidly through the nasal mucosa. Absorption is slow after transdermal application. Fentanyl is metabolised in the liver by *N*-dealkylation and hydroxylation via the cytochrome P450 isoenzyme CYP3A4. Metabolites and some unchanged drug are excreted mainly in the urine. The short duration of action is probably due to rapid redistribution into the tissues rather than metabolism and excretion. The relatively longer elimination half-life reflects slower release from tissue depots. About 80% has been reported to be bound to plasma proteins. Fentanyl appears in the CSF. It crosses the placenta and has been detected in breast milk.

Marked differences in results of pharmacokinetic studies of fentanyl have been attributed[1] to differences in assay methods. The need for sensitive assay methods has been emphasised because the potency of fentanyl means that small doses are used. However, there are differences in pharmacokinetics between bolus doses and prolonged infusion with highly lipophilic drugs such as fentanyl.[2] Terminal half-lives ranging from 2 to 7 hours have been reported in healthy subjects and surgical patients. However, the duration of action of fentanyl after a single intravenous dose of up to 100 micrograms may be only 30 to 60 minutes as a result of rapid redistribution into the tissues. US licensed product information has given values for a three-compartment pharmacokinetic model with a distribution time of 1.7 minutes, a redistribution time of 13 minutes, and a terminal elimination half-life of 219 minutes. Giving repeated or large doses, or continuous infusions, may result in accumulation and a more prolonged action.

The clinical significance of secondary peak plasma-fentanyl concentrations and the possible role of enterosystemic recirculation[3] has been controversial, but some[4] considered that irregular decay curves were not unlikely for lipophilic compounds such as fentanyl, especially in patients undergoing operations and subject to large changes in blood flow. Unexpectedly high plasma-fentanyl concentrations in a patient following epidural use were thought to be a result of aortic clamping and might reflect the effect of changes in blood flow.[5]

The main metabolites of fentanyl, which are excreted in the urine, have been identified as 4-*N*-(*N*-propionylanilino) piperidine and 4-*N*-(*N*-hydroxypropionylanilino) piperidine; 1-(2-phenethyl)-4-*N*-(*N*-hydroxypropionylanilino) piperidine is a minor metabolite.[6] Fentanyl has no active or toxic metabolites.[4]

1. Mather LE. Clinical pharmacokinetics of fentanyl and its newer derivatives. *Clin Pharmacokinet* 1983; 8: 422–46.
2. Scholz J, *et al.* Clinical pharmacokinetics of alfentanil, fentanyl and sufentanil: an update. *Clin Pharmacokinet* 1996; 31: 275–92.
3. Bennett MRD, Adams AP. Postoperative respiratory complications of opiates. *Clin Anaesthesiol* 1983; 1: 41–56.
4. Moore RA, *et al.* Opiate metabolism and excretion. *Bailliere's Clin Anaesthesiol* 1987; 1: 829–58.
5. Bullingham RES, *et al.* Unexpectedly high plasma fentanyl levels after epidural use. *Lancet* 1980; i: 1361–2.
6. Goromaru T, *et al.* Identification and quantitative determination of fentanyl metabolites in patients by gas chromatography-mass spectrometry. *Anesthesiology* 1984; 61: 73–7.

Administration. Some references to the pharmacokinetics of fentanyl after constant rate intravenous infusion,[1] transdermal application,[2-5] use of the oral sublingual[6] and transmucosal[7-11] routes, intranasal dosage,[12,13] subcutaneous infusion,[14] and epidural use.[15-17]

1. Duthie DJR, *et al.* Pharmacokinetics of fentanyl during constant rate iv infusion for the relief of pain after surgery. *Br J Anaesth* 1986; 58: 950–6.
2. Grond S, *et al.* Clinical pharmacokinetics of transdermal opioids: focus on transdermal fentanyl. *Clin Pharmacokinet* 2000; 38: 59–89.
3. Solassol I, *et al.* Inter- and intraindividual variabilities in pharmacokinetics of fentanyl after repeated 72-hour transdermal applications in cancer pain patients. *Ther Drug Monit* 2005; 27: 491–8.
4. Marier J-F, *et al.* Pharmacokinetics, tolerability, and performance of a novel matrix transdermal delivery system of fentanyl relative to the commercially available reservoir formulation in healthy subjects. *J Clin Pharmacol* 2006; 46: 642–53.
5. Marier J-F, *et al.* Comparative bioequivalence study between a novel matrix transdermal delivery system of fentanyl and a commercially available reservoir formulation. *Br J Clin Pharmacol* 2007; 63: 121–4.
6. Lennernäs B, *et al.* Pharmacokinetics and tolerability of different doses of fentanyl following sublingual administration of a rapidly dissolving tablet to cancer patients: a new approach to treatment of incident pain. *Br J Clin Pharmacol* 2005; 59: 249–53.
7. Streisand JB, *et al.* Absorption and bioavailability of oral transmucosal fentanyl citrate. *Anesthesiology* 1991; 75: 223–9.
8. Darwish M, *et al.* Pharmacokinetics and dose proportionality of fentanyl effervescent buccal tablets in healthy volunteers. *Clin Pharmacokinet* 2005; 44: 1279–86.
9. Darwish M, *et al.* Comparison of equivalent doses of fentanyl buccal tablets and arteriovenous differences in fentanyl pharmacokinetics. *Clin Pharmacokinet* 2006; 45: 843–50.
10. Darwish M, *et al.* Single-dose and steady-state pharmacokinetics of fentanyl buccal tablet in healthy volunteers. *J Clin Pharmacol* 2007; 47: 56–63.
11. Darwish M, *et al.* Absolute and relative bioavailability of fentanyl buccal tablet and oral transmucosal fentanyl citrate. *J Clin Pharmacol* 2007; 47: 343–50.
12. Walter SH, *et al.* Pharmacokinetics of intranasal fentanyl. *Br J Anaesth* 1993; 70 (suppl 1): 108.
13. Foster D, *et al.* Pharmacokinetics and pharmacodynamics of intranasal versus intravenous fentanyl in patients with pain after oral surgery. *Ann Pharmacother* 2008; 42: 1380–7.
14. Miller RS, *et al.* Plasma concentrations of fentanyl with subcutaneous infusion in palliative care patients. *Br J Clin Pharmacol* 1995; 40: 553–6.
15. Gourlay GK, *et al.* Pharmacokinetics of fentanyl in lumbar and cervical CSF following lumbar epidural and intravenous administration. *Pain* 1989; 38: 253–9.

16. Bader AM, *et al.* Maternal and neonatal fentanyl and bupivacaine concentrations after epidural infusion during labor. *Anesth Analg* 1995; 81: 829–32.
17. Moises EC, *et al.* Pharmacokinetics and transplacental distribution of fentanyl in epidural anesthesia for normal pregnant women. *Eur J Clin Pharmacol* 2005; 61: 517–22.

Cardiopulmonary bypass. In general, studies[1,2] indicate that serum concentrations of fentanyl during cardiopulmonary bypass decrease initially and then remain stable. The fall in concentrations has been attributed to haemodilution although adsorption to the bypass apparatus has also been found.

1. Buylaert WA, *et al.* Cardiopulmonary bypass and the pharmacokinetics of drugs: an update. *Clin Pharmacokinet* 1989; 17: 10–26.
2. Gedney JA, Ghosh S. Pharmacokinetics of analgesics, sedatives and anaesthetic agents during cardiopulmonary bypass. *Br J Anaesth* 1995; 75: 344–51.

Children. The disposition of intravenous fentanyl 10 to 50 micrograms/kg in 14 neonates undergoing various major surgical procedures was highly variable.[1] The mean elimination half-life of 317 minutes and other pharmacokinetic parameters including volume of distribution and total body clearance were greater than reported in adults, but both pharmacodynamic and pharmacokinetic mechanisms appeared responsible for the very prolonged respiratory depression that can occur in neonates after fentanyl anaesthesia. In 9 premature neonates given fentanyl 30 micrograms/kg intravenously for induction of anaesthesia[2] the elimination half-life ranged from 6 to 32 hours, but cautious interpretation was advised because of the method of calculation.

1. Koehntop DE, *et al.* Pharmacokinetics of fentanyl in neonates. *Anesth Analg* 1986; 65: 227–32.
2. Collins C, *et al.* Fentanyl pharmacokinetics and hemodynamic effects in preterm infants during ligation of patent ductus arteriosus. *Anesth Analg* 1985; 64: 1078–80.

The elderly. In one study the elimination half-life of intravenous fentanyl increased from 265 minutes in patients with a mean age of 36 years to 945 minutes in those with a mean age of 67 years.[1] The authors of another study were critical of the relatively short sampling time used and in contrast found that major fentanyl pharmacokinetic parameters did not correlate with age.[2] However, elderly patients had increased brain sensitivity to intravenous fentanyl, as shown by EEG changes[2] and lower doses might be indicated in older patients for pharmacodynamic rather than pharmacokinetic reasons.

1. Bentley JB, *et al.* Age and fentanyl pharmacokinetics. *Anesth Analg* 1982; 61: 968–71.
2. Scott JC, Stanski DR. Decreased fentanyl and alfentanil dose requirements with age: a simultaneous pharmacokinetic and pharmacodynamic evaluation. *J Pharmacol Exp Ther* 1987; 240: 159–66.

Hepatic impairment. The pharmacokinetics of fentanyl were not affected significantly in surgical patients with cirrhosis of the liver.[1] A 1987 review[2] considered that fentanyl had not been associated with clinical problems when given to patients with liver dysfunction.

1. Haberer JP, *et al.* Fentanyl pharmacokinetics in anaesthetized patients with cirrhosis. *Br J Anaesth* 1982; 54: 1267–70.
2. Moore RA, *et al.* Opiate metabolism and excretion. *Baillieres Clin Anaesthesiol* 1987; 1: 829–58.

Renal impairment. Clearance of fentanyl from plasma was reported to be enhanced in surgical patients with end-stage renal disease,[1] although clearance was reduced and elimination half-life increased in patients with renal failure undergoing transplantation,[2] possibly because of the influence of uraemia on metabolism in the liver. Nevertheless, a 1987 review[2] noted that fentanyl had no active or toxic metabolites and had not been associated with clinical problems when given to patients with renal dysfunction.

1. Corall IM, *et al.* Plasma concentrations of fentanyl in normal surgical patients and those with severe renal and hepatic disease. *Br J Anaesth* 1980; 52: 101P.
2. Moore RA, *et al.* Opiate metabolism and excretion. *Baillieres Clin Anaesthesiol* 1987; 1: 829–58.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Durogesic; Fentax; Gray-F; Nafluvent; Sublimaze; Talnur; ***Austral.***: Actiq; Denpax; Durogesic; Sublimaze; ***Austria***: Actiq; Durogesic; Effentora; Fentamed; Fentaplast; Fentoron; Instanyl; Matrifen; ***Belg.***: Abstral; Durogesic; Instanyl; Matrifen; ***Braz.***: Biofent; Durogesic; Fentabbott; Fentanest; Fentatil; Unifental; ***Canad.***: Abstral; Duragesic; Onsolis†; ***Chile***: Durogesic; ***China***: Durogesic (多瑞吉); ***Cz.***: Adolor; Dolforin; Durogesic; Effentora; Fentagesic†; Fentahexal†; Fentalis; Instanyl; Lunaldin; Matrifen; PecFent; Tocril; Wintanyl†; ***Denm.***: Abstral; Actiq; Breakyl; Dermagesic†; Durogesic; Haldid; Instanyl; Lafene; Matrifen; ***Fin.***: Abstral; Actiq†; Breakyl; Durogesic; Matrifen; ***Fr.***: Abstral; Actiq; Durogesic; Effentora; Instanyl; Matrifen; PecFent; ***Ger.***: Abstral; Actiq; Durogesic; Effentora; Fentadolon; FentaMat†; Instanyl; Matrifen; PecFent; Ribofentanyl†; ***Gr.***: Abstral; Actiq; Demogyl; Dolfen; Durogesic; Fentadur; Instanyl; Matrifen; Meganyl; Myfene; ***Hong Kong***: Durogesic; ***Hung.***: Dolforin; Durogesic; Matrifen; Sedaton; ***India***: Durogesic; Fendrop; Fenilate; Fenstud; Fent; Trofentyl; ***Indon.***: Durogesic; ***Irl.***: Abstral; Actiq; Breakyl; Durogesic; Effentora; Fentadur; Fental; Fetanex; Instanyl; Matrifen; Mytanyl; PecFent; Sublimaze; ***Israel***: Abstral; Actiq; Durogesic†; Fenta; Tanyl; ***Ital.***: Actiq; Durogesic; Fentanest; Fenvel; Matrifen; Quatrofen; ***Jpn***: Durotep; E-fen; OneDuro; ***Malaysia***: Durogesic; Talgesil; ***Mex.***: Durogesic; Penodid; Fentanest; Filtaten; ***Neth.***: Abstral; Actiq; Breakyl; Durogesic; Effentora; Fenylat; Instanyl; PecFent; ***Norw.***: Abstral; Actiq†; Buquel; Durogesic; Instanyl; Leptanal; Matrifen†; ***NZ***: Durogesic; Sublimaze; ***Philipp.***: Durogesic; Sublimax; Sublimaze; Trofentyl; ***Pol.***: Dolforin; Durogesic; Effentora; Fenta MX; Fentagesic; Fentahexal†; Instanyl; Lunaldin; Matrifen; PecFent; ***Port.***: Actiq; Ardicat; Durogesic; Effentora; Fentanest; Instanyl; Nilfene; PecFent; ***Rus.***: Durogesic (Дюрогезик); Fendivia (Фендивия); ***S.Afr.***: Durogesic; Sublimaze; Tanyl†; ***Singapore***: Durogesic; Fantamax; ***Spain***: Abstral; Actiq; Durogesic; Effentora; Fendivia; Fentanest; Instanyl; Matrifen; PecFent; Quidorfen†; ***Swed.***: Abstral; Actiq; Durogesic; Instanyl; Leptanal; Matrifen; ***Switz.***: Abstral; Actiq; Durogesic; Effentora; Matrifen; Sintenyl; ***Thai.***: Durogesic; ***Turk.***: Actiq; Durogesic; ***UK***: Abstral; Actiq; Breakyl; Durogesic; Effentora; Fentalis; Instanyl; Matrifen; Mezolar; Opiodur; Osmach; Osmanil; PecFent; Sublimaze; Tilofyl; ***Ukr.***: Matrifen (Матрифен)†; ***USA***: Abstral; Actiq; Duragesic; Fentora; Ionsys†; Lazanda; Onsolis†; Sublimaze; Subsys; ***Venez.***: Durogesic.

Multi-ingredient Preparations. ***Arg.***: Disifelit; ***Austral.***: Marcain with Fentanyl; Naropin with Fentanyl; ***Braz.***: Nilperidol; ***Gr.***: Thalamonal; ***NZ***: Bupafen; Marcain with Fentanyl; Naropin with Fentanyl; ***UK***: Bufyl.

Pharmacopoeial Preparations
BP 2014: Bupivacaine and Fentanyl Injection; Fentanyl Injection;
USP 36: Fentanyl Citrate Injection.

Fentiazac *(BAN, USAN, rINN)*

BR-700; Fentiazaco; Fentiazacum; Wy-21894; Фентиазак.
[4-(4-Chlorophenyl)-2-phenylthiazol-5-yl]acetic acid.
$C_{17}H_{12}ClNO_2S$=329.8
CAS — 18046-21-4.
ATC — M01AB10; M02AA14.
ATC Vet — QM01AB10; QM02AA14.
UNII — 0YHF6E6NLS.

Profile

Fentiazac is an NSAID (p. 102.3) that has been used for the relief of pain and inflammation associated with musculoskeletal, joint, peri-articular, and soft-tissue disorders. It has also been used in the treatment of fever. Fentiazac has been given orally; it has also been applied topically and has been given rectally as the calcium salt.

Fenyramidol Hydrochloride *(BANM, rINNM)*

Feniramidol, hidrocloruro de; Feniramidol Hidroklorür; Fényramidol, Chlorhydrate de; Fenyramidoli Hydrochloridum; Hidrocloruro de feniramidol; IN-511; MJ-505; NSC-17777; Phenyramidol Hydrochloride (USAN); Phenyramidol Hydrochloride; Фенирамидола Гидрохлорид.
1-Phenyl-2-(2-pyridylamino)ethanol hydrochloride; α-(2-Pyridylaminomethyl)benzyl alcohol hydrochloride.
$C_{13}H_{14}N_2O,HCl$=250.7
CAS — 553-69-5 (fenyramidol); 326-43-2 (fenyramidol hydrochloride).
ATC — M03BX03.
ATC Vet — QM03BX03.
UNII — M574V6XQH7.

Profile

Fenyramidol hydrochloride has analgesic and skeletal muscle relaxant properties and has been used in the treatment of muscular pain and stiffness.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Cabral; ***Turk.***: Cabral; Capral.

Fepradinol *(rINN)*

Fépradinol; Fepradinolum; Фепрадинол.
(±)-α-[[(2-Hydroxy-1,1-dimethylethyl)amino]methyl]benzyl alcohol.
$C_{12}H_{19}NO_2$=209.3
CAS — 63075-47-8.
UNII — 860MHI4WBA.

Profile

Fepradinol is an NSAID (p. 102.3) that has been used topically in a concentration of 6% for the relief of pain and inflammation. The hydrochloride has been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Mex.***: Sinalgia; ***Spain***: Dalgen.

Feprazone *(BAN, rINN)*

DA-2370; Feprazona; Féprazone; Feprazonum; Phenylprenazone; Prenazone; Фепразон.
4-(3-Methylbut-2-enyl)-1,2-diphenylpyrazolidine-3,5-dione.
$C_{20}H_{20}N_2O_2$=320.4
CAS — 30748-29-9 (feprazone); 57148-60-4 (feprazone piperazine salt 1:1).
ATC — M01AX18; M02AA16.
ATC Vet — QM01AX18; QM02AA16.
UNII — 78VX6J0CGR.

Profile

Feprazone, a phenylbutazone (p. 125.1) derivative, is an NSAID (p. 102.3). It has been given orally in the treatment of mild to moderate pain, fever, and inflammation associated with musculoskeletal and joint disorders. Feprazone has also been given rectally and used topically as a 5% cream.

Pinazone, the piperazine salt of feprazone, has been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Xitong (希同); ***Ital.***: Zepelin; ***Spain***: Brotazona†; ***Venez.***: Vapesin.

Firocoxib *(USAN, rINN)*

Firocoxiburn; ML-1785713; Фирококсиб.
3-(Cyclopropylmethoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]furan-2(5*H*)-one.
$C_{17}H_{20}O_5S$=336.4
CAS — 189954-96-9.
ATC Vet — QM01AH90.
UNII — Y6V2W4S4WT.

Profile

Firocoxib, a selective cyclo-oxygenase-2 (COX-2) inhibitor, is an NSAID (p. 102.3) used in veterinary medicine for the treatment of inflammation and pain associated with osteoarthritis in dogs.

Floctafenine *(BAN, USAN, rINN)*

Floctafenina; Floctafénine; Floctafeninum; R-4318; RU-15750; Флоктафенин.
2,3-Dihydroxypropyl *N*-(8-trifluoromethyl-4-quinolyl)anthranilate.
$C_{20}H_{17}F_3N_2O_4$=406.4
CAS — 23779-99-9.
ATC — N02BG04.
ATC Vet — QN02BG04.
UNII — O04HVX6A9Q.

Uses and Administration

Floctafenine, an anthranilic acid derivative, is an NSAID (p. 102.3) used in oral doses of up to 800 mg daily, in divided doses, for the short-term relief of pain.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3.

Anaphylactic shock has been reported, and may be preceded by minor allergic manifestations; floctafenine should be stopped in any patient who develops signs suggestive of allergy (such as pruritus or urticaria). Reactions may also involve the liver.

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Pharmacokinetics

Floctafenine is absorbed from the gastrointestinal tract and peak plasma concentrations occur 1 to 2 hours after ingestion. Its plasma half-life is about 8 hours. It is

metabolised in the liver to floctafenic acid. It is excreted mainly as glucuronide conjugates in the urine and bile.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Idarac; *Thai.*: Idarac.

Flufenamic Acid *(BAN, USAN, rINN)*

Acide Flufénamique; Ácido flufenámico; Acidum Flufenamicum; CI-440; CN-27554; Flufenaamihappo; Flufenámico, ácido; Flufenamsyra; INF-1837; Kwas flufenamowy; NSC-82699; Флуфенамовая Кислота.

N-(αααα-Trifluoro-*m*-tolyl)anthranilic acid.

$C_{14}H_{10}F_3NO_2$=281.2

CAS — 530-78-9 (flufenamic acid); 61891-34-7 (flufenamate aluminium); 16449-54-0 (flufenamate aluminium).

ATC — M01AG03.

ATC Vet — QM01AG03.

UNII — 60GCX7Y6BH.

Uses and Administration

Flufenamic acid, an anthranilic acid derivative related to mefenamic acid (p. 86.1), is an NSAID (p. 102.3). Flufenamic acid is mainly used topically in a concentration of 3 or 3.5% for the relief of pain and inflammation associated with musculoskeletal, joint, and soft-tissue disorders. Flufenamic acid and its aluminium salt have also been given orally.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving flufenamic acid, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

An early study[2] found that only very small amounts of flufenamic acid were excreted into breast milk after oral doses.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 01/11/07)
2. Buchanan RA, *et al.* The breast milk excretion of flufenamic acid. *Curr Ther Res* 1969; **11**: 533–8.

Effects on the gastrointestinal tract. Acute proctocolitis has been associated with oral flufenamic acid.[1]

1. Ravi S, *et al.* Colitis caused by non-steroidal anti-inflammatory drugs. *Postgrad Med J* 1986; **62**: 773–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Mobilat Intens; *Jpn*: Opyrin.

Multi-ingredient Preparations. *Austria*: Mobilisin plus; Mobilisin; Rheugesal†; Traumasal; *Belg.*: Mobilisin; *Braz.*: Mobilisin Composto; *Gr.*: Movilisin; *India*: Movelisin; *Ital.*: Mobilisin; *Port.*: Latesil; Mobilisin; Mobilisin; *Spain*: Movilisin†; *Switz.*: Assan thermo; Assan; Mobilat Intense; Mobilisin†; Sportusal assan thermo.

Flunixin Meglumine *(BANM, USAN, rINNM)*

Fluniksiinimeglumiini; Flunixin megluminová sůl; Flunixine méglumine; Flunixini Megluminum; Flunixinmeglumin; Flunixino meglumina; Flunixinum Megluminicum; Meglumini Flunixinum; Sch-14714 (flunixin); Меглумина Флуниксин.

2-{[2-Methyl-3-(trifluoromethyl)phenyl]amino}-3-pyridinecarboxylic acid compounded with 1-deoxy-1-(methylamino)-D-glucitol (1:1); 2-(α³,α³,α³-Trifluoro-2,3,-xylidino)nicotinic acid compounded with 1-deoxy-1-(methylamino)-D-glucitol (1:1).

$C_{14}H_{11}F_3N_2O_2$,$C_7H_{17}NO_5$=491.5

CAS — 38677-85-9 (flunixin); 42461-84-7 (flunixin meglumine).

UNII — 8Y3JK0JW3U.

Pharmacopoeias. In *Eur.* (see p. vii) and *US* for veterinary use only.

Ph. Eur. 8: (Flunixin Meglumine for Veterinary Use; Flunixin Meglumine BP(Vet) 2014). A white to almost white crystalline powder. Freely soluble in water and in methyl alcohol; practically insoluble in acetone. A 5% solution in water has a pH of 7.0 to 9.0.

USP 36: (Flunixin Meglumine). A white to off-white crystalline powder. Soluble in water, in alcohol, and in methyl alcohol; practically insoluble in ethyl acetate. pH of a 5% solution in water is between 7.0 and 9.0. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Profile

Flunixin meglumine is an NSAID (p. 102.3) used in veterinary medicine for the relief of pain and inflammation in acute and chronic disorders and as adjunctive therapy in the treatment of endotoxic or septic shock and mastitis.

Flupirtine Maleate *(BANM, USAN, rINNM)*

D-9998; Flupirtina, maleato de; Flupirtine, Maléate de; Flupirtini Maleas; Maleato de flupirtina; W-2964M; Флупиртина Малеат.

Ethyl 2-amino-6-(4-fluorobenzylamino)-3-pyridylcarbamate maleate.

$C_{15}H_{17}FN_4O_2$,$C_4H_4O_4$=420.4

CAS — 56995-20-1 (flupirtine); 75507-68-5 (flupirtine maleate).

ATC — N02BG07.

ATC Vet — QN02BG07.

UNII — 0VCI53PK4A.

Profile

Flupirtine maleate is an analgesic that has been given for the relief of pain (see Choice of Analgesic, p. 4.2) in usual doses of 100 mg three or four times daily orally, or 150 mg three or four times daily as a rectal suppository; daily doses of up to 600 mg orally or 900 mg rectally have been used where necessary. Flupirtine has also been given by intramuscular injection as the gluconate in the management of acute pain. It is also being investigated for the treatment of fibromyalgia.

There has been some interest in the potential of flupirtine to treat prion diseases such as Creutzfeldt-Jakob disease (see below).

References.

1. Friedel HA, Fitton A. Flupirtine: a review of its pharmacological properties and therapeutic efficacy in pain states. *Drugs* 1993; **45**: 548–69.
2. Klawe C, Maschke M. Flupirtine: pharmacology and clinical applications of a nonopioid analgesic and potentially neuroprotective compound. *Expert Opin Pharmacother* 2009; **10**: 1495–1500.
3. Devulder J. Flupirtine in pain management: pharmacological properties and clinical use. *CNS Drugs* 2010; **24**: 867–81.

Creutzfeldt-Jakob disease. A double-blind placebo-controlled study[1] from 2004 in 28 patients with Creutzfeldt-Jakob disease (CJD) found flupirtine to have beneficial effects on cognitive function.

1. Otto M, *et al.* Efficacy of flupirtine on cognitive function in patients with CJD: a double-blind study. *Neurology* 2004; **62**: 714–18.

Overdosage. A 17-year-old girl who had had symptoms of headache, blurred vision, shivering, drowsiness, disturbed speech, ataxia, and syncope was found to have bright green urine and high concentrations of flupirtine.[1] A strong green discoloration of the urine has also been reported in another patient who abused flupirtine.[2] A further patient who had taken an overdose of flupirtine was drowsy and on neurological examination had cortical hyperexcitability with intermittent myoclonus, tremor of the extremities, nystagmus, and a pronounced cerebellar syndrome.[3] Blood-flupirtine concentrations were 10.9 micrograms/mL nine hours after ingestion, compared with a therapeutic range of 0.5 to 1.5 micrograms/mL. Flupirtine was undetectable at 3 days post-ingestion. No specific treatment was given.

1. Hufschmidt A, *et al.* A girl with headache, confusion and green urine. *J Neurol* 2009; **256**: 1169–70.
2. Maier A, *et al.* Green urine following exposure to flupirtine. *Am J Kidney Dis* 2010; **56**: 1014–15.
3. Hoffmann O, *et al.* Paradoxical cerebral cortical hyperexcitability following flupirtine overdose. *J Toxicol Clin Toxicol* 2004; **42**: 913–16.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Katadolon; *China*: Katadolon (科达得龙); *Ger.*: Flupigil; Katadolon; Trancolong; Trancopal Dolo; *Israel*: Katadolon; *Ital.*: Efiret; *Pol.*: Katadolon; *Port.*: Metanor; Novocebrin†; *Rus.*: Katadolon (Катадолон); *Ukr.*: Katadolon (Катадолон).

Flurbiprofen *(BAN, USAN, rINN)*

BTS-18322; Flurbiprofeeni; Flurbiprofén; Flurbiprofenas; Flurbiprofène; Flurbiprofeno; Flurbiprofenum; U-27182; Флурбипрофен.

2-(2-Fluorobiphenyl-4-yl)propionic acid.

$C_{15}H_{13}FO_2$=244.3

CAS — 5104-49-4.

ATC — M01AE09; M02AA19; R02AX01; S01BC04.

ATC Vet — QM01AE09; QM02AA19; QR02AX01; QS01BC04.

UNII — 5GRO578KLP.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Flurbiprofen). A white or almost white crystalline powder. Practically insoluble in water; freely soluble in alcohol and in dichloromethane; dissolves in aqueous solutions of alkali hydroxides and carbonates.

USP 36: (Flurbiprofen). A white crystalline powder. Practically insoluble in water; freely soluble in dehydrated alcohol, in acetone, in ether, and in methyl alcohol; soluble in acetonitrile. Store in airtight containers.

Flurbiprofen Sodium *(BANM, rINNM)*

Flurbiprofène Sodique; Flurbiprofeno sódico; Natrii Flurbiprofenum; Натрий Флурбипрофен.

Sodium (±)-2-(2-fluoro-4-biphenylyl)propionate dihydrate.

$C_{15}H_{12}FNaO_2$,$2H_2O$=302.3

CAS — 56767-76-1.

ATC — R02AX01.

ATC Vet — QR02AX01.

UNII — Z5B97MU9K4.

Pharmacopoeias. In *Br.* and *US*.

BP 2014: (Flurbiprofen Sodium). A white to creamy-white, crystalline powder. Sparingly soluble in water; soluble in alcohol; practically insoluble in dichloromethane.

Uses and Administration

Flurbiprofen, a propionic acid derivative, is an NSAID (p. 102.3). It is used in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis, in soft-tissue disorders such as sprains and strains, for postoperative pain, and in mild to moderate pain including dysmenorrhoea and migraine. Flurbiprofen is also used as lozenges in the symptomatic relief of sore throat. Flurbiprofen sodium is used in eye drops to inhibit intraoperative miosis and to control postoperative inflammation of the anterior segment of the eye.

For **pain and inflammation**, flurbiprofen is given in usual oral doses of 150 to 200 mg daily in divided doses, increased to 300 mg daily in acute or severe conditions if necessary. A modified-release preparation for once-daily use is also available. Patients with dysmenorrhoea may be given an initial dose of 100 mg followed by 50 to 100 mg every four to six hours to a maximum total daily dose of 300 mg. Flurbiprofen has also been given rectally as suppositories in doses similar to those given orally.

For the **relief of sore throat**, a lozenge containing 8.75 mg of flurbiprofen may be sucked or allowed to dissolve slowly in the mouth every 3 to 6 hours to a maximum daily dose of 5 lozenges. It is recommended that treatment should be limited to a maximum of 3 days.

To inhibit intra-operative miosis during **ocular surgery** one drop of flurbiprofen sodium 0.03% is instilled into the eye every 30 minutes beginning 2 hours before surgery and ending not less than 30 minutes before surgery. To control postoperative inflammation the same dosage regimen is used before ocular surgery followed 24 hours after surgery by the instillation of one drop 4 times daily for 1 to 3 weeks. Flurbiprofen sodium eye drops have also been used in the topical treatment of cystoid macular oedema.

Flurbiprofen axetil has been given in some countries by intravenous injection for severe pain.

The *R*-enantiomer, tarenflurbil, has been investigated in the management of Alzheimer's disease but the results of phase III studies have been disappointing.

Adverse Effects and Treatment

As for NSAIDs in general, p. 104.3.

Minor symptoms of ocular irritation including transient burning and stinging have been reported on instillation of flurbiprofen sodium eye drops; there may be increased bleeding from ocular surgery and wound healing may be delayed. Local irritation has also followed rectal use, and local effects including a sensation of warming or burning in the mouth may be seen after using flurbiprofen lozenges.

Incidence of adverse effects. Reports from the manufacturers on the range and incidence of the adverse effects of flurbiprofen.[1,2]

1. Sheldrake FE, *et al.* A long-term assessment of flurbiprofen. *Curr Med Res Opin* 1977; **5**: 106–16.
2. Brooks CD, *et al.* Clinical safety of flurbiprofen. *J Clin Pharmacol* 1990; **30**: 342–51.

Effects on the CNS. A severe symmetrical parkinsonian syndrome developed in a 52-year-old man who had taken flurbiprofen for 7 days.[1]

1. Enevoldson TP, *et al.* Acute parkinsonism associated with flurbibrofen [sic]. *BMJ* 1990; **300**: 540–1.

Effects on the kidneys. Renal papillary necrosis has been described in a patient who had used flurbiprofen for many years.[1] Acute flank pain and reversible renal dysfunction has been reported in 2 patients treated with flurbiprofen.[2,3] Membranous nephropathy also developed in a patient who took flurbiprofen daily for 12 to 18 months.[4]

1. Nafrła EC, *et al.* Renal papillary necrosis induced by flurbiprofen. *DICP Ann Pharmacother* 1991; 25: 870–1.
2. Kaufhold J, *et al.* Flurbiprofen-associated tubulointerstitial nephritis. *Am J Nephrol* 1991; 11: 144–6.
3. McIntire SC, *et al.* Acute flank pain and reversible renal dysfunction associated with nonsteroidal anti-inflammatory drug use. *Pediatrics* 1993; 92: 459–60.
4. MacKay K. Membranous nephropathy associated with the use of flurbiprofen. *Clin Nephrol* 1997; 47: 279–80.

Effects on the liver. Cholestatic jaundice probably due to flurbiprofen has been reported.[1]

1. Kotowski KE, Grayson MF. Side effects of non-steroidal anti-inflammatory drugs. *BMJ* 1982; 285: 377.

Effects on the skin. Cutaneous vasculitis apparently due to flurbiprofen occurred in a 59-year-old woman with long-standing rheumatoid arthritis.[1] Contact dermatitis has also been seen in a 22-year-old woman who applied a poultice containing flurbiprofen to her wrist.[2]

1. Wei N. Flurbiprofen and cutaneous vasculitis. *Ann Intern Med* 1990; 112: 550–1.
2. Kawada A, *et al.* Contact dermatitis due to flurbiprofen. *Contact Dermatitis* 2000; 42: 167–8.

Hypersensitivity. A diffuse, pruritic, maculopapular rash developed in a patient 48 hours after taking a second dose of flurbiprofen.[1] Two days later, the rash had become urticarial, and angioedema and hypotension were also noted. Patch testing with flurbiprofen powder was positive.

See also Effects on the Skin, above.

1. Romano A, Pieturantonio F. Delayed hypersensitivity to flurbiprofen. *J Intern Med* 1997; 241: 81–3.

Precautions

As for NSAIDs in general, p. 107.1.

Breast feeding. Small amounts of flurbiprofen are distributed into breast milk; licensed product information advises to avoid in breast-feeding mothers.

Herpes simplex keratitis. Whether flurbiprofen can exacerbate infection when used to treat ocular herpes simplex is unclear from *animal* studies,[1,2] but licensed product information for flurbiprofen sodium eye drops recommends that they should not be used in patients with active epithelial herpes simplex keratitis. Patients with a history of herpes simplex keratitis should also be monitored closely when undergoing treatment with these eye drops.

1. Trousdale MD, *et al.* Effect of flurbiprofen on herpes simplex keratitis in rabbits. *Invest Ophthalmol Vis Sci* 1980; 19: 267–70.
2. Hendricks RL, *et al.* The effect of flurbiprofen on herpes simplex virus type 1 stromal keratitis in mice. *Invest Ophthalmol Vis Sci* 1990; 31: 1503–11.

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Parasympathomimetics. Licensed product information for acetylcholine chloride ophthalmic preparations and for flurbiprofen sodium eye drops states that there have been reports that *acetylcholine* and *carbachol* have been ineffective when used in patients treated with topical (ophthalmic) NSAIDs.

Pharmacokinetics

Flurbiprofen is readily absorbed from the gastrointestinal tract after oral doses and peak plasma concentrations occur about 1 to 2 hours after ingestion. Absorption after rectal doses may be more rapid. It is about 99% bound to plasma proteins and has a plasma half-life of about 3 to 6 hours. It is metabolised mainly by hydroxylation (via the cytochrome P450 isoenzyme CYP2C9) and conjugation in the liver and excreted in urine. Flurbiprofen is distributed into breast milk.

Flurbiprofen is a chiral compound given as the racemate and the above pharmacokinetic characteristics refer to the racemic mixture. Allowance may have to be made for the different activities of the enantiomers.

References.

1. Aarons L, *et al.* Plasma and synovial fluid kinetics of flurbiprofen in rheumatoid arthritis. *Br J Clin Pharmacol* 1986; 21: 155–63.
2. Smith U, *et al.* Flurbiprofen in post-partum women: plasma and breast milk disposition. *J Clin Pharmacol* 1989; 29: 174–84.
3. Kean WF, *et al.* The pharmacokinetics of flurbiprofen in younger and elderly patients with rheumatoid arthritis. *J Clin Pharmacol* 1992; 32: 41–8.
4. Davies NM. Clinical pharmacokinetics of flurbiprofen and its enantiomers. *Clin Pharmacokinet* 1995; 28: 100–14.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Clinadol; Flurbic; Luarprofeno; Tolerane; ***Austral.***: Ocufen; Strepfen†; ***Austria***: Strepfen†; Strepsils; ***Belg.***: Froben; Strepfen; ***Braz.***: Ocufen; Strepsils; Targus; ***Canad.***: Ansaid; Novo-Flurprofen; Ocufen†; ***Chile***: Ansaid; Distex; Ocufen; ***China***: Kai Fen (凯纷); Ocufen (欧可芬); ***Cz.***: Strepfen; ***Denm.***: Flurofen†; Strefen; ***Fr.***: Cebutid; Ocufen; Strefen; ***Ger.***: Dobendan Direkt; Ocuflur; ***Gr.***: Bedice; Bonatol-R; Demoval; Eyeflur; Fievrinol; Fladolef-B; Flodisona; Flurofen; Fluroptic; Inflaflur; Iovic; Kirik; Neliacan; Ocuflur; Pizar; Rograpon; Strepfen; ***Hung.***: Flugalin; Strepfen; ***India***: Arflur; Brufen Gel; Cadiflur; Eyefen; FBN; Fludrop; Flufen; Flur; Flurofen; Froben; Laboflur; Lorphen; Mep-Fovea; Ocuflur; Optifen; Optiflur; Oxiber; ***Irl.***: Froben; Strepsils Intensive; ***Ital.***: Benactiv; Flubifix; Froben; Ocufen; Tantum Activ Gola; Transact Lat; ***Jpn***: Ropion; ***Malaysia***: Acustop Cataplasma; ***Mex.***: Ansaid; Ocufen; ***Mon.***: Antadys; ***Neth.***: Froben†; Strepfen; Strepflam; ***NZ***: Ocufen; Strepfen; ***Pol.***: Flugalin; Strepsils Intensive; ***Port.***: Edolfene; Froben; Strepfen; Transact Lat; ***Rus.***: Raxtan (Ракстан); Strepfen (Стрепфен); ***S.Afr.***: Froben†; Ocufen†; Strepsils Intensive; TransAct; ***Singapore***: Acustop Cataplasma; Froben; Ocufen†; Strepfen; ***Spain***: Froben; Strefen; ***Switz.***: Froben; Strepfen; ***Thai.***: Flurozin†; ***Turk.***: Ansaid; Flurflex; Fortine; Frolix; Majezik; Maxaljin; Maximus; Ocufen; Zero-P; ***UK***: Froben; Ocufen; Strefen; ***Ukr.***: Strepsils Intensiv (Стрепсилс Интенсив); ***USA***: Ansaid†; Ocufen.

Multi-ingredient Preparations. ***India***: Binea; Flubichlor; Flubip; Flurbiren.

Pharmacopoeial Preparations

BP 2014: Flurbiprofen Eye Drops; Flurbiprofen Suppositories; Flurbiprofen Tablets;

USP 36: Flurbiprofen Sodium Ophthalmic Solution; Flurbiprofen Tablets.

Glucametacin *(rINN)*

Glucametacina; Glucamétacine; Glucametacinum; Глюкаметацин.

2-[2-[1-(4-Chlorobenzoyl)-5-methoxy-2-methylindol-3-yl] acetamido)-2-deoxy-D-glucose.

$C_{25}H_{27}ClN_2O_8$=518.9

CAS — 52443-21-7.

UNII — N1EXE5EHAN.

Profile

Glucametacin, a derivative of indometacin (p. 71.2), is an NSAID (p. 102.3) that has been given orally in musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Teoremin; ***Mex.***: Teoremac.

Multi-ingredient Preparations. ***Chile***: Fibrorelax.

Glycol Salicylate

Ethylene Glycol Monosalicylate; Glycoli Salicylas; Glykolisalisylaatti; Glykolsalicylat; Hidroksietilo salicilatas; Hidroxietil-szalicilát; Hydroksietyylisalisylaatti; Hydroxietylsalicylat; Hydroxyaethyli Salicylas; Hydroxyéthyle, salicylate d'; Hydroxyethylis Salicylas; Hydroxyethyl-salicylát; Salicilato de glicol; Гликоль Салицилат.

2-Hydroxyethyl salicylate.

$C_9H_{10}O_4$=182.2

CAS — 87-28-5.

UNII — 3I1VBB7AXH.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Hydroxyethyl Salicylate). An oily, colourless or almost colourless liquid or colourless crystals. M.p. about 21 degrees. Sparingly soluble in water; freely soluble in alcohol; very soluble in acetone and in dichloromethane. Protect from light.

Profile

Glycol salicylate is a salicylic acid derivative used similarly to methyl salicylate (p. 92.1) in topical rubefacient preparations in usual concentrations of 5 to 15% for the relief of muscular and rheumatic pain. Dipropylene glycol salicylate has been used in similar preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Dolo-Arthrosenex M; Dolo-Arthrosenex N; Etrat Sportgel HES†; Salhumin Gel.

Multi-ingredient Preparations. ***Arg.***: Venostasin; ***Austral.***: Deep Heat; ***Austria***: Ambenat†; Etrat; Mobilisin; Moviflex; Rheumex†; Rubriment; ***Belg.***: Algipan; Emerxil; Mobilisin; Percutalgine; Rado-Salil; Stilene; ***Braz.***: Hematom; Mobilisin Composto; Salonpas; ***Canad.***: Salonpas; ***Chile***: Calorub Sport; Salonpas; ***Cz.***: Arnidol; ***Fr.***: Algipan†; Cortisal; Lumbalgine; Percutalgine; ***Ger.***: Rheuma Bad†; Sportino Akut†; ***Gr.***: Air Salonpas; Bayolin; Export Salonpas; Movilisin; ***Hong Kong***: Air Salonpas†; New Patecs A†; Panadal Pain Relief Patch†; Panadol Pain Relief; Salomethyl†; Salonpas Medicated Plaster†; Salonsip Foot Patch†; Salonsip Plaster†; ***Hung.***: Air Salonpas; Deep Heat Spray; Nicoflex; ***India***: Algipan; Arjet; Movelisin; ***Irl.***: Deep Heat; Ralgex Heat Spray; Ralgex; Ralgex; ***Israel***: Deep Heat Spray; ***Ital.***: Balsamo Sifcamina; Mobilisin; Salonpas; Sloan †; ***Malaysia***: Panaflex; Salonpas; ***Neth.***: Capsicum comp; Crem or Capsici Compositus; Kruidvat Spierbalsem; ***Pol.***: Deep Heat; Lumbolin†; ***Port.***: DM Creme; DM Gel; ***Rus.***: Nicoflex (Никофлекс); ***S.Afr.***: Deep Heat Spray†; Infrarub†; ***Span***: Movilisin†; ***Switz.***: Assan rem; Assan thermo; Assan; Dolo Demotherm†; Dolo-Arthrosenex; Histalgane mite; Histalgan s; Midalgan Nouvelle Formule†; Mobilat Intense; Mobilisin †; Radalgin†; Sportusal assan thermo; Sportusal Spray sine hepa ino; Sportusal; Venucreme; Venugel; ***UK***: Cremalgin†; Deep Heat Spray; Dubam; Fiery Jack; Pain Relief Balm†; Ralgex Freeze Spray†; Ralgex Heat Spray (low-odour)†; Ralgex Salonair†; Salonpas; Transvasin Heat Spray; ***Ukr.***: Deep Heat (Дип Хит).

Gold Keratinate

Aurothiopolypeptide; Queratinato de oro.

CAS — 9078-78-8.

Profile

Gold keratinate is a gold compound with a gold content of about 13%; it has similar actions and uses to those of sodium aurothiomalate (p. 130.2). It has been given by intramuscular injection as the calcium salt for the treatment of rheumatoid arthritis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aurochobel.

Golimumab *(BAN, USAN, rINN)*

CNTO-148; Golimumabum; Голимумаб.

Immunoglobulin G1, anti-(human tumor necrosis factor α) (human monoclonal CNTO 148 γ1-chain), disulfide with human monoclonal CNTO 148 κ-chain, dimer.

CAS — 476181-74-5.

ATC — L04AB06.

ATC Vet — QL04AB06.

UNII — 91X1KLU43E.

Uses and Administration

Golimumab is a human monoclonal antibody to TNF α, a pro-inflammatory mediator, and has actions similar to other TNF inhibitors (see Infliximab, p. 74.2); it is described as a biological disease-modifying antirheumatic drug (DMARD). It is used in the treatment of moderately to severely active rheumatoid arthritis (p. 13.2), active and progressive psoriatic arthritis, and severely active ankylosing spondylitis (see Spondyloarthropathies, p. 14.3). In the UK, golimumab is licensed for use in patients with rheumatoid or psoriatic arthritis who have had an inadequate response to standard DMARDs (including the non-biological DMARD methotrexate for rheumatoid arthritis) and in those with ankylosing spondylitis who have had an inadequate response to conventional therapy; in severe and progressive rheumatoid arthritis it may also be used in patients who have not been treated with methotrexate. Golimumab is also used in the treatment of moderate to severe active ulcerative colitis (see Inflammatory Bowel Disease, p. 1811.3) in patients who show an inadequate response to or fail to tolerate other treatments, or who are corticosteroid dependent.

For the treatment of rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis, a dose of 50 mg is given by subcutaneous injection once a month. Alternatively, patients with rheumatoid arthritis may be treated with doses of 2 mg/kg given by intravenous infusion over 30 minutes; after an initial dose, the second dose is given 4 weeks later and maintenance doses are then given once every 8 weeks. Golimumab should be given with methotrexate in patients with rheumatoid arthritis; in those with psoriatic arthritis or ankylosing spondylitis it may be given alone or with other non-biological DMARDs. Regardless of indication, concurrent therapy with corticosteroids, non-biological DMARDs, and/or NSAIDs may be continued. UK licensed product information recommends that continuing therapy should be reconsidered if there is no adequate response within 12 to 14 weeks of starting subcutaneous treatment. Patients weighing more than

100 kg with an inadequate response during this period may benefit from a higher dose of 100 mg once a month; continuing therapy should be reconsidered if there is no adequate response within 12 to 14 weeks of receiving this dose.

In the treatment of ulcerative colitis an induction regimen consists of 200 mg given by subcutaneous injection followed 2 weeks later by a dose of 100 mg. Thereafter, a maintenance dose of 100 mg is given every 4 weeks.

Golimumab is also being studied for the treatment of chronic sarcoidosis and psoriasis.

References.
1. Kay J, *et al.* Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study. *Arthritis Rheum* 2008; 58: 964–75.
2. Inman RD, *et al.* Efficacy and safety of golimumab in patients with ankylosing spondylitis: results of a randomized, double-blind, placebo-controlled, phase III trial. *Arthritis Rheum* 2008; 58: 3402–12.
3. Keystone EC, *et al.* Golimumab, a human antibody to tumour necrosis factor α given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD study. *Ann Rheum Dis* 2009; 68: 789–96.
4. Kavanaugh A, *et al.* Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. *Arthritis Rheum* 2009; 60: 976–86.
5. Smolen JS, *et al.* Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. *Lancet* 2009; 374: 210–21. Correction. *ibid.*; 1422.
6. NICE. Golimumab for the treatment of psoriatic arthritis: Technology Appraisal Guidance 220 (issued April 2011). Available at: http://www.nice.org.uk/nicemedia/live/13441/54169/54169.pdf (accessed 05/08/11)
7. NICE. Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs: Technology Appraisal Guidance 225 (issued June 2011). Available at: http://www.nice.org.uk/nicemedia/live/13490/54929/54929.pdf (accessed 05/08/11)

Adverse Effects and Precautions

As for Infliximab, p. 75.3.

Most injection site reactions to golimumab are mild, with erythema being the most frequent manifestation.

Interactions

As for Infliximab, p. 77.3.

Mean steady-state trough concentrations of golimumab are reported to be up to about 52% higher when given with methotrexate but licensed product information for the former states that dosage adjustment for either drug does not appear to be necessary.

Pharmacokinetics

Golimumab shows linear pharmacokinetics. After subcutaneous injection peak concentrations occur in about 2 to 6 days and the absolute bioavailability is estimated to be about 53%. The mean terminal half-life is about 2 weeks.

References.
1. Zhou H, *et al.* Pharmacokinetics and safety of golimumab, a fully human anti-TNF-α monoclonal antibody, in subjects with rheumatoid arthritis. *J Clin Pharmacol* 2007; 47: 383–96.
2. Xu Z, *et al.* Population pharmacokinetics of golimumab, an anti-tumor necrosis factor-α human monoclonal antibody, in patients with psoriatic arthritis. *J Clin Pharmacol* 2009; 49: 1056–70.
3. Xu Z, *et al.* Subcutaneous bioavailability of golimumab at 3 different injection sites in healthy subjects. *J Clin Pharmacol* 2010; 50: 276–84.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Simponi; ***Austria***: Simponi; ***Belg.***: Simponi; ***Braz.***: Simponi; ***Canad.***: Simponi; ***Cz.***: Simponi; ***Denm.***: Simponi; ***Ger.***: Simponi; ***Gr.***: Simponi; ***Hong Kong***: Simponi; ***Hung.***: Simponi; ***Irl.***: Simponi; ***Israel***: Simponi; ***Jpn***: Simponi; ***Neth.***: Simponi; ***Norw.***: Simponi; ***NZ***: Simponi; ***Pol.***: Simponi; ***Port.***: Simponi; ***Spain***: Simponi; ***Swed.***: Simponi; ***Switz.***: Simponi; ***UK***: Simponi; ***USA***: Simponi.

Hexyl Nicotinate

Heksyylinikotinaatti; Hexylnicotinatum; Hexylnikotinat; Nicotinato de hexilo; Гексилникотинат.

n-Hexyl nicotinate.

$C_{12}H_{17}NO_2$=207.3

CAS — 23597-82-2.

UNII — BN07PB44IV.

Profile

Hexyl nicotinate is used in usual concentrations of up to 2% in topical preparations as a rubefacient.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Belg.***: Transvane; ***Irl.***: Transvasin†; ***UK***: Boots Pain Relief Heat Rub; Transvasin Heat Rub.

Hydrocodone Hydrochloride *(BANM, rINNM)*

Hidrocloruro de hidrocodona; Hidrocodona, hidrocloruro de; Hydrocodone, Chlorhydrate d'; Hydrocodoni Hydrochloridum; Гидрокодона Гидрохлорид.

$C_{18}H_{21}NO_3$,HCl,2½H_2O=380.9

CAS — 25968-91-6 (anhydrous hydrocodone hydrochloride).

ATC — R05DA03.

ATC Vet — QR05DA03.

UNII — QKZ0920OV3.

Hydrocodone Tartrate *(BANM, rINNM)*

Dihydrocodeinone Acid Tartrate; Hidrocodona, tartrato de; Hydrocodone Acid Tartrate; Hydrocodone Bitartrate (USAN); Hydrocodone, Tartrate d'; Hydrocodoni Bitartras; Hydrocodoni Tartras; Hydrocone Bitartrate; Tartrato de dihidrocodeinona; Tartrato de hidrocodona; Гидрокодона Тартрат.

6-Deoxy-3-*O*-methyl-6-oxomorphine hydrogen tartrate hemipentahydrate; (-)-(5*R*)-4,5-Epoxy-3-methoxy-9a-methylmorphinan-6-one hydrogen tartrate hemipentahydrate.

$C_{18}H_{21}NO_3.C_4H_6O_6.2½H_2O$=494.5

CAS — 125-29-1 (hydrocodone); 143-71-5 (anhydrous hydrocodone tartrate); 34195-34-1 (hydrocodone tartrate hemipentahydrate).

ATC — R05DA03.

ATC Vet — QR05DA03.

UNII — NO70W886KK.

NOTE. Compounded preparations of hydrocodone tartrate may be represented by the following names:

- Co-hycodAPAP (*PEN*)—hydrocodone tartrate and paracetamol.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of hydrocodone tartrate:

Cough Syrup; Vikes.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Hydrocodone Hydrogen Tartrate 2.5-Hydrate). White or almost white, hygroscopic, crystalline powder. Freely soluble or soluble in water; sparingly soluble in alcohol; practically insoluble in cyclohexane. A 2% solution in water has a pH of 3.2 to 3.8. Store in airtight containers. Protect from light.

USP 36: (Hydrocodone Bitartrate). Fine, white crystals or crystalline powder. Soluble in water; slightly soluble in alcohol; insoluble in chloroform and in ether. pH of a 2% solution in water is between 3.2 and 3.8. Store in airtight containers. Protect from light.

Profile

Hydrocodone, a phenanthrene derivative, is an opioid analgesic (p. 108.1) related to codeine (p. 40.2) and has similar actions, but is more potent on a weight-for-weight basis. Hydromorphone (below) is one of the metabolites of hydrocodone.

Hydrocodone is used mainly as the tartrate in combination preparations for the relief of irritant cough, though it has no particular advantage over codeine. Hydrocodone tannate has been used similarly. Hydrocodone tartrate is also used for the relief of moderate to moderately severe pain, usually with paracetamol. The usual oral dose of hydrocodone tartrate in such combination preparations is 5 to 10 mg every 4 to 6 hours.

For details of doses in children, see below.

Hydrocodone hydrochloride is given orally and also by injection. The polistirex derivative (a hydrocodone and sulfonated diethenylbenzene-ethenylbenzene copolymer complex) is used in modified-release preparations.

Hydrocodone has also been used in the treatment of dyspnoea.

Abuse. The abuse or overuse of preparations containing hydrocodone and paracetamol has been associated with *sensorineural hearing loss.*[1,2] Cochlear implants improved the hearing loss in some of the patients.

Intranasal abuse of preparations of hydrocodone and paracetamol has also been reported.[3,4]

1. Friedman RA, *et al.* Profound hearing loss associated with hydrocodone/acetaminophen abuse. *Am J Otol* 2000; 21: 188–91.
2. Ho T, *et al.* Hydrocodone use and sensorineural hearing loss. *Pain Physician* 2007; 10: 467–72.
3. Jewers WM, *et al.* Palatal perforation associated with intranasal prescription narcotic abuse. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005; 99: 594–7.
4. Sloan PA, Klimkina O. Intranasal abuse of prescription hydrocodone/acetaminophen results in oronasal fistula: a case report. *J Opioid Manag* 2009; 5: 383–5.

Administration in children. Hydrocodone tartrate may be given as part of a combination preparation for the relief of irritant cough in children aged from 6 to 12 years in usual oral doses of 2.5 mg every 4 to 6 hours. Older children may be given the usual adult dose (see above).

Pharmacokinetics. References.

1. Hutchinson MR, *et al.* CYP2D6 and CYP3A4 involvement in the primary oxidative metabolism of hydrocodone by human liver microsomes. *Br J Clin Pharmacol* 2004; 57: 287–97.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Hycodan; ***Ger.***: Dicodid†; ***Switz.***: Hydrocodeinon†; ***USA***: Zohydro.

Multi-ingredient Preparations. ***Arg.***: Hidronovag Complex; ***Canad.***: Dalmacol; Dimetane Expectorant DC; Hycomine†; Novahistex DH; Novahistine DH; ratio-Calmydone; ratio-Coristex-DH; Tussionex; Vasofrinic DH; ***China***: Norco (諾而可); ***USA***: Alor†; Anaplex HD†; Anexsia; Atuss G†; Atuss HC†; Atuss HD†; Atuss HS†; Atuss HX†; Ceta Plus†; Co-Gesic; Co-Tuss V; Codal-DH†; Codiclear DH†; Codimal DH†; Cophene XP; Cordron-HC†; Cytuss HC†; Cytuss-HC NR†; Damason-P; De-Chlor HC†; De-Chlor MR†; De-Chlor NX†; Deconamine CX†; Dolacet; Donatussin DC; Drocon-CS; Duocet; Duratuss HD†; Dytan-HC; ED Tuss HC†; ED-TLC†; Endagen-HD; Endal-HD Plus†; Endal-HD; Entex HC†; Entuss Expectorant; Entuss Expectorant; Entuss-D Jr; Entuss-D; Entuss-D; Histex HC†; Histinex D†; Histinex HC; Histinex PV†; Histussin HC; Hy-KXP†; Hy-Phen†; Hycet; HycoClear Tuss; Hycodan†; Hycomine Compound; Hycotuss†; Hydex PD†; Hydro DP†; Hydro-GP; Hydro-Tussin HG†; Hydrocet†; Hydrocodone CP; Hydrocodone GF; Hydrocodone HD; Hydrogesic; Hydromet; Hydron CP†; Hydron EX†; Hydron KGS†; Hydron PSC†; Hydropane; Hyphed†; HyTan†; Ibudone; Iodal; Iotussin HC; J-Tan D HC†; Kwelcof†; Levall 5.0; Liquicet; Lorcet 10/650; Lorcet Plus; Lorcet-HD†; Lortab ASA†; Lortab; Lortuss HC†; Marcof†; Margesic H; Maxi-Tuss HCG†; Maxi-Tuss HCX†; Maxidone; Nalex DH; Nalex Expectorant; Narcof; Nariz HC; Neo HC; Norco; Notuss PD; Notuss-Forte; Novasus; Oncet; P-V-Tussin†; Pancof XP†; Pancof-HC†; Pancof-XL†; Para-Hist HD; Pneumotussin†; Poly-Tussin†; Pro-Red†; Relacon-HC†; Relasin-HCX; Reprexain; Rezira; S-T Forte 2; SRC Expectorant; Stagesic; Su-Tuss HD†; T-Gesic; Tusana-D†; Tusdec-HC†; Tusnel-HC†; Tussafed-HCG; Tussafin Expectorant; Tussanil DH; Tussend; TussiCaps; Tussigon; Tussionex Pennkinetic; Tusso-DF; Tusso-HC†; Tussplex; Tyrodone; Unituss HC; Vanex Expectorant; Vanex-HD; Vanex-HD; Vazotuss HC†; Vicodin Tuss; Vicodin; Vicoprofen; Vitussin†; Vituz; Xodol; Z-Cof HC; Zamicet; Zolvit; Zutripro; Zydone; Zymine HC†.

Pharmacopoeial Preparations

USP 36: Hydrocodone Bitartrate and Acetaminophen Tablets; Hydrocodone Bitartrate and Homatropine Methylbromide Tablets; Hydrocodone Bitartrate Tablets.

Hydromorphone Hydrochloride

(BANM, rINNM) ⊗

Dihydromorphinone Hydrochloride; Hidrocloruro de dihidromorfinona; Hidrocloruro de hidromorfona; Hidromorfona, hidrocloruro de; Hidromorfono hidrochloridas; Hydromorfon-hydrochlorid; Hydromorfonhydroklorid; Hydromorfonihydrokloridi; Hydromorphone, Chlorhydrate d'; Hydromorphonhydrochlorid; Hydromorphoni Hydrochloridum; Гидроморфона Гидрохлорид.

6-Deoxy-7,8-dihydro-6-oxomorphine hydrochloride; (-)-(5*R*)-4,5-Epoxy-3-hydroxy-9a-methylmorphinan-6-one hydrochloride.

$C_{17}H_{19}NO_3$,HCl=321.8

CAS — 466-99-9 (hydromorphone); 71-68-1 (hydromorphone hydrochloride).

ATC — N02AA03.

ATC Vet — QN02AA03.

UNII — L960UP2KRW.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of hydromorphone:

Dillies; HillBilly Heroin; Hospital heroin.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Hydromorphone Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water; very slightly soluble in alcohol; practically insoluble in dichloromethane. Protect from light.

USP 36: (Hydromorphone Hydrochloride). A fine white, or practically white, odourless, crystalline powder. Soluble 1 in 3 of water; sparingly soluble in alcohol; practically insoluble in ether. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Incompatibility. Colour change from pale yellow to light green occurred when solutions of minocycline hydrochloride or tetracycline hydrochloride were mixed with hydromorphone hydrochloride in 5% glucose injection.[1] Mixtures of hydromorphone hydrochloride and dexamethasone sodium phosphate showed concentration-dependent incompatibility.[2] White cloudiness, haziness, or precipitation developed 4 hours after mixing thiopental sodium and hydromorphone hydrochloride.[3]

Stability of mixtures of fluorouracil and hydromorphone hydrochloride in 0.9% sodium chloride or 5% glucose depended on the concentration of fluorouracil present.[4] Hydromorphone hydrochloride 500 micrograms/mL with fluorouracil 1 mg/mL was stable for at least 7 days at 32 degrees and for at least 35 days at 23 degrees, 4 degrees, or -20 degrees. When the concentration of fluorouracil was increased to 16 mg/mL, hydromorphone was noted to decompose incurring unacceptable losses after 3 days at 32 degrees or after 7 days at 23 degrees, but was stable for at least 35 days at 4 degrees or -20 degrees.

1. Nieves-Cordero AL, *et al.* Compatibility of narcotic analgesic solutions with various antibiotics during simulated Y-site injection. *Am J Hosp Pharm* 1985; **42:** 1108–9.
2. Walker SE, *et al.* Compatibility of dexamethasone sodium phosphate with hydromorphone hydrochloride or diphenhydramine hydrochloride. *Am J Hosp Pharm* 1991; **48:** 2161–6.
3. Chiu MF, Schwartz ML. Visual compatibility of injectable drugs used in the intensive care unit. *Am J Health-Syst Pharm* 1997; **54:** 64–5.
4. Xu QA, *et al.* Stability and compatibility of fluorouracil with morphine sulfate and hydromorphone hydrochloride. *Ann Pharmacother* 1996; **30:** 756–61.

Uses and Administration

Hydromorphone hydrochloride, a phenanthrene derivative, is an opioid analgesic (p. 108.1). It is related to morphine (p. 93.2) but with a greater analgesic potency. Hydromorphone hydrochloride is used for the relief of moderate to severe pain; it has been used for the relief of non-productive cough.

In the treatment of pain, hydromorphone hydrochloride is a useful alternative to morphine for subcutaneous use since its greater solubility in water allows a smaller dose volume. After injection onset of action usually occurs within 15 minutes and analgesia is reported to last for more than 5 hours; after oral doses onset of analgesia is usually within 30 minutes. It is given by subcutaneous or intramuscular injection in initial doses of 1 to 2 mg every 4 to 6 hours as necessary. It may also be given by slow intravenous injection or by intravenous or subcutaneous infusion, with doses adjusted according to individual requirements. Higher parenteral doses may be given to opioid-tolerant patients using a highly concentrated solution containing 10 mg/mL that allows smaller dose volumes. In the UK, the initial oral dose is 1.3 mg every 4 hours; thereafter the dose may be increased as necessary. In the USA, initial oral doses of 2 mg may be given every 4 to 6 hours; doses may be increased to 4 mg or more for severe pain. Modified-release preparations are available for less frequent administration, but see Alcohol, under Interactions, below. By rectum, the usual dose is 3 mg every 6 to 8 hours.

References.

1. Bruera E, *et al.* A randomized, double-blind, double-dummy, crossover trial comparing the safety and efficacy of oral sustained-release hydromorphone with immediate-release hydromorphone in patients with cancer pain. *J Clin Oncol* 1996; **14:** 1713–17.
2. Miller MG, *et al.* Continuous subcutaneous infusion of morphine vs. hydromorphone: a controlled trial. *J Pain Symptom Manage* 1999; **18:** 9–16.
3. Quigley C. Hydromorphone for acute and chronic pain. Available in The Cochrane Database of Systematic Reviews: Issue 1. Chichester: John Wiley; 2002 (accessed 26/06/08).
4. Murray A, Hagen NA. Hydromorphone. *J Pain Symptom Manage* 2005; **29** (suppl): S57–S66.
5. Grosset AB, *et al.* Comparative efficacy of oral extended-release hydromorphone and immediate-release hydromorphone in patients with persistent moderate to severe pain: two randomized controlled trials. *J Pain Symptom Manage* 2005; **29:** 584–94.
6. Du Pen S, *et al.* Intrathecal hydromorphone for intractable nonmalignant pain: a retrospective study. *Pain Med* 2006; **7:** 10–15.
7. Chang AK, *et al.* Safety and efficacy of hydromorphone as an analgesic alternative to morphine in acute pain: a randomized clinical trial. *Ann Emerg Med* 2006; **48:** 164–72.

Dependence and Withdrawal

As for Opioid Analgesics, p. 109.1.

Adverse Effects, Treatment, and Precautions

As for Opioid Analgesics in general, p. 110.1.

UK licensed product information contra-indicates the use of hydromorphone hydrochloride in patients with hepatic impairment; however, product information in the USA permits its cautious use although doses may need to be reduced. It should also be used with caution and given in reduced doses to those with renal impairment.

Effects on the nervous system. Myoclonus has been reported[1] in a 55-year-old man given relatively low doses of intravenous hydromorphone with a total daily dose of 4 mg on day 1 and 6 mg on day 2: symptoms resolved when the drug was stopped on day 3. A chart review[2] for neuroexcitatory symptoms in 48 patients with terminal illnesses on hydromorphone found 13 cases of agitation, 9 of myoclonus, and 4 of seizures; maximal dose and treatment duration were noted to increase the risk of neurotoxicity.

1. Patel S, *et al.* A myoclonic reaction with low-dose hydromorphone. *Ann Pharmacother* 2006; **40:** 2068–70.
2. Thwaites D, *et al.* Hydromorphone neuroexcitation. *J Palliat Med* 2004; **7:** 545–50.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies hydromorphone as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/10/11)

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

Alcohol. The FDA received data from pharmacokinetic studies in healthy subjects which showed that significantly higher peak plasma concentrations of hydromorphone were achieved, as a result of dose-dumping, when alcohol was ingested with once-daily hydromorphone modified-release capsules (*Palladone; Purdue Frederick, USA*); these increases were considered potentially lethal, even in opioid-tolerant patients.[1] Subsequently, this formulation was voluntarily withdrawn by the US manufacturer in July 2005.

1. FDA. Information for healthcare professionals: hydromorphone hydrochloride extended-release capsules (marketed as Palladone) (issued July 2005). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm129288 (accessed 02/08/10)

Pharmacokinetics

Hydromorphone hydrochloride is rapidly but incompletely absorbed from the gastrointestinal tract after oral doses; peak plasma concentrations occur within 0.5 to 1 hour. Oral bioavailability is about 50% as it undergoes extensive first-pass metabolism. Hydromorphone is about 8 to 19% bound to plasma proteins. A plasma elimination half-life of about 2.5 hours has been reported after oral or intravenous doses. Hydromorphone appears to be widely distributed in the tissues; it crosses the placenta and is distributed into breast milk. It is extensively metabolised by glucuronidation in the liver and excreted in the urine mainly as conjugated hydromorphone, dihydroisomorphine, and dihydromorphine.

References.

1. Vallner JJ, *et al.* Pharmacokinetics and bioavailability of hydromorphone following intravenous and oral administration to human subjects. *J Clin Pharmacol* 1981; **21:** 152–6.
2. Parab PV, *et al.* Pharmacokinetics of hydromorphone after intravenous, peroral and rectal administration to human subjects. *Biopharm Drug Dispos* 1988; **9:** 187–99.
3. Vashi V, *et al.* Clinical pharmacology and pharmacokinetics of once-daily hydromorphone hydrochloride extended-release capsules. *J Clin Pharmacol* 2005; **45:** 547–54.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Dolonovag; *Austral.*: Dilaudid; Jurnista; *Austria*: Hydal; Jurnista; *Belg.*: Palladone; *Braz.*: Jurnista; *Canad.*: Dilaudid; Hydromorph; Jurnista; *Cz.*: Jurnista; Palladone; *Denm.*: Jurnista; Palladon; *Fin.*: Palladon; *Fr.*: Sophidone; *Ger.*: Jurnista; Palladon; *Gr.*: Palladone; *Hung.*: Jurnista; Palladone; *Irl.*: Palladone; *Israel*: Jurnista†; Palladone; *Ital.*: Jurnista; *Mex.*: Liberaxim; *Neth.*: Palladon; *Norw.*: Palladon; *Philipp.*: Jurnista; *Port.*: Jurnista; Palladone†; *Singapore*: Jurnista; *Spain*: Jurnista; Palladone; *Swed.*: Palladon; *Switz.*: Jurnista; Palladon; *Turk.*: Jurnista; *UK*: Palladone; *USA*: Dilaudid; Exalgo.

Multi-ingredient Preparations. *Swed.*: Palladon Comp†; *USA*: Dilaudid Cough†.

Pharmacopoeial Preparations

USP 36: Hydromorphone Hydrochloride Injection; Hydromorphone Hydrochloride Oral Solution; Hydromorphone Hydrochloride Tablets.

Ibuprofen *(BAN, USAN, rINN)*

Ibuprofeeni; Ibuprofén; Ibuprofenas; Ibuprofène; Ibuprofeno; Ibuprofenum; RD-13621; U-18573; Ибупрофен.

2-(4-Isobutylphenyl)propionic acid.

$C_{13}H_{18}O_2$=206.3

CAS — 15687-27-1.

ATC — C01EB16; G02CC01; M01AE01; M02AA13.

ATC Vet — QC01EB16; QG02CC01; QM01AE01; QM02AA13.

UNII — WK2XYI10QM.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Ibuprofen). A white or almost white, crystalline powder or colourless crystals. M.p. 75 degrees to 78 degrees. Practically insoluble in water; freely soluble in acetone, in dichloromethane, and in methyl alcohol; it dissolves in dilute solutions of alkali hydroxides and carbonates.

USP 36: (Ibuprofen). A white to off-white crystalline powder having a slight characteristic odour. Practically insoluble in water; very soluble in alcohol, in acetone, in chloroform, and in methyl alcohol; slightly soluble in ethyl acetate. Store in airtight containers.

Ibuprofen Lysine *(USAN)*

Ibuprofen Lysinate; Soluphene; Ибупрофен Лизин.

Lysine 2-(4-isobutylphenyl)propionate.

$C_{19}H_{32}N_2O_4$=352.5

CAS — 57469-77-9.

ATC — C01EB16; G02CC01; M01AE01; M02AA13.

ATC Vet — QC01EB16; QG02CC01; QM01AE01; QM02AA13.

UNII — N01ORX9D6S.

Stability. Solutions of ibuprofen lysine in Water for Injections stored at room temperature were found to be most stable when protected from light.[1]

1. Volonté MG, *et al.* Stability of ibuprofen in injection solutions. *Am J Health-Syst Pharm* 2005; **62:** 630–3.

Uses and Administration

Ibuprofen, a propionic acid derivative, is an NSAID (p. 102.3). Its anti-inflammatory properties may be weaker than those of some other NSAIDs.

Ibuprofen is used in the management of mild to moderate pain and inflammation in conditions such as dysmenorrhoea, headache including migraine, postoperative pain, dental pain, musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis including juvenile idiopathic arthritis, periarticular disorders such as bursitis and tenosynovitis, and soft-tissue disorders such as sprains and strains. It is also used to reduce fever.

Ibuprofen is also used as an alternative to indometacin in the treatment of patent ductus arteriosus.

The usual **oral** dose for painful conditions is 1.2 to 1.8 g daily in divided doses although maintenance doses of 600 mg to 1.2 g daily may be effective in some patients. If necessary the dose may be increased; in the UK the maximum recommended dose is 2.4 g daily whereas in the USA it is 3.2 g daily. Modified-release preparations of ibuprofen are available for once- or twice-daily dosing, although actual dosages vary with different preparations. Patients with rheumatoid arthritis generally require higher doses of ibuprofen than those with osteoarthritis. The recommended dose for fever reduction is 200 to 400 mg every 4 to 6 hours to a maximum of 1.2 g daily. For oral doses in children, see Administration in Children, below.

Ibuprofen may be given **parenterally** by intravenous infusion for the management of mild to moderate pain and as an adjunct to opioid analgesics for moderate to severe pain, and for reduction of fever. For painful conditions, 400 to 800 mg may be given every 6 hours as necessary. For fever reduction, an initial dose of 400 mg may be followed by 400 mg every 4 to 6 hours or 100 to 200 mg every 4 hours as necessary. Regardless of indication, infusion time must be no less than 30 minutes and a dose of 3.2 g daily should not be exceeded. Ibuprofen is also given parenterally for the treatment of patent ductus arteriosus in preterm infants; for details of doses, see p. 69.1.

Ibuprofen is applied **topically** as a 5% cream, foam, gel, or spray solution; a 10% gel is also available. It is also used topically as a dressing containing 500 micrograms/cm² of ibuprofen for the management of ulcers and superficial wounds.

Ibuprofen is usually given as the base but **derivatives**, including various salts, esters, and other complexes, have also been used. These include lysine (see Patent Ductus Arteriosus, p. 69.1), potassium, and sodium salts, guaiacol and pyridoxine esters, and mabuprofen (ibuprofen aminoethanol), isobutanolammonium, and meglumine derivatives.

Ibuprofen is usually given as a racemic mixture but preparations containing only the *S*-(+)-isomer dexibuprofen (p. 43.1) are available in some countries.

Administration in children. In the UK, the following oral doses of ibuprofen, given according to age, are recommended by the *BNFC* for the treatment of **pain, inflammation of soft-tissue injuries**, or **fever** in children:

- 1 to 3 months: 5 mg/kg 3 or 4 times daily
- 3 to 6 months: 50 mg 3 times daily

- 6 to 12 months: 50 mg 3 or 4 times daily
- 1 to 4 years: 100 mg 3 times daily
- 4 to 7 years: 150 mg 3 times daily
- 7 to 10 years: 200 mg 3 times daily
- 10 to 12 years: 300 mg 3 times daily
- 12 to 18 years: initially 300 to 400 mg 3 or 4 times daily increased, if necessary, to a maximum of 2.4 g daily; maintenance doses of 200 to 400 mg 3 times daily may be adequate
- for more *severe* symptoms in children aged between 3 months and 12 years, a dose of 30 mg/kg (maximum 2.4 g) daily in 3 or 4 divided doses may be given

In the USA, suggested doses for children aged 6 months and over are: for fever, 5 to 10 mg/kg (depending on the severity of the fever) and for pain, 10 mg/kg; doses may be given every 6 to 8 hours up to a maximum daily dose of 40 mg/kg.

In the treatment of **rheumatic disease** including juvenile idiopathic arthritis, the *BNFC* recommends a dose of 10 mg/kg 3 or 4 times daily (maximum 2.4 g daily) in children aged 3 months and over; if necessary up to 60 mg/kg daily in 4 to 6 divided doses (maximum 2.4 g daily) may be given in systemic juvenile idiopathic arthritis. A usual daily dose in the USA for juvenile idiopathic arthritis is 30 to 40 mg/kg in divided doses.

Similar dosage regimens are also suggested by UK licensed product information for all the above indications; however, ibuprofen use is not generally recommended in children weighing less than 5 kg or under 3 months of age.

For **post-immunisation pyrexia**, a dose of 50 mg has been recommended; a second dose may be given after 6 hours. If the pyrexia persists after the second dose, medical advice should be sought. Infants aged 2 to 3 months may also be given a 50-mg dose of ibuprofen for post-immunisation pyrexia on the advice of a doctor.

Ibuprofen or its lysine salt are also used in the treatment of **patent ductus arteriosus** in preterm infants; dosage details for this indication are given below.

Cachexia. For reference to the use of ibuprofen with megestrol to treat cancer cachexia, see p. 2289.3.

Cystic fibrosis. In patients with cystic fibrosis (see p. 179.2), the inflammatory response to chronic pulmonary infection with *Pseudomonas* organisms contributes to lung destruction. NSAIDs have been studied in patients with cystic fibrosis as an alternative to corticosteroids to reduce pulmonary inflammation. Some reviews[1,2] found evidence in support of using high-dose NSAIDs, most notably ibuprofen, to slow the progression of lung damage in patients with cystic fibrosis. However, there are limited data about the long-term safety of high doses[1] and some consider that this may have limited such use of NSAIDs;[3] others remain to be convinced that a benefit has been shown.[4] Furthermore there were sufficient data to recommend that NSAIDs be temporarily stopped when intravenous aminoglycosides or other nephrotoxic drugs are used.[1]

1. Lands LC, Stanojevic S. Oral non-steroidal anti-inflammatory drug therapy for cystic fibrosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 07/11/07).
2. Konstan MW. Ibuprofen therapy for cystic fibrosis lung disease: revisited. *Curr Opin Pulm Med* 2008; 14: 567–73.
3. Fennel PB, *et al.* Use of high-dose ibuprofen in a pediatric cystic fibrosis center. *J Cyst Fibros* 2007; 6: 153–8.
4. Bush A, Davies J. Non† to non-steroidal anti-inflammatory therapy for inflammatory lung disease in cystic fibrosis (at least at the moment). *J Pediatr* 2007; 151: 228–30.

Pain. Findings from a long-term study[1] in 585 patients (mean age of 64 years) with knee pain suggested that oral and topical ibuprofen had an equivalent analgesic effect although the former was associated with more minor adverse effects; there was no difference in the rate of major adverse effects.

Single dose, oral ibuprofen is an effective analgesic for the treatment of postoperative pain.[2]

1. Underwood M, *et al.* Topical or oral ibuprofen for chronic knee pain in older people: the TOIB study. *Health Technol Assess* 2008; 12: 1–176.
2. Derry C, *et al.* Single dose oral ibuprofen for acute postoperative pain in adults. Available in The Cochrane Database of Systematic Reviews: Issue 3. Chichester: John Wiley; 2009 (accessed 15/09/09).

Patent ductus arteriosus. Ibuprofen or its lysine salt may be given **parenterally** for the treatment of patent ductus arteriosus (p. 72.2) in preterm infants of less than 34 weeks' gestation; doses are expressed in terms of ibuprofen. Three intravenous doses (infused over 15 minutes) are given at 24-hour intervals; the initial dose is equivalent to 10 mg/kg of ibuprofen followed by two further doses of 5 mg/kg. If, 48 hours after this course of therapy the ductus remains open, a second course may be given, but if this produces no response surgery may be necessary. Ibuprofen injection, *when given as the base*, should be used undiluted, but if necessary it may be reconstituted with sodium chloride 0.9% or glucose 5% for injection. *When given as the lysine salt*, it should be diluted with sodium chloride 0.9% or glucose 5%.

For a suggestion that ibuprofen might be a better choice than indometacin for the treatment of patent ductus arteriosus, see p. 72.2.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3. Ibuprofen may be better tolerated than other NSAIDs.

Adverse effects that may be associated with the use of ibuprofen injection in premature **neonates** include intraventricular haemorrhage, periventricular leucomalacia, bronchopulmonary dysplasia, pulmonary haemorrhage, necrotising enterocolitis, intestinal perforation, oliguria, fluid retention, and haematuria; hypoxaemia and gastrointestinal haemorrhage have also been reported. In addition ibuprofen injection should not be given to neonates with life-threatening infection, with significant renal impairment, or with known or suspected necrotising enterocolitis. Infants who are bleeding (especially gastrointestinal bleeding or intracranial haemorrhage) or who have thrombocytopenia or coagulation defects should also not be given parenteral ibuprofen, and those given it should be monitored during treatment for signs of bleeding. Renal function should be monitored and if anuria or marked oliguria is evident at the time of a scheduled second or third dose, it should be delayed until renal function has returned to normal.

Symptoms of nausea, vomiting, epigastric pain, and tinnitus have been reported after ibuprofen overdosage. More serious toxicity is uncommon, but giving activated charcoal followed by supportive measures is recommended if the quantity ingested within the previous hour exceeds 400 mg/kg.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving ibuprofen, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding. The *BNF* also considers the amount of ibuprofen distributed into breast milk to be too small to be harmful to a breast-fed infant. A study[2] estimated that a breast-fed infant would ingest about 0.0008% of the maternal dose. However, licensed product information for some preparations, including some topical preparations, recommends that breast feeding should be avoided during ibuprofen treatment.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 07/11/07)
2. Walter K, Dilger C. Ibuprofen in human milk. *Br J Clin Pharmacol* 1997; 44: 211–12.

Children. An analysis[1] of the outcome of treatment of 83 915 children found that the risk of hospitalisation for gastrointestinal bleeding, renal failure, or anaphylaxis was no greater in children given ibuprofen than in those given paracetamol.

1. Lesko SM, Mitchell AA. An assessment of the safety of pediatric ibuprofen. *JAMA* 1995; 273: 929–33.

Effects on the blood. Blood disorders including agranulocytosis, aplastic anaemia,[1] pure white-cell aplasia,[2] and thrombocytopenia[3] have been reported in patients taking ibuprofen. Fatal haemolytic anaemia occurred in a man taking ibuprofen and oxazepam.[4]

1. Gryfe CI, Rubenzahl S. Agranulocytosis and aplastic anemia possibly due to ibuprofen. *Can Med Assoc J* 1976; 114: 877.
2. Mamus SW, *et al.* Ibuprofen-associated pure white-cell aplasia. *N Engl J Med* 1986; 314: 624–5.
3. Jain S. Ibuprofen-induced thrombocytopenia. *Br J Clin Pract* 1994; 48: 51.
4. Guidry JB, *et al.* Fatal autoimmune hemolytic anemia associated with ibuprofen. *JAMA* 1979; 242: 68–9.

Effects on the cardiovascular system. For a discussion of the cardiovascular effects of NSAIDs, including ibuprofen, see p. 105.1.

Effects on the CNS. Aseptic meningitis has occurred in patients taking NSAIDs. A review[1] of NSAID-related CNS adverse effects summarised 23 literature reports of NSAID-associated aseptic meningitis; 17 reports involved ibuprofen, 4 sulindac, 1 naproxen, and 1 tolmetin. Of the 23 reports, 11 were in patients with a diagnosis of SLE. Typically the reaction is seen in patients who have just restarted NSAID therapy after a gap in their treatment. Within a few hours of restarting the NSAID the patient develops fever, headache, and a stiff neck; abdominal pain may be present. The patient may become lethargic and eventually comatose. Symptoms resolve if the NSAID is stopped. It is believed to be a hypersensitivity reaction but there does not appear to be cross-reactivity between NSAIDs.

Similar conclusions have also been reported more recently.[2] After experience of 2 cases, a review of the literature identified 71 episodes of ibuprofen-induced aseptic meningitis in 36 patients; 22 patients had recurrent episodes after repeated ibuprofen use. An underlying autoimmune connective tissue disorder was noted in 22 patients of whom 14 had SLE, 6 had an undifferentiated or mixed disorder, 1 had rheumatoid arthritis, and 1 had Sjögren's syndrome. In most cases, symptoms developed within 24 hours of starting ibuprofen although 1 patient had been taking ibuprofen for 2 years before the onset of symptoms. Cross-reactivity was reported in only 1 patient who had also developed aseptic meningitis with both naproxen and rofecoxib.

1. Hoppmann RA, *et al.* Central nervous system side effects of nonsteroidal anti-inflammatory drugs: aseptic meningitis, psychosis, and cognitive dysfunction. *Arch Intern Med* 1991; 151: 1309–13.
2. Rodríguez SC, *et al.* Characteristics of meningitis caused by ibuprofen: report of 2 cases with recurrent episodes and review of the literature. *Medicine* 2006; 85: 214–20.

Effects on electrolytes. Hyponatraemia has been described in patients taking ibuprofen;[1-3] other risk factors such as pre-existing renal impairment or use with desmopressin were generally present.

1. Blum M, Aviram A. Ibuprofen induced hyponatraemia. *Rheumatol Rehabil* 1980; 19: 258–9.
2. Rault RM. Case report: hyponatremia associated with nonsteroidal antiinflammatory drugs. *Am J Med Sci* 1993; 305: 318–20.
3. García EBG, *et al.* Hyponatraemic coma induced by desmopressin and ibuprofen in a woman with von Willebrand's disease. *Haemophilia* 2003; 9: 232–4.

Effects on the eyes. Reversible amblyopia has been reported in patients taking ibuprofen.[1,2] For reference to effects on the optic nerve associated with ibuprofen, see p. 105.3.

1. Collum LMT, Bowen DL. Ocular side-effects of ibuprofen. *Br J Ophthalmol* 1971; 55: 472–7.
2. Palmer CAL. Toxic amblyopia from ibuprofen. *BMJ* 1972; 3: 765.

Effects on the gastrointestinal tract. Ibuprofen may be associated with a lower risk of upper gastrointestinal effects than some other NSAIDs, but nonetheless it can cause dyspepsia, nausea and vomiting, gastrointestinal bleeding, and peptic ulcers and perforation. Colitis and its exacerbation have occurred.[1,2]

1. Ravi S, *et al.* Colitis caused by non-steroidal anti-inflammatory drugs. *Postgrad Med J* 1986; 62: 773–6.
2. Clements D, *et al.* Colitis associated with ibuprofen. *BMJ* 1990; 301: 987.

Effects on the kidneys. Reports of adverse renal effects with ibuprofen include an increase in serum creatinine concentration,[1] acute renal failure,[2-6] and nephrotic syndrome.[7] Cystitis, haematuria, and interstitial nephritis may occur. Acute flank pain and reversible renal dysfunction has been reported in some patients treated with ibuprofen.[8,9] See also Effects on Electrolytes, above.

1. Whelton A, *et al.* Renal effects of ibuprofen, piroxicam, and sulindac in patients with asymptomatic renal failure: a prospective, randomized, crossover comparison. *Ann Intern Med* 1990; 112: 568–76.
2. Brandstetter RD, Mar DD. Reversible oliguric renal failure associated with ibuprofen treatment. *BMJ* 1978; 2: 1194–5.
3. Kimberly RP, *et al.* Apparent acute renal failure associated with therapeutic aspirin and ibuprofen administration. *Arthritis Rheum* 1979; 22: 281–5.
4. Spierto RJ, *et al.* Acute renal failure associated with the use of over-the-counter ibuprofen. *Ann Pharmacother* 1992; 26: 714.
5. Fernando AHN, *et al.* Renal failure after topical use of NSAIDs. *BMJ* 1994; 308: 533.
6. Moghal NE, *et al.* Ibuprofen and acute renal failure in a toddler. *Arch Dis Child* 2004; 89: 276–7.
7. Justiniani FR. Over-the-counter ibuprofen and nephrotic syndrome. *Ann Intern Med* 1986; 105: 303.
8. McIntire SC, *et al.* Acute flank pain and reversible renal dysfunction associated with nonsteroidal anti-inflammatory drug use. *Pediatrics* 1993; 92: 459–60.
9. Wattad A, *et al.* A unique complication of nonsteroidal anti-inflammatory drug use. *Pediatrics* 1994; 93: 693.

Effects on the liver. Raised liver transaminase values were noted in 3 patients with chronic hepatitis C infection after taking ibuprofen.[1] Values returned to normal on stopping the drug; the effect recurred in one patient who was re-exposed. Other hepatic adverse effects reported with ibuprofen include hepatitis[2] and liver failure.[3]

See also Effects on the Skin, below.

1. Riley TR, Smith JP. Ibuprofen-induced hepatotoxicity in patients with chronic hepatitis C: a case series. *Am J Gastroenterol* 1998; 93: 1563–5.
2. Borel L, *et al.* Hépatite aiguë sévère après prise d'ibuprofène. *Gastroenterol Clin Biol* 2001; 25: 430–2.
3. Rodríguez-González FJ, *et al.* Orthotopic liver transplantation after subacute liver failure induced by therapeutic doses of ibuprofen. *Am J Gastroenterol* 2002; 97: 2476–7.

Effects on the skin. Rashes may occur during hypersensitivity reactions although serious dermatological effects attributed to ibuprofen are rare. Reports of more serious effects have included Stevens-Johnson syndrome (often associated with hepatotoxicity),[1-4] photosensitivity,[5] and bullous leucocytoclastic vasculitis.[6]

1. Sternlieb P, Robinson RM. Stevens-Johnson syndrome plus toxic hepatitis due to ibuprofen. *N Y State J Med* 1978; 78: 1239–43.
2. Srivastava M, *et al.* Drug-associated acute-onset vanishing bile duct and Stevens-Johnson syndromes in a child. *Gastroenterology* 1998; 115: 743–6.

3. Taghian M, *et al.* Acute vanishing bile duct syndrome after ibuprofen therapy in a child. *J Pediatr* 2004; 143: 273–6.
4. Health Canada. Ibuprofen: Stevens-Johnson syndrome. *Can Adverse React News* 2005; 15 (3): 3. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v15n3-eng.pdf (accessed 29/08/08)
5. Bergner T, Przybilla B. Photosensitization caused by ibuprofen. *J Am Acad Dermatol* 1992; 26: 114–16.
6. Davidson KA, *et al.* Ibuprofen-induced bullous leukocytoclastic vasculitis. *Cutis* 2001; 67: 303–7.

Hypersensitivity. A fatal asthma attack occurred in a 65-year-old woman, with adult-onset asthma, 30 minutes after ingestion of ibuprofen 800 mg.[1]

For other hypersensitivity reactions or possible reactions see also Effects on the CNS (p. 69.2) and Effects on the Skin, p. 69.3.

1. Ayres JG, *et al.* Asthma death due to ibuprofen. *Lancet* 1987; i: 1082.

Meningitis. For reports of aseptic meningitis after use of ibuprofen, see Effects on the CNS, p. 69.2.

Overdosage. There was a substantial increase in the number of cases of ibuprofen overdose reported to the National Poisons Information Service of the UK in the 2 years after its introduction as an 'over-the-counter' medication.[1] However, no concurrent increase in severity of poisoning was found and in only 1 of 203 cases was ibuprofen thought to have caused serious problems. It was concluded that ibuprofen appeared to be much less toxic in acute overdose than either aspirin or paracetamol. Current advice is that doses below 100 mg/kg are unlikely to cause toxicity in *children*, whereas clinical features will occur in children who have ingested more than 400 mg/kg. In *adults* the dose-response effect is less clear cut, but those who have ingested less than 100 mg/kg are unlikely to require treatment.

Nonetheless, reports illustrate the complexity of major overdosage with ibuprofen. A syndrome of coma, hyperkalaemia with cardiac arrhythmias, metabolic acidosis, pyrexia, and respiratory and renal failure was reported[2] in a 17-year-old man after major overdosage with ibuprofen and minor overdosage with doxepin. Hyperkalaemia was not evident until 14 hours after hospital admission and was thought to be due to a combination of potassium replacement for initial hypokalaemia, acidosis, muscle damage, and ibuprofen-induced renal failure. A 6-year-old child developed[3] shock, coma, and metabolic acidosis after ingestion of a dose of ibuprofen equivalent to 300 mg/kg. Treatment consisting of intubation, mechanical ventilation, fluid resuscitation, gastric lavage, and activated charcoal proved successful. In another report,[4] in which a 21-month-old child had ingested the equivalent of 500 mg/kg of ibuprofen, the presenting symptoms were acute renal failure with severe metabolic acidosis. The child developed tonic-clonic seizures 46 hours after ingestion, with significant hypocalcaemia and hypomagnesaemia, which may have been exacerbated by use of sodium polystyrene sulfonate and furosemide. The seizures, which could not be controlled with diazepam, phenytoin, and phenobarbital, ceased on correction of electrolyte balance.

1. Perry SJ, *et al.* Ibuprofen overdose: the first two years of over-the-counter sales. *Hum Toxicol* 1987; 6: 173–8.
2. Menzies DG, *et al.* Pulminant hypetkalaemia and multiple complications following ibuprofen overdose. *Med Toxicol Adverse Drug Exp* 1989; 4: 468–71.
3. Zuckerman GB, Uy CC. Shock, metabolic acidosis, and coma following ibuprofen overdose in a child. *Ann Pharmacother* 1995; 29: 869–71.
4. Al-Harbi NN, *et al.* Hypocalcemia and hypomagnesemia after ibuprofen overdose. *Ann Pharmacother* 1997; 31: 432–4.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ibuprofen as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 23/10/11)

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Antineoplastics. For the effect of ibuprofen on the metabolism of *pemetrexed*, see p. 845.3.

Aspirin. It has been suggested that ibuprofen may reduce the cardioprotective effect of aspirin but see NSAIDs, under Interactions of Aspirin, p. 27.1.

Lipid regulating drugs. For a report of rhabdomyolysis and renal failure attributed to an interaction between ibuprofen and *ciprofibrate*, see p. 1325.2.

Muscle relaxants. *Baclofen* toxicity may develop after starting ibuprofen; for further details, see p. 2017.1.

Pharmacokinetics

Ibuprofen is absorbed from the gastrointestinal tract and peak plasma concentrations occur about 1 to 2 hours after ingestion. Ibuprofen is also absorbed on rectal use. It is partially absorbed after topical application to the skin; some licensed product information state that percutaneous absorption from topical gel is about 5% of that from an oral dose form. Ibuprofen is 90 to 99% bound to plasma proteins and has a plasma half-life of about 2 hours. It is rapidly excreted in the urine mainly as metabolites and their conjugates. About 1% is excreted in the urine as unchanged ibuprofen and about 14% as conjugated ibuprofen. There appears to be little, if any, distribution into breast milk.

The above figures refer to racemic ibuprofen. However, ibuprofen's disposition is stereoselective and there is some metabolic conversion of the inactive *R*-(-)-enantiomer to the active *S*-(+)-enantiomer, dexibuprofen (p. 43.1).

References.
1. Davies NM. Clinical pharmacokinetics of ibuprofen: the first 30 years. *Clin Pharmacokinet* 1998; 34: 101–54.
2. Sharma PK, *et al.* Pharmacokinetics of oral ibuprofen in premature infants. *J Clin Pharmacol* 2003; 43: 968–73.
3. Gregoire N, *et al.* Population pharmacokinetics of ibuprofen enantiomers in very premature neonates. *J Clin Pharmacol* 2004; 44: 1114–24.
4. Han EE, *et al.* Pharmacokinetics of ibuprofen in children with cystic fibrosis. *Clin Pharmacokinet* 2004; 43: 145–56.
5. Hao H, *et al.* Enantioselective pharmacokinetics of ibuprofen and involved mechanisms. *Drug Metab Rev* 2005; 37: 215–34.
6. Kyllonen M, *et al.* Perioperative pharmacokinetics of ibuprofen enantiomers after rectal administration. *Paediatr Anaesth* 2005; 15: 566–73.
7. Kokki H, *et al.* Cerebrospinal fluid distribution of ibuprofen after intravenous administration in children. Abstract: *Pediatrics* 2007; 120: 882. Full version: http://pediatrics.aappublications.org/cgi/reprint/120/4/e1002 (accessed 15/09/09)
8. Gregoire N, *et al.* Population pharmacokinetic analysis of ibuprofen enantiomers in preterm newborn infants. *J Clin Pharmacol* 2008; 48: 1460–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Actron; Acuilfem; Afebril; Atomo Desinflamante Ibu; Butidiona; Causalon Ibu; Copiron; Dolorsyn; Druisel; Fabogesic; Febratic; Fontol; Ibu Evanol; Ibu-Novalgina; Ibu; Ibubenitol; Ibucalmin; Ibucler; Ibufabra; Ibulix; Ibufull; Ibulam; Ibulgia; Ibumar; Ibumultin; Ibup; Ibupirac; Ibupiretas; Ibuprofenix; Ibuprofex; Ibusi; Ibusol; Ibusumal†; Ibutenk; Ibuxfar; Ibuxim; Ibuzidine; Matrix; Novo Geniol; Oxibut; Pakurat; Ponstil Mujer; Ponstin; Ponstinetas; Salivia; Sindol; Teprix; Tonal; Vefren; ***Austral.***: ACT-3†; Actiprofen†; Advil; Brufen; Dimetapp Pain & Fever Relief; Nurofen Migraine; Nurofen Zavance; Nurofen; Proven; Rafen; Tri-Profen†; ***Austria***: Adolorin Ibufortе; Aktren; Brufen; Dismenol Neu; Dolgit; Dolofort; Duafen†; Duanibu; Ibumetin; Ibutop; Kratalgin; Momento†; Nureflex; Nurofen; Pedea; ratioDolor; ***Belg.***: Adulfen Lysine†; Advil Mono†; Brufen; Buprophar; Dolofin; Epsilon; Extrapan; Ibumed; Ibutop; Malafene; Nurofen; Optalidon Nieuwe Formule; Pedea; Perdofemina; Perdophen; Perviam†; Spidifen; ***Braz.***: Actiprofen; Advil; Algi-Reumatril; Algiflex; Alivium; Artril; Buprovil; Buscofem; Dalsy; Doraliv; Dorigren; Febsen; Ibuflex; Ibufran; Ibupril; Ibuprofan; Ibuvix; Lombalgina; Maxifen; Motrin; Novalfem; Pararrrin; Spidufen; Uniprofen; Vantil; ***Canad.***: Advil; Caldolor; Europrofen; Infants Motrin; Motrin; Novo-Profen; Pamprin Ibuprofen; ***Chile***: Actron; Bediatil; Deucodol; Dolorub; Esanterm; Fortapal†; Ibu; Ibucon; Ibupirac; Ipson; Kin; Motrin; Niofen; Pediaprofen; Pironal; Pyriped; ***China***: Advil (雅维); An Rui Ke (安瑞克); Bang Qi (邦奇); Bei De Fen (倍得芬); Bei Fen (倍芬); Childrens Motrin (美林); Di Er Nuo (迪尔诺); Efficover (芬克); Etibufen (布洛芬缓释); Fen Su (芬苏); Fenbid (芬必得); Fennikang (芬尼康); Fu Er Da (抚尔达); Fu Er Shuan (福尔栓); Huanshifen (缓士芬); Jie Le (捷乐); Jihao (吉浩); Jiubaofen (久保芬); Qin Fu (琴福); Qing Fen (清芬); Sai Ke (赛可); Spedifen (司百得); Tai Bao (泰宝); Tian Qian (恬倩); Tuen (托恩); Xin Di Fen (欣获芬); Xin Wei (欣卫); Yi Fen Ning (怡芬宁); Zefen (泽芬); ***Cz.***: Advil; Baroc†; Brufen; Dolgit; Ibalgin; Ibuberl; Ibudolor; Ibumax; Iburion; Nurofen Advance†; Nurofen Stopgrip; Nurofen; Pabiprofen†; Panafen; Pedea; Solpaflex†; Tomaflex†; Urgo†; ***Denm.***: Brufen; Burana; Fenasol; Ibumax; Ibumetin; Ibumil; Ibustar; Ibutop; Ipren; Nurofen; Pedea; Xpri; ***Fin.***: Burana; Ibumax; Ibumetin; Ibusal; Ibutabs; Ibuxin: MIG; ***Fr.***: Advil; Advilcaps; Advilliff; Adviltab; Anadvil†; Antarene Codeine; Antarene; Biatain-Ibu; Brufen; Dolgit; Doltaque†; Ergix Douleur et Fievre; Expanfen†; Gelufene; Hemagene Tailleur; Ibutop; Intralgis; Nureflex; Nurofen; Nurofenfem; Nurofenflash; Nurofenpro; Nurofentabs; Pedea; Solufen†; Spedifen; Spifen; Tiburon; Upfen; ***Ger.***: Advel†; Aktren; Analgin Akut; Anco†; Biatain-Ibu; Dismenol N; Dolgit; Dolo Sanol†; Dolo-Puren†; Dolobene Ibu; Dolodoc†; Dolormin; Espreni†; Eudorlin Extra; Eudorlin Migrane; Gyno-Neuralgin; Ib-u-ron; ibu-Attritin†; Ibu-Lysin; Ibu-ratiopharm; Ibu; Ibubeta; Ibudolor; Ibuflam†; Ibuhexal†; Ibutad†; Ibutop†; Imbun; Kontagripp†; Mensoton; Migranin Ibuprofen†; Neuralgin extra; Nurofen; Optalidon Ibu†; Opturem†; Pedea; Pfeil; Schmerz-Dolgit†; Spidifen; Tabalon†; Tispol Ibu-DD; Trauma-Dolgit; Tussamag Fieber- und Schmerztablettent†; Urem; ***Gr.***: Advil; Algofren; Brufen; Buscofem; Chrobifen; Drin; Fenbid; Focus; Forbiphen; Ibodezil; Ibugel†; Ibuspel; Londodact; Nurofen; Pedea; Pinafor; Rozovin; ***Hong Kong***: Bifen; Brufen; Brumed; Cortal Ibuprofen†; Ibufac; Ibupen†; Infacalm; Maprofen†; Neutropain; Nurofen; Perofen; Profen; Rafen†; Schufen; Spedifen; Synprofen†; Zofen; ***Hung.***: Advil; Algoflex; Dolgit; Ibumax; Ibutop; Melfen; Nurofen; Solpaflex†; Spedifen; ***India***: Alfam; Bren; Brufen; Cipgesic; Ibrumac; Ibu; Ibubid; Ibucon; Ibuf; Ibugesic; Ibugin; Ibupal; Ibuspan; Ibusynth; Inflapen; Mybu; Myofen; Norswel; Nurom; ***Indon.***: Anafen; Arfen; Arthrifen; Bufect; Dofen; Dolofer-F; Ethifen; Farsifen; Febryn†; Fenatic; Fenris; Iprox; Lexaprol; Mofen; Nofena†; Ostarin; Prifen†; Profen; Proris; Prosic; Prosinal; Rhelafen; Ribunal; Shelrofen†; Spedifen; Yariven; ***I.L.***: Actiprofen; Advil; Brufen; Bufigen†; Buplex; Easofen; Feloprofine; Ibugel; Ibuleve†; Melfen; Nurofen Advance; Nurofen; Pedea; Phorpain; Proflex†; Provin; ***Israel***: Adex; Advil; Artofen; Iboo; Ibufen; Ibuleve; Nurofen; Tiptipot Ibutaf; ***Ital.***: Algofen; Antalfebal; Antalfort; Antalgil; Antalisin; Arfen; Brufen; Busofen; Calmine; Cibalgina Dol; Cibalgina Due Fast; Cibalginafor; Dolofast: Edenil; Gineflor; Ginenorm; Ibupas; Kendo; Momeat; Momentact; Nureflex†; Nurofast†; Nurofen; Nuroflash; Nurosolv; Pedea; Sinilev; Spidifen; Stibupatch; Subitene; Vicks Febbre e Dolore; Visquo; ***Malaysia***: Bifen; Brufen; Ibufac; Nurofen; Perofen†; Spedifen; ***Mex.***: ABKI; Actron; Adivon†; Advil; Afrasil; Ainex†; Aldofen; Algidol; Bestafen; Carone; Citalgan; Daicil; Days; Dibufen†; Dipofen; Diprodol; Dolprin; Dolprofen†; Dolval; Dolver; Eufenil; Febratic†; Fidoin-Q; Flexafen; Gelidol; Gobrosan; Ibuflam; Ibuflex; Ifentil; Inpained; Maxifen; Medifen; Motrin; Nafendol; Pro-XB; Proartinal†; Probuxil; Quadrax; Realdrax; Ribufen†; Tabalon; Zoafalet-H; ***Neth.***: Advil; Brufen; Burana; Femapirin†; Ibosure†; Nurofen; Pedea; Roco†; Sarixe; Spidifen; Zafen; ***Norw.***: Brufen; Burana; Ibumetin; Ibuprox; Ibux; Pedea; ***NZ***: ACT-3; Brufen; Fenpaed; Ibucare†; Nurofen Migraine; Nurofen Tension Headache; Nurofen; Panafen; ***Philipp.***: Advil; Brufen†; Dolafen; Dolan; Faspic; Genselax; Ibupe; Idyl; Medbufen; Medicol; Midol; Rheuxan; ***Pol.***: Aprofen; Bolnet†; Bufenik; Dolgit; Ibalgin; Ibufen; Ibum; Ibupar; Ibuprox; Iburion; Kidofen; MIG; Nurofen Migrenol†; Nurofen; Pedea; ***Port.***: Anadvil; Arfen; Baroc; Brufen; Calbrun†; Dolocyl; Dolomate; Faspic; Fenibu†; Fenpic; Frenidor; Kifen; Liderfen; Moment; Nolofene; Norvectan; Nurofen; Ozonol: Pedea; Perdofen; Seclodin†; Solufen; Solvium; Spidifen; Sporfen; Tricalm; Trifene; Zafen; Zip-A-Dol; ***Rus.***: Aldospray (Альдоспрей); Artrocam (АртроКам); Bonifen (Бонифен); Brufen (Бруфен); Burana (Бурана); Dolgit (Долгит); Faspic (Фаспик); Ibalgin (Ибалгин); Ibufen (Ибуфен); Iburom (Ибупром); Mig (Миг); Nurofen (Нурофен); Pedea (Педеа); Solpaflex (Солпафлекс); ***S.Afr.***: Adfen†; Advil; Betagesic; Betaprofen; Bren; Brufen; Dynofen; Iboflam; IBU; Ibugesic; Ibuleve; Ibumax; Ibumed; Ibunate; Inza; Lenafen; Norflam T; Nurofen: Pedea; Ranfen; ***Singapore***: Bifen; Brufen; Children's Advil; Ibufen; Ibuleve; Nurofen; Perofen; Sugafen; Zofen; ***Spain***: Advil†; Aldospray Analgesico; Algiasdin; Algidrin; Algifast; Alogesia; Aprofeno; Aragel; Articalm; Bexistar†; Brufen; Dadosel†; Dalsy; Dersindol; Diltix Doctril; Dolencar; Dolorac; Doltra; Dorival†; Espididol; Espidifen; Factopan†; Femaprin†; Feminalin†; Fenomas†; Fenospin Fiedosin†; Frenatermin†; Gelobufen; Gelofeno; Gelopiril†; Ibufarmalid; Ibufen; Ibukey; Ibumac; Ibuprox†; Ibustick; Junifen Levedol; Liderferme; Narfen†; Neobrufen; Nodolfen; Normodol Norvectan; Nurofen; Oberdol†; Optajun†; Paidofebril; Pedea Pirexin; Ratiodol†; Saetil; Solvium; Termalfeno†; Todalgil; Unodol; ***Swed.***: Alindrin; Brufen; Burana; Ibumax; Ibumetin; Ibuzin; Ipren; Nurofen; Pedea; ***Switz.***: Alges-X; Algifor; Artofen†; Brufen; Contre-Douleurs IL; Dismenol; Dolgit; Dolo-Spedifen, Dolocyl; Ecoprofen†; Grefen; Ibu; Ibufen-L; Ibuscent†; Ibusifar; Iproben; Irfen; Nurofen; Optifen; Perskindol Ibuprofen acute; Saridon N; Spedifen; Treupel Dolo Ibuprofen; ***Thai.***: Ambufen; Anbifen†; Anufen; Aprofen; Borafen; Borakid†; Brufen†; Brufenin; Brugin; Bruprin; Brusil; Buflex; Bumed; Bunofen; Cefen; Cenbufen; Coprofen; Duran; Eufen; Fafen; Faspic†; G-Fen; Gesica; Gofen; Greatofen; Heidi; I Fen F; I-Profen; Ibrofen; Ibu†; Ibufac; Ibufex; Ibugan; Ibukids; Ibulan; Ibulium; Ibuman; Ibumax; Ibupac; Junimol; Mano-Bruzone; Nurofen; P-Fen†; Pippen; Probue†; Probufen; Profen; Profeno; Rabufen; Rheumanox; Rumasian†; Rumatifen†; S-Pro; Sanofen†; Schufen; Sinprofen; Skelan IB†; Spedifen; Suphen; Tofen; Trofen; Tyhofen; Umafen†; ***Turk.***: Advil; Algifen; Artril; Balafen; Bebol†; Berkofen; Biophen; Brufen; Dolgit; Dolven; Gerofen; Ibu-600; Ibufen; Kiddyfen; Nurofen Plus; Nurofen; Pedifen; Profen; Repozal; Rofen; Siyafen; Suprafen; Ternsofen†; Ultrafen; Upren; ***UAE***: Profinal; ***UK***: Advil; Anadin Ibuprofen; Anadin Joint Pain; Anadin LiquiFast; Anadin Ultra; Arthrofen; Biatain-Ibu; Brufen; Calprofen; Cuprofen; Ebufac; Fenbid; Fenpaed; Feverfen; Galprofen; Hedex Ibuprofen; Ibrufhalal; Ibufem; Ibugel; Ibuleve; Ibumousse; Ibuspray; Ibutop Cuprofen; Ibutop Ralgex†; Librofem; Mandafen; Manorfen; Mentholatum Ibuprofen; Migrafen; Novaprin; Nurofen Migraine; Nurofen; Obifen; Orbifen; Pacifene; Pedea; Phor Pain; Proflex†; Radian-B Ibuprofen; Relcofen; Rimafen; ***Ukr.***: Bofen (Бофен); Caffetin Lady (Каффетин Леди); Dolgit (Долгит); Ibufen (Ибуфен); Ibuprom (Ибупром); Ibutard (Ибутард); Imet (Имет); Irfen (Ирфен); Nortafen (Нортафен)†; Nurofen (Нурофен); Pedea (Педеа); ***USA***: Advil Migraine; Advil; Anadar; Caldolor; Duexis; Ibu-Tab; Ibu-4, -6, -8; Ibu; Ibutab; Menadol; Midol Cramp & Body Aches; Motrin; NeoProfen; PediaCare Childrens Pain Reliever Fever Reducer IB; PediaCare Infants Pain Reliever Fever Reducer; Saleto-200; ***Venez.***: Advil; Brugesic; Buprodol; Dologesic; Femicaps; Femmex Plus; Ibucaps; Ibufen; Iburin; Ibutan; Lumbax; Max; Maydol; Mestral; Motrin; Pedibu.

Multi-ingredient Preparations. ***Arg.***: Aliviagrip; Buscapina Fem; Dexprofeno†; Espasmo Ibuprofeno; Espasmofin; Feminity; Gobbigesic†; Ibu Evanol Extra; Ibu Evanol Plus; Ibu-Buscapina; Ibu-Tetralgin; Ibudolofrix; Ibudristan; Ibufem; Ibunastizol; Ibupirac Fem; Ibupirac Flex; Ibupirac Migra; Ibuxim Fem; Labsyna Caf; Labsyna Fem; Mensalgin; Migral II; Roveril; Supragesic; Teprix Fem; Vefren Flex; ***Austral.***: Dimetapp Headcold & Flu;

Nurofen Cold & Flu; Nurofen Plus; Panafen Plus; Proven Plus; Rafen Plus; Sudafed PE Sinus + Anti-inflammatory Pain Relief; Sudafed Sinus & Anti-inflammatory Pain Relief†; ***Braz.***: Reuplex†; ***Canad.***: Advil Cold & Sinus Nighttime; Advil Cold & Sinus Plus; Advil Cold & Sinus; Advil Nighttime; Analgesic and Muscle Relaxant Caplets; Childrens Advil Cold; Cold + Sinus; Motrin Cold & Sinus; Robax Platinum; Sudafed Sinus Advance; Summit Ultra; Vicks DayQuil Sinus & Pain Relief; ***Chile***: Adona†; Artritapsin; Butartrol; Deucodol Plus; Dolnix; Dolo Winasorb; Dolo-Niofen; Dolo-Octirona; Dolonase; Ibu Kitadol; Ibupirac Compuesto; Ibupirac Flu; Ipson-D; Neo Butartrol; Niofen Cold HBP; Niofen Flu; Pironal Flu; Precenid; Predual; Termo-Niofen; ***China***: Ai Fei Le (爱菲乐); Bo Shu (伯舒); Brustan (保施泰); Chen Gong Zai Xin (臣功再欣); De Er (得尔); Fenshida (芬世达); Gan Ning (敢宁); Kang Tai Ke Qing (康泰克清); Ke Tai Shu (可泰舒); Keluoqu (克洛曲); Nuo He (诺合); Pu Feng Qing (扑风清); Pu Luo Bi Da (普洛必达); Shuang Ji (双信); Si Wei Pu (思为普); Tuoan (托安); Ya Ke (雅克); Ya Zhou Kang (牙周康); Zaikang (再康); ***Cz.***: Advil Cold†; Ibu-Hepa; Modafen; ***Fin.***: Ardinex; Burana-C; ***Fr.***: Adviltab Rhume†; Cliptol; Nurofen Rhume; Rhinadvil; Rhinureflex; ***Gr.***: Nurofen Cold & Flu; Vicks†; ***Hong Kong***: Neuroquick†; ***Hung.***: Advil Cold†; Algoflex-M; Deep Relief; Nurofen Cold & Flu; Rhinathiol Cold; ***India***: Abufen-C; Acks†; Actimol-P; Adiflam Plus; Alcofen; Anaflam; Answell; Arcure; Armix; Arpa; Artifen Plus; Artigesic; Bestofen; Bestoflame; Bren Plus; Brenfed; Brenlax; Briflam; Bruace; Brucet; Brufamol-M; Brufamol; Brufen-MR; Brupal; Brustin; Bufex Kid; Bufex Plus; Bufex-C; Buwin Plus; C-Gesic; Calpol Plus; Cipgesic Plus; Codistar Plus; Combiflam; Decofed-DS; Dolocrat; Dolomed-MR; Dolomed; Dolomed; DT-Ibuflam; Dualflam; Duoflam Plus; Duoflam; Efen; Emflam Plus; Fenceta; Fentrex; Fitflam; Flexon-MR; Flexon; Iben Forte; Iben Plus; Ibruvon Forte; Ibu-Proxyvon; Ibubid Plus; Ibucet; Ibuclin; Ibucon Plus; Ibudol-A Kid; Ibudol; Ibuflamar-P; Ibugesic Plus; Ibugesic-M; Ibumac Plus; Ibumet P; Ibumol; Ibun; Ibunij; Ibupar-M; Ibura; Iburic Plus; Ibuspan-P; Ibutop; Ibuwin; Icparil; Imol Plus; Imol; Ipecee; IPM; Lederflam Plus; Lobain; Lumbril-T; Lupiflam-C; Lupiflam; Magadol; Maxofen; New Artifen Plus; Nuren-Ace; Orthodex Plus; Orthodex; Ospidyne; Osyfen Plus; Oxymark; Paraflax; Parvon Forte; Reactine Forte; Robiflam; Somaflam; ***Indon.***: Aknil†; Arthrifen Plus; Axalan†; Bodrex Extra; Iremax; Limasip†; Neo Rheumacyl Neuro; Neo Rheumacyl; Neuralgin; Oskadon SP; Profenal; Shelrod-Plus†; ***Irl.***: Advil Cold & Flu; Nurofen Cold & Flu; Nurofen Plus; Vicks Action†; ***Israel***: Advil Cold & Sinus; Deep Relief†; Nurofen Cold & Flu; Nurofen Plus; ***Ital.***: Nurofen Influenza e Raffreddore; Vicks Flu-Action; ***Jpn***: Colgen Kowa IB; ***Mex.***: Actron Plus; Algitrin; Buscapina Fem; Carbager-Plus; Dualgos; Eufenil M28; Gelidol-X-Press; Sinutab Advance†; ***NZ***: Ibucode Plus; Maxigesic; Nurofen Cold & Flu†; Nurofen Plus; ***Philipp.***: Alaxan; Anoflam; Brustan†; Fladexon; Flexan; Flexigesic; I-Laxx; Muskelax; Proflex; Relievo; Restolax; Selxan; ***Pol.***: Acatar Zatoki; Ardinex†; Dip Rilif; Ibalgin Sport; Ibum Grip; Ibum; Ibuprom Zatoki; Metafen; Modafen; Nurofen Antigrip; Nurofen Plus; ***Rus.***: Brustan (Брустан); Deep Relief (Дип Рилиф); Ibuclin (Ибуклин); Novigan (Новиган); Nurofen Plus (Нурофен Плюс); Pentabufen (Пентабуфен); Theraflex Advance (Терафлекс Адванс); ***S.Afr.***: Advil CS†; Benylin For Colds; Dentopain Forte; Dentopain; Gen-Payne; Ibucod; Ibumol; Ibupain Forte; Ibupain; Lotem; Mybucod; Mybulen; Mypaid; Myprodol; Nurofen Cold & Flu; Nurofen Plus†; Panado Plus; Sinumax Cold & Flu; Sinutab 3-Way; ***Singapore***: Nurofen Cold & Flu; ***Spain***: Astefor; Hyltrin; Ibucod; Neobrufen con Codeina; Nidol; Salvarina; ***Swed.***: Ardinex; ***Switz.***: Ibufen-L; ***Thai.***: Alaxan PI†; Bruno; Brustan; Cetan†; Dologen; Lofen; Panofen; Parafen; Rumatifen-Plus†; Skelan†; ***Turk.***: Dolorin Cold; Iburamin Cold; Nurofen Cold & Flu; ***UAE***: Profinal Cold & Sinus; Profinal FM†; Profinal XP; ***UK***: Cuprofen Plus; Deep Relief; Lemsip Flu 12Hr; Lemsip Max All Day Cold & Flu; Lemsip Max All Day Flu Relief; Lemsip Max All Night Cold & Flu; Lemsip Max All Night Flu Relief; Lemsip Pharmacy Powercaps†; Non-Drowsy Sudafed Dual Relief Max; Nurofen All Night Cold & Flu; Nurofen All Night Flu Relief; Nurofen Cold & Flu Relief; Nurofen Cold & Flu; Nurofen Plus; Nurofen Sinus†; Nuromol; Orbifen Cold & Flu; Soleve; Solpadeine Migraine; Solpaflex; ***Ukr.***: Deep Relief (Дип Рилиф); Ibuprom Sinus (Ибупром Синус)†; Novigan (Новиган); Tamipul (Тамипул); Theraflex Advance (Терафлекс Адванс); ***USA***: Advil Allergy Sinus; Advil Cold & Sinus; Advil PM; Anadar Cold & Flu; Childrens Advil Cold; Childrens Ibuprofen Cold; Childrens Motrin Cold; Combunox†; Dimetapp Childrens Cold & Fever; Dimetapp Sinus; Dristan Sinus; Ibudone; Motrin IB Sinus; Reprexain; Sine-Aid IB; Vicoprofen; ***Venez.***: Brudol; Brugesic Plus; Brugesina; Colfene; Femmexultra; Ibucoden.

Pharmacopoeial Preparations

BP 2014: Ibuprofen Cream; Ibuprofen Gel; Ibuprofen Oral Suspension; Ibuprofen Tablets; Prolonged-release Ibuprofen Capsules; Prolonged-release Ibuprofen Tablets:

USP 36: Diphenhydramine Citrate and Ibuprofen Tablets; Ibuprofen and Pseudoephedrine Hydrochloride Tablets; Ibuprofen Oral Suspension; Ibuprofen Tablets.

Iguratimod *(rINN)*

Iguratimodum; T-614; Игуратимод.

N-{7-[(Methylsulfonyl)amino]-4-oxo-6-phenoxy-4*H*-1-benzopyran-3-yl}formamide.

$C_{17}H_{14}N_2O_6S$=374.4

CAS — 123663-49-0.

UNII — 4IHY34Y2NV.

Profile

Iguratimod is a disease-modifying antirheumatic drug (DMARD) used in the treatment of rheumatoid arthritis.

References.

1. Hara M, *et al.* Long-term safety study of iguratimod in patients with rheumatoid arthritis. *Mod Rheumatol* 2007; 17: 10–16.
2. Hara M, *et al.* Efficacy and safety of iguratimod compared with placebo and salazosulfapyridine in active rheumatoid arthritis: a controlled, multicenter, double-blind, parallel-group study. *Mod Rheumatol* 2007; 17: 1–9.
3. Mucke HA. Iguratimod: a new disease-modifying antirheumatic drug. *Drugs Today* 2012; 48: 577–86.
4. Ishiguro N, *et al.* Iguratimod-Clinical Study Group. Concomitant iguratimod therapy in patients with active rheumatoid arthritis despite stable doses of methotrexate: a randomized, double-blind, placebo-controlled trial. *Mod Rheumatol* 2012;.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Iremod (艾得辛); ***Jpn***: Careram; Kolbet.

Imidazole Salicylate *(rINN)*

Imidazole, Salicylate d'; Imidazoli Salicylas; Salicilato de imidazol; Имидазола Салицилат.

Imidazole compounded with salicylic acid.

$C_{10}H_{10}N_2O_3$=206.2

CAS — 36364-49-5.

ATC — N02BA16.

ATC Vet — QN02BA16.

UNII — 4JVD4X01MJ.

Profile

Imidazole salicylate is a salicylic acid derivative (see Aspirin, p. 22.2) that has been used in the treatment of fever and inflammatory respiratory-tract and otorhinolaryngeal disorders. Imidazole salicylate has been given in oral doses of up to 2.25 g daily in divided doses. It has also been given as a rectal suppository and has been applied topically as a 5% gel for the relief of muscular and rheumatic pain.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Chulai (楚来); ***Ital.***: Selezen.

Indometacin *(BAN, rINN)*

Indometacina; Indometacinas; Indométacine; Indometacinum; Indometacyna; Indometasiini; Indometasin; Indomethacin (USAN); Indomethacin; Индометацин.

[1-(4-Chlorobenzoyl)-5-methoxy-2-methylindol-3-yl]acetic acid.

$C_{19}H_{16}ClNO_4$=357.8

CAS — 53-86-1.

ATC — C01EB03; M01AB01; M02AA23; S01BC01.

ATC Vet — QC01EB03; QM01AB01; QM02AA23; QS01BC01.

UNII — XXE1CET956.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Indometacin). A white or yellow, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol. Protect from light.

USP 36: (Indomethacin). A pale yellow to yellow-tan, crystalline powder having not more than a slight odour. It exhibits polymorphism. Practically insoluble in water; soluble 1 in 50 of alcohol, 1 in 30 of chloroform, and 1 in 40 of ether. Protect from light.

Stability. Indometacin is unstable in alkaline solution.

Indometacin Sodium *(BANM, rINNM)*

Indometacina sódica; Indométacine Sodique; Indometacin Sodium (USAN); Indomethacin Sodium Trihydrate; Natrii indometacinum; Натрий Индометацин.

Sodium 1-(4-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetate, trihydrate.

$C_{19}H_{15}ClNNaO_4.3H_2O$=433.8

CAS — 74252-25-8.

UNII — 0IMX38M2GG.

Pharmacopoeias. In *US*.

USP 36: (Indomethacin Sodium). Protect from light.

Incompatibility. Indometacin sodium injection is reconstituted with preservative-free sodium chloride for injection 0.9% or preservative-free water for injection. Preparations containing glucose should not be used; reconstitution at a pH below 6 may cause precipitation of indometacin. Visual incompatibility has been reported between indometacin sodium injection and tolazoline hydrochloride,[1] 7.5 and 10% glucose injection, calcium gluconate, dobutamine, dopamine, cimetidine,[2] gentamicin sulfate, levofloxacin,[3] and tobramycin sulfate.[4] A pH below 6 may account for the visual incompatibility of indometacin sodium and several of these drugs.

1. Marquardt ED. Visual compatibility of tolazoline hydrochloride with various medications during simulated Y-site injection. *Am J Hosp Pharm* 1990; 47: 1802–3.
2. Ishisaka DY, *et al.* Visual compatibility of indomethacin sodium trihydrate with drugs given to neonates by continuous infusion. *Am J Hosp Pharm* 1991; 48: 2442–3.
3. Saltsman CL, *et al.* Compatibility of levofloxacin with 34 medications during simulated Y-site administration. *Am J Health-Syst Pharm* 1999; 56: 1458–90.
4. Thompson DF, Heflin NR. Incompatibility of injectable indomethacin with gentamicin sulfate or tobramycin sulfate. *Am J Hosp Pharm* 1992; 49: 836–8.

Stability. A reconstituted solution of indometacin sodium 500 micrograms/mL was stable for 14 days when stored at 2 degrees to 6 degrees in either the manufacturer's original glass vial or in a polypropylene syringe.[1]

1. Walker SE, *et al.* Stability of reconstituted indomethacin sodium trihydrate in original vials and polypropylene syringes. *Am J Health-Syst Pharm* 1998; 55: 154–8.

Uses and Administration

Indometacin, an indole acetic acid derivative, is an NSAID (p. 102.3). It is used in musculoskeletal and joint disorders including ankylosing spondylitis, osteoarthritis, rheumatoid arthritis, and acute gout, and in peri-articular disorders such as bursitis and tendinitis. It may also be used in inflammation, pain, and oedema following orthopaedic procedures, in mild to moderate pain in conditions such as dysmenorrhoea, and it has been used in the management of postoperative pain as an adjunct to opioids, and in the treatment of fever. Indometacin is also used as the sodium salt to close patent ductus arteriosus in premature infants (see p. 72.2).

The usual initial oral dose in **chronic musculoskeletal and joint disorders** is 25 mg two or three times daily increased, if required, by 25 to 50 mg at weekly intervals to 150 to 200 mg daily. To alleviate night pain and morning stiffness, up to 100 mg of the total daily dose may be given orally, or rectally as a suppository, on retiring. Alternatively, the total daily dose may be given rectally as 100 mg in the morning and at night. The total daily combined oral and rectal dose should not exceed 200 mg. In acute gout the daily dose is 150 to 200 mg in divided doses until all symptoms and signs subside; in dysmenorrhoea up to 75 mg daily has been suggested. Modified-release preparations of indometacin are available for use once or twice daily. For doses in children, see below.

Indometacin is used as 0.1% eye drops to **prevent miosis during cataract surgery**; the usual dose is 2 drops, repeated after 2 hours, on the day before surgery, then 2 drops 3 hours before and 2 drops 1 hour before surgery. To prevent **cystoid macular oedema**, 1 drop may then be instilled postoperatively 4 times daily for 15 days, decreasing to 3 times daily thereafter; treatment should be continued until inflammatory signs have disappeared. A 0.5% eye drop is also available for the prevention of miosis and inflammation associated with cataract surgery. Indometacin eye drops are also used in **other inflammatory eye disorders**; the usual dose is 1 drop of the 0.1% strength 4 to 6 times daily until symptoms are resolved.

Meglumine indometacin and indometacin farnesil, a lipid soluble ester of indometacin ($C_{34}H_{40}ClNO_4$ = 562.1), have also been given for painful and inflammatory conditions. A complex of indometacin and L-arginine, known as indoarginine, has also been used.

Administration in children. Although indometacin is not licensed in the UK for the treatment of **rheumatic diseases** such as juvenile idiopathic arthritis in children, the *BNFC* suggests an oral dose of 0.5 to 1 mg/kg twice daily in those aged 1 month to 18 years; higher doses may be used under specialist supervision

Indometacin is also used in the treatment of **patent ductus arteriosus** in premature infants; see p. 72.2 for further details including doses.

Bartter's syndrome. The treatment of Bartter's syndrome can often be difficult (see p. 1779.3). Blocking the kinin-prostaglandin axis with a cyclo-oxygenase inhibitor such as indometacin improves hypokalaemia and other clinical features (including growth retardation) in children with the syndrome.[1-3]

1. Littlewood JM, *et al.* Treatment of childhood Bartter's syndrome with indomethacin. *Lancet* 1976; II: 795.
2. Seidel C, *et al.* Pre-pubertal growth in the hyperprostaglandin E syndrome. *Pediatr Nephrol* 1995; 9: 723–8.
3. Craig JC, Falk MC. Indomethacin for renal impairment in neonatal Bartter's syndrome. *Lancet* 1996; 347: 550.

4. Mourani CC, *et al.* Bartter syndrome in a neonate: early treatment with indomethacin. *Pediatr Nephrol* 2000; **14:** 143–5.
5. Vaisbich MH, *et al.* Bartter syndrome: benefits and side effects of long-term treatment. *Pediatr Nephrol* 2004; **19:** 858–63.

Diabetes insipidus. Indometacin and other prostaglandin synthetase inhibitors have been reported to decrease urine volume in all types of nephrogenic diabetes insipidus (p. 2348.2).

References.

1. Rosen GH, *et al.* Indomethacin for nephrogenic diabetes insipidus in a four-week-old infant. *Clin Pharm* 1986; **5:** 254–6.
2. Libber S, *et al.* Treatment of nephrogenic diabetes insipidus with prostaglandin synthesis inhibitors. *J Pediatr* 1986; **108:** 305–11.
3. Allen BM, *et al.* Indomethacin in the treatment of lithium-induced nephrogenic diabetes insipidus. *Arch Intern Med* 1989; **149:** 1123–6.
4. Martinez EJ, *et al.* Lithium-induced nephrogenic diabetes insipidus treated with indomethacin. *South Med J* 1993; **86:** 971–3.
5. Hohler T, *et al.* Indomethacin treatment in amphotericin B induced nephrogenic diabetes insipidus. *Clin Investig* 1994; **72:** 769–71.
6. Lam SS, Kjellstrand C. Emergency treatment of lithium-induced diabetes insipidus with nonsteroidal anti-inflammatory drugs. *Ren Fail* 1997; **19:** 183–8.

Malignant neoplasms. In common with some other NSAIDs (see p. 104.1) it has been suggested that indometacin might possess some antineoplastic activity.[1] Some NSAIDs such as indometacin may also be of value for the differential diagnosis and the management of neoplastic fever, as they appear to be more effective in reducing this type of fever than against fever associated with infections.[2] Indometacin has also been tried for the treatment of fever and flu-like symptoms associated with interleukin-2 therapy although there has been concern over exacerbation of renal toxicity (see NSAIDs, under Interactions, p. 812.1).

1. Mertens WC, *et al.* Effect of indomethacin plus ranitidine in advanced melanoma patients on high-dose interleukin-2. *Lancet* 1992; **340:** 397–8.
2. Engervall P, *et al.* Antipyretic effect of indomethacin in malignant lymphoma. *Acta Med Scand* 1986; **219:** 501–5.

Neonatal intraventricular haemorrhage. Indometacin has been tried prophylactically to prevent the development of intraventricular haemorrhage in neonates at risk (see p. 1128.3). Several mechanisms have been proposed for its possible action including reduction of cerebral flow as a result of vasoconstriction, reduction of oxygen free-radical damage, and accelerated maturation of blood vessels around the ventricles. Early studies[1-3] of the use of indometacin for prevention of intraventricular haemorrhage produced conflicting results. A subsequent large multicentre study[4] (the Indomethacin Intraventricular Haemorrhage Prevention Trial, IIHP) suggested that indometacin could reduce the incidence and severity of intraventricular haemorrhage, especially for the more severe forms. Neonates with a birth-weight of 600 to 1250 g were given indometacin in a dose of 100 micrograms/kg intravenously at 6 to 12 hours after delivery and then every 24 hours for 2 additional doses. There was, however, concern[5] that an unusually large number of neonates with severe intraventricular haemorrhage in the control group might have biased the findings.

A concern with the use of indometacin is the possibility that it may produce cerebral ischaemia due to its vasoconstrictor action and therefore increase the risk of developmental handicaps. Follow-up at 3 years,[6] at 4½ years,[7] and at 8 years of age[8] in the infants included in the IIHP study reported no adverse effects on cognitive or motor development. However, another large multicentre study[9] (the Trial of Indomethacin Prophylaxis in Preterms, TIPP) in extremely-low-birth-weight infants (less than 1000 g) found that although indometacin reduced the incidence of severe haemorrhage, it did not improve survival without neurosensory impairment at 18 months. A subsequent systematic review[10] also concluded that indometacin prophylaxis did not improve survival free of neurosensory disability although, again, the incidence of severe intraventricular haemorrhage was reduced.

Further analysis of the data from the IIHP study has suggested that indometacin might reduce intraventricular haemorrhage in boys but have little effect in girls;[11] verbal scores at ages 3 to 8 years were also higher in those boys treated with indometacin when compared with a control group of boys treated with saline; no differences in scores were noted in indometacin-treated girls and their control group. Re-analysis of data from the TIPP study[12] in extremely-low-birth-weight neonates suggested a weak gender difference in the effect of indometacin treatment when all primary outcomes such as death, cerebral palsy, cognitive delay, and severe intraventricular haemorrhage were considered; however, when outcomes were considered individually, there was a significant reduction in intraventricular haemorrhage in boys when compared with girls. The authors considered the results to be a consequence of an unfavourable effect of indometacin in girls rather than any positive effects in boys. Any true difference in effect between the sexes remains to be confirmed.

Indometacin does not appear to prevent the progression of existing haemorrhage.[13]

1. Ment LR, *et al.* Randomized indomethacin trial for prevention of intraventricular hemorrhage in very low birth weight infants. *J Pediatr* 1985; **107:** 937–43.
2. Rennie JM, *et al.* Early administration of indomethacin to preterm infants. *Arch Dis Child* 1986; **61:** 233–8.
3. Bada HS, *et al.* Indomethacin reduces the risks of severe intraventricular hemorrhage. *J Pediatr* 1989; **115:** 631–7.
4. Ment LR, *et al.* Low-dose indomethacin and prevention of intraventricular hemorrhage: a multicenter randomized trial. *Pediatrics* 1994; **93:** 543–50.
5. Volpe JJ. Brain injury caused by intraventricular hemorrhage: is indomethacin the silver bullet for prevention? *Pediatrics* 1994; **93:** 673–7.
6. Ment LR, *et al.* Neurodevelopmental outcome at 36 months' corrected age of preterm infants in the multicenter indomethacin intraventricular hemorrhage prevention trial. *Pediatrics* 1996; **98:** 714–18.
7. Ment LR, *et al.* Outcome of children in the indomethacin intraventricular hemorrhage prevention trial. *Pediatrics* 2000; **105:** 485–91.
8. Vohr BR, *et al.* School-age outcomes of very low birth weight infants in the indomethacin intraventricular hemorrhage prevention trial. Abstract: *Pediatrics* 2003; **111:** 874. Full version: http://pediatrics.aappublications.org/cgi/content/full/111/4/e340 (accessed 07/11/07)
9. Schmidt B, *et al.* Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. *N Engl J Med* 2001; **344:** 1966–72.
10. Fowlie PW, Davis PG. Prophylactic indomethacin for preterm infants: a systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal Ed* 2003; **88:** F464–F466.
11. Ment LR, *et al.* Prevention of intraventricular hemorrhage by indomethacin in male preterm infants. *J Pediatr* 2004; **145:** 832–4.
12. Ohlsson A, *et al.* Male/female differences in indomethacin effects in preterm infants. *J Pediatr* 2005; **147:** 860–2.
13. Ment LR, *et al.* Low-dose indomethacin therapy and extension of intraventricular hemorrhage: a multicenter randomized trial. *J Pediatr* 1994; **124:** 951–5.

Patent ductus arteriosus. In the fetal circulation the ductus arteriosus connects the pulmonary artery and the descending aorta. After birth, various mechanisms, including a fall in prostaglandin concentration, trigger its closure but in some infants the ductus arteriosus fails to close, a condition known as persistent patent ductus arteriosus. This condition may be found in infants with congenital heart defects but is more commonly seen in premature neonates, especially those with respiratory distress syndrome.

- Some infants may be asymptomatic or have only slight clinical symptoms and no immediate intervention is required. In many cases spontaneous closure will occur after several months, or else surgical ligation may be performed if clinical symptoms persist.
- In some infants a patent ductus arteriosus is necessary for maintaining some oxygenation of the blood, for example in pulmonary artery atresia or transposition of the great arteries. These infants require treatment with a prostaglandin such as *alprostadil* or *dinoprostone* to maintain patency of the ductus arteriosus until surgery can be performed to correct the malformation.
- Infants with haemodynamically significant ductus arteriosus, signs of heart failure, and who require ventilation should undergo treatment to close the patent ductus arteriosus.

Initial **management** involves fluid restriction, diuretics, correction of anaemia, and support of respiration. *Chlorothiazide* and *furosemide* are diuretics commonly used. There has been concern that furosemide might delay closure in infants with respiratory distress syndrome.[1,2] A systematic review[3] concluded that this did not seem to be the case, and that the diuretic might reduce adverse renal effects of indometacin; however, the evidence for this was limited and it was felt that there was not enough evidence to support the use of furosemide in infants treated with indometacin.

If initial treatment fails to control symptoms after 24 to 48 hours then *indometacin* is generally given to promote closure of the ductus.[1,4-8] The benefits of treatment with indometacin as soon as symptoms become apparent, rather than delaying treatment until signs of congestive failure develop, have been debated.[7,8] Early treatment may significantly reduce the morbidities arising from a persistent patent ductus arteriosus.[7] However, delaying treatment until the end of the first week of life can allow for spontaneous closure and avoid the need of exposing infants to the toxic effects of indometacin.[8]

Indometacin probably leads to closure of the ductus through inhibition of prostaglandin synthesis. It is given as the sodium salt in three intravenous doses at 12- to 24-hour intervals; each dose should be infused over 20 to 30 minutes. Indometacin sodium injection is reconstituted with preservative-free sodium chloride 0.9% for injection or water for injection; glucose solutions should not be used (see Incompatibility, p. 71.2). The dose of indometacin sodium (expressed as indometacin) depends upon the age of the neonate and the following doses have been suggested based upon the age at the first dose:

- less than 48 hours old: 200 micrograms/kg initially followed by two further doses of 100 micrograms/kg each
- 2 to 7 days old: three doses of 200 micrograms/kg each
- over 7 days old: 200 micrograms/kg initially followed by two further doses of 250 micrograms/kg each

If 48 hours after this course of therapy the ductus remains open or re-opens, a second course may be used, but if this produces no response (which may be the case in 25% of infants treated[4,9]) surgery may be necessary.

Indometacin has been given orally where the injection is unavailable, but absorption of oral indometacin is poor and incomplete in premature neonates.

A decreased need for surgical closure and reduced recurrences were seen in neonates in whom standard intravenous indometacin therapy was then followed by maintenance therapy (intravenous indometacin 200 micrograms/kg daily for an additional 5 days).[10] Prolonged therapy using high doses of up to 1 mg/kg as a single dose every 12 hours has also been used with some success in a few infants who have not responded to standard regimens.[1] Similar beneficial findings were reported[12] in infants given prolonged low-dose indometacin therapy (100 micrograms/kg daily for 6 days). An additional benefit was a lower incidence of adverse effects; fewer infants had a rise in serum creatinine or urea concentrations. However, a systematic review[13] has suggested that such regimens are no more effective than the shorter standard regimens, and found an increased rather than decreased incidence of adverse effects (including a trend towards increased risk of necrotising enterocolitis[1,6]). Prolonged treatment with indometacin could not be recommended.[13] Prophylactic treatment or treatment of asymptomatic ductus with indometacin has been tried in premature infants, and there is good evidence to suggest that this is effective in reducing the risk of symptomatic patent ductus arteriosus and intraventricular haemorrhage (see above) in such patients;[7,14,15] however, prophylactic treatment has not been shown to significantly reduce the risk of short-term pulmonary complications such as bronchopulmonary dysplasia. Systematic reviews[14,15] have also found no evidence of either benefit or harm in neurological development or other longer term outcomes.

Some other NSAIDs have also been tried in the treatment of patent ductus arteriosus. A recent systematic review[16] found that ibuprofen was as effective as indometacin, and also reduced the risk of necrotising enterocolitis and transient renal impairment. Given its lower risk of adverse effects, the authors suggested that ibuprofen is the drug of choice; however, data on longer term outcomes are needed before any recommendations regarding the use of indometacin or ibuprofen can be made. Ibuprofen is also effective when used prophylactically; however, there have been reports of pulmonary hypertension with such use and ibuprofen is not recommended.[17]

Oral therapy with ibuprofen has also been tried.[18,19]

1. Bhatt V, Nahata MC. Pharmacologic management of patent ductus arteriosus. *Clin Pharm* 1989; **8:** 17–33.
2. Anonymous. Delayed closure of the ductus. *Lancet* 1983; **ii:** 436.
3. Brion LP, Campbell DE. Furosemide for prevention of morbidity in indomethacin-treated infants with patent ductus arteriosus. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2001 (accessed 07/11/07).
4. Silove ED. Pharmacological manipulation of the ductus arteriosus. *Arch Dis Child* 1986; **61:** 827–9.
5. Barst RJ, Gersony WM. The pharmacological treatment of patent ductus arteriosus: a review of the evidence. *Drugs* 1989; **38:** 249–66.
6. Archer N. Patent ductus arteriosus in the newborn. *Arch Dis Child* 1993; **69:** 529–32.
7. Clyman RI. Recommendations for the postnatal use of indomethacin: an analysis of four separate treatment strategies. *J Pediatr* 1996; **128:** 601–7.
8. Van Overmeire B, *et al.* Early versus late indomethacin treatment for patent ductus arteriosus in premature infants with respiratory distress syndrome. *J Pediatr* 2001; **138:** 205–11.
9. Gersony WM, *et al.* Effects of indomethacin in premature infants with patent ductus arteriosus: results of a national collaborative study. *J Pediatr* 1983; **102:** 895–906.
10. Hammerman C, Aramburo MJ. Prolonged indomethacin therapy for the prevention of recurrences of patent ductus arteriosus. *J Pediatr* 1990; **117:** 771–6.
11. Sperandio M, *et al.* Effectiveness and side effects of an escalating, stepwise approach to indomethacin treatment for symptomatic patent ductus arteriosus in premature infants below 33 weeks of gestation. *Pediatrics* 2005; **116:** 1361–6.
12. Rennie JM, Cooke RWI. Prolonged low dose indomethacin for persistent ductus arteriosus of prematurity. *Arch Dis Child* 1991; **66:** 55–8.
13. Herrera C, *et al.* Prolonged versus short course of indomethacin for the treatment of patent ductus arteriosus in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 07/11/07).
14. Fowlie PW, Davis PG. Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 07/11/07).
15. Cooke L, *et al.* Indomethacin for asymptomatic patent ductus arteriosus in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 07/11/07).
16. Ohlsson A, *et al.* Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2010 (accessed 16/08/10).
17. Shah SS, Ohlsson A. Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 07/11/07).
18. Heyman E, *et al.* Closure of patent ductus arteriosus with oral ibuprofen suspension in premature newborns: a pilot study. Abstract: *Pediatrics* 2003; **112:** 1170. Full version: http://pediatrics.aappublications.org/cgi/reprint/112/5/e354.pdf (accessed 07/11/07)
19. Cherif A, *et al.* Randomized pilot study comparing oral ibuprofen with intravenous ibuprofen in very low birth weight infants with patent ductus arteriosus. Abstract: *Pediatrics* 2008; **122:** 1361–2. Full version: http://pediatrics.aappublications.org/cgi/reprint/122/6/e1256 (accessed 16/09/09)

Polyhydramnios. Indometacin may be of benefit in the management of polyhydramnios (an excessive accumulation of amniotic fluid).[1-3] Polyhydramnios is a feature of the neonatal variant of Bartter's syndrome (see also p. 71.3).

1. Cabrol D, *et al.* Treatment of symptomatic polyhydramnios with indomethacin. *Eur J Obstet Gynecol Reprod Biol* 1996; **66**: 11–15.
2. Abhyankar S, Salvi VS. Indomethacin therapy in hydramnios. *J Postgrad Med* 2000; **46**: 176–8.
3. Kriplani A, *et al.* Indomethacin therapy in the treatment of polyhydramnios due to placental chorioangioma. *J Obstet Gynaecol Res* 2001; **27**: 245–8.

Premature labour. The most common approach to postponing premature labour (p. 2131.1) with drugs has historically been with a selective beta$_2$ agonist. However, as prostaglandins have a role in uterine contraction and cervical ripening and dilatation, prostaglandin synthetase inhibitors such as indometacin have also been used. Comparative studies[1,2] have shown that indometacin and ritodrine are equally effective in inhibiting uterine contractions and delaying delivery in patients in preterm labour who have intact membranes and in whom the gestational age is less than or equal to 34 weeks. In one study[2] an initial oral loading dose of indometacin 50 mg was given, followed by 25 to 50 mg orally every 4 hours until contractions stopped and then by a maintenance dose of 25 mg every 4 to 6 hours. In the other comparative study[1] indometacin was given as a 100-mg rectal suppository followed by 25 mg orally every 4 hours for 48 hours; if regular uterine contractions persisted 1 to 2 hours after the initial suppository, an additional 100-mg suppository was given before beginning oral therapy. Terbutaline was given for maintenance therapy.

Unfortunately indometacin can constrict the ductus arteriosus,[3-5] which may lead to pulmonary hypertension,[2] and has also been associated with bronchopulmonary dysplasia,[6] reduced volume of amniotic fluid (oligohydramnios)[2,4] and possible renal damage (see Effects on the Kidneys, below) in the fetus. Another complication is that prenatal indometacin exposure may increase both the incidence and severity of patent ductus arteriosus in premature infants,[7,8] as shown by the increased need for post-natal indometacin therapy and surgical ligation in such infants. However, there is evidence to suggest that there is no significant increase in the risk of neonatal complications in infants exposed to indometacin tocolysis when compared with control groups of infants who received either no treatment or tocolysis with drugs other than indometacin.[9,10]

The evidence for any overall benefit of indometacin in delaying labour is equivocal,[11-13] and it is generally reserved as a second-line tocolytic or for use with an intravenous tocolytic when an additive effect is required.

1. Morales WJ, *et al.* Efficacy and safety of indomethacin versus ritodrine in the management of preterm labor: a randomized study. *Obstet Gynecol* 1989; **74**: 567–72.
2. Besinger RE, *et al.* Randomized comparative trial of indomethacin and ritodrine for the long-term treatment of preterm labor. *Am J Obstet Gynecol* 1991; **164**: 981–8.
3. Moise KJ, *et al.* Indomethacin in the treatment of premature labor: effects on the fetal ductus arteriosus. *N Engl J Med* 1988; **319**: 327–31.
4. Hallak M, *et al.* Indomethacin for preterm labor: fetal toxicity in a dizygotic twin gestation. *Obstet Gynecol* 1991; **78**: 911–13.
5. Vermillion ST, *et al.* The effect of indomethacin tocolysis on fetal ductus arteriosus constriction with advancing gestational age. *Am J Obstet Gynecol* 1997; **177**: 256–61.
6. Eronen M, *et al.* Increased incidence of bronchopulmonary dysplasia after antenatal administration of indomethacin to prevent preterm labor. *J Pediatr* 1994; **124**: 782–8.
7. Norton ME, *et al.* Neonatal complications after the administration of indomethacin for preterm labor. *N Engl J Med* 1993; **329**: 1602–7.
8. Hammerman C, *et al.* Indomethacin tocolysis increases post-natal patent ductus arteriosus severity. Abstract: *Pediatrics* 1998; **102**: 1202–3. Full version: http://pediatrics.aappublications.org/cgi/content/full/102/5/e56 (accessed 07/11/07)
9. Vermillion ST, Newman RB. Recent indomethacin tocolysis is not associated with neonatal complications in preterm infants. *Am J Obstet Gynecol* 1999; **181**: 1083–6.
10. Loe SM, *et al.* Assessing the neonatal safety of indomethacin tocolysis: a systematic review with meta-analysis. *Obstet Gynecol* 2005; **106**: 173–9.
11. Macones GA, Robinson CA. Is there justification for using indomethacin in preterm labor? An analysis of neonatal risks and benefits. *Am J Obstet Gynecol* 1997; **177**: 819–24.
12. Panter KR, *et al.* The effect of indomethacin tocolysis in preterm labour on perinatal outcome: a randomised placebo-controlled trial. *Br J Obstet Gynaecol* 1999; **106**: 467–73.
13. Macones GA, *et al.* The controversy surrounding indomethacin for tocolysis. *Am J Obstet Gynecol* 2001; **184**: 264–72.

Adverse Effects and Treatment

As for NSAIDs in general, p. 104.3.

Adverse effects are more frequent with indometacin than with many other NSAIDs, the most common being gastrointestinal disturbances, headache, vertigo, dizziness, and lightheadedness. Gastrointestinal perforation, ulceration, and bleeding may also occur; rarely, intestinal strictures have been reported. Other adverse effects include depression, drowsiness, tinnitus, confusion, insomnia, psychiatric disturbances, syncope, convulsions, coma, peripheral neuropathy, blurred vision, corneal deposits and other ocular effects, oedema and weight gain, hypertension, haematuria, rashes, pruritus, urticaria, stomatitis, alopecia, and hypersensitivity reactions. Leucopenia, purpura, thrombocytopenia, aplastic anaemia, haemolytic anaemia, agranulocytosis, epistaxis, hyperglycaemia, hypoaldosteronism and hyperkalaemia, and vaginal bleeding have been reported. There have also been reports of hepatitis, jaundice, and renal failure. Hypersensitivity reactions may also occur in aspirin-sensitive patients. Rectal irritation and bleeding have been reported occasionally in patients who have received indometacin suppositories.

Adverse effects associated with the use of indometacin injection in premature **neonates** may also include haemorrhagic, renal, gastrointestinal, metabolic, and coagulation disorders; pulmonary hypertension, intracranial bleeding, fluid retention, and exacerbation of infection may also occur.

Effects on the blood. There were 1261 reports of adverse reactions to indometacin reported to the UK CSM between June 1964 and January 1973. These included 157 reports of blood disorders (25 fatal) including thrombocytopenia (35; 5 fatal), aplastic anaemia (17; no fatalities), and agranulocytosis or leucopenia (21; 3 fatal).[1] Subsequently, the First Report from the International Agranulocytosis and Aplastic Anemia Study confirmed a significant relationship between the use of indometacin and agranulocytosis and aplastic anaemia.[2] Neutropenia has also been noted in a premature infant with patent ductus arteriosus after use of indometacin.[3]

Although use of indometacin in 20 women being treated for premature labour did not affect maternal prothrombin or activated partial thromboplastin time, maternal bleeding time during therapy was increased.[4] However, no cases of neonatal intraventricular haemorrhage or maternal postpartum haemorrhage were seen.

1. Cuthbert MF. Adverse reactions to non-steroidal antirheumatic drugs. *Curr Med Res Opin* 1974; **2**: 600–10.
2. The International Agranulocytosis and Aplastic Anemia Study. Risks of agranulocytosis and aplastic anemia: a first report of their relation to drug use with special reference to analgesics. *JAMA* 1986; **256**: 1749–57.
3. Bengtsson B-OS, *et al.* Indomethacin-associated neutropenia with subsequent Gram-negative sepsis in a preterm infant: cause or coincidence? *J Perinatol* 2006; **26**: 381–3.
4. Lunt CC, *et al.* The effect of indomethacin tocolysis on maternal coagulation status. *Obstet Gynecol* 1994; **84**: 820–2.

Effects on cerebral blood flow. See Patent Ductus Arteriosus under Uses and Administration, p. 72.2.

Effects on the eyes. Severe and irreversible retinopathy, presumably due to long-term ingestion of high doses of indometacin occurred in a 33-year-old man.[1] A summary of previous literature reports of indometacin-induced ocular effects indicated that indometacin was retinotoxic, although to what degree was uncertain. For reference to effects on the optic nerve associated with indometacin, see p. 105.3.

1. Graham CM, Blach RK. Indomethacin retinopathy: case report and review. *Br J Ophthalmol* 1988; **72**: 434–8.

Effects on the gastrointestinal tract. Nausea, vomiting, dyspepsia, gastrointestinal lesions, and serious reactions including gastrointestinal bleeding, ulceration, and perforation have occurred in patients receiving indometacin. Although it is well established that NSAIDs can produce adverse effects on the upper gastrointestinal tract, indometacin and other NSAIDs can also affect the large intestines.[1] Giving indometacin to preterm neonates increases the risk of small bowel perforation and necrotising enterocolitis.[2-4] Risk seems to be increased in very-low-birthweight or extremely premature infants.

1. Oren R, Ligumsky M. Indomethacin-induced colonic ulceration and bleeding. *Ann Pharmacother* 1994; **28**: 883–5.
2. Grosfeld JL, *et al.* Increased risk of necrotizing enterocolitis in premature infants with patent ductus arteriosus treated with indomethacin. *Ann Surg* 1996; **224**: 350–7.
3. Shorter NA, *et al.* Indomethacin-associated bowel perforations: a study of possible risk factors. *J Pediatr Surg* 1999; **34**: 442–4.
4. Fujii AM. Neonatal necrotizing enterocolitis with intestinal perforation in extremely premature infants receiving early indomethacin treatment for patent ductus arteriosus. *J Perinatol* 2002; **22**: 535–40.

Effects on the joints. For references to concern that NSAIDs such as indometacin may accelerate the rate of cartilage destruction in patients with osteoarthritis, see Effects on Bone, under NSAIDs, p. 104.3.

Effects on the kidneys. Acute renal failure,[1] nephrotic syndrome,[2] and renal papillary necrosis[3] have been reported in patients given indometacin. There have been suggestions that misoprostol might reduce the risk of indometacin-induced renal toxicity.[4,5]

Renal impairment has also occurred in **neonates** given indometacin intravenously for patent ductus arteriosus. Although rare, and usually reversible, the effect may be serious in neonates with pre-existing renal disorders.[6] Serious or fatal renal toxicity has been reported in neonates exposed to indometacin due to maternal ingestion.[7] The renal effects of prenatal indometacin may be prolonged.[8]

1. Chan X. Fatal renal failure due to indomethacin. *Lancet* 1987; **ii**: 340.
2. Boiskin I, *et al.* Indomethacin and the nephrotic syndrome. *Ann Intern Med* 1987; **106**: 776–7.
3. Mitchell H, *et al.* Indomethacin-induced renal papillary necrosis in juvenile chronic arthritis. *Lancet* 1982; **ii**: 558–9.
4. Weir MR, *et al.* Minimization of indomethacin-induced reduction in renal function by misoprostol. *J Clin Pharmacol* 1991; **31**: 729–35.
5. Wong F, *et al.* The effect of misoprostol on indomethacin-induced renal dysfunction in well-compensated cirrhosis. *J Hepatol* 1995; **23**: 1–7.
6. Cuzzolin L, *et al.* NSAID-induced nephrotoxicity from the fetus to the child. *Drug Safety* 2001; **24**: 9–18.
7. van der Heijden BJ, *et al.* Persistent anuria, neonatal death, and renal microcystic lesions after prenatal exposure to indomethacin. *Am J Obstet Gynecol* 1994; **171**: 617–23.
8. Butler-O'Hara M, D'Angio CT. Risk of persistent renal insufficiency in premature infants following the prenatal use of indomethacin for suppression of preterm labor. *J Perinatol* 2002; **22**: 541–6.

Effects on the liver. Cholestasis occurred in a 52-year-old woman several days after starting indometacin;[1] liver function values returned to normal once indometacin was stopped.

1. Cappell MS, *et al.* Indomethacin-associated cholestasis. *J Clin Gastroenterol* 1988; **10**: 445–7.

Hypersensitivity. Hypersensitivity reactions including acute asthma have been reported after use of indometacin suppositories,[1] eye drops,[2] or capsules[3] by patients who were aspirin-sensitive or had a history of asthma.

1. Timperman J. A fatal asthmatic attack following administration of an indomethacin suppository. *J Forensic Med* 1971; **18**: 30–2.
2. Sheehan GJ, *et al.* Acute asthma attack due to ophthalmic indomethacin. *Ann Intern Med* 1989; **111**: 337–8.
3. Johnson NM, *et al.* Indomethacin-induced asthma in aspirin-sensitive patients. *BMJ* 1977; **2**: 1291.

Precautions

As for NSAIDs in general, p. 107.1.

Indometacin should be used with caution in patients with epilepsy, parkinsonism, or psychiatric disorders. Dizziness may affect the performance of skilled tasks such as driving. Patients on long-term indometacin therapy should be examined regularly for adverse effects, and the *BNF* particularly recommends periodic blood and ophthalmic examinations. Rectal use should be avoided in patients with proctitis and haemorrhoids.

In addition indometacin should not be given to **neonates** with untreated infection, with significant renal impairment, or with necrotising enterocolitis. Infants who are bleeding (especially gastrointestinal bleeding or intracranial haemorrhage) or who have thrombocytopenia or coagulation defects should not be given indometacin and those receiving indometacin should be monitored during treatment for signs of bleeding. Electrolytes and renal function should also be monitored and if anuria or marked oliguria is evident at the time of a scheduled second or third dose, it should be delayed until renal function has returned to normal.

False-negative results in the dexamethasone suppression test have been reported in patients taking indometacin.

Breast feeding. Convulsions in a one-week old breast-fed infant appeared to be associated with maternal ingestion of indometacin;[1] the child had normal motor and mental development at the age of 1 year and seizures had not recurred.

Indometacin has been detected in breast milk, but some workers[2,3] and the *BNF* consider that the amount is too small to be harmful to a breast-fed infant. The American Academy of Pediatrics[4] also states that indometacin is usually compatible with breast feeding despite acknowledging the above case report of convulsions. However, licensed product information recommends that indometacin should not be used in nursing mothers.

1. Eeg-Olofsson O, *et al.* Convulsions in a breast-fed infant after maternal indomethacin. *Lancet* 1978; **ii**: 215.
2. Beaulac-Baillargeon L, Allard G. Distribution of indomethacin in human milk and estimation of its milk to plasma ratio in vitro. *Br J Clin Pharmacol* 1993; **36**: 413–16.
3. Lebedevs TH, *et al.* Excretion of indomethacin in breast milk. *Br J Clin Pharmacol* 1991; **32**: 751–4.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 07/11/07)

The elderly. After a study[1] of the pharmacokinetics of indometacin in the elderly it was suggested that the maintenance dose of indometacin in elderly patients should be reduced by 25%. The total clearance of indometacin in elderly subjects had been reduced when compared with that in young subjects; this was thought to be due to reduced hepatic metabolism in the elderly.

1. Oberbauer R, *et al.* Pharmacokinetics of indomethacin in the elderly. *Clin Pharmacokinet* 1993; **24**: 428–34.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies indometacin as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 23/10/11)

Pregnancy. See Premature Labour under Uses and Administration, p. 73.1.

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Anti-inflammatory doses of aspirin decrease indometacin blood concentrations by about 20%. Diflunisal decreases the renal clearance and increases plasma concentrations of indometacin. Use of diflunisal with indometacin has also resulted in fatal gastrointestinal haemorrhage, and the two should not be used together. Plasma concentrations of indometacin are likely to be increased in patients receiving probenecid.

Antibacterials. Indometacin has been reported to increase plasma concentrations of *aminoglycosides*.

Antipsychotics. Severe drowsiness and confusion have been reported in patients given *haloperidol* with indometacin.[1]

1. Bird HA, *et al.* Drowsiness due to haloperidol/indomethacin in combination. *Lancet* 1983; i: 830–1.

Bone modulating drugs. Indometacin has been reported to increase the bioavailability of *tiludronate*, see p. 1192.3.

Desmopressin. The effect of desmopressin may be enhanced by indometacin.

Digoxin. In addition to increasing digoxin serum concentrations (see p. 1358.1), combination of digoxin with indometacin has been reported to reduce the half-life of the latter in premature neonates (see Half-life under Pharmacokinetics, below).

Parasympathomimetics. Licensed product information for acetylcholine chloride ophthalmic preparations has stated that there have been reports that *acetylcholine* and *carbachol* have been ineffective when used in patients treated with topical (ophthalmic) NSAIDs.

Pharmacokinetics

Indometacin is readily absorbed from the gastrointestinal tract in adults; peak plasma concentrations occur about 2 hours after a dose. Absorption may be slowed by food or by aluminium- or magnesium-containing antacids. In premature neonates, absorption of oral indometacin is poor and incomplete. The bioavailability of rectal suppositories in adults has been reported to be comparable with or slightly less than the bioavailability with oral dosage forms.

Indometacin is about 99% bound to plasma proteins. It is distributed into synovial fluid, the CNS, and placenta. Low concentrations have been distributed into breast milk. The terminal plasma half-life has been reported to range from 2.6 to 11.2 hours in adults. The terminal half-life in neonates has been reported to be between 12 and 28 hours (see also below). Indometacin is metabolised in the liver to its glucuronide conjugate and to desmethylindometacin, desbenzoylindometacin, desmethyl-desbenzoylindometacin, and to their glucuronides. Some indometacin undergoes *N*-deacylation. Indometacin and its conjugates undergo enterohepatic circulation. Excretion of indometacin and its metabolites is mainly in the urine with lesser amounts appearing in the faeces.

References.

1. Moise KJ, *et al.* Placental transfer of indomethacin in the human pregnancy. *Am J Obstet Gynecol* 1990; 162: 549–54.
2. Mannila A, *et al.* Plasma and cerebrospinal fluid concentrations of indomethacin in children after intravenous administration. *J Clin Pharmacol* 2007; 47: 94–100.

Half-life. The plasma half-life of indometacin in premature infants can be variable but appears to be inversely proportional to post-natal age and weight.[1,2] One population model suggests that for an infant of 1.17 kg, half-life would be 22.3 hours at a post-natal age of 8 days, but 16.1 hours at 25 days (and only 11.2 hours if also receiving digoxin).[2]

1. Wiest DB, *et al.* Population pharmacokinetics of intravenous indomethacin in neonates with symptomatic patent ductus arteriosus. *Clin Pharmacol Ther* 1991; 49: 550–7.
2. Smyth JM, *et al.* Intravenous indometacin in preterm infants with symptomatic patent ductus arteriosus: a population pharmacokinetic study. *Br J Clin Pharmacol* 2004; 58: 249–58.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Agilex; IM 75; Indogesic; Indotex; Klonametacina; *Austral.*: Arthrexin; Indocid PDA; Indocid; *Austria*: Indobene; Indocid; Indocollyre; Indomelan; Luiflex; *Belg.*: Dolcidium; Indocid; Indocollyre; Sportiflex; *Braz.*: Agilisin; Indocid; *Canad.*: Indocid PDA†; Novo-Methacin; Nu-Indo; Pro-Indo; Rhodacine†; *Chile*: Flexono; Moviflex†; *China*: Bi Nuo (比诺); Di Ke Shi (狄克施); He Lin Kou Fu Ye (鹤临口服液); Indocontin (意施丁); Lu Qi (露奇); Meidaxin (美达新); Patecs (必艾得); *Cz.*: Elmetacin; Indobene; Indocollyre; Vonum Cutan; *Denm.*: Confortid; *Fin.*: Indocid†; Indometin; *Fr.*: Chrono-Indocid; Indocid; Indocollyre; *Ger.*: Indo EDO; Indo Top; Indo-paed†; Indo; Indocolir; Indomet-ratiopharm; Mobilat Schmerzspray; Rheubalmin Indo; *Gr.*: Afardin; Algibron; Bavilon; Begincalm; Bonatol; Cindol; Dolcispray; Dolopas; Fortathrin; Frangerton; Hastel; Indocid; Indocontin; Indomethol; Intobutaz; Intomin; Itapredin; Labestran; Nuricon; Reumacid; Reumadolor; Reumastop; Rheumafar; *Hong Kong*: Arthrexin†; Indocap†; Indocid; Indocin PDA; Indocollyre; Indoxen; Methacin†; *Hung.*: Elmetacin; Indobene; Indocollyre; *India*: Artisid; Ducain; Idicin; Indocap; Indocid; Indoflam; Indoriv; Inmecin; Inocin; Microcid; *Indon.*: Dialon; *Irl.*: Flexin Continus†; Indocid PDA†; *Israel*: Indocin; Indocollyre; Indomed; Indotard†; Indovis; *Ital.*: Indocid; Indocollirio; Indom; Indoxen; Liometacen; Metacen; *Jpn*: Catlep; Idomethine; Infree; Inteban; *Malaysia*: Indo; Indomen; *Mex.*: Antalgin; Artaxol; Biometacin; Draxil; Indaflex; Indocarsil†; Indocid; Indoman; Indotrin; Italon; Malival; Mefazil; Soltacina†; Stratasin; *Neth.*: Indocid PDA†; Indocid†; Indocollyre; *Norw.*: Confortid†; Indocid†; *NZ*: Arthrexin; Indocid PDA; Rheumacin†; *Philipp.*: Infree; Vi-Gel; *Pol.*: Elmetacin; Indocollyre; Metindol; *Port.*: Autritis; Dolovin†; Elmetacin; Indocid; Indocollyre; Reumacide; *Rus.*: Indocollyre (Индоколлир); Indomin (Индомин)†; Indovis (Индовис); Metindol (Метиндол); *S.Afr.*: Acuflex†; Adco-Indogel; Aflamin†; Amdocin; Arthrexin; Betacin; Elmetacin; Famethacin; Flamaret†; Flamecid; Indocid; Mediflex; Methocaps; Nisaid; Restameth-SR; *Singapore*: HD-Methacin; Indo; Indocap; Indocid; Indocin; Indocollyre; Indomen; Methacid; *Spain*: Aliviosin; Artrinovo; Flogoter; Inacid; Indolgina†; Indonilo; Reusin; *Swed.*: Confortid; Indomee†; *Switz.*: Bonidon†; Elmetacin; Indocid; Indophtal; *Thai.*: Ammi-Indocin; Andocit; Docin; Elmego; Elmetacin; IDC; Incosit; Indo-Mathacin†; Indo-Trustman; Indo; Indocid†; Indocin; Indocollyre†; Indoman; Indomed; Indometh; Indometin; Indono; Inflamate†; Inthacine; Liometacen†; M-CIN; Metindo; S-Docid; Satogesic; Zonema; *Turk.*: Endol; Endosetin; Indocid; Indocolir; Inomet; *UAE*: Rothacin; *UK*: Indocid PDA; Indocid; Indolar SR; Pardelprin; Rimacid†; Slo-Indo; *Ukr.*: Indocollyre (Индоколлир); Metindol (Метиндол); *USA*: Indocin; Indocin; *Venez.*: Cevimin; Elmetacin; Indocid.

Multi-ingredient Preparations. *Austria*: Vonum; *China*: Ai Mei Xing (爱美幸); Compound Indometacin (复方吲哚美辛); Vantelinkowa (万特力); *Fin.*: Indalgin; *Fr.*: Indobiotic; *Hong Kong*: Artrolin-F†; *India*: Inmecin-P; *Ital.*: Difmetre; *Jpn*: Vantelin; *Mex.*: Ardosons; Artridol; Artridol; Deximet; Indarzona; Malival Compuesto; Morlan; Reupat; *Port.*: Indobiotic; *Rus.*: Indovasin (Индовазин); *Spain*: Artri†; Fiacin†; *Thai.*: Dometa; Sancago; *Turk.*: Indobiotic; *Ukr.*: Indovenol (Индовенол).

Pharmacopoeial Preparations

BP 2014: Indometacin Capsules; Indometacin Suppositories;
USP 36: Indomethacin Capsules; Indomethacin Extended-release Capsules; Indomethacin for Injection; Indomethacin Oral Suspension; Indomethacin Suppositories; Indomethacin Topical Gel.

Infliximab *(BAN, rINN)*

cA2; CenTNF; Infliksimab; Infliksimabi; Infliximabum; Инфликсимаб.

Immunoglobulin G (human-mouse monoclonal cA2 heavy chain anti-human tumor necrosis factor), disulfide with human-mouse monoclonal cA2 light chain, dimer.

CAS — 170277-31-3.
ATC — L04AB02.
ATC Vet — QL04AB02.
UNII — B72HH48FLU.

Uses and Administration

Infliximab is a chimeric monoclonal antibody to TNF α, a pro-inflammatory mediator. Elevated levels of TNF have been found in the affected tissues and fluids of patients with rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis, and Crohn's disease and ulcerative colitis. Elevated TNF levels are also found in psoriatic plaques. Infliximab is described as a biological disease-modifying antirheumatic drug (DMARD).

Infliximab is given by intravenous infusion over a usual period of not less than 2 hours; shorter infusion times have been used in some patients with rheumatoid arthritis (see below for further details).

Infliximab is used with methotrexate in the management of moderate to severe, active **rheumatoid arthritis** (p. 75.2). In the UK it is licensed for use in patients who have had an inadequate response to standard DMARDs although, in severe progressive cases, it may be used in patients not previously treated with methotrexate or other DMARDs; in the USA it may be used for treating early rheumatoid arthritis. Infliximab is given in a dose of 3 mg/kg, repeated at 2 and 6 weeks, then every 8 weeks thereafter. For the first 3 doses infliximab should be infused for at least 2 hours; however, UK licensed product information suggests that subsequent infusion times may be reduced to a minimum period of 1 hour in those who tolerate the initial infusions. A clinical response is usually achieved within 12 weeks of starting treatment. Patients with an inadequate response during this period or who later relapse may benefit by increasing the dose: in the UK, a maximum dose of 7.5 mg/kg every 8 weeks (with increases made in steps of 1.5 mg/kg) is recommended whereas, in the USA, a maximum dose of 10 mg/kg is allowed. Alternatively, a dose of 3 mg/kg may be given as often as every 4 weeks in such patients. Continuing therapy in those who show no response within the first 12 weeks of treatment or after dose adjustment should be carefully reconsidered: in the UK NICE recommends that infliximab be withdrawn if there is no adequate response within 3 months of starting treatment.

Infliximab is used in the treatment of severe, active **Crohn's disease** (see Inflammatory Bowel Disease, p. 75.1) unresponsive to conventional treatment; in the USA, it is also licensed for use in moderate disease. Patients may be given an initial single dose of 5 mg/kg. This may be followed by a maintenance regimen of additional infusions of 5 mg/kg at 2 and 6 weeks after the initial infusion and then every 8 weeks thereafter, or the drug may be readministered when signs and symptoms of the disease recur (but see below). UK licensed product information does not recommend further doses in patients who are unresponsive after the first 2 doses; in the USA, a patient is not considered to be unresponsive until 3 doses have been given. US product information also suggests that doses of up to 10 mg/kg may be used in patients who relapse after an initial response. A similar regimen is used in patients with fistulising Crohn's disease although therapy should not be considered ineffective until after the third dose of infliximab. Infliximab is also used in the treatment of moderate to severe, active **ulcerative colitis** (see Inflammatory Bowel Disease, p. 75.1) in patients unresponsive to conventional therapy; the recommended dose is 5 mg/kg given in a regimen similar to that used for Crohn's disease (see above). Therapy should not be considered ineffective until after the third dose of infliximab.

In the treatment of active **ankylosing spondylitis** (see Spondyloarthropathies, p. 75.2), UK licensed product information recommends that infliximab should only be used in patients with severe disease who have had an inadequate response to conventional treatment; however, in the USA it may be used in early treatment. The initial dose is 5 mg/kg, repeated at 2 and 6 weeks and then every 6 to 8 weeks thereafter; if there is no response after 2 doses no further treatment should be given.

Infliximab is also used in the treatment of active and progressive **psoriatic arthritis** (see Spondyloarthropathies, p. 75.2); in the UK, its use is limited to patients who have had an inadequate response to standard DMARDs but, as before, US licensed product information allows earlier use. In the USA, it may be given with or without methotrexate; however, UK product information only recommends use without methotrexate in those patients who are intolerant of, or have contra-indications to, such treatment. It is given in a single dose of 5 mg/kg, repeated at 2 and 6 weeks and then every 8 weeks thereafter. Guidance issued by NICE in the UK recommends that treatment with infliximab is stopped after 12 weeks in those who show an inadequate response.

Infliximab is used in the treatment of severe **plaque psoriasis** (p. 75.2) in patients unresponsive to, or intolerant of, conventional systemic therapy including photochemotherapy; in the UK, it is also licensed for use in moderate disease. Infliximab is given in a dose of 5 mg/kg, repeated at 2 and 6 weeks, then every 8 weeks thereafter. Treatment should be stopped after 14 weeks (4 doses) in patients who show no response.

If the signs and symptoms of rheumatoid arthritis or Crohn's disease recur infliximab may be readministered if within 16 weeks of the last infusion. **Readministration** after a drug-free interval of more than 16 weeks may be associated with an increased risk of delayed hypersensitivity (see Delayed Reactions, p. 76.3) and consequently is not recommended. Recommendations regarding the readministration of infliximab for other indications (other than those detailed above) have not been established. Limited data from readministration with a single dose of infliximab in psoriasis after an interval of 20 weeks suggest reduced efficacy and a higher incidence of mild to moderate infusion reactions when compared with the initial regimen.

For details of infliximab use in children, see p. 75.1.

Administration in children. Infliximab is licensed for use in moderate to severe, active Crohn's disease and ulcerative colitis in children aged 6 years and over who have not responded to conventional therapy, or who have contra-indication for or are intolerant of such treatments; doses are the same as those used in adults (see p. 74.2). In the treatment of Crohn's disease, UK licensed product information suggests that the dosage interval may be adjusted to maintain any benefits; however, further treatment is unlikely to be of use in patients not responding within the first 10 weeks. In ulcerative colitis, further treatment is not recommended in those who do not respond within the first 8 weeks.

Although unlicensed for such use in the UK, infliximab has also been used in children with fistulising Crohn's disease; the *BNFC* recommends that those aged 6 to 18 years may be treated with the same dosage regimen that is used for this indication in adults (see p. 74.2).

Asthma. TNF inhibitors such as infliximab have been investigated in the treatment of refractory asthma (p. 1195.2).[1,2] There is some evidence that only a minority of patients will respond to such therapy, and that the benefits and risks must therefore be carefully assessed.[2]

1. Erin EM, *et al.* The effects of a monoclonal antibody directed against tumor necrosis factor-α in asthma. *Am J Respir Crit Care Med* 2006; **174:** 753–62.
2. Brightling C, *et al.* Targeting TNF-alpha: a novel therapeutic approach for asthma. *J Allergy Clin Immunol* 2008; **121:** 5–10.

Hidradenitis suppurativa. TNF inhibitors such as infliximab and adalimumab have been used[1-3] with some success in the treatment of hidradenitis suppurativa, a chronic skin disease characterised by purulent inflammation of occluded hair follicles and sebaceous glands typically in intertriginous areas such as the axillae and groin.

1. Haslund P, *et al.* Treatment of hidradenitis suppurativa with tumour necrosis factor-α inhibitors. *Acta Derm Venereol* 2009; **89:** 595–600.
2. Kimball AB, *et al.* Adalimumab for the treatment of moderate to severe hidradenitis suppurativa: a parallel randomized trial. *Ann Intern Med* 2012; **157:** 846–55.
3. van Rappard DC, *et al.* The off-label treatment of severe hidradenitis suppurativa with TNF-α inhibitors: a systematic review. *J Dermatolog Treat* 2013; **24:** 392–404.

Inflammatory bowel disease. Infliximab is used in adults for the treatment of Crohn's disease[1-6] and ulcerative colitis[2,7-9] (p. 1811.3); it is also used in children.[10-13]

In the treatment of ulcerative colitis, guidance issued by NICE recommends against the use of infliximab in subacute manifestations of moderately to severely active disease (defined as that which would normally be managed in an outpatient setting, and does not require hospitalisation or the consideration of urgent surgical intervention).[14] In the treatment of acute exacerbations of severely active ulcerative colitis, NICE guidance recommends use of infliximab only in patients in whom ciclosporin is contra-indicated or clinically inappropriate; otherwise, it should only be used for such treatment in the context of clinical studies.[15]

1. Siddiqui MAA, Scott LJ. Infliximab: a review of its use in Crohn's disease and rheumatoid arthritis. *Drugs* 2005; **65:** 2179–2208. Correction. *ibid.* 2006; **66:** 1359.
2. Rutgeerts P, *et al.* Review article: infliximab therapy for inflammatory bowel disease—seven years on. *Aliment Pharmacol Ther* 2006; **23:** 451–63.
3. Osterman MT, Lichtenstein GR. Infliximab in fistulizing Crohn's disease. *Gastroenterol Clin North Am* 2006; **35:** 795–820.
4. Eichevers MJ, *et al.* Optimizing the use of tumour necrosis factor inhibitors in Crohn's disease: a practical approach. *Drugs* 2010; **70:** 109–20.
5. NICE. Infliximab (review) and adalimumab for the treatment of Crohn's disease (includes a review of NICE technology appraisal guidance 40): Technology Appraisal Guidance 187 (issued May 2010). Available at: http://www.nice.org.uk/nicemedia/live/12985/48552/48552.pdf (accessed 19/10/10)
6. Behrn BW, Bickston SJ. Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 04/05/12).
7. Lawson MM, *et al.* Tumour necrosis factor alpha blocking agents for induction of remission in ulcerative colitis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 13/06/08).
8. Aberra FN, Lichtenstein GR. Infliximab in ulcerative colitis. *Gastroenterol Clin North Am* 2006; **35:** 821–36.
9. Gisbert JP, *et al.* Systematic review: infliximab therapy in ulcerative colitis. *Aliment Pharmacol Ther* 2007; **25:** 19–37.
10. de Ridder L, *et al.* Infliximab use in children and adolescents with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2007; **45:** 3–14.
11. Veres G, *et al.* Infliximab therapy in children and adolescents with inflammatory bowel disease. *Drugs* 2007; **67:** 1703–23.
12. Parashette KR, *et al.* Infliximab therapy in pediatric Crohn's disease: a review. *Clin Exp Gastroenterol* 2010; **3:** 57–63.
13. Hyams J, *et al.* T72 Study Group. Induction and maintenance therapy with infliximab for children with moderate to severe ulcerative colitis. *Clin Gastroenterol Hepatol* 2012; **10:** 391–9.
14. NICE. Infliximab for subacute manifestations of ulcerative colitis: Technology Appraisal Guidance 140 (issued April 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA140Guidance.pdf (accessed 28/07/08)
15. NICE. Infliximab for acute exacerbations of ulcerative colitis: Technology Appraisal Guidance 163 (issued December 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA163Guidance.pdf (accessed 27/10/09)

Leprosy. Infliximab has been used[1] in the treatment of recurrent type 2 (erythema nodosum leprosum) lepra reactions (p. 190.3). However, 2 cases of rapidly progressive leprosy developing in patients given infliximab for rheumatoid arthritis have also been described;[2] reversal (type 1) reactions occurred in both when infliximab was stopped.

1. Faber WR, *et al.* Treatment of recurrent erythema nodosum leprosum with infliximab. *N Engl J Med* 2006; **355:** 739.
2. Scollard DM, *et al.* Development of leprosy and type 1 leprosy reactions after treatment with infliximab: a report of 2 cases. *Clin Infect Dis* 2006; **43:** e19–e22.

Psoriasis. Infliximab is used in the treatment of moderate to severe plaque psoriasis (p. 1688.1).[1-8] However, TNF inhibitors have been associated with various adverse effects on the skin, see Effects on the Skin, p. 77.1.

1. Benoit S, *et al.* Treatment of recalcitrant pustular psoriasis with infliximab: effective reduction of chemokine expression. *Br J Dermatol* 2004; **150:** 1009–12.
2. Gottlieb AB, *et al.* Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol* 2004; **51:** 534–42.
3. Reich K, *et al.* EXPRESS study investigators. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet* 2005; **366:** 1367–74.
4. Reich K, *et al.* Improvement in quality of life with infliximab induction and maintenance therapy in patients with moderate-to-severe psoriasis: a randomized controlled trial. *Br J Dermatol* 2006; **154:** 1161–8.
5. Smith CH, *et al.* Infliximab for severe, treatment-resistant psoriasis: a prospective, open-label study. *Br J Dermatol* 2006; **155:** 160–9.
6. Menter A, *et al.* A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. *J Am Acad Dermatol* 2006; **56:** 31. e1–15.
7. Poulalhon N, *et al.* A follow-up study in 28 patients treated with infliximab for severe recalcitrant psoriasis: evidence for efficacy and high incidence of biological autoimmunity. *Br J Dermatol* 2007; **156:** 329–36.
8. NICE. Infliximab for the treatment of adults with psoriasis: Technology Appraisal Guidance 134 (issued January 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA134Guidance.pdf (accessed 22/08/08)

Rheumatoid arthritis. TNF inhibitors play an increasingly important role in the management of rheumatoid arthritis; they tend to be reserved for patients who are unresponsive to more conventional disease-modifying antirheumatic drugs (DMARDs), although some favour use earlier in management.

Some references[1-10] to the use of infliximab in rheumatoid arthritis (p. 13.2) and juvenile idiopathic arthritis (p. 12.1).

1. Maini R, *et al.* ATTRACT Study Group. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. *Lancet* 1999; **354:** 1932–9.
2. Lipsky PE, *et al.* Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. Infliximab and methotrexate in the treatment of rheumatoid arthritis. *N Engl J Med* 2000; **343:** 1594–1602.
3. Maini RN, *et al.* Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. *Arthritis Rheum* 2004; **50:** 1051–65.
4. Quinn MA, *et al.* Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2005; **52:** 27–35.
5. Voulgari PV, *et al.* Infliximab therapy in established rheumatoid arthritis: an observational study. *Am J Med* 2005; **118:** 515–20.
6. Chen Y-F, *et al.* NHS Health Technology Assessment Programme. A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness (issued November 2006). Available at: http://www.hta.ac.uk/fullmono/mon1042.pdf (accessed 31/10/08)
7. Ruperto N, *et al.* Paediatric Rheumatology International Trials Organisation. Pediatric Rheumatology Collaborative Study Group. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. *Arthritis Rheum* 2007; **56:** 3096–3106.
8. NICE. Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis (includes a review of technology appraisal guidance 36): Technology Appraisal Guidance 130 (issued October 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/TA130guidance.pdf (accessed 03/11/08)
9. NICE. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (part review of NICE technology appraisal guidance 36 and review of NICE technology appraisal guidance 126 and 141): Technology Appraisal Guidance 195 (issued August 2010). Available at: http://www.nice.org.uk/nicemedia/live/13108/50413/50413.pdf (accessed 04/11/10)
10. Wiens A, *et al.* Meta-analysis of the efficacy and safety of adalimumab, etanercept, and infliximab for the treatment of rheumatoid arthritis. *Pharmacotherapy* 2010; **30:** 339–53.

Sarcoidosis. For a mention of possible benefit from infliximab in sarcoidosis, see p. 1612.2. However, there have been individual case reports of TNF-inhibitor-induced sarcoidosis (see p. 77.3).

Spondyloarthropathies. References[1-9] to the use of infliximab in the treatment of ankylosing spondylitis and psoriatic arthritis (p. 14.3). Guidance issued by NICE in the UK does not recommend the use of infliximab for the treatment of ankylosing spondylitis; adalimumab or etanercept are preferred.[7]

1. Brandt J, *et al.* Infliximab in the treatment of active and severe ankylosing spondylitis. *Clin Exp Rheumatol* 2002; **20** (suppl 28): S106–S110.
2. Brandt J, *et al.* Successful short term treatment of severe undifferentiated spondyloarthropathy with the anti-tumor necrosis factor-alpha monoclonal antibody infliximab. *J Rheumatol* 2002; **29:** 118–22.
3. Collantes-Estévez E, *et al.* Infliximab in refractory spondyloarthropathies: a multicentre 38 week open study. *Ann Rheum Dis* 2003; **62:** 1239–40.
4. Robinson DM, Keating GM. Infliximab: in ankylosing spondylitis. *Drugs* 2005; **65:** 1283–91.
5. Rott S, *et al.* Successful treatment of severe psoriatic arthritis with infliximab in an 11-year-old child suffering from linear psoriasis along lines of Blaschko. *Br J Dermatol* 2007; **157:** 191–2.
6. McLeod C, *et al.* NHS Health Technology Assessment Programme. Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation (issued August 2007). Available at: http://www.hta.ac.uk/fullmono/mon1128.pdf (accessed 31/10/08)
7. NICE. Adalimumab, etanercept and infliximab for ankylosing spondylitis: Technology Appraisal Guidance 143 (issued May 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA143Guidance.pdf (accessed 31/10/08)
8. Baraliakos X, Braun J. Anti-TNF-α therapy with infliximab in spondyloarthritides. *Expert Rev Clin Immunol* 2010; **6:** 9–19.
9. NICE. Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (review of technology appraisal guidance 104 and 125): Technology Appraisal Guidance 199 (issued August 2010). Available at: http://www.nice.org.uk/nicemedia/live/13110/50422/50422.pdf (accessed 19/10/10)

Uveitis. Infliximab has been tried[1-12] with some success in the treatment of uveitis (p. 1615.1) including that associated with Behçet's syndrome (p. 1601.1). Uveitis can also develop as a complication of other inflammatory disorders such as rheumatoid arthritis; treatment with infliximab may improve ocular symptoms in addition to its effect on the primary disorder.

1. Murphy CC, *et al.* Tumor necrosis factor alpha blockade with infliximab for refractory uveitis and scleritis. *Ophthalmology* 2004; **111:** 352–6.
2. Bodaghi B, *et al.* Therapeutic use of infliximab in sight threatening uveitis: retrospective analysis of efficacy, safety, and limiting factors. *Ann Rheum Dis* 2005; **64:** 962–4.
3. Braun J, *et al.* Decreased incidence of anterior uveitis in patients with ankylosing spondylitis treated with the anti-tumor necrosis factor agents infliximab and etanercept. *Arthritis Rheum* 2005; **52:** 2447–51.
4. Richards JC, *et al.* Infliximab for juvenile idiopathic arthritis-associated uveitis. *Clin Experiment Ophthalmol* 2005; **33:** 461–8.
5. Lindstedt EW, *et al.* Anti-TNF-α therapy for sight threatening uveitis. *Br J Ophthalmol* 2005; **89:** 533–6.
6. Saurenmann RK, *et al.* Tumour necrosis factor alpha inhibitors in the treatment of childhood uveitis. *Rheumatology (Oxford)* 2006; **45:** 982–9.
7. Kahn P, *et al.* Favorable response to high-dose infliximab for refractory childhood uveitis. *Ophthalmology* 2006; **113:** 860–4.
8. Guignard S, *et al.* Efficacy of tumour necrosis factor blockers in reducing uveitis flares in patients with spondylarthropathy: a retrospective study. *Ann Rheum Dis* 2006; **65:** 1631–4.
9. Tynjälä P, *et al.* Infliximab and etanercept in the treatment of chronic uveitis associated with refractory juvenile idiopathic arthritis. *Ann Rheum Dis* 2007; **66:** 548–50.
10. Ardoin SP, *et al.* Infliximab to treat chronic noninfectious uveitis in children: retrospective case series with long-term follow-up. *Am J Ophthalmol* 2007; **144:** 844–9.
11. Pipitone N, *et al.* Infliximab for the treatment of Neuro-Behçet's disease: a case series and review of the literature. *Arthritis Rheum* 2008; **59:** 285–90.
12. Yamada Y, *et al.* Comparison of infliximab versus ciclosporin during the initial 6-month treatment period in Behçet disease. *Br J Ophthalmol* 2010; **94:** 284–8.

Vasculitic syndromes. For a preliminary report on the use of infliximab in Takayasu's arteritis, see p. 1614.3. Infliximab has also been investigated in the management of Kawasaki disease (p. 2405.2) in patients who are unresponsive to standard treatment.[1-4]

1. Burns JC, *et al.* Infliximab treatment for refractory Kawasaki syndrome. *J Pediatr* 2005; **146:** 662–7.
2. Sajl T, Kemmotsu Y. Infliximab for Kawasaki syndrome. *J Pediatr* 2006; **149:** 426.
3. O'Connor MJ, Saulsbury FT. Incomplete and atypical Kawasaki disease in a young infant: severe, recalcitrant disease responsive to infliximab. *Clin Pediatr (Phila)* 2007; **46:** 345–8.
4. Burns JC, *et al.* Infliximab treatment of intravenous immunoglobulin-resistant Kawasaki disease. *J Pediatr* 2008; **153:** 833–8.

Adverse Effects, Treatment, and Precautions

Acute infusion reactions during or within 1 to 2 hours of infusion are common with infliximab, and other TNF inhibitors, particularly with the first or second dose. Symptoms include fever, chills, pruritus, urticaria, dyspnoea, chest pain, and hypertension or hypotension. Mild reactions may respond to a reduced rate of infusion or a temporary interruption. If reactions are more severe, therapy should be stopped. Pretreatment with paracetamol, corticosteroids, and antihistamines may be considered. TNF inhibitors should only be given where facilities for resuscitation are available. Delayed reactions have occurred 3 to 12 days after infliximab treatment; symptoms include myalgia, arthralgia, fever, and rash. Similar delayed reactions may also be seen when infliximab has been restarted after an extended period without treatment (see p. 76.3).

Other, common, adverse effects include nausea and vomiting, abdominal pain, diarrhoea, fatigue, dizziness, headache, and back pain. Antibodies to infliximab (human antichimeric antibodies) may develop, and are associated with an increased incidence of hypersensitivity reactions. Antinuclear antibodies and anti-double-stranded-DNA antibodies have also developed with TNF inhibitor therapy. A lupus-like syndrome has occurred rarely; treatment should be stopped if it develops. Sarcoidosis or a sarcoid-like reaction has also been reported rarely.

Infections are common in patients treated with infliximab or other drugs that inhibit TNF, and most often affect the upper respiratory tract and the urinary tract. TNF inhibitors have also been associated rarely with the development of serious opportunistic infections, sepsis, pneumonia, and onset or reactivation of tuberculosis (see Infection, p. 77.2), particularly in patients with underlying conditions predisposing them to infections; in some cases death has resulted. TNF inhibitors should not be given to patients with severe infection, including active tuberculosis, abscesses, and opportunistic infections, and should be stopped if these develop. Patients should be evaluated for latent and active tuberculosis before beginning therapy; if evidence of latent tuberculosis is found, the risks and benefits of treatment should be considered carefully and chemoprophylaxis should be started before giving a TNF inhibitor. They should also be used with care in those with chronic infections, a history of recurrent infections, or with underlying conditions that may predispose to infections. Patients with fistulising Crohn's disease with suppurative fistulas should not be given infliximab until possible infection sources such as abscesses have been ruled out. Patients should be instructed to seek medical advice if symptoms suggestive of tuberculosis (such as persistent cough, weight loss, or low grade fever) occur. Patients should be monitored for signs of infection after stopping treatment: for those TNF inhibitors with long half-lives (such as adalimumab, certolizumab, golimumab, and infliximab) monitoring should continue for up to 6 months; because of its relatively shorter half-life, the elimination of etanercept may be quicker.

There have been rare reports of severe hepatic reactions such as acute liver failure, jaundice, hepatitis, and cholestasis with infliximab; some cases have been fatal or required transplantation. Patients with signs or symptoms of hepatotoxicity should be evaluated and infliximab should be stopped in those patients with jaundice or marked elevations in liver enzyme values. Infliximab and other TNF inhibitors have also been associated with the reactivation of hepatitis B in chronic carriers, which has resulted in fatalities in some cases. Patients at risk of hepatitis B infection should be screened before starting treatment; it is recommended that carriers treated with a TNF inhibitor are closely monitored during, and for several months after stopping, treatment.

Blood dyscrasias, including leucopenia, thrombocytopenia, pancytopenia, and aplastic anaemia, have been reported rarely with TNF inhibitors; in some cases the outcome was fatal. They should be used with caution in patients with a history of blood dyscrasias.

Rare, and sometimes fatal, cases of interstitial lung disease including pulmonary fibrosis and pneumonitis have been reported with TNF inhibitors.

Infliximab and other TNF inhibitors are also associated with an increased incidence of malignancies including lymphomas and leukaemias (see also Carcinogenicity, below), although occurrences are rare. Some groups of patients treated with TNF inhibitors may already have an increased background risk of developing malignancies, regardless of drug treatment. Care has been advocated in patients with a history of malignancy.

Anaphylactic reactions have been reported rarely with TNF inhibitors. Infliximab should be avoided in patients with a history of hypersensitivity to the drug or other murine proteins.

TNF inhibitors have been associated in rare cases with seizures and clinical or radiological worsening of demyelinating disorders such as multiple sclerosis or optic neuritis; care is required in prescribing it to patients with such disorders or symptoms suggestive of their onset.

Worsening and, in some cases, new-onset heart failure has been reported with TNF inhibitors (see Effects on the Heart, below). In the UK, infliximab is contra-indicated in patients with moderate to severe heart failure (NYHA class III or IV); however, US licensed product information advises that doses up to 5 mg/kg may be used in such patients. It should be used with caution in patients with mild heart failure (NYHA class I or II). All patients with heart failure should be closely monitored and infliximab stopped in those who develop new or worsening symptoms of heart failure. Similar recommendations are given for the TNF inhibitors adalimumab, certolizumab, etanercept, and golimumab although UK licensed information for etanercept only advises caution in patients with heart failure.

General references.

1. Hansen RA, *et al.* Serious adverse events with infliximab: analysis of spontaneously reported adverse events. *Clin Gastroenterol Hepatol* 2007; 5: 729–35.
2. Lecluse LLA, *et al.* Review and expert opinion on prevention and treatment of infliximab-related infusion reactions. *Br J Dermatol* 2008; 159: 527–36.
3. Zabana Y, *et al.* Infliximab safety profile and long-term applicability in inflammatory bowel disease: 9-year experience in clinical practice. *Aliment Pharmacol Ther* 2010; 31: 553–60.
4. O'Donnell S, *et al.* Safety of infliximab in 10 years of clinical practice. *Eur J Gastroenterol Hepatol* 2011; 23: 603–6.

Carcinogenicity. Malignancies, especially lymphomas, have been seen in patients treated with TNF inhibitors for rheumatoid arthritis and Crohn's disease;[1] however, the suggestion of a causal relationship is controversial. A meta-analysis[2] in 2006 identified 24 published reports of malignancies in 3493 study patients with rheumatoid arthritis who had received at least one dose of a TNF inhibitor (adalimumab or infliximab) along with 2 cases in 1512 control patients; further, unpublished, cases were also found using FDA data to give 29 malignancies in the treatment groups and 3 in the control groups. Based on these figures, there was a 3.3-fold increase in the risk of malignancy in patients receiving TNF inhibitors when compared with controls. These results have, however, been criticised[3] on several points including the difficulty in applying them to current practice because etanercept was not included in the analysis, and, in particular, the unexpectedly low rate of malignancies in the control groups. Other studies in patients with rheumatoid arthritis[4–6] and Crohn's disease[7] have generally concluded that the overall risk of malignancies is not significantly increased in patients taking TNF inhibitors when compared with patients who have not taken these drugs. Some studies[4,8] in patients with rheumatoid arthritis have, however, shown a possible increased risk of lymphoma with TNF inhibitor treatment, but caution in interpreting these results was recommended as they were based on a small number of cases; in addition, the background risk of lymphoma is increased in rheumatoid arthritis regardless of treatment.

Rare cases of hepatosplenic T-cell lymphoma have been seen in adolescents and young adults given infliximab for the treatment of Crohn's disease. In July 2006, the manufacturer was aware of 6 cases of this type of lymphoma in 5 adolescents aged 12 to 19 years and one 31-year-old adult;[9] 4 of the 6 cases occurred in males. The treatment duration ranged from 1 or 2 infusions to over 4 years of therapy; in all cases, patients were also taking or had taken azathioprine or 6-mercaptopurine. This type of lymphoma is aggressive and 5 of the above patients died. A causal relationship was not clearly established although it could neither be excluded. Further cases have since been reported.[10] Hepatosplenic T-cell lymphoma has also been associated with adalimumab. In July 2008, the manufacturer was aware of 3 cases;[11] of these, 2 had occurred in young men also taking azathioprine or 6-mercaptopurine for inflammatory bowel disease. (Details of the third case were not provided).

Concerns about the risk of cancer in children and adolescents receiving TNF inhibitors prompted the FDA[12] to review all cases of cancer in children taking adalimumab, etanercept, or infliximab. (Certolizumab and golimumab were not included in the review as neither were licensed for use in children and were minimally used during the review period.) In August 2009, their findings were reported. Forty eight cases of malignancies in children and adolescents were identified; of these, about half were lymphomas, including Hodgkin's and non-Hodgkin's lymphomas. Other reported malignancies included leukaemia, melanoma, and solid organ cancers; malignancies that are rare in children such as leiomyosarcoma, hepatic malignancies, and renal cell carcinoma were also reported. About 88% of the 48 patients were also taking other immunosuppressants such as azathioprine and methotrexate. There were 11 fatalities reported, comprising 9 cases of hepatosplenic T-cell lymphoma, 1 of T-cell lymphoma, and 1 of sepsis after achieving remission of the lymphoma. The FDA considered that there is an increased risk of malignancy with TNF inhibitors although they were unable to characterise the strength of this association due to factors such as the relatively rare occurrence of these cancers, the limited number of paediatric patients on TNF inhibitor therapy, and the possible role of concurrent immunosuppressants.

In a second analysis the FDA[12] reviewed 147 reports of leukaemia associated with TNF inhibitors in all patients, including adults. Of these, the most frequently reported were acute myeloid leukaemia (44 cases), chronic lymphocytic leukaemia (31 cases), and chronic myeloid leukaemia (23 cases). About 61% of the patients were also receiving other immunosuppressants. There were 30 fatalities reported; of these, 26 were due to leukaemia. The average time to onset of leukaemia was within the first 2 years of TNF inhibitor therapy. Based on the available data, the FDA concluded that there is a possible association between TNF inhibitor therapy and leukaemia.

1. Brown SL, *et al.* Tumor necrosis factor antagonist therapy and lymphoma development: twenty-six cases reported to the Food and Drug Administration. *Arthritis Rheum* 2002; 46: 3151–8.
2. Bongartz T, *et al.* Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA* 2006; 295: 2275–85. Correction. *ibid.*: 2482.
3. Dixon W, Silman A. Is there an association between anti-TNF monoclonal antibody therapy in rheumatoid arthritis and risk of malignancy and serious infection? Commentary on the meta-analysis by Bongartz et al. *Arthritis Res Ther* 2006; 8: 111.
4. Geborek P, *et al.* Tumour necrosis factor blockers do not increase overall tumour risk in patients with rheumatoid arthritis, but may be associated with an increased risk of lymphomas. *Ann Rheum Dis* 2005; 64: 699–703.
5. Setoguchi S, *et al.* Tumor necrosis factor α antagonist use and cancer in patients with rheumatoid arthritis. *Arthritis Rheum* 2006; 54: 2757–54. Correction. *ibid.*; 3134.
6. Askling J, *et al.* Cancer risk in patients with rheumatoid arthritis treated with anti-tumor necrosis factor α therapies: does the risk change with the time since start of treatment? *Arthritis Rheum* 2009; 60: 3180–9.
7. Biancone L, *et al.* Infliximab and newly diagnosed neoplasia in Crohn's disease: a multicentre matched pair study. *Gut* 2006; 55: 228–33.
8. Wolfe F, Michaud K. Lymphoma in rheumatoid arthritis: the effect of methotrexate and anti-tumor necrosis factor therapy in 18,572 patients. *Arthritis Rheum* 2004; 50: 1740–51.
9. Schering Canada. Health Canada endorsed important safety information on Remicade (infliximab) (issued 24th July, 2006). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/remicade_3_hpc-cps-eng.pdf (accessed 29/08/08)
10. Mackey AC, *et al.* Hepatosplenic T cell lymphoma associated with infliximab use in young patients treated for inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2007; 44: 265–7.
11. Abbott, UK. Direct healthcare professional communication on report of hepatosplenic T-cell lymphoma in patients treated with Humira (adalimumab) (issued 16th July, 2008). Available at: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON023075 (accessed 03/11/08)
12. FDA. Information for healthcare professionals: tumor necrosis factor (TNF) blockers (marketed as Remicade, Enbrel, Humira, Cimzia, and Simponi) (issued 4th August, 2009). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm174474.htm (accessed 26/10/09)

Delayed reactions. Ten of 37 patients with Crohn's disease re-treated with infliximab after a 2- to 4-year period without treatment had delayed hypersensitivity reactions, of which 6 were considered serious. None of the patients had had infusion-related adverse effects with their original infliximab therapy. Adverse reactions developed in 9 of the 23 patients originally treated with a discontinued liquid formulation, and in 1 of the 14 patients who previously received the marketed formulation, leading to speculation that the formulation may have been a contributing factor.

Effects on blood lipids. A 35-year-old man with psoriatic arthritis and psoriasis developed markedly elevated triglyceride levels and a mildly increased total cholesterol level after a single infusion of infliximab;[1] previous tests had shown a mild hypertriglyceridaemia for which he had received no treatment. No further doses of infliximab were given and his triglyceride levels subsequently improved. Similarly, hypertriglyceridaemia and hypercholesterolaemia developed in a 39-year-old man with psoriatic arthritis and psoriasis after 8 weeks of treatment with adalimumab;[2] triglyceride levels were markedly elevated after 3 months of therapy although total cholesterol level remained unchanged. Levels improved 4 weeks after stopping the drug.

1. Antoniou C, *et al.* Elevated triglyceride and cholesterol levels after intravenous antitumour necrosis factor-α therapy in a patient with psoriatic arthritis and psoriasis vulgaris. *Br J Dermatol* 2007; 156: 1090–1.
2. Stinco G, *et al.* Hypertriglyceridaemia during treatment with adalimumab in psoriatic arthritis. *Br J Dermatol* 2007; 157: 1273–4.

Effects on the CNS. Aseptic meningitis developed in a patient after his fifth injection of infliximab for rheumatoid arthritis.[1] Similar symptoms also occurred after a sixth injection.

Two patients with inflammatory bowel disease developed acute motor neuropathy with multiple conduction blocks after infliximab treatment; both patients improved after infliximab was stopped.[2] Similar adverse effects were reported in 2 further patients:[3] one was taking etanercept for rheumatoid arthritis and the other infliximab for ankylosing spondylitis. Three cases of bilateral optic neuropathy associated with infliximab therapy have also been reported.[4] Other neuropathies have been associated with TNF inhibitor treatment, including Guillain-Barré syndrome.[5]

1. Marotte H, *et al.* Infliximab-induced aseptic meningitis. *Lancet* 2001; 358: 1784.
2. Singer OC, *et al.* Acute neuropathy with multiple conduction blocks after TNFα monoclonal antibody therapy. *Neurology* 2004; 63: 1754.
3. Richez C, *et al.* Neuropathy resembling CIDP in patients receiving tumor necrosis factor-α blockers. *Neurology* 2005; 64: 1468–70.
4. ten Tusscher MPM, *et al.* Bilateral anterior toxic optic neuropathy and the use of infliximab. *BMJ* 2003; 326: 579.
5. Stübgen J-P. Tumor necrosis factor-α antagonists and neuropathy. *Muscle Nerve* 2008; 37: 281–92.

Effects on the heart. The FDA has reported[1] on 47 patients who developed heart failure during long-term therapy with TNF antibodies (etanercept and infliximab) for arthritic conditions or Crohn's disease. Of these, 38 developed new-onset heart failure, 19 having documented risk factors for heart failure, and 9 had exacerbation of existing heart failure. The median time to new-onset heart failure was 3.5 months. However, studies[2–4] investigating a possible association between TNF inhibitors and the development of heart failure have been equivocal and further investigation is warranted.

Preliminary investigations on the use of infliximab in the treatment of moderate to severe heart failure failed to show any clinical improvement in patients given infliximab 5 mg/kg or 10 mg/kg when compared with placebo;[5] in addition, those given the higher dose had an increased risk of death or hospitalisation due to worsening heart failure.

1. Kwon HJ, *et al.* Case reports of heart failure after therapy with a tumor necrosis factor antagonist. *Ann Intern Med* 2003; 138: 807–11.
2. Jacobsson LTH, *et al.* Treatment with tumor necrosis factor blockers is associated with a lower incidence of first cardiovascular events in patients with rheumatoid arthritis. *J Rheumatol* 2005; 32: 1213–18.
3. Curtis JR, *et al.* Heart failure among younger rheumatoid arthritis and Crohn's patients exposed to TNF-α antagonists. *Rheumatology (Oxford)* 2007; 46: 1688–93.
4. Listing J, *et al.* Does tumor necrosis factor α inhibition promote or prevent heart failure in patients with rheumatoid arthritis? *Arthritis Rheum* 2008; 58: 667–77.
5. Chung ES, *et al.* Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-α, in patients with moderate-to-severe heart failure: results of the Anti-TNF Therapy Against Congestive Heart failure (ATTACH) trial. *Circulation* 2003; 107: 3133–40.

Effects on the lungs. Infliximab treatment has been associated with a fatal exacerbation of previously asymptomatic fibrosing alveolitis in 3 patients with chronic rheumatoid arthritis;[1] all 3 patients were also taking azathioprine and prednisolone. There was no evidence of infection or other underlying causes for the decline in respiratory function.

1. Ostor AJK, *et al.* Fatal exacerbation of rheumatoid arthritis associated fibrosing alveolitis in patients given infliximab. *BMJ* 2004; 329: 1266.

Effects on the skin. Patients with rheumatoid arthritis receiving TNF inhibitor therapy are more likely to develop adverse skin reactions than those who are not.[1] Of 289 patients taking TNF inhibitors (*infliximab, etanercept, adalimumab,* and lenercept), 72 (25%) reported 128 dermatological events including skin infections, eczema, drug-related eruptions, and malignancies such as actinic keratosis; of the 289 patients not taking TNF inhibitors, 37 (13%) reported dermatological events.

In another review,[2] cutaneous adverse effects were seen in 35 out of 150 patients receiving TNF inhibitors (adalimumab, etanercept, or infliximab) for rheumatic disorders; cases included dermatitis herpetiformis and leucocytoclastic vasculitis although eczematous and skin infections were more common or infectious. Perhaps unexpectedly, psoriasis-like lesions were seen in 8 patients, 6 of whom had no history of psoriasis; similar effects have also been noted in other patients with rheumatoid arthritis[3,4] or Crohn's disease[5,6] (see also below).

Rare cases of serious skin reactions have been associated with TNF inhibitor treatment.[7] Since approval in 1998, the FDA has received 15 cases of erythema multiforme, 5 cases of Stevens-Johnson syndrome, and 1 case of toxic epidermal necrolysis associated with infliximab; cases for etanercept, approved in the same year, included 13 reports of erythema multiforme, and 4 reports each of Stevens-Johnson syndrome and toxic epidermal necrolysis. For adalimumab, which was marketed late in 2002, there have been 4 cases of erythema multiforme and 2 of Stevens-Johnson syndrome.

In August 2009, the FDA[8] reported that it had reviewed 69 cases of new-onset psoriasis, including pustular (17 cases) and palmoplantar (15 cases) psoriasis, in all patients receiving TNF inhibitor therapy for auto-immune and rheumatic disorders other than psoriasis and psoriatic arthritis; of these, 2 cases were of children and 12 had resulted in hospitalisation. The time to onset of psoriasis ranged from weeks to years after starting TNF inhibitor therapy; symptoms improved in the majority of patients after stopping the drug. None of the cases had reported pre-existing psoriasis.

Cutaneous pseudolymphoma has been reported after 2 doses of adalimumab in a patient with psoriasis and recurred when infliximab treatment was introduced;[9] both eruptions resolved completely on withdrawal of the drug. Etanercept has also been associated with cutaneous pseudolymphoma[10] in a patient with rheumatoid arthritis. The eruption occurred after one year of treatment and resolved on withdrawal; subsequent treatment with adalimumab did not induce the skin reaction.

For reports of drug-induced lupus or lupus-like syndrome associated with TNF inhibitors, see Lupus, below.

1. Flendrie M, *et al.* Dermatological conditions during TNF-α-blocking therapy in patients with rheumatoid arthritis: a prospective study. *Arthritis Res Ther* 2005; 7: R666–R676.
2. Lee H-H, *et al.* Cutaneous side-effects in patients with rheumatic diseases during application of tumour necrosis factor-α antagonists. *Br J Dermatol* 2007; 156: 486–91.
3. Dereure O, *et al.* Psoriatic lesions induced by antitumour necrosis factor-α treatment: two cases. *Br J Dermatol* 2004; 151: 506–7.
4. Teraki Y, *et al.* A case of generalized psoriasiform and pustular eruption induced by infliximab: evidence for skin-homing Th17 in the pathogenesis. *Br J Dermatol* 2010; 163: 1347–51.
5. Verea MM, *et al.* Psoriasiform eruption induced by infliximab. *Ann Pharmacother* 2004; 38: 54–7.
6. Conklin LS, *et al.* Rash induced by anti-tumor necrosis factor agents in an adolescent with Crohn's disease. *Nat Rev Gastroenterol Hepatol* 2010; 7: 174–7.
7. FDA. Tumor necrosis factor alpha (TNF-α) antagonists. Infliximab (marketed as Remicade), etanercept (marketed as Enbrel), and adalimumab (marketed as Humira). Serious skin reactions. *FDA Drug Safety Newsletter* 2007; 1: 18–20. Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/DrugSafetyNewsletter/ucm109169 (accessed 28/07/10)
8. FDA. Information for healthcare professionals: tumor necrosis factor (TNF) blockers (marketed as Remicade, Enbrel, Humira, Cimzia, and Simponi) (issued 4th August, 2009). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm174474.htm (accessed 27/10/09)
9. Imafuku S, *et al.* Cutaneous pseudolymphoma induced by adalimumab and reproduced by infliximab in a patient with arthropathic psoriasis. *Br J Dermatol* 2012; 166: 675–8.
10. Guis S, *et al.* Cutaneous pseudolymphoma associated with a TNF-alpha inhibitor treatment: etanercept. *Eur J Dermatol* 2008; 18: 474–6.

Infection. TNF inhibitors (such as infliximab, adalimumab, certolizumab, etanercept, and golimumab) are known to suppress the immune system and infections are commonly reported with these drugs. However, serious, life-threatening, opportunistic infections involving multiple organ systems and sites have also been reported rarely in patients taking TNF inhibitors.[1-7] Of particular concern are bacterial infections such as legionellosis, leprosy (see also under Uses and Administration, p. 75.1), listeriosis, nocardiosis, tuberculosis, and nontuberculous mycobacteria, invasive fungal infections such as aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, and pneumocystosis, viruses such as hepatitis B, and parasitic organisms. Infections frequently have been disseminated rather than localised.

The risk for developing an opportunistic infection is higher for patients who are 65 years of age and older and for those taking concomitant immunosuppressive agents. Delay in diagnosis and treatment of infections, especially fungal, has resulted in fatalities; patients should be closely monitored for signs and symptoms of systemic infection before, during, and after treatment with TNF inhibitors. Empirical antifungal therapy may be considered in those thought to be at risk of endemic fungal infections.[8,9]

There have been reports of onset or reactivation of tuberculosis in patients treated with infliximab and other TNF inhibitors, including cases of miliary tuberculosis and unusual extrapulmonary disease.[1,2,4,5] Guidelines have therefore been issued by the British Thoracic Society[10] to quantify the risks of reactivation of tuberculosis with TNF inhibitors and to advise on the treatment of such infection in patients being assessed for TNF inhibitor therapy. Other guidelines[11] have also been issued based on a review of the literature and current national recommendations.

1. CSM/MCA. Infliximab (Remicade) and tuberculosis. *Current Problems* 2001; 27: 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007458&RevisionSelectionMethod=LatestReleased (accessed 13/06/08)
2. Schaible TF [Centocor, Inc. Important drug warning (issued 5th October, 2001). Available at: http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm174242 (accessed 28/07/10)
3. Wallis RS, *et al.* Granulomatous infectious diseases associated with tumor necrosis factor antagonists. *Clin Infect Dis* 2004; 38: 1261–5. Correction. *ibid.*; 39: 1254–5.
4. Health Canada. Infliximab (Remicade) and etanercept (Enbrel): serious infections and tuberculosis. *Can Adverse React News* 2004; 14 (4): 2–3. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v14n4-eng.pdf (accessed 29/08/08)
5. Mohan AK, *et al.* Tuberculosis following the use of etanercept, a tumor necrosis factor inhibitor. *Clin Infect Dis 2004;* 39: 295–9.
6. Tsiodras S, *et al.* Fungal infections complicating tumor necrosis factor α blockade therapy. *Mayo Clin Proc* 2008; 83: 181–94.
7. FDA. Drug safety communication: drug labels for the tumor necrosis factor-alpha (TNFα) blockers now include warnings about infection with Legionella and Listeria bacteria (issued 7th September, 2011). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm270849.htm (accessed 11/10/11)
8. FDA. Information for healthcare professionals: Cimzia (certolizumab pegol), Enbrel (etanercept), Humira (adalimumab), and Remicade (infliximab) (issued 4th September, 2008). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124185.htm (accessed 27/10/09)
9. Smith JA, Kauffman CA. Endemic fungal infections in patients receiving tumour necrosis factor-α inhibitor therapy. *Drugs* 2009; 69: 1403–15.
10. British Thoracic Society Standards of Care Committee. BTS recommendations for assessing risk and for managing Mycobacterium tuberculosis infection and disease in patients due to start anti-TNF-α treatment. *Thorax* 2005; 60: 800–5. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Anti%20TNF%20Treatment/Guidelines/antitnf_treatment.pdf (accessed 13/06/08)
11. Perlmutter A, *et al.* Tuberculosis and tumour necrosis factor-α inhibitor therapy: a report of three cases in patients with psoriasis—comprehensive screening and therapeutic guidelines for clinicians. *Br J Dermatol* 2009; 160: 8–15.

Lupus. In June 2009, the Australian Adverse Drug Reactions Advisory Committee (ADRAC)[1] stated that 36 out of 87 reports of drug-induced lupus erythematosus or lupus-like syndrome received since 2003 were associated with TNF inhibitor therapy. Of these, 21 reports were associated with infliximab, 10 with adalimumab, and 5 with etanercept.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Drug-induced lupus erythematosus: an emerging association with TNF inhibitors. *Aust Adverse Drug React Bull* 2009; 28: 10–11. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0906.pdf (accessed 27/10/09)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies infliximab as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 15/11/11)

Sarcoidosis. Although infliximab has been tried in the treatment of sarcoidosis, the TNF inhibitors adalimumab, etanercept, and infliximab have been associated with reports of sarcoidosis in patients being treated for rheumatoid or psoriatic arthritis or plaque psoriasis.[1,2] Non-specific respiratory symptoms typically developed within about 2 years of starting treatment, and generally resolved within a year of stopping the drug.

1. Massara A, *et al.* Sarcoidosis appearing during anti-tumor necrosis factor α therapy: a new "class effect" paradoxical phenomenon. Two case reports and literature review. *Semin Arthritis Rheum* 2010; 39: 313–19.
2. Fink AE, *et al.* The development of sarcoidosis on antitumour necrosis factor therapy: a paradox. *Br J Dermatol* 2010; 163: 648–9.

Interactions

Live vaccines should not be given with infliximab or other drugs that inhibit TNF as the effect of such drugs on vaccine efficacy or the risk of infection transmission is unknown. The use of TNF inhibitors with the interleukin-1 receptor antagonist anakinra may increase the risk of serious infections and neutropenia; such combinations are not recommended. A similar interaction has been seen with TNF inhibitors and the co-stimulation blocker abatacept.

Abatacept. Use of the TNF inhibitor etanercept with abatacept has resulted in an increase in the incidence of serious adverse effects including serious infections; in addition, there was no increase in clinical benefit.[1] Combinations of abatacept with TNF inhibitors are not recommended by UK licensed product information.

1. Weinblatt M, *et al.* Selective costimulation modulation using abatacept in patients with active rheumatoid arthritis while receiving etanercept: a randomised clinical trial. *Ann Rheum Dis* 2007; 66: 228–34.

Anakinra. The incidence of serious infections, injection site reactions, and neutropenia is increased when anakinra is given with the TNF inhibitor etanercept.[1] In addition, the combination did not provide any further clinical benefit when compared with etanercept alone. Similar findings may be expected if anakinra is given with other TNF inhibitors.

1. Genovese MC, *et al.* Combination therapy with etanercept and anakinra in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate. *Arthritis Rheum* 2004; 50: 1412–19.

Pharmacokinetics

Infliximab shows linear pharmacokinetics. It is distributed mainly in the vascular compartment and, after single doses, has a terminal elimination half-life of 8 to 9.5 days. After repeated doses, infliximab has been detected in serum for at least 8 weeks.

References.

1. Nestorov I. Clinical pharmacokinetics of tumor necrosis factor antagonists. *J Rheumatol* 2005; 74 (suppl): 13–18.
2. Klotz U, *et al.* Clinical pharmacokinetics and use of infliximab. *Clin Pharmacokinet* 2007; 46: 645–60.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Remicade; *Austral.*: Remicade; *Austria*: Remicade; *Belg.*: Remicade; *Braz.*: Remicade; *Canad.*: Remicade; *Chile*: Remicade; *China*: Remicade (类克); *Cz.*: Remicade; *Denm.*: Remicade; *Fin.*: Remicade; *Fr.*: Remicade; *Ger.*: Remicade; *Gr.*: Remicade; *Hong Kong*: Remicade; *Hung.*: Remicade; *Indon.*: Remicade; *Irl.*: Remicade; *Israel*: Remicade; *Ital.*: Remicade; *Jpn*: Remicade; *Malaysia*: Remicade; *Mex.*: Remicade; *Neth.*: Remicade; *Norw.*: Remicade; *NZ*: Remicade; *Philipp.*: Remicade; *Pol.*: Remicade; *Port.*: Remicade; *Rus.*: Remicade (Ремикейд); *S.Afr.*: Revellex; *Singapore*: Remicade; *Spain*: Remicade; *Swed.*: Remicade; *Switz.*: Remicade; *Thai.*: Remicade; *Turk.*: Remicade; *UK*: Remicade; *Ukr.*: Remicade (Ремикейд); *USA*: Remicade; *Venez.*: Remicade.

Interleukin-6 Receptor Antagonists

Tocilizumab *(USAN, rINN)*

Atlizumab; MRA; R-1569; Tocilizumabum; Тоцилизумаб. Immunoglobulin G1, anti-(human interleukin 6 receptor) (human-mouse monoclonal MRA heavy chain), disulfide with human-mouse monoclonal MRA κ-chain, dimer.

CAS — 375823-41-9.

ATC — L04AC07.

ATC Vet — QL04AC07.
UNII — I031V2H011.

Uses and Administration

Antagonists to the interleukin-6 receptor block the actions of interleukin-6 (p. 2534.1) and are under investigation for rheumatoid arthritis, systemic-onset juvenile idiopathic arthritis, adult-onset Still's disease, Crohn's disease, and haemolytic anaemia.

Tocilizumab is a recombinant monoclonal antibody that targets the interleukin-6 receptor and is used for the treatment of rheumatoid arthritis (p. 13.2) and some forms of juvenile idiopathic arthritis (p. 12.1). It is also used for the treatment of Castleman's disease, a rare lymphoproliferative disorder.

Tocilizumab is given with methotrexate (p. 822.2) for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have not responded to, or are intolerant of, disease-modifying antirheumatic drugs including TNF antagonists. It may also be given as monotherapy in patients who are unable to tolerate methotrexate or in whom methotrexate would otherwise be inappropriate. Tocilizumab is given every 4 weeks by intravenous infusion over 1 hour in a dose of 8 mg/kg; the initial dose may be 4 or 8 mg/kg and the maximum dose per infusion is 800 mg. For doses in children with juvenile idiopathic arthritis see Administration in Children, below.

Neutrophil and platelet counts and liver enzyme values should be monitored during treatment, and in the event of altered or abnormal counts or levels, tocilizumab treatment may need to be suspended until there is improvement, or treatment stopped altogether.

References.

1. Nishimoto N, *et al.* Improvement in Castleman's disease by humanized anti-interleukin-6 receptor antibody therapy. *Blood* 2000; 95: 56–61.
2. Ito H, *et al.* A pilot randomized trial of a human anti-interleukin-6 receptor monoclonal antibody in active Crohn's disease. *Gastroenterology* 2004; 126: 989–96.
3. Nishimoto N. Clinical studies in patients with Castleman's disease, Crohn's disease, and rheumatoid arthritis in Japan. *Clin Rev Allergy Immunol* 2005; 28: 221–30.
4. Maini RN, *et al.* Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. *Arthritis Rheum* 2006; 54: 2817–29.
5. Paul-Pletzer K. Tocilizumab: blockade of interleukin-6 signaling pathway as a therapeutic strategy for inflammatory disorders. *Drugs Today* 2006; 42: 559–76.
6. Nishimoto N, Kishimoto T. Interleukin 6: from bench to bedside. *Nat Clin Pract Rheumatol* 2006; 2: 619–26. Correction. *ibid.*; 691.
7. Kanda J, *et al.* Reversible cardiomyopathy associated with multicentric Castleman disease: successful treatment with tocilizumab, an anti-interleukin 6 receptor antibody. *Int J Hematol* 2007; 85: 207–11.
8. Matsuyama M, *et al.* Anti-interleukin-6 receptor antibody (tocilizumab) treatment of multicentric Castleman's disease. *Intern Med* 2007; 46: 771–4.
9. Smolen JS, *et al.* OPTION Investigators. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. *Lancet* 2008; 371: 987–97.
10. Sebba A. Tocilizumab: the first interleukin-6-receptor inhibitor. *Am J Health-Syst Pharm* 2008; 65: 1413–8.
11. Genovese MC, *et al.* Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. *Arthritis Rheum* 2008; 58: 2968–80.
12. Emery P, *et al.* IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. *Ann Rheum Dis* 2008; 67: 1516–23.
13. Oldfield V, *et al.* Tocilizumab: a review of its use in the management of rheumatoid arthritis. *Drugs* 2009; 69: 609–32.
14. Jones G, *et al.* Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. *Ann Rheum Dis* 2010; 69: 88–96.
15. NICE. Tocilizumab for the treatment of rheumatoid arthritis (rapid review of technology appraisal guidance 198). Technology Appraisal Guidance 247 (issued February 2012). Available at: http://www.nice.org.uk/nicemedia/live/13669/58202/58202.pdf (accessed 02/08/13)
16. Gabay C, *et al.* Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. *Lancet* 2013; 381: 1541–50.

Administration in children. Tocilizumab may be used alone or with methotrexate for the treatment of active systemic juvenile idiopathic arthritis or juvenile idiopathic polyarthritis, in children aged 2 years and over.[1-5] The recommended dose in systemic juvenile idiopathic arthritis is 12 mg/kg in children weighing less than 30 kg, or 8 mg/kg in those weighing 30 kg and over; doses should be given once every 2 weeks as an intravenous infusion over 1 hour. The recommended dose in juvenile idiopathic polyarthritis is 10 mg/kg in children weighing less than 30 kg, or 8 mg/kg in those weighing 30 kg and over; doses should be given once every 4 weeks as an intravenous infusion over 1 hour.

1. Yokota S, *et al.* Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. *Lancet* 2008; 371: 998–1006.
2. NICE. Tocilizumab for the treatment of systemic juvenile idiopathic arthritis: Technology Appraisal Guidance 238 (issued December 2011). Available at: http://www.nice.org.uk/nicemedia/live/13627/57489/57489.pdf (accessed 02/08/13)
3. Decelle K, Horton ER. Tocilizumab for the treatment of juvenile idiopathic arthritis. *Ann Pharmacother* 2012; 46: 822–9.
4. De Benedetti F, *et al.* PRINTO. PRCSG. Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. *N Engl J Med* 2012; 367: 2385–95.
5. Imagawa T, *et al.* Safety and efficacy of tocilizumab, an anti-IL-6-receptor monoclonal antibody, in patients with polyarticular-course juvenile idiopathic arthritis. *Mod Rheumatol* 2012; 22: 109–15.

Adverse Effects and Precautions

The adverse effects reported most commonly with tocilizumab are headache, hypertension, nasopharyngitis, respiratory-tract infections, hypercholesterolaemia, and increased liver enzyme values. Conjunctivitis, dizziness, gastritis, mouth ulceration, pruritus, and rash have also been reported. Infusion reactions and hypersensitivity have also occurred and fatal anaphylaxis has been reported. If a hypersensitivity reaction is suspected, the infusion should be stopped immediately and appropriate treatment given. Tocilizumab treatment should be permanently discontinued in those patients.

Treatment with tocilizumab should not be started in patients with active infections. If a patient develops a serious infection during treatment, tocilizumab should be interrupted until the infection has been controlled. Tocilizumab should be used with caution in patients with a history of recurrent or chronic infections or with underlying disorders (e.g. diverticulitis, diabetes mellitus) that may increase the risk of developing infections. Patients should be screened for latent tuberculosis infection before starting tocilizumab treatment.

Complications of diverticulitis have occasionally been reported with tocilizumab, and it should therefore be used with caution in patients with a history of this condition or of gastrointestinal ulceration. Patients presenting with symptoms such as abdominal pain, haemorrhage, or unexplained change in bowel habits with fever that might indicate complicated diverticulitis should be evaluated promptly.

As raised liver enzyme values have been reported with tocilizumab, particularly when given with methotrexate, it should be used with caution in patients with hepatic impairment since its safety in such patients has not been adequately studied.

Decreases in neutrophil and platelet counts have occurred with tocilizumab given with methotrexate, and the risk of neutropenia may be increased in patients previously treated with a tumour necrosis factor antagonist. Tocilizumab should therefore be used with caution in patients with low neutrophil or platelet counts; it should not be started in treatment-naive patients if the absolute neutrophil count is below 2000 cells/microlitre.

Live or attenuated vaccines should not be given at the same time as tocilizumab because of lack of safety data. For similar reasons, tocilizumab is not recommended for use with other biological agents used in the treatment of rheumatoid arthritis.

Dizziness has been reported with tocilizumab; if affected, patients should avoid driving or operating machinery.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tocilizumab as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Interactions

During inflammation the expression of cytochrome P450 isoenzymes is suppressed by cytokines such as interleukin-6, and cytochrome P450 expression may therefore be normalised when treatment with a cytokine inhibitor such as tocilizumab is started. Also, since tocilizumab has a long elimination half-life, its effect on cytochrome P450 isoenzyme activity may last for several weeks after stopping treatment. Therefore when starting or stopping therapy with tocilizumab, patients being treated with drugs that are metabolised by cytochrome P450 isoenzymes CYP1A2, CYP2C9, CYP2C19, and CYP3A4, (e.g. atorvastatin, calcium-channel blockers, theophylline, warfarin, phenytoin, ciclosporin, or benzodiazepines) should be monitored as doses of these drugs may need to be adjusted.

References.

1. Kim S, *et al.* Interleukin-6 and cytochrome-P450, reason for concern? *Rheumatol Int* 2012; 32: 2601–4.

Pharmacokinetics

Tocilizumab undergoes biphasic elimination from the circulation after intravenous dosing. Its clearance and half-life are concentration-dependent; at low serum concentrations, clearance is non-linear due to binding of tocilizumab to the interleukin-6 receptor, while at higher concentration the non-linear pathway is saturated and clearance is dominated by a linear clearance pathway mediated by the reticuloendothelial system. Furthermore the non-linear pathway is not saturated continuously within a 4-week dosing interval, and half-life declines within the dosing period.

In adults with rheumatoid arthritis, tocilizumab has a half-life of up to 11 days at steady-state dosing of 4 mg/kg every 4 weeks, and up to 13 days with 8 mg/kg every 4 weeks. The half-life in patients with systemic juvenile idiopathic arthritis is up to 23 days, and up to 16 days for those with juvenile idiopathic polyarthritis.

References.

1. Frey N, *et al.* Population pharmacokinetic analysis of tocilizumab in patients with rheumatoid arthritis. *J Clin Pharmacol* 2010; 50: 754–66.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Actemra; *Austral.*: Actemra; *Austria*: RoActemra; *Belg.*: RoActemra; *Braz.*: Actemra; *Canad.*: Actemra; *Chile*: Actemra; *Cz.*: RoActemra; *Denm.*: RoActemra; *Fr.*: RoActemra; *Ger.*: RoActemra; *Gr.*: RoActemra; *Hong Kong*: Actemra; *Hung.*: RoActemra; *Irl.*: RoActemra; *Israel*: Actemra; *Jpn*: Actemra; *Mex.*: RoActemra; *Neth.*: RoActemra; *Norw.*: RoActemra; *NZ*: Actemra; *Philipp.*: Actemra; *Pol.*: RoActemra; *Port.*: RoActemra; *Rus.*: Actemra (Актемра); *Spain*: RoActemra; *Swed.*: RoActemra; *Switz.*: Actemra; *Thai.*: Actemra; *UK*: RoActemra; *Ukr.*: Actemra (Актемра); *USA*: Actemra.

Isonixin *(rINN)*

Isonixine; Isonixino; Isonixinum; Изониксин.
2-Hydroxy-*N*-(2,6-dimethylphenyl)nicotinamide.
$C_{14}H_{14}N_2O_2$=242.3
CAS — 57021-61-1.
UNII — BYX6E7M5QE.

Profile

Isonixin is an NSAID (p. 102.3) that has been used in the management of pain and inflammation associated with musculoskeletal and joint disorders. It has been used in doses of 400 mg two to four times daily orally or by rectal suppository. It has also been applied topically as a 2.5% cream.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Spain*: Nixyn.

Multi-ingredient Preparations. *Spain*: Nixyn.

Kebuzone *(rINN)*

Kebuzona; Kébuzone; Kebuzonum; Ketophenylbutazone; Кебузон.
4-(3-Oxobutyl)-1,2-diphenylpyrazolidine-3,5-dione.
$C_{19}H_{18}N_2O_3$=322.4
CAS — 853-34-9.
ATC — M01AA06.
ATC Vet — QM01AA06.
UNII — 4VD83UL6Y6.

Profile

Kebuzone, a phenylbutazone derivative, is an NSAID (p. 102.3). It has been given for musculoskeletal, joint, and soft-tissue disorders in oral doses of up to 1.5 g daily in divided doses. Kebuzone has also been given as the sodium salt by intramuscular injection in doses equivalent to 1 g of base once or twice daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Rheumesser.

Ketobemidone Hydrochloride *(BANM, rINNM)*

Cetobemidona, hidrocloruro de; Cétobémidone, Chlorhydrate de; Cetobemidone Hydrochloride; Cetobemidoni Hydrochloridum; Hidrocloruro de cetobemidona; Ketobemidonhydrochlorid; Ketobemidon-hydrochlorid; Ketobemidonhydroklorid; Ketobemidoni Hydrochloridum; Ketobemidonihydrokloridi; Ketobemidono hidrochloridas; Кетобемидона Гидрохлорид.
1-(4-*m*-Hydroxyphenyl-1-methyl-4-piperidyl)propan-1-one hydrochloride.

$C_{15}H_{21}NO_2$,HCl=283.8
CAS — 469-79-4 (ketobemidone); 5965-49-1 (ketobemidone hydrochloride).
ATC — N02AB01.
ATC Vet — QN02AB01.
UNII — U9U6LTV80K.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Ketobemidone Hydrochloride). White or almost white, crystalline powder. Freely soluble in water; soluble in alcohol; very slightly soluble in dichloromethane. A 1% solution in water has a pH of 4.5 to 5.5.

Profile

Ketobemidone is an opioid analgesic (p. 108.1). It has been given as the hydrochloride orally, by injection, or rectally, sometimes with an antispasmodic.

References.
1. Al-Shurbaji A, Tokics L. The pharmacokinetics of ketobemidone in critically ill patients. *Br J Clin Pharmacol* 2002; **54**: 583–6.
2. Jylli L, *et al.* Comparison of the analgesic efficacy of ketobemidone and morphine for management of postoperative pain in children: a randomized, controlled study. *Acta Anaesthesiol Scand* 2004; **48**: 1256–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ketobemidone as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Norw.*: Ketorax; *Swed.*: Ketogan Novum.

Multi-ingredient Preparations. *Denm.*: Ketogan; *Norw.*: Ketogan; *Swed.*: Ketogan.

Ketoprofen (BAN, USAN, rINN)

Ketoprofeeni; Ketoprofén; Ketoprofenas; Kétoprofène; Ketoprofeno; Ketoprofenum; RP-19583; Кетопрофен.
(*RS*)-2-(3-Benzoylphenyl)propionic acid.
$C_{16}H_{14}O_3$=254.3
CAS — 22071-15-4 (ketoprofen); 57469-78-0 (ketoprofen lysine); 57495-14-4 (ketoprofen sodium).
ATC — M01AE03; M02AA10.
ATC Vet — QM01AE03; QM02AA10.
UNII — 90Y4QC304K.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Ketoprofen). A white or almost white, crystalline powder. M.p. 94 degrees to 97 degrees. Practically insoluble in water; freely soluble in alcohol, in acetone, and in dichloromethane.

USP 36: (Ketoprofen). Store in airtight containers.

Dexketoprofen Trometamol (BANM, rINNM)

(*S*)-(+)-Dexketoprofen Trometamol; Dexkétoprofène Trométamol; Dexketoprofeno trometamol; Dexketoprofenum Trometamolum; Декскетопрофен Трометамол.
CAS — 22161-81-5 (dexketoprofen).
ATC — M01AE17.
ATC Vet — QM01AE17.
UNII — N674F7L21E.

Uses and Administration

Ketoprofen, a propionic acid derivative, is an NSAID (p. 102.3). Its anti-inflammatory properties may be weaker than those of some other NSAIDs. Ketoprofen is a racemic mixture; in *animal* studies the *S*-(+) enantiomer, dexketoprofen, has about twice the analgesic activity of ketoprofen by weight.

Ketoprofen is used in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis, and in peri-articular disorders such as bursitis and tendinitis. It is also used in dysmenorrhoea, postoperative pain, in painful and inflammatory conditions such as acute gout or soft-tissue disorders, and to reduce fever. Dexketoprofen is used in the treatment of mild to moderate pain such as musculoskeletal pain, dysmenorrhoea, or dental pain.

In the treatment of rheumatic disorders a usual oral daily dose of ***ketoprofen*** is 100 to 200 mg in 2 to 4 divided doses; modified-release formulations taken once daily may also be used. Some licensed product information suggests initial oral doses of 75 mg three times daily or 50 mg four times daily increased as needed to a maximum of 300 mg daily in divided doses. Ketoprofen may also be given rectally as suppositories in a dose of 100 mg at night or 100 mg twice daily. It is recommended that the total daily combined oral and rectal dose should not exceed 200 mg. The usual oral dose for the treatment of other painful conditions including dysmenorrhoea is 25 to 50 mg every 6 to 8 hours. For details on the use of ketoprofen in patients with hepatic or renal impairment, see below.

Ketoprofen may be given by deep intramuscular injection into the gluteal muscle for acute exacerbations of musculoskeletal, joint, peri-articular, and soft-tissue disorders, and in the management of pain after orthopaedic surgery. Doses of 50 to 100 mg may be given every 4 hours, up to a maximum dose of 200 mg in 24 hours for up to 3 days. In some countries, ketoprofen has also been given intravenously in similar doses.

Ketoprofen may be applied as a 2.5% gel for local pain relief. Doses vary slightly between preparations: typically, they are applied 2 to 4 times daily for up to 10 days.

Dexketoprofen is given orally as the trometamol salt. Doses are expressed in terms of the base; dexketoprofen trometamol 36.9 mg is equivalent to about 25 mg of dexketoprofen. Usual doses are 12.5 mg every 4 to 6 hours or 25 mg every 8 hours; the total daily dose should not exceed 75 mg. Elderly patients should be started on a total daily dose not exceeding 50 mg. Dose reductions are also necessary in patients with hepatic or renal impairment, see below. It is usually recommended that NSAIDs are taken with or after food to reduce any adverse gastrointestinal effects; however, licensed product information for dexketoprofen states that absorption is delayed if the drug is taken with food and therefore recommends that in acute pain dexketoprofen should be given at least 30 minutes before food.

Ketoprofen has also been used as the hydrochloride, lysine, and sodium salts.

Reviews.
1. Mauleón D, *et al.* Preclinical and clinical development of dexketoprofen. *Drugs* 1996; **52**: 24–46.
2. Moore RA, Barden J. Systematic review of dexketoprofen in acute and chronic pain. *BMC Clin Pharmacol* 2008; **8**: 11. Available at: http://www.biomedcentral.com/content/pdf/1472-6904-8-11.pdf (accessed 17/09/09)

Administration in hepatic or renal impairment. No specific dosage recommendations for racemic *ketoprofen* in patients with hepatic or renal impairment are given by UK licensed product information, although the drug is contra-indicated in severe renal impairment and it is advised that the dose be kept as low as possible and renal function be monitored in more moderate renal impairment (but see also Renal Impairment, below). In the USA, however, it has been recommended that patients with hepatic impairment and a serum albumin concentration of less than 3.5 g/dL should be given a maximum initial daily dose of 100 mg orally. Patients with mild renal impairment should be given a maximum daily dose of 150 mg and those with more severe impairment (GFR less than 25 mL/minute per 1.73 m^2 or end-stage renal impairment) should not exceed a maximum daily dose of 100 mg.

UK licensed product information for *dexketoprofen* recommends a reduced initial daily dose of 50 mg orally in patients with mild to moderate hepatic or mild renal impairment. Dexketoprofen should not be used in patients with severe hepatic or moderate to severe renal impairment.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3.

When ketoprofen is given intramuscularly there may be pain at the injection site and occasionally tissue damage. Topical preparations containing ketoprofen may cause application site reactions. Ketoprofen suppositories may cause local irritation; rectal use should be avoided in patients with a history of proctitis or haemorrhoids. Ketoprofen should be used with caution in patients with renal or hepatic impairment; it should not be used in those with severe renal impairment.

Dexketoprofen should be avoided in patients with moderate to severe renal or severe hepatic impairment, and in those with severe heart failure.

Effects on the skin. Contact and photoallergic dermatitis have been seen after topical use of ketoprofen.[1,2] A retrospective study[3] found that of the 139 cases of contact reactions to topical NSAIDs reported to the Spanish Pharmacovigilance System between 1996 and 2001, 84 involved ketoprofen (16 allergy; 68 photoallergy). Totals for other NSAIDs included piroxicam (21), etofenamate (10), piketoprofen (5), salicylates (4), fepradinol (3), diclofenac (3), indometacin (2), phenylbutazone (2), benzydamine (2), aceclofenac (1), naproxen (1), and mabuprofen (1). Analysis indicated that the number of reports for topical ketoprofen was disproportionately high in relation to its usage.

1. Matthieu L, *et al.* Contact and photocontact allergy to ketoprofen: the Belgian experience. *Contact Dermatitis* 2004; **50**: 238–41.
2. Hindsén M, *et al.* Photoallergic contact dermatitis from ketoprofen in southern Sweden. *Contact Dermatitis* 2006; **54**: 150–7.
3. Diaz RL, *et al.* Greater allergenicity of topical ketoprofen in contact dermatitis confirmed by use. *Contact Dermatitis* 2006; **54**: 239–43.

Hypersensitivity. Life-threatening asthma, urticaria, and angioedema developed in 2 aspirin-sensitive patients after taking ketoprofen 50 mg orally.[1] Cardiac and respiratory arrest occurred in an asthmatic patient shortly after taking ketoprofen.[2] Life-threatening asthma has also occurred after topical application of ketoprofen.[3]

Delayed skin hypersensitivity was seen in a patient who used a topical gel containing ketoprofen.[4] The reaction recurred on rechallenge to ketoprofen gel but not to a similar gel containing diclofenac. The authors of the report noted that the UK CSM had received 15 reports of skin reactions to ketoprofen gel, including two each of dermatitis and urticaria.

See also Effects on the Skin, above.
1. Frith P, *et al.* Life-threatening asthma, urticaria, and angioedema after ketoprofen. *Lancet* 1978; **ii**: 847–8.
2. Schreuder G. Ketoprofen: possible idiosyncratic acute bronchospasm. *Med J Aust* 1990; **152**: 332–3.
3. Kashiwabara K, Nakamura H. Analgesic-induced asthma caused by 2.0% ketoprofen adhesive agents, but not by 0.3% agents. *Intern Med* 2001; **40**: 124–6.
4. Oh VMS. Ketoprofen gel and delayed hypersensitivity dermatitis. *BMJ* 1994; **309**: 512.

Myasthenia gravis. A cholinergic crisis was precipitated by a single oral dose of ketoprofen 50 mg in a patient with well-controlled myasthenia gravis.[1] The patient had previously noted a similar but milder reaction with aspirin, but not with paracetamol.

1. McDowell IFW, McConnell JB. Cholinergic crisis in myasthenia gravis precipitated by ketoprofen. *BMJ* 1985; **291**: 1094.

Pancreatitis. Pancreatitis has been associated with ketoprofen use.[1,2]

1. Cobb TK, Pierce JR. Acute pancreatitis associated with ketoprofen. *South Med J* 1992; **85**: 430–1.
2. Métè D, *et al.* Pancréatite aiguë et kétoprofène. *Gastroenterol Clin Biol* 2001; **25**: 721–2.

Photosensitivity. Ketoprofen causes photosensitivity reactions[1,2] and cross-sensitivity to other drugs, notably the fibrates bezafibrate, ciprofibrate, and fenofibrate, has also been reported. The cross reactions were attributed to the benzoyl ketone structure that the drugs have in common.

See also Effects on the Skin (above).
1. Bagheri H, *et al.* Photosensitivity to ketoprofen: mechanisms and pharmacoepidemiological data. *Drug Safety* 2000; **22**: 339–49.
2. Veyrac G, *et al.* Bilan de l'enquête nationale sur les effets indésirables cutanés du kétoprofène gel enregistrés entre le 01/09/1996 et le 31/08/2000. *Therapie* 2002; **57**: 55–64.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ketoprofen as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 23/10/11)

Renal impairment. The elimination half-life and unbound plasma concentrations of dexketoprofen are increased in patients with renal impairment given racemic ketoprofen;[1,2] this appears to be mainly attributable to impaired renal clearance of the acyl-glucuronide conjugates in a stereoselective fashion, with subsequent hydrolysis of the unstable conjugate back to the aglycone producing increased plasma-ketoprofen concentrations.[2,3] The authors of one study suggested[3] that dosage adjustments of racemic ketoprofen were indicated only for patients with moderately severe renal failure (creatinine clearance of less than 20 mL/minute).

For advice on the dose of dexketoprofen in patients with renal impairment see under Uses and Administration, above. See also Adverse Effects and Precautions, above.
1. Hayball PJ, *et al.* The influence of renal function on the enantioselective pharmacokinetics and pharmacodynamics of ketoprofen in patients with rheumatoid arthritis. *Br J Clin Pharmacol* 1993; **36**: 185–93.
2. Grubb NG, *et al.* Stereoselective pharmacokinetics of ketoprofen and ketoprofen glucuronide in end-stage renal disease: evidence for a 'futile cycle' of elimination. *Br J Clin Pharmacol* 1999; **48**: 494–500.
3. Skeith KJ, *et al.* The influence of renal function on the pharmacokinetics of unchanged and acyl-glucuroconjugated ketoprofen enantiomers after 50 and 100 mg racemic ketoprofen. *Br J Clin Pharmacol* 1996; **42**: 163–9.

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Probenecid delays the excretion of ketoprofen and decreases its extent of protein binding resulting in increased plasma-ketoprofen concentrations. Not unexpectedly, a similar interaction may be seen with dexketoprofen and probenecid.

Pharmacokinetics

Ketoprofen is readily absorbed from the gastrointestinal tract; peak plasma concentrations occur about 0.5 to 2 hours after an oral dose. When ketoprofen is given with food, the

bioavailability is not altered but the rate of absorption is slowed. Ketoprofen is well absorbed from the intramuscular and rectal routes; only a small amount of percutaneous absorption occurs after topical application. Ketoprofen is 99% bound to plasma proteins and substantial concentrations of drug are found in the synovial fluid. The elimination half-life in plasma is about 1.5 to 4 hours. Ketoprofen is metabolised mainly by conjugation with glucuronic acid, and is excreted mainly in the urine.

Ketoprofen possesses a chiral centre. It is usually given as the racemate but its pharmacological actions appear to be due largely to the *S*-enantiomer, dexketoprofen. The pharmacokinetics of ketoprofen appear to show little stereoselectivity (but see under Renal Impairment, p. 79.3).

References.

1. Debruyne D, *et al.* Clinical pharmacokinetics of ketoprofen after single intravenous administration as a bolus or infusion. *Clin Pharmacokinet* 1987; 12: 214–21.
2. Flouvat B, *et al.* Pharmacokinetics of ketoprofen in man after repeated percutaneous administration. *Arzneimittelforschung* 1989; 39: 812–15.
3. Jamali F, Brocks DR. Clinical pharmacokinetics of ketoprofen and its enantiomers. *Clin Pharmacokinet* 1990; 19: 197–217.
4. Geisslinger G, *et al.* Pharmacokinetics of ketoprofen enantiomers after different doses of the racemate. *Br J Clin Pharmacol* 1995; 40: 73–5.
5. Barbanoj MJ, *et al.* Pharmacokinetics of dexketoprofen trometamol in healthy volunteers after single and repeated oral doses. *J Clin Pharmacol* 1998; 38: 335–40S.
6. Kokki H, *et al.* Pharmacokinetics of ketoprofen syrup in small children. *J Clin Pharmacol* 2000; 40: 354–9.
7. Barbanoj M-J, *et al.* Clinical pharmacokinetics of dexketoprofen. *Clin Pharmacokinet* 2001; 40: 245–62.
8. Kokki H, *et al.* Pharmacokinetics of intravenous and rectal ketoprofen in young children. *Clin Pharmacokinet* 2003; 42: 373–9.
9. Valles J, *et al.* Clinical pharmacokinetics of parenteral dexketoprofen trometamol in healthy subjects. *Methods Find Exp Clin Pharmacol* 2006; 28 (suppl A): 7–12.
10. Valles J, *et al.* Single and repeated dose pharmacokinetics of dexketoprofen trometamol in young and elderly subjects. *Methods Find Exp Clin Pharmacol* 2006; 28 (suppl A): 13–19.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Enantyum; Helenil; Ketfren; Salicrem K; *Austral.*: Orudis; Oruvail; *Austria*: Enantyum; Fastum; Ketesse; Ketospray; Profenid; *Belg.*: Bi-Rofenid; Enantyum; Fastum; Ketesse; Rofenid; *Braz.*: Artrifenil; Artrinid; Artrosil; Bi-Profenid; Ceprofen; Cetofenid; Flamador; Profenid; *Canad.*: Apo-Keto; Novo-Keto†; *Chile*: Bonil; Cirus; Desketo; Dolo-Ketazon; Dolofar; Dolostat; Fastum†; Flogofin; Profenid; Relatene; Talflex; *China*: Ao Ding Ni (奥丁尼); Arket (琪和); Fastum (法斯通); Fen Li (芬利); Ketotop (基多托); Kui La Lan (舜拉兰); Ricfen (锐迈); San Si Teng (散斯腾); Shu Li Ang (枢力昂); Wei Kang Li (维康利); Youbaifen (优百芬); *Cz.*: Dexoket; Fastum; Keplat; Ketesse; Ketonal; Profenid; Prontoflex; Prontoket†; *Denm.*: Enantyum†; Fastum; Ketesse; Ketospray; Orofen†; Orudis†; *Fin.*: Enantyum†; Ketesse; Keto; Ketomex; Ketorin; Orudis; Zon†; *Fr.*: Bi-Profenid; Ketesse; Ketum; Profemigr; Profenid; Topfena†; Toprec; *Ger.*: Advel†; Alrheumun; Dolormin mit Ketoprofen†; Effekton mit Ketoprofen; Gabrilen; Phardol Schmerz; Spondylon†; Sympal; *Gr.*: Drastirel; Farbovil; Ketodur; Menaril; Nosatel; Oruvail; Profinject; Solu-Ket; Totifen; Viaxal; Vofen; *Hong Kong*: Apo-Keto-E†; Fastum; Mohrus; Orudis; Oruvail†; *Hung.*: Algoflex; Fastum; Keplat; Ketodex; Ketospray; Profenid; Prontoket†; *India*: Fastum; Infen; Ketofen; Ketopatch; Ostofen; *Indon.*: Altofen; Fetik; Gatofen; Kaltrofen; Ketesse; Ketros; Lantiflam; Molaflam; Nasaflam; Nazovell; Noflam; Ovurila; Profecom; Profenid; Profika; Pronalges; Protofen; Remapro; Rematof†; Rhetoflam; Rofiden; Suprafenid; *Irl.*: Fastum; Keral; Orugesic†; Oruvail; *Israel*: Fastum†; Ketospray; Profenid; *Ital.*: Alket; Ardbeg; Artrosilene; Desketo; Dolgosin; Enantyum; Euketos; Fastum; Flexen; Hiruflog; Ibifen; Isofenal; Keplat; Ketartrium†; Ketesse; Ketodol; Ketofarm; Ketoplus; Ketoselect; Ketum; Lasoartro; Lasonil Gel; Liotondol; Oki; Orudis; Steofen; *Jpn*: Mohrus; *Malaysia*: Apo-Keto; Fastum; KefenTech; Kenhancer; Kenofen; Ketofen; Orudis; *Mex.*: Arket†; Arthril; Bi-Profenid; Bibix†; Efiken; K-Profen; Keral; Ketoflex; Oki 3A; Orudis; Painsik; Profenid; Stadium; *Neth.*: Enantyum; Orudis; Oruvail; Oscorel; Rilies; Stadium; *Norw.*: Orudis; Zon†; *NZ*: Orudis†; Oruvail; *Philipp.*: Fastum; Floramil; Keon; Ketofen†; Ketotop; Orudis; Udzapen†; *Pol.*: Bi-Profenid; Dexak; Fastum; Febrofen; Ketonal; Ketoprom; Ketopronil; Ketores; Ketospray; Profenid; Refastin; Ultrafastin; *Port.*: Enantyum; Fastum; Keplat; Ketesse; Profenid; *Rus.*: Artrosilen (Артрозилен); Artrum (Артрум); Bystrumgel (Быструмгель); Dexalgin (Дексалгин); Fastum (Фастум); Febrofid (Феброфид); Flamax (Фламакс); Flexen (Флексен); Ketonal (Кетонал); Oki (Оки); *S.Afr.*: Fastum; Ketoflam; Myproflam; Oruvail†; *Singapore*: Apo-Keto; Fastum; KefenTech; Kenhancer; Ketesse; Oruvail; Pronalges; *Spain*: Adolquir; Arcental; Enangel; Enantyum; Extraplus; Fastum; Ketesgel; Ketesse; Orudis; Quiralam; Quirgel; *Swed.*: Enantyum; Ketesse; Ketoflex†; Orudis; Siduro; Zon†; *Switz.*: Fastum; Ketesse; *Thai.*: Fastum; Kaprofen†; Lolita; Oruvail; Profenid†; Rhumafen; Rofepain; Vestam; *Turk.*: Arveles; Bi-Profenid; Fastjel; Ketesse; Keto; Ketofen†; Profenid; Proflam; *UK*: Axorid; Keral; Ketocid; Ketovail; Larafen; Orudis; Oruvail; Powergel; Tiloket; *Ukr.*: Dexalgin (Дексалгин); F-Gel (Ф-Гель); Fastum (Фастум); Ketonal (Кетонал); Ketum (Кетум)†; Ultrafastin (Ультрафастин); Valusal (Валусал); *Venez.*: Dolomax; Kelfen; Keto; Ketoprof; Keydol; Lindilan; Orofeno; Peindol; Profenid.

Multi-ingredient Preparations. *Gr.*: Profenil Complex; *India*: Ketonal-D; Lupiflex; *Mex.*: Bifebral; Dolo Bedoyecta; Reumophan Alka; Reumophan Vit.

Pharmacopoeial Preparations

BP 2014: Ketoprofen Capsules; Ketoprofen Gel;
USP 36: Ketoprofen Extended-Release Capsules.

Ketorolac Trometamol *(BANM, rINNM)*

Ketorolaakkitrometamoli; Ketorolac-Trometamol; Kétorolac Trométamol; Ketorolac Tromethamine (USAN); Ketorolaco trometamol; Ketorolacum Trometamoli; Ketorolacum trometamolum; Ketorolak Trometamol; Ketorolak z trometamolem; Ketorolak-trometamol; Ketorolaktrometamol; RS-37619-00-31-3; RS-37619 (Ketorolac); Кеторолак Трометамол.

(±)-5-Benzoyl-2,3-dihydro-1*H*-pyrrolizine-1-carboxylic acid compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1).

$C_{19}H_{24}N_2O_6$=376.4

CAS — 74103-06-3 (ketorolac); 74103-07-4 (ketorolac trometamol).

ATC — M01AB15; S01BC05.

ATC Vet — QM01AB15; QS01BC05.

UNII — 4EVES946BQ.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Ketorolac Trometamol). A white or almost white, crystalline powder. Freely soluble in water and in methyl alcohol; slightly soluble in alcohol; practically insoluble in dichloromethane. A 1% solution in water has a pH of 5.7 to 6.7. Protect from light.

USP 36: (Ketorolac Tromethamine). A white to off-white, crystalline powder. Freely soluble in water and in methyl alcohol; slightly soluble in alcohol, in dehydrated alcohol, and in tetrahydrofuran; practically insoluble in acetone, in acetonitrile, in butyl alcohol, in dichloromethane, in dioxan, in ethyl acetate, in hexane, and in toluene. pH of a 1% solution in water is between 5.7 and 6.7. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Ketorolac, a pyrrolizine carboxylic acid derivative structurally related to indometacin (p. 71.2), is an NSAID (p. 102.3). It is used mainly as an analgesic.

Ketorolac is used intramuscularly, intravenously, or orally as the trometamol salt in the short-term management of moderate to severe **postoperative pain**. However, it should be noted that because of concerns over the high incidence of reported adverse effects with ketorolac its dosage and maximum duration of use are restricted. The recommended maximum duration for parenteral therapy is 2 days in the UK; if required, patients should be transferred to oral therapy with another analgesic. In the USA it is recommended that the maximum combined duration of use of parenteral and oral ketorolac should not exceed 5 days.

- In the UK the recommended initial dose by the *parenteral* route is 10 mg of ketorolac trometamol followed by 10 to 30 mg every 4 to 6 hours as required, although ketorolac may be given as often as every 2 hours in the initial postoperative period if required. The total maximum daily dose is 90 mg (60 mg in the elderly, patients with mild renal impairment, and in those weighing less than 50 kg). Intravenous injections should be given over at least 15 seconds.
- Regimens in use in the USA include a single intramuscular dose of 60 mg or a single intravenous dose of 30 mg, or a multiple-dose regimen comprising 30 mg every 6 hours intramuscularly or intravenously, up to a maximum of 120 mg daily. These doses should be halved in the elderly (aged 65 years or older), the renally impaired, and those weighing less than 50 kg.
- In the USA ketorolac trometamol may also be given *orally* as continuation therapy from parenteral dosing. The recommended dose is 20 mg (10 mg in the elderly, the renally impaired, and those weighing under 50 kg), followed by 10 mg every 4 to 6 hours to a maximum of 40 mg daily.

For doses in children see Administration in Children, below.

In the USA, ketorolac trometamol is also approved for the short-term management of moderate to moderately severe **acute pain** as an *intranasal* spray. It is recommended that the maximum duration of use either alone or with other ketorolac preparations should not exceed 5 days; it should not be used at the same time as other ketorolac preparations. The recommended dose is 15.75 mg in each nostril every 6 to 8 hours to a total maximum daily dose of 126 mg. In patients aged 65 years or older, the renally impaired, and those weighing less than 50 kg, the recommended dose is 15.75 mg in one nostril every 6 to 8 hours to a total maximum daily dose of 63 mg.

Ketorolac trometamol is used as 0.5% eye drops to relieve **ocular itching** associated with seasonal allergic conjunctivitis. Ketorolac trometamol eye drops 0.5% have also been used for the topical treatment of **cystoid macular oedema** and for the prevention and reduction of **inflammation** associated with ocular surgery. In the USA, 0.4 or 0.45% eye drops are also available for postoperative ocular inflammation.

Reviews.

1. Gillis JC, Brogden RN. Ketorolac: a reappraisal of its pharmacodynamic and pharmacokinetic properties and therapeutic use in pain management. *Drugs* 1997; 53: 139–88.
2. Di Massa A, *et al.* Ketorolac for paediatric postoperative pain: a review. *Minerva Anestesiol* 2000; 66: 749–56.
3. Arora S, *et al.* Myth: parenteral ketorolac provides more effective analgesia than oral ibuprofen. *CJEM* 2007; 9: 30–2.
4. Schechter BA. Ketorolac tromethamine 0.4% as a treatment for allergic conjunctivitis [sic]. *Expert Opin Drug Metab Toxicol* 2008; 4: 507–11.
5. Sinha VR, *et al.* Ketorolac tromethamine formulations: an overview. *Expert Opin Drug Deliv* 2009; 6: 961–75.

Administration in children. Ketorolac trometamol may be used for the short-term management of moderate to severe postoperative pain in children. In the USA, children aged between 2 to 16 years may be given a single intramuscular dose of 1 mg/kg of ketorolac trometamol up to a maximum of 30 mg or a single intravenous dose of 500 micrograms/kg up to a maximum of 15 mg. In the UK, parenteral ketorolac is only licensed for those aged 16 and over; doses are as for adults (see above). However, the *BNFC* suggests that children aged 6 months to 16 years may be given an initial intravenous injection of 0.5 to 1 mg/kg (maximum of 15 mg), followed by 0.5 mg/kg (maximum of 15 mg) every 6 hours as required, to a maximum daily dose of 60 mg.

Oral ketorolac is not licensed for use in children.

Administration in renal impairment. Ketorolac is contra-indicated in patients with moderate to severe renal impairment; for suggested doses in less advanced renal impairment, see Uses and Administration, above.

Adverse Effects and Treatment

As for NSAIDs in general, p. 104.3.

Concern over the high incidence of reported adverse effects with ketorolac trometamol has led to its withdrawal in some countries while in others its permitted dosage and maximum duration of treatment have been reduced.

Adverse effects reported include gastrointestinal disturbances including gastrointestinal bleeding (especially in the elderly), perforation, and peptic ulceration. Hypersensitivity reactions such as anaphylaxis, rash, bronchospasm, laryngeal oedema, and hypotension have also occurred. Other adverse effects reported include drowsiness, dizziness, headache, mental and sensory changes, psychotic reactions, sweating, dry mouth, thirst, fever, convulsions, myalgia, aseptic meningitis, hypertension, dyspnoea, pulmonary oedema, bradycardia, chest pain, palpitations, fluid retention, increases in blood urea and creatinine, acute renal failure, oedema, hyponatraemia, hyperkalaemia, urinary frequency or retention, nephrotic syndrome, flank pain with or without haematuria, purpura, thrombocytopenia, epistaxis, inhibition of platelet aggregation, increased bleeding time, postoperative wound haemorrhage, haematoma, flushing or pallor, and pancreatitis. Severe skin reactions including Stevens-Johnson syndrome and Lyell's syndrome have been reported. Liver function changes may occur; hepatitis and liver failure have been reported. There may be pain at the site of injection.

The most frequently reported adverse effects of ketorolac intranasal spray were mild and transient local reactions such as nasal discomfort or irritation.

Ketorolac eye drops may produce transient stinging and other minor symptoms of ocular irritation. As with some other NSAIDs used in the eye, ketorolac has been implicated in reports of corneal toxicity (see Effects on the Eyes, p. 50.1).

Incidence of adverse effects. Adverse effects reported with ketorolac are mainly those common to all NSAIDs with gastrointestinal reactions being the most frequent followed by haematological, renal, hypersensitivity, and then neurological reactions. From 1990 to 1993, 97 reactions with a fatal outcome were reported worldwide.[1] The causes of death were: gastrointestinal bleeding or perforation (47 cases); renal impairment or insufficiency (20 cases); anaphylaxis or asthma (7 cases); haemorrhagic reactions (4 cases); and unexplained or miscellaneous causes (19 cases). Concern over the safety of ketorolac has led to adverse reactions being monitored closely and to the implementation of restrictions on dose and duration of treatment (see Uses and Administration, above). A post-marketing surveillance study[2] examined the risks of parenteral ketorolac in 9900 patients given 10272 courses of

ketorolac. The results indicated a dose-response relationship with average daily ketorolac dose for both gastrointestinal bleeding and operative site bleeding, the expected major risks, and an association between gastrointestinal bleeding and therapy for over 5 days. The risk of serious gastrointestinal bleeding and operative site bleeding was higher for elderly patients [licensed product information recommends that the elderly should not receive daily parenteral doses greater than 60 mg]. Although the overall associations between ketorolac use and both gastrointestinal bleeding and operative site bleeding are small, the risk becomes clinically important as doses increase, in elderly patients, and, for gastrointestinal bleeding only, when used for longer than 5 days.

US product information has consequently emphasised that ketorolac is a potent NSAID and is indicated only for the short-term management of moderate to severe pain and not for minor or chronic painful conditions; its use carries many risks and related adverse effects can be serious especially when used inappropriately. After examining data from the above study the EU Committee for Proprietary Medicinal Products adopted the opinion that ketorolac had a narrow therapeutic margin but that it was indicated for the short-term management of moderate to severe acute postoperative pain.

Further references to ketorolac's adverse effects are given below.[3-12]

1. CSM/MCA. Ketorolac: new restrictions on dose and duration of treatment. *Current Problems* 1993; 19: 5–6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024455&RevisionSelectionMethod=LatestReleased (accessed 07/11/07)
2. Strom BL, *et al.* Parenteral ketorolac and risk of gastrointestinal and operative site bleeding: a postmarketing surveillance study. *JAMA* 1996; 275: 376–82.
3. Rotenberg FA, Giannini VS. Hyperkalemia associated with ketorolac. *Ann Pharmacother* 1992; 26: 778–9.
4. Boras-Uber LA, Brackett NC. Ketorolac-induced acute renal failure. *Am J Med* 1992; 92: 450–2. Correction *ibid.*; 93: 117.
5. Schoch PH, *et al.* Acute renal failure in an elderly woman following intramuscular ketorolac administration. *Ann Pharmacother* 1992; 26: 1233–6.
6. Goetz CM, *et al.* Anaphylactoid reaction following ketorolac tromethamine administration. *Ann Pharmacother* 1992; 26: 1237–8.
7. Randi ML, *et al.* Haemolytic uraemic syndrome during treatment with ketorolac trometamol. *BMJ* 1993; 306: 186.
8. Fong J, Gora ML. Reversible renal insufficiency following ketorolac therapy. *Ann Pharmacother* 1993; 27: 510–12.
9. Corelli RL, Gericke KR. Renal insufficiency associated with intramuscular administration of ketorolac tromethamine. *Ann Pharmacother* 1993; 27: 1055–7.
10. Buck ML, Norwood VF. Ketorolac-induced acute renal failure in a previously healthy adolescent. *Pediatrics* 1996; 98: 294–6.
11. Feldman HI, *et al.* Parenteral ketorolac: the risk for acute renal failure. *Ann Intern Med* 1997; 126: 193–9.
12. Reinhart DJ, *et al.* Minimising the adverse effects of ketorolac. *Drug Safety* 2000; 22: 487–97.

Precautions

As for NSAIDs in general, p. 107.1.

In light of the concern over its toxicity, licensed product information for ketorolac recommends that it should not be used during pregnancy or labour, nor given to mothers who are breast feeding (but see below).

Ketorolac is contra-indicated in patients with a history of hypersensitivity to aspirin or other NSAIDs, a history of asthma, nasal polyps, bronchospasm, or angioedema, a history of peptic ulceration or gastrointestinal bleeding, in patients with moderate or severe renal impairment, and in those with hypovolaemia or dehydration. Ketorolac should not be given to patients with coagulation or haemorrhagic disorders or those with confirmed or suspected cerebrovascular bleeding. It is contra-indicated as a prophylactic analgesic before surgery and for intraoperative use because of its inhibitory effects on platelets; it should also not be given postoperatively to those who have undergone procedures with a high risk of haemorrhage.

The total daily dose of ketorolac should be reduced in the elderly and in patients weighing less than 50 kg. It is recommended that patients with mild renal impairment should receive a reduced dose of ketorolac and undergo close monitoring of renal function. Ketorolac should be used with caution in heart failure, hepatic impairment, and conditions leading to reduction in blood volume or in renal blood flow. Ketorolac should be withdrawn if clinical symptoms of hepatotoxicity develop.

Drowsiness and dizziness may affect the performance of skilled tasks such as driving.

Breast feeding. The concentration of ketorolac distributed into breast milk is very low and a study[1] considered that the amount ingested by the infant would probably be too small to be harmful. The American Academy of Pediatrics[2] also states that there have been no reports of any clinical effect on the infant associated with the use of ketorolac by breast-feeding mothers, and that therefore it may be considered to be usually compatible with breast feeding. Similarly, the *BNF* considers the amount to be too small to be harmful to breast-fed infants and US licensed product information permits its use. However, UK product information recommends that ketorolac should be avoided in mothers who are breast feeding.

1. Wischnik A, *et al.* The excretion of ketorolac tromethamine into breast milk after multiple oral dosing. *Eur J Clin Pharmacol* 1989; 36: 521–4.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 07/11/07)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ketorolac trometamol as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 23/10/11)

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Ketorolac should not be given to patients already receiving anticoagulants or to those who will require prophylactic anticoagulant therapy, including low-dose heparin. The risk of ketorolac-associated bleeding is also increased by other NSAIDs or aspirin and by pentoxifylline and use together should be avoided. Probenecid increases the half-life and plasma concentrations of ketorolac and the two drugs should not be given together.

Parasympathomimetics. Licensed product information for acetylcholine chloride ophthalmic preparations states that there have been reports that *acetylcholine* and *carbachol* have been ineffective when used in patients treated with topical (ophthalmic) NSAIDs.

Pharmacokinetics

Ketorolac trometamol is absorbed after intramuscular or oral doses. At physiological pH ketorolac trometamol dissociates to form an anionic ketorolac molecule which is less hydrophilic than the trometamol salt. Peak plasma concentrations of ketorolac occur within about 30 to 60 minutes; absorption after intramuscular injection may be slower than that after oral doses in some individuals. Ketorolac is over 99% bound to plasma proteins. It does not readily penetrate the blood-brain barrier. Ketorolac crosses the placenta and small amounts of drug are distributed into breast milk. The terminal plasma half-life is about 4 to 6 hours, but is about 6 to 7 hours in the elderly and 9 to 10 hours in patients with renal dysfunction. The major metabolic pathway is glucuronic acid conjugation; there is some *para*-hydroxylation. About 90% of a dose is excreted in urine as unchanged drug and conjugated and hydroxylated metabolites, the remainder is excreted in the faeces.

References.

1. Kauffman RE, *et al.* Enantiomer-selective pharmacokinetics and metabolism of ketorolac in children. *Clin Pharmacol Ther* 1999; 65: 382–8.
2. Hamunen K, *et al.* Stereoselective pharmacokinetics of ketorolac in children, adolescents and adults. *Acta Anaesthesiol Scand* 1999; 43: 1041–6.
3. Dsida RM, *et al.* Age-stratified pharmacokinetics of ketorolac tromethamine in pediatric surgical patients. *Anesth Analg* 2002; 94: 266–70.
4. McAleer SD, *et al.* Pharmacokinetics and safety of ketorolac following single intranasal and intramuscular administration in healthy volunteers. *J Clin Pharmacol* 2007; 47: 13–18.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Acular; Blocadol; Dolten; Kelac; Kemanat; Kerarer; Ketopharm; Klenac; Poenkerat; Sinalgico; Teledol; Tenkdol; Unicalm; ***Austral.***: Acular; Ketoral; Toradol; ***Austria***: Acular; ***Belg.***: Aculare; Taradyl; ***Braz.***: Acular; Cetrolac; Optilar; Toradol; Toragesic; ***Canad.***: Acular; Acuvail; Toradol; ***Chile***: Acular; Brodifac; Burten; Dilox; Dolgenal; Netaf; Poenkerat†; Syndol; ***China***: Acular (安贺拉); Ni Song (尼松); ***Denm.***: Acular; Toradol; ***Fin.***: Acular; Toradol; ***Fr.***: Acular; ***Ger.***: Acular; ***Gr.***: Acular; Errkes; Toradol; ***Hong Kong***: Acular; Keto; Toradol; ***India***: Acular; Alexis; Apsolox; Cadolac; Centagesic; Doloket; Ked; Kelac; Kenalfin; Ketanov; Ketin; Ketlac; Ketlur; Ketodrops; Ketofan; Ketolas; Ketonic; Ketorol; Ketroc; Ketrol; Ketzy; Key; Labolac; Nato; Nodine; Oculac; Torolac; ***Indon.***: Dolac; Farpain; K-Pain; Ketopain; Ketrobat; Lactor; Lantipain; Matolac; Remopain; Rolac; Scelto; Teranol; Toradol; Toramine; Torasic; Torpain; Trolac; Xevolac; ***Irl.***: Acular; ***Ital.***: Acular; Benketol; Girolac; Kevindol; Lixidol; Nasvical; Rolacsin; Tora-Dol; ***Malaysia***: Acular; Keto; Toradol; ***Mex.***: Acularen; Ainelac†; Aitornet; Alidol†; Apotoke; Brunacol; Celfax; Dobelor; Doket; Dolac; Dolcoplaz; Dolikan; Drometak; Efimerol; Estopein; Exorol; Finlac; Geldako; Gesilac†; Glicima; Godek; Italker†; Katamisine; Kendol; Kendolit; Koprak; Lacdol; Lacomin; Landaco; Lenaken; Lokefar; Lorotec; Mavidol; Onemer; Plusindol; Poenkerat; Ranketo†; Rapix; Rolesen; Rolodiquim; Rometran-K; Sebapain; Supradol; Toloran; Toral; Torkol; Trodorol; Tromedal; Ultilap; Voydol; Zafidol; ***Neth.***: Acular; ***Norw.***: Toradol; ***NZ***: Acular; ***Philipp.***: Acular; Eurolac; Inco; Ketanov; Ketero; Keto; Ketodol; Ketomed; Kortezor; Remopain; Teromac; Togesic; Toradol; Tral; ***Port.***: Acular; Elipa; Toradol; ***Rus.***: Adolor (Адолор); Dolac (Долак); Dolomine (Доломин); Ketalgin (Кеталгин); Ketanov (Кетанов); Ketofreel (Кетофрил); Ketolac (Кеталак); Ketorol (Кеторол); ***S.Afr.***: Acular; Bedoral; Tora-Dol; ***Singapore***: Acular; Keto; Toradol; ***Spain***: Acular; Algikey†; Droal†; Toradol; ***Swed.***: Toradol; ***Switz.***: Acular; Tora-Dol; ***Thai.***: Acular; Ketolac; ***Turk.***: Acular; ***UK***: Acular; Toradol; ***Ukr.***: Emodol (Эмодол)†; Ketanov (Кетанов); Ketolong (Кетолонг); Novalket (Новалькет); ***USA***: Acular; Acuvail; Sprix; ***Venez.***: Dolak; Kelac; Notolac; Ocudol; Poenkerat.

Multi-ingredient Preparations. ***India***: Doloket-O; Ketlur Plus; Keto-PC; Ketoflox; Milflox Plus; Omeflox-KT; ***Mex.***: Gammadol; Sinergix; Supradol-F; Voydol-C.

Pharmacopoeial Preparations

USP 36: Ketorolac Tromethamine Injection; Ketorolac Tromethamine Tablets.

Leflunomide *(BAN, USAN, rINN)*

HWA-486; Leflunomid; Leflunomida; Léflunomide; Leflunomidi; Leflunomidum; RS-34821; SU-101; Лефлуномид.

α,α,α-Trifluoro-5-methyl-4-isoxazolecarboxy-*p*-toluidide.

$C_{12}H_9F_3N_2O_2$=270.2

CAS — 75706-12-6.

ATC — L04AA13.

ATC Vet — QL04AA13.

UNII — G162GK9U4W.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Leflunomide). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; freely soluble in methyl alcohol; sparingly soluble in dichloromethane. Protect from light.

USP 36: (Leflunomide). White to almost white powder. Practically insoluble in water; freely soluble in acetone, in acetonitrile, in alcohol, in chloroform, in ethyl acetate, in isopropyl alcohol, and in methyl alcohol. Store at a temperature not exceeding 30 degrees.

Uses and Administration

Leflunomide has immunosuppressant and antiproliferative properties. It is used as a disease-modifying antirheumatic drug (DMARD) in the treatment of active rheumatoid arthritis (below). It is also used in the treatment of active psoriatic arthritis (see Spondyloarthropathies, p. 82.1) and has been investigated in the management of various solid neoplasms.

Because of the long half-life of the principal metabolite, a loading dose of leflunomide is required to reach steady-state concentrations relatively rapidly. Therapy should start with an oral loading dose of 100 mg once daily for 3 days. However, in practice, the loading dose may be omitted in those patients at an increased risk of adverse effects, particularly haematological or hepatic effects. The maintenance dose is 10 to 20 mg once daily for rheumatoid arthritis and 20 mg once daily for psoriatic arthritis. Dose adjustments may be necessary in patients who develop abnormal liver enzyme values, see below. The therapeutic effect usually starts after 4 to 6 weeks of therapy and further improvements may occur for up to 6 months.

Administration in hepatic impairment. Leflunomide is contra-indicated in patients with hepatic impairment. Patients who develop moderate elevations of liver enzyme values (defined as transaminase levels 2 to 3 times the normal upper limit) while receiving leflunomide treatment should have their dose reduced to 10 mg daily; if necessary, monitoring of liver enzyme values should also be performed at weekly intervals. If moderate elevations persist or if severe elevations occur, leflunomide should be stopped and washout procedures started (see p. 82.3).

Inflammatory bowel disease. Leflunomide has been tried, with some success, in the management of Crohn's disease[1] (p. 1811.3).

1. Prajapati DN, *et al.* Leflunomide treatment of Crohn's disease patients intolerant to standard immunomodulator therapy. *J Clin Gastroenterol* 2003; 37: 125–8.

Rheumatoid arthritis. References[1-5] to the use of leflunomide in rheumatoid arthritis (p. 13.2).

1. Strand V, *et al.* Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. *Arch Intern Med* 1999; 159: 2542–50.
2. Prakash A, Jarvis B. Leflunomide: a review of its use in active rheumatoid arthritis. *Drugs* 1999; 58: 1137–64.
3. Emery P, *et al.* A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. *Rheumatology (Oxford)* 2000; 39: 655–65.
4. McCarey DW, *et al.* Leflunomide in treatment of rheumatoid arthritis. *Lancet* 2002; 359: 1158.
5. Miceli-Richard C, Dougados M. Leflunomide for the treatment of rheumatoid arthritis. *Expert Opin Pharmacother* 2003; 4: 987–97.

6. Maddison P, *et al.* Leflunomide in rheumatoid arthritis: recommendations through a process of consensus. *Rheumatology (Oxford)* 2005; 44: 280–6. Correction. *ibid.*; 569.
7. Silverman E, *et al.* Long-term open-label preliminary study of the safety and efficacy of leflunomide in patients with polyarticular-course juvenile rheumatoid arthritis. *Arthritis Rheum* 2005; 52: 554–62.
8. Silverman E, *et al.* Leflunomide in Juvenile Rheumatoid Arthritis (JRA) Investigator Group. Leflunomide or methotrexate for juvenile rheumatoid arthritis. *N Engl J Med* 2005; 352: 1655–66.

Spondyloarthropathies. References[1-6] to the use of leflunomide in ankylosing spondylitis and psoriatic arthritis (p. 14.3).

1. Cuchacovich M, Soto L. Leflunomide decreases joint erosions and induces reparative changes in a patient with psoriatic arthritis. *Ann Rheum Dis* 2002; 61: 942–3.
2. Kaltwasser JP, *et al.* Treatment of Psoriatic Arthritis Study Group. Efficacy and safety of leflunomide in the treatment of psoriatic arthritis and psoriasis: a multinational, double-blind, randomized, placebo-controlled clinical trial. *Arthritis Rheum* 2004; 50: 1939–50.
3. Haibel H, *et al.* Six months open label trial of leflunomide in active ankylosing spondylitis. *Ann Rheum Dis* 2005; 64: 124–6.
4. van Denderen JC, *et al.* Double blind, randomised, placebo controlled study of leflunomide in the treatment of active ankylosing spondylitis. *Ann Rheum Dis* 2005; 64: 1761–4.
5. Schmin J, Wozel G. Psoriasis-arthritis—Langzeit-therapie zweier Patienten mit Leflunomid. *J Dtsch Dermatol Ges* 2005; 2: 763–6.
6. Nash P, *et al.* Leflunomide improves psoriasis in patients with psoriatic arthritis: an in-depth analysis of data from the TOPAS study. *Dermatology* 2006; 212: 238–49.

Adverse Effects, Treatment and Precautions

Common adverse effects seen with leflunomide are hypertension, gastrointestinal disturbances (particularly diarrhoea), weight loss, headache, dizziness, leucopenia, asthenia, paraesthesia, joint disorders and synovitis, upper respiratory-tract infections, alopecia, eczema, and dry skin. Hypersensitivity reactions may occur and a few cases of Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, or vasculitis have been reported. Hepatotoxicity has occurred. It is usually mild and reversible but rare cases of severe, sometimes fatal, liver disease, including acute hepatic necrosis, have been seen particularly in the first 6 months of therapy. Other adverse effects that have been reported include anxiety, peripheral neuropathy, hypokalaemia, and mild hyperlipidaemia. There have been rare reports of pancytopenia, agranulocytosis, and thrombocytopenia; these effects are more common when leflunomide is given with other myelosuppressive drugs (see Interactions, below). There have been occasional reports of pancreatitis, interstitial lung disease, and severe infections, including fatal sepsis. Renal failure has also been reported.

The active metabolite of leflunomide, A-771726, has a half-life of about 2 weeks. Consequently, the adverse effects of leflunomide may continue even after therapy has been stopped. When severe reactions occur, a drug washout procedure (see below) may be required.

Leflunomide should not be given to immunocompromised patients or to patients with severe infections, hepatic or moderate to severe renal impairment, severe hypoproteinaemia, or bone-marrow dysplasia. Patients with a history of tuberculosis should be carefully monitored because of the possibility of reactivation of the infection. Intra-uterine devices should be used with caution during immunosuppressive treatment as there is an increased risk of infection. Live vaccines should be avoided for the same reason. Blood pressure should be monitored regularly during therapy.

In the UK, licensed product information recommends that liver enzyme values should be checked before beginning therapy and at fortnightly intervals during the first 6 months of treatment; US product information recommends monthly monitoring for the first 6 months. Subsequent monitoring should be carried out at 6- to 8-week intervals. Dosage should be reduced if moderate elevations of liver enzyme values occur (see Administration in Hepatic Impairment, p. 81.3); for persistent or more severe elevations leflunomide should be stopped and washout procedures begun. Monitoring of liver enzymes should be continued after stopping therapy until they return to within the normal range. Blood counts should also be checked at the same time as liver enzyme values.

References.

1. Alcorn N, *et al.* Benefit-risk assessment of leflunomide: an appraisal of leflunomide in rheumatoid arthritis 10 years after licensing. *Drug Safety* 2009; 32: 1123–34.

Effects on the lungs. Up to December 2006, the Australian Adverse Drug Reactions Advisory Committee (ADRAC) had received 142 reports of respiratory symptoms with leflunomide use since its introduction in 2000.[1] Of these, 22 reports mentioned at least one of the following serious reactions: pneumonitis (8), interstitial lung disease (9), lung infiltration (4), or pulmonary fibrosis (3); it was considered that all these were likely to represent interstitial lung disease. Four patients died, but relative causality was difficult to assign as methotrexate was also given in many cases, however, several patients had been on methotrexate long-term without any problems. It was recommended that the pulmonary status of patients should be considered before starting leflunomide and monitored during treatment; if symptoms such as cough or dyspnoea develop or worsen, leflunomide may need to be stopped. ADRAC subsequently reported[2] that in June 2009 the number of reports of respiratory symptoms with leflunomide had increased to 196. Of these, 153 reports mentioned use with methotrexate including 23 of the 39 reports of interstitial lung disease.

The risk of interstitial lung disease with leflunomide has also been assessed using data from a large cohort study.[3] This study found that, overall, there was a twofold increase in the risk of interstitial lung disease in patients treated with leflunomide compared with those who did not receive leflunomide. However, subgroup analysis showed that this increase was limited to those patients with a history of methotrexate use or interstitial lung disease; in those with no previous methotrexate use or no history of interstitial lung disease, there was no increased risk with leflunomide. See also under Interactions, below.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Leflunomide and interstitial lung disease. *Aust Adverse Drug React Bull* 2006; 25: 22–3. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0612.pdf (accessed 13/06/08)
2. Adverse Drug Reactions Advisory Committee (ADRAC). Is it leflunomide lung? *Aust Adverse Drug React Bull* 2009; 28: 15. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0908.pdf (accessed 23/10/09)
3. Suissa S, *et al.* Leflunomide use and the risk of interstitial lung disease in rheumatoid arthritis. *Arthritis Rheum* 2006; 54: 1435–9.

Effects on the nervous system. Peripheral neuropathy has been associated with leflunomide use.[1-5] Up to October 2006, the Australian Adverse Drug Reactions Advisory Committee had received 659 reports of adverse reactions associated with leflunomide, 30 of which mentioned neuropathy or peripheral neuropathy;[4] leflunomide was the sole suspected drug in 24 of these cases. Recovery was noted after drug withdrawal in 6 patients, of whom 3 underwent washout procedures; however, 15 patients had not recovered at the time of the reports and there was no information on the remaining cases. More recently, up to October 2009, Health Canada[5] had received 26 reports of peripheral neuropathy symptoms associated with leflunomide. Of these, 9 reports had specified peripheral neuropathy; the duration of leflunomide therapy ranged from 2 months to 2 years and the reaction abated after stopping leflunomide.

1. Bonnel RA, Graham DJ. Peripheral neuropathy in patients treated with leflunomide. *Clin Pharmacol Ther* 2004; 75: 580–5.
2. Martin K, *et al.* Neuropathy associated with leflunomide: a case series. *Ann Rheum Dis* 2005; 64: 649–50.
3. Metzler C, *et al.* Peripheral neuropathy in patients with systemic rheumatic diseases treated with leflunomide. *Ann Rheum Dis* 2005; 64: 1798–1800.
4. Adverse Drug Reactions Advisory Committee (ADRAC). Leflunomide and peripheral neuropathy. *Aust Adverse Drug React Bull* 2006; 25: 18–19. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0610.pdf (accessed 13/06/08)
5. Health Canada. Leflunomide and peripheral neuropathy. *Can Adverse React News* 2010; 20 (2): 1–2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/medeff/bulletin/carn-bcei_v20n2-eng.pdf (accessed 07/05/10)

Effects on the skin. A 58-year-old woman developed lupus erythematosus 1 month after starting leflunomide 20 mg daily for treatment of Sjögren's syndrome.[1] The rash resolved within 4 weeks of stopping leflunomide but recurred on 2 separate occasions when she took the drug again.

1. Gensburger D, *et al.* Lupus erythematosus with leflunomide: induction or reactivation? *Ann Rheum Dis* 2005; 64: 153–5.

Overdose. Unintentional overdoses with leflunomide have been reported in 2 patients. In one case, no adverse effects were seen in a 40-year-old woman who had mistakenly taken both a 100-mg and a 20-mg tablet daily for 28 days;[1] in another case, a 70-year-old man who took 100 mg weekly, in addition to 20 mg daily, for over 2 years was found to have interstitial nephritis which improved after leflunomide was stopped.[2] In both cases, the 100-mg dose was meant to be taken for 2 or 3 days only as a loading dose.

1. Kamali S, *et al.* An unusual overdose of leflunomide in a patient with rheumatoid arthritis. *Ann Pharmacother* 2004; 38: 1320–1.
2. Haydar AA, *et al.* Chronic overdose of leflunomide inducing interstitial nephritis. *Nephrol Dial Transplant* 2004; 19: 1334–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies leflunomide as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 15/11/11)

Pregnancy. Leflunomide is contra-indicated during pregnancy as its active metabolite has been shown to be teratogenic in *animals*. Pregnancy should therefore be excluded before beginning therapy, and licensed product information states that reliable contraception should be used in women of child-bearing potential (UK product information also recommends reliable contraception in men treated with leflunomide). Women wishing to become pregnant should wait for 2 years after stopping therapy, or if this is infeasible, a washout procedure (see below) should be performed and a waiting period of 6 weeks be observed from the time plasma concentrations of the metabolite fall below 20 nanograms/mL before attempting conception. A washout procedure with a waiting period of at least 3 months is recommended in men who wish to father children. Women who become pregnant during therapy should also undergo a washout procedure.

Washout procedure. If serious adverse effects occur during leflunomide therapy, licensed product information recommends that a drug washout procedure is performed. This may also be considered if a patient becomes pregnant while taking leflunomide, or if it is necessary to swap to another disease-modifying antirheumatic drug such as methotrexate.

For the washout procedure, either 8 g of colestyramine is given orally 3 times daily or 50 g of activated charcoal is given orally or via a nasogastric tube 4 times daily. Therapy is normally continued for 11 days, but should be repeated until plasma concentrations of the primary metabolite A-771726 are below 20 nanograms/mL, verified by two separate tests at least 14 days apart.

Interactions

Increased adverse effects may occur if leflunomide is given with other hepatotoxic or myelosuppressive drugs; these effects may also be seen when leflunomide treatment is followed by such drugs without a drug washout procedure (above). The risks of combined use with other disease-modifying antirheumatic drugs, particularly in the long term, have not been studied and such use is not advised in the UK; however, US licensed product information recommends that if long-term combined use is necessary, liver enzyme values and blood counts should be monitored monthly, for the first 6 months, rather than every 6 to 8 weeks (see Adverse Effects, Treatment, and Precautions, above).

See above for precautions about use with live vaccines.

Anticoagulants. For reference to the effect of leflunomide on the activity of *warfarin*, see under Immunosuppressants, p. 1534.2.

Methotrexate. Leflunomide therapy has been rarely associated with pancytopenia. Of the 18 cases (median age 65.5 years) reported in one series, 14 patients were also receiving methotrexate therapy.[1] The pancytopenia was typically severe and required hospitalisation; 5 patients had died, 4 of whom were also taking methotrexate. Time to onset of pancytopenia ranged from 11 days to 4 years. The authors concluded that the risk of pancytopenia during leflunomide treatment appeared to increase when used with methotrexate, and emphasised the importance of ongoing monitoring of blood counts.

Leflunomide therapy with or without methotrexate has also been rarely associated with interstitial lung disease including interstitial pneumonitis (see above). Up to March 2006, the Centre for Adverse Reactions Monitoring in New Zealand[2] had received 7 reports of pneumonitis associated with leflunomide in patients who were also taking methotrexate. Of these, 4 had taken methotrexate (which is also associated with pneumonitis) for more than 1 year. Respiratory symptoms developed 12 to 36 weeks after starting leflunomide therapy; 5 patients recovered, 1 died, and another improved but had some persisting respiratory impairment.

For advice on a drug washout procedure, see above.

1. Chan J, *et al.* Leflunomide-associated pancytopenia with or without methotrexate. *Ann Pharmacother* 2004; 38: 1206–11.
2. Savage R. Leflunomide and pneumonitis. *Prescriber Update* 2006; 27: 7–9.

Pharmacokinetics

After oral doses leflunomide undergoes rapid first-pass metabolism in the liver and gut wall to teriflunomide (A-771726), which is responsible for the majority of the *in vivo* activity. The bioavailability of leflunomide after oral doses ranges from 82 to 95%. Peak plasma concentrations of the active metabolite may occur from 1 to 24 hours after a dose.

For details on the distribution and elimination of teriflunomide, see p. 2626.3.

References.

1. Rozman B. Clinical pharmacokinetics of leflunomide. *Clin Pharmacokinet* 2002; 41: 421–30.
2. Shi J, *et al.* Population pharmacokinetics of the active metabolite of leflunomide in pediatric subjects with polyarticular course juvenile rheumatoid arthritis. *J Pharmacokinet Pharmacodyn* 2005; 32: 419–39.
3. Chan V, *et al.* Population pharmacokinetics and association between A771726 plasma concentrations and disease activity measures following administration of leflunomide to people with rheumatoid arthritis. *Br J Clin Pharmacol* 2005; 60: 257–64.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Afiancen; Arava; Filartros; Inmunoartro; Lefluar; *Austral.*: Arabloc; Arava; *Austria*: Arava; *Belg.*: Arava; *Braz.*: Arava; *Canad.*: Arava; *Chile*: Arava; Artrilab; Artrimod†; Leflucross; *China*: Airuohua (爱若华); Aokelu (奥克鲁); Guanping (关平); Hepai (赫派); Tuo Shu (妥抒); Youtong (优通); *Cz.*: Arava; Repso; *Denm.*: Arava; *Fin.*: Arava; *Fr.*: Arava; *Ger.*: Arava; *Gr.*: Arava; *Hong Kong*: Arava; *Hung.*: Arava; *India*: Arava; Cleft; Lefno; Lefra; Lefumide; Lisifen; Rumalef; *Indon.*: Arava; *Irl.*: Arava; Repso; *Israel*: Arava; *Ital.*: Arava; *Malaysia*: Arava; *Mex.*: Arava; *Neth.*: Arava; Repso; *Norw.*: Arava; *NZ*: Arava; *Philipp.*: Arava; *Pol.*: Arava; *Port.*: Arava; *Rus.*: Arava (Арава); *S.Afr.*: Arava; *Singapore*: Arava; *Spain*: Arava; *Swed.*: Arava; *Switz.*: Arava; *Thai.*: Arava; *Turk.*: Arava; *UK*: Arava; *Ukr.*: Arava (Арава); *USA*: Arava; *Venez.*: Arava.

Pharmacopoeial Preparations
USP 36: Leflunomide Tablets.

Levacetylmethadol *(rINN)*

l-α-Acetylmethadol; LAAM (levacetylmethadol or levacetylmethadol hydrochloride); LAM; Levacetilmetadol; Levacetylmetadol; Lévacétylméthadol; Levacetylmethadolum; Levasetyylimetadoli; Levomethadyl Acetate (USAN); *l*-Methadyl Acetate; Левацетилметадол.
(-)-4-Dimethylamino-1-ethyl-2,2-diphenylpentyl acetate.
$C_{23}H_{31}NO_2$=353.5
CAS — 1477-40-3 (levomethadyl); 34433-66-4 (levacetylmethadol).
ATC — N07BC03.
ATC Vet — QN07BC03.
UNII — R3B637Y991.

Levacetylmethadol Hydrochloride *(rINNM)*

Hidrocloruro de levacetilmetadol; LAAM (levacetylmethadol or levacetylmethadol hydrochloride); Levacetilmetadol, hidrocloruro de; Lévacétylméthadol, Chlorhydrate de; Levacetylmethadoli Hydrochloridum; Levomethadyl Acetate Hydrochloride (USAN); Levomethadyl Acetate Hydrochloride; MK-790; Левацетилметадола Гидрохлорид.
(-)-(3*S*,6*S*)-6-(Dimethylamino)-4,4-diphenyl-3-heptanol acetate hydrochloride.
$C_{23}H_{31}NO_2$,HCl=390.0
CAS — 43033-72-3.
ATC — N07BC03.
ATC Vet — QN07BC03.
UNII — B54CW5KG52.

Profile

Levacetylmethadol, a diphenylheptane derivative, is a long-acting opioid analgesic (p. 108.1); it is a derivative of methadone (p. 88.3). It was used as the hydrochloride in the management of opioid dependence. However, the proarrhythmic effects led to its withdrawal in the EU and the USA.

Levomethadone Hydrochloride *(rINNM)* ⊗

Hidrocloruro de levometadona; Levometadona, hidrocloruro de; Levometadonhidrokloridi; Levometadonhydrokloridi; Levometadonihydrokloridi; Levometadono hidrocloridas; Lévométhadone, Chlorhydrate de; Levomethadon-hydrochlorid; Levomethadonhydrochlorid; Levomethadoni Hydrochloridum; (-)-Methadone Hydrochloride; Левометадона Гидрохлорид.
(-)-6-Dimethylamino-4,4-diphenylheptan-3-one hydrochloride.
$C_{21}H_{27}NO$,HCl=345.9
CAS — 125-58-6 (levomethadone); 5967-73-7 (levomethadone hydrochloride).
UNII — V57LC776C0.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Levomethadone Hydrochloride). A white or almost white, crystalline powder. Soluble in water; freely soluble in alcohol. Protect from light.

Profile

Levomethadone is an opioid analgesic (p. 108.1). It is the active isomer of racemic methadone (p. 88.3) and is used similarly, as the hydrochloride, in the treatment of severe pain and in the management of opioid dependence.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: L-Polamidon.

Levorphanol Tartrate *(BANM, rINNM)*

Levorfanol, tartrato de; Levorphan Tartrate; Levorphanol Bitartrate; Lévorphanol, Tartrate de; Levorphanoli Tartras; Methorphinan Tartrate; Tartrato de levorfanol; Леворфанола Тартрат.
(-)-9a-Methylmorphinan-3-ol hydrogen tartrate dihydrate.
$C_{17}H_{23}NO,C_4H_6O_6,2H_2O$=443.5
CAS — 77-07-6 (levorphanol); 125-72-4 (anhydrous levorphanol tartrate); 5985-38-6 (levorphanol tartrate dihydrate).
UNII — 04WQU6T9QI.

Pharmacopoeias. In *US.*

USP 36: (Levorphanol Tartrate). A practically white, odourless, crystalline powder. Soluble 1 in 50 of water and 1 in 120 of alcohol; insoluble in chloroform and in ether. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Profile

Levorphanol tartrate, a phenanthrene derivative, is a potent opioid analgesic (p. 108.1) used in the management of moderate to severe pain. The analgesic effect usually begins about 10 to 60 minutes after oral doses and lasts up to about 8 hours. A usual initial oral dose of levorphanol tartrate is 2 mg repeated in 6 to 8 hours if necessary; the dose may be increased to 3 mg every 6 to 8 hours, adjusted according to response. The maximum initial daily dose in non-opioid tolerant patients should not exceed 12 mg. Elderly or debilitated patients may require lower doses; initial doses should be reduced by 50% or more.

Levorphanol tartrate has also been given by intramuscular, subcutaneous, or slow intravenous injection for pain relief and for premedication.

References.
1. Prommer E. Levorphanol: the forgotten opioid. *Support Care Cancer* 2007; 15: 259–64.

Preparations

Pharmacopoeial Preparations
USP 36: Levorphanol Tartrate Injection; Levorphanol Tartrate Tablets.

Licofelone *(rINN)*

Licofelona; Licofélone; Licofelonum; ML-3000; Ликофельон.
[6-(4-Chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1*H*-pyrrolizin-5-yl]acetic acid.
$C_{24}H_{22}ClNO_2$=379.9
CAS — 156897-06-2.
UNII — P5T6BYS22Y.

Profile

Licofelone is an NSAID (p. 102.3) stated to be both a cyclooxygenase and lipoxygenase inhibitor. It has been investigated for the treatment of osteoarthritis.

References.
1. Kulkarni SK, Singh VP. Licofelone—a novel analgesic and anti-inflammatory agent. *Curr Top Med Chem* 2007; 7: 251–63.
2. Fischer L, *et al.* The molecular mechanism of the inhibition by licofelone of the biosynthesis of 5-lipoxygenase products. *Br J Pharmacol* 2007; 152: 471–80.
3. Raynaud JP, *et al.* Canadian Licofelone Study Group. Protective effects of licofelone, a 5-lipoxygenase and cyclo-oxygenase inhibitor, versus naproxen on cartilage loss in knee osteoarthritis: a first multicentre clinical trial using quantitative MRI. *Ann Rheum Dis* 2009; 68: 938–47.

Lornoxicam *(BAN, USAN, rINN)*

Chlorotenoxicam; Chlortenoxicam; CTX; Lornoksikaami; Lornoksikam; Lornoxicamum; Lornoxicanum; Lornoxikam; Ro-13-9297; TS-110; Лорноксикам.
6-Chloro-4-hydroxy-2-methyl-*N*-2-pyridyl-2*H*-thieno[2,3-e][1,2]-thiazine-3-carboxamide 1,1-dioxide.
$C_{13}H_{10}ClN_3O_4S_2$=371.8
CAS — 70374-39-9.
ATC — M01AC05.
ATC Vet — QM01AC05.
UNII — ER09126G7A.

Profile

Lornoxicam, an oxicam derivative, is an NSAID (p. 102.3). It is used in musculoskeletal and joint disorders such as osteoarthritis and rheumatoid arthritis; it is also used in the treatment of other painful conditions including postoperative pain.

In the treatment of osteoarthritis and rheumatoid arthritis lornoxicam is given in an initial oral daily dose of 12 mg in two or three divided doses; if necessary the daily dose may be increased to a maximum of 16 mg.

Lornoxicam is given in oral doses of 8 to 16 mg daily for the treatment of pain; similar doses may be given by intravenous or intramuscular injection.

The hydrochloride salt has also been used.

References.
1. Balfour JA, *et al.* Lornoxicam: a review of its pharmacology and therapeutic potential in the management of painful and inflammatory conditions. *Drugs* 1996; 51: 639–57.
2. Skjodt NM, Davies NM. Clinical pharmacokinetics of lornoxicam: a short half-life oxicam. *Clin Pharmacokinet* 1998; 34: 421–8.
3. Frizziero L, *et al.* Studio a lungo termine su efficacia e sicurezza terapeutica di lornoxicam nell'artrite reumatoide. *Minerva Med* 2002; 93: 315–20.
4. Thienthong S, *et al.* Treatment of pain after spinal surgery in the recovery room by single dose lornoxicam: a randomized, double blind, placebo-controlled trial. *J Med Assoc Thai* 2004; 87: 650–5.
5. Zhao H, *et al.* Application of lornoxicam to patient-controlled analgesia in patients undergoing abdominal surgeries. *Chin Med Sci J* 2005; 20: 59–62.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lornoxicam as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 23/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Hypodol; Xefo; *Austria*: Xefo; *Braz.*: Xefo; *China*: Da Lu (达路); Qinda (沁达); Xafon (可塞风); Zheng Ting (正庭); *Cz.*: Xefo; *Denm.*: Xefo; *Ger.*: Telos†; *Gr.*: Xefo; *Hung.*: Xefo; *India*: C-Cum; Camri; Plexilor; Lenor; Lofecam; Loni; Lormoto; Lornica; Lornistar; Lorniz; Lornofan; Lornoxi; Lorox; Lorsaid; Lorwalk; Loxcam; Mitilor; Movilor; Neucam; Nextcam; Noxi; *Irl.*: Xefo; *Israel*: Xefo; *Ital.*: Noxon; Taigalor; *Jpn*: Lorcam; *Neth.*: Xefo†; *Pol.*: Xefo; *Port.*: Acabel; Bosporon; *Rus.*: Xefocam (Ксефокам); *S.Afr.*: Xefo; *Spain*: Acabel; Bosporon; *Swed.*: Xefo; *Switz.*: Xefo; *Turk.*: Xefo; *Ukr.*: Xefocam (Ксефокам); *Venez.*: Acabel.

Multi-ingredient Preparations. *India*: Campar; Cincam-P; Lenor-P; Lezdes-P; Lolira-P; Loni-Plus; Lorbit-P; Lorchek-MR; Lorchek-P; Lorflam-P; Lormoto-P; Lornistar-P; Lornofan-P; Lornoxi-P; Lorsaid-P; Lorter-P; Lorthox-P; Lorup Plus; Lorwalk-P; Loxcam-P; Loxicam-P; Luloxy-P; Movilor-P; Neucam-P; Nextcam-P; Noxi-P; Orilox-P; Paratel-LC.

Loxoprofen Sodium *(rINNM)*

CS-600 (loxoprofen); Loxoprofène Sodique; Loxoprofeno sódico; Natrii Loxoprofenum; Натрий Локсопрофен.
Sodium (±)-*p*-[(2-oxocycloperityl)methyl]hydratropate dihydrate.
$C_{15}H_{17}O_3Na,2H_2O$=304.3
CAS — 68767-14-6 (loxoprofen); 80382-23-6 (loxoprofen sodium); 226721-96-6 (loxoprofen sodium dihydrate).
UNII — NDC2M7395S (anhydrous loxoprofen sodium); Z2DR42L11Y (loxoprofen sodium dihydrate).

Pharmacopoeias. In *Jpn.*

Profile

Loxoprofen sodium is an NSAID (p. 102.3) used in painful and inflammatory conditions. It is given as the dihydrate although doses are expressed in terms of the anhydrous salt. Anhydrous loxoprofen sodium 10 mg is equivalent to about 11.3 mg of loxoprofen sodium dihydrate.

For the management of pain and inflammation associated with musculoskeletal and joint disorders, or operative procedures, a usual oral dose equivalent to 60 mg of the anhydrous form has been given three times daily. It has also been applied topically as a poultice containing the equivalent of 100 mg of the anhydrous form or as a 1% gel.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Oxeno; *Braz.*: Loxonin; *China*: An Pu Luo (安普洛); Bei Luo (倍珞); Loxonin (乐松); Luo Lie Tong (洛列通); Luo Na (洛那); Qing Fu (庆福); Ruo Mai (若迈); Sai Ke Tong (赛克同); San Yuan Shu Xing (三元舒星); Weikang DiKe (康威迪克); Zhen Tong Yan (真痛言); *Jpn*: Lobu; Loxonin; *Mex.*: Loxonin; *Philipp.*: Loxonin†; *Thai.*: Loxonin; *Venez.*: Loxonin.

Lumiracoxib *(BAN, USAN, rINN)*

Cox-189; Lumiracoxibum; Лумиракоксиб.

2-[(2-Chloro-6-fluorophenyl)amino]-5-methylphenyl]acetic acid.

$C_{15}H_{13}ClFNO_2$=293.7.

CAS — 220991-20-8.

ATC — M01AH06.

ATC Vet — QM01AH06.

UNII — V91T9204HU.

Uses and Administration

Lumiracoxib is an NSAID (p. 102.3) reported to be a selective inhibitor of cyclo-oxygenase-2 (COX-2). It has been withdrawn in many countries after reports of hepatotoxicity. Lumiracoxib has been used in the treatment of osteoarthritis of the knee and hip in an oral dose of 100 mg once daily. Higher doses of up to 400 mg daily have also been used but may be associated with an increased risk of hepatotoxicity (see Effects on the Liver, below).

References.

1. Lyseng-Williamson KA, Curran MP. Lumiracoxib. *Drugs* 2004; 64: 2237–46.
2. Bannwarth B, Berenbaum F. Clinical pharmacology of lumiracoxib, a second-generation cyclooxygenase 2 selective inhibitor. *Expert Opin Invest Drugs* 2005; 14: 521–33.
3. Rordorf CM, *et al.* Clinical pharmacology of lumiracoxib: a selective cyclo-oxygenase-2 inhibitor. *Clin Pharmacokinet* 2005; 44: 1247–66.
4. Schnitzer TJ, *et al.* Lumiracoxib in the treatment of osteoarthritis, rheumatoid arthritis and acute postoperative dental pain: results of three dose-response studies. *Curr Med Res Opin* 2005; 21: 151–61.
5. Berenbaum F, *et al.* Efficacy of lumiracoxib in osteoarthritis: a review of nine studies. *J Int Med Res* 2005; 33: 21–41.
6. Sheldon E, *et al.* Efficacy and tolerability of lumiracoxib in the treatment of osteoarthritis of the knee: a 13-week, randomized, double-blind comparison with celecoxib and placebo. *Clin Ther* 2005; 27: 64–77.
7. Fleischmann R, *et al.* Lumiracoxib is effective in the treatment of osteoarthritis of the knee: a prospective randomized 13-week study versus placebo and celecoxib. *Clin Rheumatol* 2006; 25: 42–53.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3.

Hypersensitivity reactions including anaphylaxis and angioedema have occurred in patients receiving lumiracoxib; it should be stopped at the first signs of hypersensitivity.

Lumiracoxib use, particularly at high doses, may cause severe liver toxicity (see Effects on the Liver, below) and its use is contra-indicated in patients with hepatic disease. It should also not be used in those with a history of drug-induced increases in transaminase values greater than 3 times the upper limit of normal (ULN) or in those taking other drugs known to cause clinically significant hepatotoxicity. All patients should have baseline liver function tests before starting lumiracoxib treatment; those in whom transaminases are more than 1.5 times the ULN should not start treatment. Liver function tests should be repeated monthly and lumiracoxib should be stopped in those patients with an increase in transaminases greater than 3 times the ULN; in those with an increase greater than 2 times the ULN, liver function tests should be repeated in 7 days. Patients should be advised to report any symptoms suggestive of liver toxicity such as anorexia, nausea, vomiting, abdominal pain, fatigue, dark urine, and jaundice.

Lumiracoxib should not be used in patients with ischaemic heart disease, cerebrovascular disease, or peripheral arterial disease. It should be used with caution in patients with significant risk factors for cardiovascular disease such as hypertension, hyperlipidaemia, and diabetes mellitus.

Lumiracoxib is also contra-indicated in patients with inflammatory bowel disease, moderate to severe heart failure (NYHA class II to IV), and moderate to severe renal impairment associated with a creatinine clearance of less than 50 mL/minute. Caution is recommended when using lumiracoxib in dehydrated patients; it may be advisable to rehydrate patients before giving lumiracoxib.

Effects on the cardiovascular system. There have been concerns about the adverse cardiovascular effects of selective cyclo-oxygenase-2 (COX-2) inhibitors after the worldwide withdrawal of rofecoxib (see p. 128.3). The cardiovascular safety of lumiracoxib has been assessed in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET)[1] which involved over 18 000 patients with osteoarthritis. Lumiracoxib 400 mg daily (2 to 4 times the recommended dose) was compared against either naproxen 1 g daily, or ibuprofen 2.4 g daily; low-dose aspirin (100 mg daily or less) was also allowed where indicated. After a planned treatment duration of 1 year, the incidence of myocardial infarction, stroke, or cardiovascular death with lumiracoxib was found to be similar to that for ibuprofen or naproxen. More events were noted in the lumiracoxib versus naproxen subgroup than in the lumiracoxib versus ibuprofen group; however, this difference was not statistically significant and the authors considered that the higher number of patients with a history of vascular risk in the lumiracoxib versus naproxen subgroup could explain this finding. In addition, it was noted that the incidence of heart failure was less frequent with lumiracoxib although, again, this was not significant; however, blood pressure changes from baseline were significantly less likely with lumiracoxib than with ibuprofen or naproxen.

More recently, a meta-analysis[2] by the manufacturer (which included the above study along with other published and unpublished clinical studies of lumiracoxib in the treatment of osteoarthritis and rheumatoid arthritis) has also found no evidence that the risk of thrombotic events with lumiracoxib is significantly increased when compared with placebo, with naproxen (1 g daily), or with the NSAIDs diclofenac (150 mg daily), ibuprofen (2.4 g daily), celecoxib (up to 400 mg daily), and rofecoxib (25 mg daily) as a group.

For further details on the relative risk of cardiovascular thrombotic events with NSAIDs, see p. 105.1.

For discussion and advice on the use of selective COX-2 inhibitors in patients with cardiovascular or cerebrovascular disease, see under Celecoxib, p. 37.3.

1. Farkouh ME, *et al.* Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), cardiovascular outcomes: randomised controlled trial. *Lancet* 2004; 364: 675–84.
2. Matchaba P, *et al.* Cardiovascular safety of lumiracoxib: a meta-analysis of all randomized controlled trials ≥ 1 week and up to 1 year in duration of patients with osteoarthritis and rheumatoid arthritis. *Clin Ther* 2005; 27: 1196–1214.

Effects on the gastrointestinal tract. It is generally accepted that the inhibition of cyclo-oxygenase-1 (COX-1) plays a role in the adverse gastrointestinal effects of the NSAIDs, and that the selective inhibition of the other isoform, COX-2, by NSAIDs such as lumiracoxib may cause less gastrotoxicity than that seen with the non-selective inhibition of the traditional NSAIDs. However, licensed product information has stated that upper gastrointestinal ulceration and bleeds, in some cases fatal, have occurred with lumiracoxib treatment; consequently it should be used with caution in patients at risk of such events.

Results from controlled studies confirm that NSAIDs selective for COX-2 are associated with a lower incidence of serious gastrointestinal effects. A study[1] in patients with osteoarthritis taking lumiracoxib at supratherapeutic doses (400 mg daily) concluded that there was a lower incidence of definite or probable upper gastrointestinal ulcer complications (bleeding, perforation, or obstruction) after 12 months of treatment when compared with non-selective NSAIDS (ibuprofen 2.4 g daily or naproxen 1 g daily). The incidence of endoscopically-detected ulcers was also less with lumiracoxib than with non-selective NSAIDs. However, the use of low-dose aspirin appeared to nullify any protective gastrointestinal effect of lumiracoxib.

An analysis[2] of pooled data from 15 pre-licensing studies in patients with rheumatoid arthritis or osteoarthritis has also concluded that the risk of upper gastrointestinal ulcers and ulcer complications is less with lumiracoxib than with non-selective NSAIDs (diclofenac, naproxen, and ibuprofen).

1. Schnitzer TJ, *et al.* Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), reduction in ulcer complications: randomised controlled trial. *Lancet* 2004; 364: 665–74.
2. Hawkey CJ, *et al.* Gastrointestinal tolerability of lumiracoxib in patients with osteoarthritis and rheumatoid arthritis. *Clin Gastroenterol Hepatol* 2006; 4: 57–66.

Effects on the kidneys. Limited evidence of the renal toxicity of the selective cyclo-oxygenase-2 (COX-2) inhibitors such as lumiracoxib suggests that these NSAIDs appear to have effects on renal function similar to those of the non-selective NSAIDs (see p. 106.2).

Effects on the liver. In August 2007, the regulatory authority in Australia withdrew lumiracoxib from the market after reports of hepatotoxicity.[1,2] In the 6 months since marketing, there had been 8 reports of serious adverse liver reactions resulting in 2 deaths and 2 transplantations. There was some concern that pre-licensing clinical study data seemed to suggest that those patients who developed elevated liver function tests while on lumiracoxib would recover once the drug was stopped; however, in the 8 Australian cases, some patients did not improve because of the severity of the hepatic damage.

In response to the Australian data, the MHRA in the UK reported that it had received 16 reports of suspected adverse reactions to lumiracoxib;[3] of these, one was a case of hepatotoxicity in which the patient recovered after the drug was withdrawn. Worldwide, the MHRA was aware of 11 reports of serious hepatotoxicity including 9 cases of liver failure, 2 deaths, and 3 liver transplants suspected to be at least possibly related to lumiracoxib use. The dose used in most of the cases was higher than the maximum dose of 100 mg daily that is recommended in the UK and other European countries. (Higher maximum daily doses have been licensed in other countries; in Australia, the licensed maximum dose was 400 mg daily for some conditions.) At that time in the UK, new prescribing restrictions on the use of lumiracoxib in osteoarthritis were issued (see Adverse Effects and Precautions, above) while its safety continued to be reviewed by European regulatory authorities. After a review in October 2007, the MHRA reiterated its earlier prescribing restrictions for lumiracoxib and stated the issue of hepatotoxicity would continue to be monitored. They also advised that, worldwide up until then, there had been 19 cases of severe liver reactions, including 13 of liver failure, 2 deaths, and 3 liver transplants suspected to be possibly related to use of lumiracoxib.[4] At about the same time, lumiracoxib was withdrawn from the Canadian market after Health Canada noted 4 cases of severe hepatotoxicity, including 2 in Canada, associated with the 100-mg dose of lumiracoxib.[5] Subsequently, in November 2007, the MHRA suspended the product licence for lumiracoxib after a further review of worldwide safety data showed an increased number of serious liver reactions with the 100-mg dose which, in some cases, occurred with short-term use.[6] In addition, the EMEA[7] has recommended its withdrawal in the EU.

1. Australian Therapeutic Goods Administration. Urgent advice regarding management of patients taking lumiracoxib (Prexige) (issued 13th August, 2007). Available at: http://www.tga.gov.au/alerts/prexige.htm (accessed 08/11/07)
2. Adverse Drug Reactions Advisory Committee (ADRAC). Withdrawal of lumiracoxib in Australia. *Aust Adverse Drug React Bull* 2008; 27: 6–7. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0804.pdf (accessed 17/07/08)
3. MHRA. New (interim) restrictions on prescription of lumiracoxib following concerns over liver safety (issued 24th August, 2007). Available at: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON2032098 (accessed 29/08/08)
4. MHRA. Lumiracoxib and liver adverse reactions (issued 16th October 2007). Available at: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON2032831 (accessed 29/08/08)
5. Health Canada. Withdrawal of market authorisation for Prexige. (issued 4th October, 2007). Available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2007/2007_141_e.html (accessed 30/10/07)
6. MHRA. Lumiracoxib (Prexige): suspension of marketing authorisations (issued 19th November, 2007). Available at: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON2033073 (accessed 29/08/08)
7. EMEA. European Medicines Agency recommends withdrawal of the marketing authorisations for lumiracoxib-containing medicines (issued 13th December, 2007). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/PR_Lumiracoxib_57930107en.pdf (accessed 17/07/08)

Interactions

For interactions associated with NSAIDs in general, see p. 107.3. Lumiracoxib may cause liver toxicity and consequently it should not be used with other drugs known to cause clinically significant hepatotoxicity.

There is the possibility that lumiracoxib may decrease the clearance of drugs that are cytochrome P450 CYP2C9 substrates and caution is advised when it is given with CYP2C9 substrates that have a narrow therapeutic index such as phenytoin and warfarin.

Pharmacokinetics

Lumiracoxib is absorbed from the gastrointestinal tract after oral use and peak plasma concentrations occur in about 2 hours. Protein binding is at least 98%. Lumiracoxib undergoes extensive hepatic metabolism; several enzymes appear to be involved including glucuronosyltransferase and cytochrome P450 isoenzymes. The main oxidative pathway is mediated by the CYP2C9 isoenzyme; however, this does not appear to be the major pathway. Three major metabolites have been identified: 4′-hydroxy-lumiracoxib, 5-carboxy-lumiracoxib, and 4′-hydroxy-5-carboxy-lumiracoxib. The 4′-hydroxy metabolite is active as a cyclo-oxygenase-2 (COX-2) inhibitor although it is less potent than lumiracoxib. The plasma half-life of lumiracoxib is about 4 hours. Slightly more of a dose is excreted in the urine (54%) than in the faeces (about 43%); only about 5% of a dose is excreted unchanged.

References.

1. Scott G, *et al.* Pharmacokinetics of lumiracoxib in plasma and synovial fluid. *Clin Pharmacokinet* 2004; 43: 467–78.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Prexige; *Austria*: Prexige†; *Braz.*: Prexige; *Chile*: Prexige†; *Gr.*: Frexocel; Prexige; *Hung.*: Prexige†; *Indon.*: Prexige†; *NZ*: Prexige†; *Swed.*: Prexige†; *Turk.*: Prexige.

Lysine Aspirin

Acetilsalicilato de lisina; Aspirin DL-Lysine; Lysiiniasetyylisalisylaatti; Lysinacetylsalicylat; DL-Lysine Acetylsalicylate; Lysine Acetylsalicylate; Lysinum Acetylsalicylicum; Лизин-Аспирин.

$C_{15}H_{22}N_2O_6$=326.3
CAS — 62952-06-1.
UNII — 2JJ274J145.

Pharmacopoeias. In *Fr.*

Uses and Administration

Lysine aspirin has analgesic, anti-inflammatory, and antipyretic actions similar to those of aspirin (p. 22.3). When given, lysine aspirin dissociates into lysine and aspirin; aspirin is then hydrolysed to salicylic acid. Lysine aspirin 900 mg is equivalent to about 500 mg of aspirin.

Lysine aspirin is used in the treatment of pain, fever, and rheumatic disorders. It is given in oral doses equivalent to 0.5 to 1 g of aspirin, repeated every 4 to 8 hours as needed up to a maximum of 3 g of aspirin daily (2 g daily in the elderly) for pain and fever. The dose for rheumatic disorders is equivalent to 3 to 6 g of aspirin daily in 3 or 4 divided doses. Lysine aspirin is also given intramuscularly or intravenously in similar doses; the maximum daily parenteral dose is equivalent to 4 g of aspirin for very severe pain and to 6 g of aspirin for rheumatic disorders.

Lysine aspirin is also used with metoclopramide in the treatment of migraine.

Lysine aspirin has also been used in the management of thromboembolic disorders.

Headache. Some references to the use of lysine aspirin, often with metoclopramide, in the treatment of migraine.

1. Tfelt-Hansen P, *et al.* The effectiveness of combined oral lysine acetylsalicylate and metoclopramide compared with oral sumatriptan for migraine. *Lancet* 1995; **346**: 923–6.
2. Diener HC. Efficacy and safety of intravenous acetylsalicylic acid lysinate compared to subcutaneous sumatriptan and parenteral placebo in the acute treatment of migraine. A double-blind, double-dummy, randomized, multicenter, parallel group study. *Cephalalgia* 1999; **19**: 581–8.
3. Tfelt-Hansen P. The effectiveness of combined oral lysine acetylsalicylate and metoclopramide (Migpriv) in the treatment of migraine attacks: comparison with placebo and oral sumatriptan. *Funct Neurol* 2000; **15** (suppl 3): 196–201.

Nasal polyps. Two long-term controlled studies[1] suggested that topical (endonasal) lysine aspirin may be effective in preventing the recurrence of nasal polyps after surgical removal (see p. 1608.2) in both aspirin-tolerant and aspirin-sensitive patients. This effect may be attributed to the non-specific anti-inflammatory properties of lysine aspirin. Although no adverse effects were reported in this study, hypersensitivity reactions have been seen after use of salicylates in the presence of nasal polyps (see Hypersensitivity under Adverse Effects of Aspirin, p. 25.2).

In another study[2] intranasal lysine aspirin did not show significant clinical benefit in preventing the recurrence of nasal polyps when compared with placebo. However, significant improvement at a microscopic level was noted.

1. Nucera E, *et al.* Effects of lysine-acetylsalicylate (LAS) treatment in nasal polyposis: two controlled long term prospective follow up studies. *Thorax* 2000; **55** (suppl 2): S75–78.
2. Parikh AA, Scadding GK. Intranasal lysine-aspirin in aspirin-sensitive nasal polyposis: a controlled trial. *Laryngoscope* 2005; **115**: 1385–90.

Adverse Effects, Treatment, and Precautions

As for Aspirin, p. 24.2. Anaphylactic shock has been reported in patients given lysine aspirin by injection.

Lysine aspirin, like aspirin, should not generally be given to children because of the risk of Reye's syndrome.

Hypersensitivity. For a suggestion that inhaled or intranasal lysine aspirin might be more suitable than aspirin for the diagnosis of sensitivity to NSAIDs, see under Hypersensitivity on p. 25.2.

Interactions

For interactions associated with aspirin, see p. 26.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Aspirina; Decitriol; Yectaspirin†; *Belg.*: Aspegic; Cardegic; *China*: Lai Bi Lin (来比林); *Cz.*: Kardegic; *Fr.*: Aspegic; Cardiosolupsan†; Kardegic; *Gr.*: Aspicalm; Draspir; Egicalm Cardio†; Egicalm; Ogiflegon; *Hung.*: Aspegic; Kardegic; *Ital.*: Aspegic†; Cardirene; Flectadol; *Mex.*: Coraspir; Kardegic; *Neth.*: Aspegic; *Pol.*: Laspal†; *Port.*: Aspegic; Inespirin†; Intraspir†; Kardegic†; Lisaspin; *Spain*: Inyespirin; *Switz.*: Alcacyl instantanee; Aspegic; Kardegic; *Turk.*: Aspegic; *Ukr.*: Acelysin (Ацелізин).

Multi-ingredient Preparations. *Belg.*: Migpriv; *Chile*: Dolotol 12; *Fin.*: Migpriv†; *Fr.*: Aspegic Codeine†; Migpriv; *Gr.*: Egityl; Premig; *Hung.*: Migpriv; *India*: Biospirin; *Ital.*: Migpriv; Migraprim; *Mex.*: Antigram; *Neth.*: Migrafin; *Pol.*: Migpriv; *Swed.*: Migpriv†; *Switz.*: Migpriv†; *Turk.*: Migprin; *UK*: Migramax.

Magnesium Salicylate

Salicilato magnésico; Магния Салицилат.
$C_{14}H_{10}MgO_6.4H_2O$=370.6
CAS — 18917-89-0 (anhydrous magnesium salicylate); 18917-95-8 (magnesium salicylate tetrahydrate).
UNII — 41728CY7UX (magnesium salicylate); JQ69D454N1 (anhydrous magnesium salicylate).

Pharmacopoeias. In *Chin.* and *US.*

USP 36: (Magnesium Salicylate). A white, odourless, efflorescent, crystalline powder. Soluble in water and in alcohol; slightly soluble in ether; freely soluble in methyl alcohol. Store in airtight containers.

Uses and Administration

Magnesium salicylate has analgesic, anti-inflammatory, and antipyretic actions similar to those of aspirin (see p. 22.3). Anhydrous magnesium salicylate 1 g is equivalent to about 1.2 g of aspirin. It is used in the treatment of pain and fever and has been used in the management of inflammatory conditions such as osteoarthritis, rheumatoid arthritis, and other arthritides. Usual oral doses of magnesium salicylate, expressed in terms of anhydrous magnesium salicylate, are about 300 to 600 mg every 4 hours for pain or fever.

Adverse Effects, Treatment, and Precautions

As for Aspirin, p. 24.2. Magnesium salicylate should also be used with caution in renal impairment because of the risk of hypermagnesaemia.

The use of aspirin and other acetylated salicylates is generally not recommended for children because of the risk of Reye's syndrome, unless specifically indicated. Some licensed product information extends this precaution to magnesium salicylate.

Interactions

For interactions associated with salicylates, see Aspirin, p. 26.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Herbogesic†; *USA*: Backache Maximum Strength Relief; Bayer Select Maximum Strength Backache; Doans; Magan; Mobidin; Momentum Muscular Backache Formula; MST.

Multi-ingredient Preparations. *Cz.*: Cholagol; *Hung.*: Cholagol; *Rus.*: Cholagol (Холагол); *Ukr.*: Cholagol (Холагол); *USA*: Back Pain-Off; Cafgesic Forte†; Combiflex ES†; Durabac Forte; Extra Strength Doans PM; Painaid Back Relief; Painaid BRP Back Relief Formula; Tetra-Mag†.

Pharmacopoeial Preparations
USP 36: Magnesium Salicylate Tablets.

Meclofenamic Acid *(BAN, USAN, rINN)*

Acide Méclofénamique; Ácido meclofenámico; Acidum Meclofenamicum; CI-583; INF-4668; Meclofenámico, ácido; Меклофенамовая Кислота.
N-(2,6-Dichloro-*m*-tolyl)anthranilic acid.
$C_{14}H_{11}Cl_2NO_2$=296.1
CAS — 644-62-2.
ATC — M01AG04; M02AA18.
ATC Vet — QM01AG04; QM02AA18.
UNII — 48ISLU4ZWD.

Pharmacopoeias. In *BP(Vet).*

BP(Vet) 2014: (Meclofenamic Acid). A white or almost white, crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in chloroform; sparingly soluble in ether; soluble in dimethylformamide and in 1M sodium hydroxide.

Meclofenamate Sodium *(BANM, USAN, rINNM)*

Méclofénamate de Sodium; Meclofenamato sódico; Natrii Meclofenamas; Натрий Меклофенамат.
$C_{14}H_{10}Cl_2NNaO_2.H_2O$=336.1
CAS — 6385-02-0.
UNII — 94N818U2W.

Pharmacopoeias. In *US.*

USP 36: (Meclofenamate Sodium). A white to creamy white, odourless to almost odourless, crystalline powder. Freely soluble in water, the solution sometimes being somewhat turbid due to partial hydrolysis and absorption of carbon dioxide; the solution is clear above pH 15. Slightly soluble in chloroform; practically insoluble in ether; soluble in methyl alcohol. Store in airtight containers. Protect from light.

Uses and Administration

Meclofenamic acid, an anthranilic acid derivative similar to mefenamic acid (p. 86.1), is an NSAID (p. 102.3). It is given orally as the sodium salt in musculoskeletal and joint disorders such as osteoarthritis and rheumatoid arthritis, in mild to moderate pain, and in dysmenorrhoea and menorrhagia.

Doses of meclofenamate sodium are expressed in terms of the equivalent amount of meclofenamic acid. Meclofenamic acid 100 mg is equivalent to about 113.5 mg of meclofenamate sodium. In arthritic conditions it is given in doses equivalent to 200 to 400 mg daily; daily doses are usually given in 3 or 4 divided doses. For relief of mild to moderate pain doses are 50 to 100 mg every 4 to 6 hours; the daily dose should not exceed 400 mg. The dose in the treatment of dysmenorrhoea and menorrhagia is 100 mg three times daily for up to 6 days during menstruation.

Meclofenamic acid has been given as a rectal suppository and is also used in veterinary medicine.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3.

Incidence of adverse effects. The commonest adverse effect in 2500 patients given meclofenamate sodium was gastrointestinal disturbance.[1] Diarrhoea occurred in 11.2% of patients in double-blind studies and 32.8% of patients in long-term studies (up to 3 years). Ulcers were detected in 22 patients during therapy and rashes occurred in 4% of patients. Transient increases in serum aminotransferases and BUN occurred in some patients.

1. Preston SN. Safety of sodium meclofenamate (Meclomen™). *Curr Ther Res* 1978; **23** (suppl 4S): S107–S112.

Effects on the blood. Case reports of agranulocytosis[1] and thrombocytopenia[2] associated with meclofenamate therapy.

1. Wishner AJ, Milburn PB. Meclofenamate sodium-induced agranulocytosis and suppression of erythropoiesis. *J Am Acad Dermatol* 1985; **13**: 1052–3.
2. Rodriguez J. Thrombocytopenia associated with meclofenamate. *Drug Intell Clin Pharm* 1981; **15**: 999.

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Pharmacokinetics

Meclofenamate sodium is readily absorbed when given orally. Peak plasma concentrations occur about 0.5 to 2 hours after ingestion. Meclofenamate is over 99% bound to plasma proteins. The plasma elimination half-life of meclofenamate sodium is about 2 to 4 hours. It is metabolised by oxidation, hydroxylation, dehalogenation, and conjugation with glucuronic acid and excreted in urine mainly as glucuronide conjugates of the metabolites. About 20 to 30% is recovered in the faeces. One of the metabolites, a 3-hydroxymethyl compound, is reported to be active although to a lesser extent than the parent drug.

References.
1. Koup JR, *et al.* A single and multiple dose pharmacokinetic and metabolism study of meclofenamate sodium. *Biopharm Drug Dispos* 1990; **11**: 1–15.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Chile*: Meclomen; *Gr.*: Meclomen; *Ital.*: Lenidolor; Movens.

Pharmacopoeial Preparations
USP 36: Meclofenamate Sodium Capsules.

Mefenamic Acid *(BAN, USAN, rINN)*

Acide Méfénamique; Ácido mefenámico; Acidum Mefenamicum; CI-473; CN-35355; INF-3355; Kwas mefenamowy; Kyselina mefenamová; Mefenaamihappo; Mefenámico, ácido; Mefenamik Asit; Mefenaminsäure; Mefenaminsav; Mefenamo rūgštis; Mefenamsyra; Мефенамовая Кислота.
N-(2,3-Xylyl)anthranilic acid.
$C_{15}H_{15}NO_2$=241.3
CAS — 61-68-7.
ATC — M01AG01.
ATC Vet — QM01AG01.
UNII — 367589PJ2C.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Mefenamic Acid). A white to almost white, microcrystalline powder. It exhibits polymorphism. Practically insoluble in water; slightly soluble in alcohol and in dichloromethane; dissolves in dilute solutions of alkali hydroxides.

USP 36: (Mefenamic Acid). A white to off-white, crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in methyl alcohol; sparingly soluble in chloroform; soluble in solutions of alkali hydroxides. Store in airtight containers. Protect from light.

Uses and Administration

Mefenamic acid, an anthranilic acid derivative, is an NSAID (p. 102.3), although its anti-inflammatory properties are considered to be minor.

It is used in mild to moderate pain including headache, dental pain, postoperative and postpartum pain, and dysmenorrhoea, in musculoskeletal and joint disorders such as osteoarthritis and rheumatoid arthritis, and in menorrhagia.

In the UK, the usual oral dose is 500 mg three times daily. US licensed product information recommends an initial dose of 500 mg followed by 250 mg every 6 hours as needed. In addition, in the USA, when mefenamic acid is used in the treatment of mild to moderate pain in adults and adolescents aged 14 years and over, it is also recommended that it should not be given for longer than 7 days at a time.

For doses of mefenamic acid in children, see below.

Mefenemate sodium has also been used.

Administration in children. In the UK, licensed product information states that mefenamic acid may be used in children for the treatment of Still's disease (see Juvenile Idiopathic Arthritis, p. 12.1) and fever, and for dysmenorrhoea in older children; a suggested oral dose in those over 6 months of age is 25 mg/kg daily in divided doses. Treatment in children should be given for no longer than 7 days unless they are receiving mefenamic acid for Still's disease. However, the *BNFC* only recommends mefenamic acid for acute pain, including dysmenorrhoea and menorrhagia, in those aged 12 years and over who may be given the usual adult dose (see above).

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3.

Treatment should be stopped if diarrhoea and rashes occur. Other effects reported include drowsiness, and effects on the blood such as thrombocytopenia, occasionally haemolytic anaemia, and rarely aplastic anaemia. Convulsions may occur on overdosage.

Mefenamic acid is contra-indicated in patients with inflammatory bowel disease. Licensed product information recommends that blood counts and liver and renal function should be monitored during long-term therapy. Drowsiness may affect the performance of skilled tasks.

Mefenamic acid may give a false positive in some tests for the presence of bile in the urine.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were given mefenamic acid, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding. The *BNF* also considers that the amount of mefenamic acid distributed into breast milk is too small to be harmful to a breast-fed infant. An early study[2] confirms that the distribution of mefenamic acid into breast milk is minimal. However, licensed product information contra-indicates the use of mefenamic acid in nursing mothers.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/11/07)
2. Buchanan RA, *et al.* The breast milk excretion of mefenamic acid. *Curr Ther Res* 1968; 10: 592–6.

Effects on the blood. References to haematological reactions in patients taking mefenamic acid including haemolytic anaemia,[1] leucopenia,[2] neutropenia,[3] and agranulocytosis.[4]

1. Scott GL, *et al.* Autoimmune haemolytic anaemia and mefenamic acid therapy. *BMJ* 1968; 3: 534–5.
2. Burns A, Young RE. Mefenamic acid induced leucopenia in the elderly. *Lancet* 1984; ii: 46.
3. Handa SI, Preestone S. Mefenamic acid-induced neutropenia and renal failure in elderly females with hypothyroidism. *Postgrad Med J* 1990; 66: 557–9.
4. Muroi K, *et al.* Treatment of drug-induced agranulocytosis with granulocyte-colony stimulating factor. *Lancet* 1989; ii: 55.

Effects on the gastrointestinal tract. Reversible steatorrhoea has occurred[1] with mefenamic acid; it may also provoke colitis in patients without a history of this condition.[2]

1. Marks JS, Gleeson MH. Steatorrhoea complicating therapy with mefenamic acid. *BMJ* 1975; 4: 442.
2. Ravi S, *et al.* Colitis caused by non-steroidal anti-inflammatory drugs. *Postgrad Med J* 1986; 62: 773–6.

Effects on the kidneys. Nonoliguric renal failure has occurred in elderly patients who had had diarrhoea and vomiting while taking mefenamic acid and had continued to take the drug. It is normally recommended that mefenamic acid be stopped in the event of diarrhoea and it was suggested that in these patients the gastrointestinal toxicity had led to fluid and electrolyte depletion, thus predisposing these patients to mefenamic acid's nephrotoxicity.[1] There has been a subsequent report[2] of nonoliguric renal failure in elderly patients given mefenamic acid for musculoskeletal pain.

1. Taha A, *et al.* Non-oliguric renal failure during treatment with mefenamic acid in elderly patients: a continuing problem. *BMJ* 1985; 291: 661–2.
2. Grant DJ, MacConnachie AM. Mefenamic acid is more dangerous than most. *BMJ* 1995; 311: 392.

Effects on the skin. Bullous pemphigoid, together with haemolytic anaemia and diarrhoea,[1] and fixed drug eruptions[2-4] have been associated with the use of mefenamic acid. Additionally, Stevens-Johnson syndrome, together with cholestatic hepatitis and haemolytic anaemia, in one patient has been attributed to mefenamic acid.[5] It is generally recommended that mefenamic acid should be withdrawn if skin reactions develop.

1. Shepherd AN, *et al.* Mefenamic acid-induced bullous pemphigoid. *Postgrad Med J* 1986; 62: 67–8.
2. Wilson CL, Otter A. Fixed drug eruption associated with mefenamic acid. *BMJ* 1986; 293: 1243.
3. Long CC, *et al.* Fixed drug eruption to mefenamic acid: a report of three cases. *Br J Dermatol* 1992; 126: 409–11.
4. Rallis E. Dalmatian dog'-like skin eruption (two cases of multifocal fixed drug eruption induced by mefenamic acid). *J Eur Acad Dermatol Venereol* 2005; 19: 753–5.
5. Chan JCN, *et al.* A case of Stevens-Johnson syndrome, cholestatic hepatitis and haemolytic anaemia associated with use of mefenamic acid. *Drug Safety* 1991; 6: 230–4.

Overdosage. Mefenamic acid overdose has been associated with CNS toxicity, especially with convulsions.[1] Coma[2,3] has also been reported.

1. Court H, Volans GN. Poisoning after overdose with non-steroidal anti-inflammatory drugs. *Adverse Drug React Acute Poisoning Rev* 1984; 3: 1–21.
2. Gössinger H, *et al.* Coma in mefenamic acid poisoning. *Lancet* 1982; ii: 384.
3. Hendrickse MT. Mefenamic acid overdose mimicking brainstem stroke. *Lancet* 1988; ii: 1019.

Pancreatitis. A report of pancreatitis associated with mefenamic acid.[1]

1. van Walraven AA, *et al.* Pancreatitis caused by mefenamic acid. *Can Med Assoc J* 1982; 126: 894.

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Pharmacokinetics

Mefenamic acid is absorbed from the gastrointestinal tract. Peak plasma concentrations occur about 2 to 4 hours after ingestion. The plasma elimination half-life is reported to be about 2 to 4 hours. Mefenamic acid is more than 90% bound to plasma proteins. It is distributed into breast milk. Mefenamic acid is metabolised by the cytochrome P450 isoenzyme CYP2C9 to 3-hydroxymethyl mefenamic acid, which may then be oxidised to 3-carboxymefenamic acid. Over 50% of a dose may be recovered in the urine, as unchanged drug or, mainly, as conjugates of mefenamic acid and its metabolites.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Ponstil; *Austral.*: Mefic†; Ponstan; *Austria*: Mefenabene; Parkemed; *Braz.*: Ponsdril; Ponstan; Pontin; Pontrex; Standor; *Canad.*: Ponstan; *Chile*: Adesna; Algex; Algifemin; Flipal; Sicadol; T-Nol; Tanston; Templadol; Truasinol; *Fin.*: Ponstan; *Fr.*: Ponstyl; *Gr.*: Acinic; Aidol; Algopress; Calmin; Demostan; Kpeitton; Padomil; Penta; Ponstan; Vidan; *Hong Kong*: Gynogesic†; Hamitan†; Hostan†; Medicap; Mefa; Mefamic†; Mefen; Mefenac†; Mefencid†; Mefic; Metsyn†; Namic; Napan; Painnox†; Pekaso†; Pongesic; Ponsis†; Ponstan; Pontacid†; Sefmic; Uni-Fenamic†; *Hung.*: Ponmel; *India*: Dysmen 500; Mefac; Mefacid; Mefdol; Meflup; Mefsine; Meftal; Ponstan; *Indon.*: Analspec; Asam; Asimat; Benostan; Cetalmic; Corstanal; Datan; Dogesic; Dolfenal†; Dolos; Dystan†; Femisic; Fensik; Gitaramin; Grafix; Lapistan; Licostan; Maxtan; Mectan†; Mefast; Mefinal; Mefinter; Mefix; Menin; Molasic; Nichostan; Opistan; Pehastan; Ponalar; Poncofen; Pondex; Ponsamic; Ponstan; Ponstelax; Solasic; Stanalin; Stanza†; Stelpon†; Teamic; Topgesic; Tropistan; *Irl.*: Mefac; Ponalgic; Ponmel†; Ponstan; *Ital.*: Lysalgo; *Malaysia*: Beafemic; Mefic†; Namic; Napan; Ponstan; Pontacid; Pontalon; Sefmic; *Mex.*: Artriden; Namifen; Ponstan; *NZ*: Ponstan; *Philipp.*: Acidan; Afligec; Algifort; Analcid; Analmin; Aprostal†; Arthran; Atnose; Belfedane; Calibral; Dolfenal; Dolmetine†; Dolsten; Escandar†; Eurostan; Finox; Fromefen; Gardan; Gisfen; Hispen; Inflasic; Isagesic; Istan; Kramon; Laffed; Marfen; Mecid A; Medianon; Mefan; Mefenax; Mefril†; Metaflam; MFE; Neostan; Penomor; Ponser; Ponstan; Pontaser; Ralgec; Remifein; Revalan; Selmac; Senflam†; Spegic; Stangesic; Suprazen; Totagesic; Tynostan; Vamgesic†; Vandifen†; Zanovic; ZapAn†; Zestan; *Pol.*: Mefacit; *Port.*: Ponstan; *S.Afr.*: Fenamin; Ponac; Ponstan; Ponstel; *Singapore*: Alfoxan; Beafemic; Fenagesic; Hostan; Medicap; Mefenix; Mefril; Napan; Pontacid; Pontalon; Pontyl; SP-Famic; Zeet; *Spain*: Coslan; *Switz.*: Mefenacid; Mefenamin; Mefenaminacid†; Mephadolor; Ponstan; Spiralgine; Sportusal†; *Thai.*: Anagan; Anagic; Coly; Conamic; Dismen; Dolfen; Fastan; Femen; Femic; Fenamic; Fennic; Gandin; Gynogesic; Locpan; Manic; Manomic; Masafen†; Meditan; Mednil; Mefa; Mefamed; Mefamic; Mefen; Mefenac; Mefenan; Mefnasic; Menamic; Nalgesin; Namic; Nufemic; Pacamic; Painnox; Panamic†; Pefamic; Ponacap; Ponatap; Pondnadysmen; Pongesics; Ponnac; Ponnesia; Ponstan; Pontalon; Pronamic; Prostan; Pynamic; Sefmic† TV Gin; Vestan; *Turk.*: Ponstan; Roladol; Rolan; *UK*: Ponstan *USA*: Ponstel; *Venez.*: Ponstan.

Multi-ingredient Preparations. *India*: Abdowin; Apodrot; Baralgan-DM; Bio-Stat-MF; Chromostat; Clip-MF; Coastat-Gyne Coease-M; Coligon Plus; Colimef; Colispas; Cyclocos-TX; Cyclocos; Cyclomeff; Cyclopam Plus; Cyclosym-TX; Cyclosym; Dam Spas; Decolic-V; Detrim; Divo-M; Dora-M; Dortsil-M; Dotarin MF; Dotra-M; Dozee-M; Drat-MF; Drobel-MF; Drofem; Drofic Drolid-M; Drosym-MF; Drotikind-M; Drotin-M; Drotmic; Drotwell-M; Dubatran-MF; Dutora-M; DVN Plus; Dymef; Dynamet Dysmen Forte; Dysmen; Dysmeryl; Efespas; Eginor; Eklot-MF Eldrot-Plus; Emverin-MF; Etosys-MF; Examic-MF; Fenamic Fetran-MF; Fibran-M; Florasyl-MF; Fodro-M; Gefplus; Gefspass; Griprid; Gynae-Pil Forte; Hamodam-M; HMT; Inorine-M Kolispas; Lenagesic; Maff-D; Mafia; Majispa; MD-MF; Mef-T Mefac Spas; Mefacid Forte; Mefamic-D; Mefar-PD; Mefatin-Spas; Mefcil Spas; Mefdi; Mefdic; Mefdol Spas; Mefegesic; Meffnex; Mefitrax; Meflam; Meflaxin; Meflup Forte; Mefmin Spas; Mefnex; Mefnic Spas; Mefnic-D; Mefsaid-D; Mefsaid; Mefsym-Spas; Mefsyn-TX; Meftagesic; Meftagesic; Meftal Forte; Meftal-MR; Meftal-Spas; Meftal-TX; Meftrax; Mefze Spas; Mefzys; Menogia-MF; Menospan-MF; Menotran; Mepar; Mespas; Mouzex-MF; Neurospas-MF; No Blos For; Noblifen; Normospas; Novaspas; NTSpass; Pal-MF; Paraspas; Spasmonil Forte; Spasmonil Plus; Tranfib MF; Ze-Spas; *Singapore*: Orcigesic; *Thai.*: Anpuzz; Difemic; Mainnox; *Ukr.*: No-Spasma (Но-Спазма)†.

Pharmacopoeial Preparations

BP 2014: Mefenamic Acid Capsules; Mefenamic Acid Tablets;
USP 36: Mefenamic Acid Capsules.

Meloxicam *(BAN, USAN, rINN)*

Meloksikaami; Meloksikam; Méloxicam; Meloxicamum; Meloxikam; UH-AC-62; UH-AC-62XX; Мелоксикам.

4-Hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide.

$C_{14}H_{13}N_3O_4S_2$=351.4

CAS — 71125-38-7.

ATC — M01AC06.

ATC Vet — QM01AC06.

UNII — VG2QF83CGL

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Meloxicam). A pale yellow powder. It exhibits polymorphism. Practically insoluble in water; very slightly soluble in alcohol; soluble in dimethylformamide. Protect from light. A pale yellow powder. Practically insoluble in water; very slightly soluble in alcohol and in methyl alcohol; slightly soluble in acetone; soluble in dimethylformamide.

USP 36: (Meloxicam). A pale yellow powder. Practically insoluble in water; very slightly soluble in alcohol and in methyl alcohol; slightly soluble in acetone; soluble in dimethylformamide.

Uses and Administration

Meloxicam, an oxicam derivative, is an NSAID (p. 102.3). It is reported to be a selective inhibitor of cyclo-oxygenase-2 (COX-2). Meloxicam is used in the management of rheumatoid arthritis, for the short-term symptomatic treatment of acute exacerbations of osteoarthritis, and for the symptomatic treatment of ankylosing spondylitis. It may also be used in the treatment of juvenile idiopathic arthritis.

In the treatment of rheumatoid arthritis and ankylosing spondylitis, meloxicam is given in a usual oral dose of 15 mg daily as a single dose. Those with an increased risk of adverse reactions should be started on 7.5 mg daily. A dose of 7.5 mg daily is recommended for long-term treatment in the elderly. In the treatment of acute exacerbations of osteoarthritis the usual oral daily dose of meloxicam is 7.5 mg, increased if necessary to a maximum of 15 mg daily given as a single dose.

For dosage details in children, see below.

Meloxicam may be given by rectal suppository in doses similar to those used orally.

For the dose of meloxicam in patients with renal impairment, see p. 87.1.

Administration in children. In the USA, meloxicam is used in the treatment of juvenile idiopathic arthritis in children aged 2 years and over. The recommended oral dose is 125 micrograms/kg once daily, up to a maximum of 7.5 mg daily. In the UK, licensed product information states that meloxicam should not be used in children aged under 16 years. However, the *BNFC* has suggested the following oral doses, according to body-weight, for the relief

of pain and inflammation in juvenile idiopathic arthritis and other musculoskeletal disorders in those aged 12 to 18 years who are intolerant of other NSAIDs:
- less than 50 kg: 7.5 mg once daily
- over 50 kg: 15 mg once daily

Administration in renal impairment. Meloxicam is normally contra-indicated in patients with severe renal impairment. However, in dialysed patients, meloxicam may be given in a dose of 7.5 mg daily orally or rectally as suppositories. No dose reduction is required in those with mild to moderate renal impairment (creatinine clearance of greater than 25 mL/min).

Musculoskeletal and joint disorders. Meloxicam is used in the treatment of osteoarthritis (p. 12.3), rheumatoid arthritis (p. 13.2) including juvenile idiopathic arthritis (p. 12.1), and ankylosing spondylitis (see Spondyloarthropathies, p. 14.3). However, in the UK, the use of meloxicam and other selective cyclo-oxygenase-2 (COX-2) inhibitors is limited to those patients with good cardiovascular health and at high risk of developing serious gastrointestinal problems if given a non-selective NSAID (see p. 105.3).

References.

1. Lemmel EM, *et al.* Efficacy and safety of meloxicam in patients with rheumatoid arthritis. *J Rheumatol* 1997; **24:** 282–90.
2. Yocum D, *et al.* Safety and efficacy of meloxicam in the treatment of osteoarthritis: a 12-week, double-blind, multiple-dose, placebo-controlled trial. The Meloxicam Osteoarthritis Investigators. *Arch Intern Med* 2000; **160:** 2947–54.
3. Combe B, *et al.* Comparison of intramuscular and oral meloxicam in rheumatoid arthritis patients. *Inflamm Res* 2001; **50** (suppl 1): S10–S16.
4. Fleischmann R, *et al.* Meloxicam. *Expert Opin Pharmacother* 2002; **3:** 1501–12.

Veterinary use. For the suggestion that meloxicam should be used as an alternative to diclofenac in cattle in South Asia (to reduce toxicity to vultures who may consume their carcasses), see under Precautions of Diclofenac, p. 50.2

Adverse Effects and Treatment

As for NSAIDs in general, p. 104.3.

Incidence of adverse effects. Between September 1996, when meloxicam was first marketed in the UK, and mid-June 1998 the UK CSM had received a total of 773 reports of 1339 suspected adverse reactions for meloxicam.[1] Of all the reactions 41% were gastrointestinal and of these 18% involved gastrointestinal perforation, ulceration and/or bleeding; the mean age of the patients involved was 64 years. Although most patients recovered after withdrawal of meloxicam and/or treatment, 5 died. A total of 193 reactions involved the skin, the most common being pruritus, rash, and urticaria. There were also reports of angioedema (25 reports), photosensitivity (12 reports), and bullous dermatoses, including erythema multiforme and Stevens-Johnson syndrome (5 reports). No patients died from skin reactions and most recovered after meloxicam was withdrawn. Other frequently reported reactions were neurological (mostly headache), cardiovascular (oedema and palpitations), dizziness, flushing, and fatigue. A prescription event monitoring study has also analysed events reported with meloxicam use.[2] In a cohort of 19 087 patients who had received meloxicam some time between December 1996 and March 1997, 203 patients had had 252 events considered to be suspected adverse reactions. The majority of reactions were not serious or were labelled adverse effects of meloxicam. Rare, serious suspected adverse reactions included 2 reports of thrombocytopenia and 1 each of interstitial nephritis and idiosyncratic liver abnormality. The most frequent gastrointestinal event was dyspepsia; other more serious gastrointestinal events occurring during meloxicam exposure included upper gastrointestinal bleeding (33 reports) and peptic ulcer (19 reports). However, it was considered that the incidence of gastrointestinal disturbance was low in the absence of gastrointestinal risk factors. Adverse drug reactions reported during the first year of marketing of meloxicam to the Swedish Medical Products Agency suggested a similar safety profile to other NSAIDs.[3] Of the 15 reports, 6 were for gastrointestinal disturbances and 5 involved skin reactions.

1. CSM/MCA. Meloxicam (Mobic): gastrointestinal and skin reactions. *Current Problems* 1998; **24:** 13. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE6dDocName=CON2023216RevisionSelectionMethod=LatestReleased (accessed 08/11/07)
2. Martin RM, *et al.* The incidence of adverse events and risk factors for upper gastrointestinal disorders associated with meloxicam use amongst 19 087 patients in general practice in England: cohort study. *Br J Clin Pharmacol* 2000; **50:** 35–42.
3. Anonymous. Meloxicam safety similar to other NSAIDs. *WHO Drug Information* 1998; **12:** 147.

Effects on the gastrointestinal tract. It is generally accepted that inhibition of cyclo-oxygenase-1 (COX-1) plays a role in the adverse gastrointestinal effects of NSAIDs, and that selective inhibition of the other isoform, COX-2, by NSAIDs such as meloxicam may cause less gastrotoxicity than that seen with the non-selective inhibition of traditional NSAIDs. However, there has been little convincing evidence that the risk of severe gastrointestinal events is lower with meloxicam than with other NSAIDs at equi-effective doses.[1] Two large multicentre studies[2,3] have reported a lower incidence of gastrointestinal adverse effects with meloxicam than with non-selective cyclo-oxygenase inhibitors (diclofenac[2] or piroxicam[3]) but in one of these[2] the dose of meloxicam given also appeared to be less effective than the reference drug. A more recent systematic review[4] also found a lower risk of serious gastrointestinal toxicity with meloxicam 7.5 mg daily when compared with diclofenac (100 or 150 mg daily), naproxen (500 mg twice daily), or piroxicam (20 mg daily); however, when given at a dose of 15 mg daily, the risk of toxicity with meloxicam was significantly lower only when compared with piroxicam.

Individual case reports of gastrointestinal toxicity with meloxicam included one of ischaemic colitis associated with high-dose (15 mg daily) meloxicam treatment.[5]

1. Anonymous. Meloxicam—a safer NSAID? *Drug Ther Bull* 1998; **36:** 62–4.
2. Hawkey C, *et al.* Gastrointestinal tolerability of meloxicam compared to diclofenac in osteoarthritis patients. *Br J Rheumatol* 1998; **37:** 937–45.
3. Dequeker J, *et al.* Improvement in gastrointestinal tolerability of the selective cyclooxygenase (COX)-2 inhibitor, meloxicam, compared with piroxicam: results of the safety and efficacy large-scale evaluation of COX-inhibiting therapies (SELECT) trial in osteoarthritis. *Br J Rheumatol* 1998; **37:** 946–51.
4. Singh G, *et al.* Risk of serious upper gastrointestinal and cardiovascular thromboembolic complications with meloxicam. *Am J Med* 2004; **117:** 100–106.
5. Garcia B, *et al.* Ischaemic colitis in a patient taking meloxicam. *Lancet* 2001; **357:** 690.

Precautions

As for NSAIDs in general, p. 107.1.

Meloxicam should be avoided in severe hepatic impairment, in bleeding disorders, and in patients with renal failure unless receiving dialysis. Rectal use should be avoided in patients with a history of proctitis, haemorrhoids, or rectal bleeding.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies meloxicam as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 23/10/11)

Renal impairment. The pharmacokinetics of meloxicam were not substantially altered in patients with a creatinine clearance (CC) of 41 to 60 mL/minute compared with those with normal renal function.[1] In those with a CC of 20 to 40 mL/minute, total plasma-meloxicam concentrations were lower but meloxicam free fractions were higher. Such free meloxicam concentrations were similar to the other groups. On the basis of these results, it was suggested that it was not necessary to reduce meloxicam doses in patients with a CC greater than 20 mL/minute.

1. Boulton-Jones JM, *et al.* Meloxicam pharmacokinetics in renal impairment. *Br J Clin Pharmacol* 1997; **43:** 35–40.

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Colestyramine increases the clearance and decreases the half-life of meloxicam.

Pharmacokinetics

Meloxicam is well absorbed after oral or rectal doses and peak plasma concentrations occur within 6 hours. It is 99% bound to plasma proteins. Meloxicam has a plasma-elimination half-life of about 20 hours. It is extensively metabolised, mainly by oxidation to its major metabolite, 5'-carboxymeloxicam. *In vitro* studies suggest that the cytochrome P450 isoenzyme CYP2C9 plays an important role in the metabolism of meloxicam with CYP3A4 involved to a lesser degree. Meloxicam, in the form of metabolites, is excreted in similar amounts in the urine and in the faeces; less than 5% of a dose is excreted unchanged. The volume of distribution is increased in renal failure.

References.

1. Nafes H, *et al.* Pharmacokinetics and tolerability of meloxicam after i.m. administration. *Br J Clin Pharmacol* 1996; **41:** 135–9.
2. Türck D, *et al.* Clinical pharmacokinetics of meloxicam. *Arzneimittelforschung* 1997; **47:** 253–8.
3. Davies NM, Skjodt NM. Clinical pharmacokinetics of meloxicam: a cyclooxygenase-2 preferential nonsteroidal anti-inflammatory drug. *Clin Pharmacokinet* 1999; **36:** 115–26.
4. Meineke I, Türck D. Population pharmacokinetic analysis of meloxicam in rheumatoid arthritis patients. *Br J Clin Pharmacol* 2003; **55:** 32–8.
5. Burgos-Vargas R, *et al.* Pharmacokinetics of meloxicam in patients with juvenile rheumatoid arthritis. *J Clin Pharmacol* 2004; **44:** 866–72.

Renal impairment. For reference to the pharmacokinetics of meloxicam in renal impairment, see under Precautions, above.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Bronax; Dominadol; Flexidol; Flexium; Loxitenk; Meloracˆ; Meloxid; Mextran; Miolox; Mobic; Telaroid†; Tenaron; ***Austral.***: Meloxibell; Mobic; Movalis; Moxicam; ***Austria***: Metosan; Movalis; ***Belg.***: Docmeloxi†; Mobic; ***Braz.***: Alivian; Bioflac; Dormelox; Flamatec; Inicox; Leutrol; Loxam; Loxiflan; Melocox; Melotec; Meloxigran; Meloxil; Menoxiton; Mevamox; Movacox; Movatec; Movoxicam; ***Canad.***: Mobicox; ***Chile***: Anposel; Ecax; Hyflex; Isox; Melic; Melodol; Mexan; Mexilal; Mibloc FT; Mioflam; Mobex; Sition; Tenaron; ***China***: An Li Qing (安立青); He Chang (和畅); Hong Qiang (宏强); Ji Kang Ning (吉康宁); Jie Zong (节宗); Keyi (可伊); Luo Guan Jian (络贯健); Luo Ke (洛珂); Mei Er Tong (美尔同); Mi Nuo Xi (米诺希); Mo Le Xin (莫乐新); Mobic (莫比可); Mokelin (莫利林); Nai Bang (奈邦); PuLiLuo (普利洛); Qing Qing (清轻); Sai Ke Si (赛可斯); Sai Ou Si (塞欧斯); Si Lai Mei (斯莱美); Tong Ke (统克); Wu Yan (吾琰); You Ni (优尼); Ze Li (则立); ***Cz.***: Antrend; Artrilom; Duplicam†; Enaros; Galoxiway†; Melobax; Melocox; Melovis; Meloxistad; Movalis; Movmaks; Noflamen; Oramellox; Recoxa; ***Denm.***: Celomix; Loxime; ***Fin.***: Latonid†; Mobic; ***Fr.***: Mobic; ***Ger.***: Melox†; Mobec; ***Gr.***: Arsitec; Arthrox; Auroxicam; Brosiral; Doctinon; Examel; Farmelox; Flelox; Flumidon; Iamaxicam; Iaten; Iconal; Infomel; Loxitan; Mecalox; Medoxicam; Melcam; Melice; Melocalm; Melock; Melocox; Melodim; Meloprol; Melorem; Melorilif; Melotec; Melotop; Melox; Meloxeron; Meloxil; Meloxitor; Melus; Meomel; Movatec; Movaxin; Moxalid; Notpel; Parogal; Partial; Philipon-S; Rentilox; Reumotec; Reumotherm; Sanetron; Saniflam; Starmelox; Supercad; Transantor; Tropofin; Valoxin; Vexicam; Zametrixal; Zerelin; ***Hong Kong***: Arrox; Melcam; Melflam; Melox; Mobic; Partial; ***Hung.***: Borbin; Camelox; Melodyn; Melogen; Melox; Meloxan; Movalis; Moxicam; Noflamen; ***India***: Ecwin; M-Cam; Mel-OD; Melflam; Melogesic; Melone; Melosuganril; Mexam; Movac; Muvera; Muvik; ***Indon.***: Arimed; Artrilox; Cameloc; Flamoxi; Flasicox; Loxil; Loxinic; Mecox; Meflam; Meloxin; Mevilox; Mexpharm; Mobiflex; Movi-Cox; Movix; Moxam; Moxic; Nulox; Ostelox; Paxicam; Relox; Remacam; Rhemacox; Velcox; X-Cam; ***Irl.***: Areloger; Melcam; Mobic; Mobicam; Mobiglan; Movox; ***Ital.***: Gixal; Leutrol; Mobic; ***Jpn***: Mobic; ***Malaysia***: Arrox; Avegesic; Mel-OD; Melartin; Melocam; Melox; Mobic; Rafree; ***Mex.***: Aflamid; Anpre; Auricam†; Coxylan; Dolocam; Exel; Flexiver; Flexol; Lexpram; Loxam†; Loxibach; Loxibest; Mavicam; Maxoflam; Meflen; Melarthryl; Melican; Melosteral; Menflixil; Mobicox; Promotion; Reosan; Retoflam; ***Neth.***: Movalis†; Movicox; ***Norw.***: Mobic†; ***NZ***: Melorex; Mobic; ***Philipp.***: Bexxam; Caxlem; Cloxim; Meflam; Mel-OD; Melart; Melcom; Melocox; Meloflam; Melora; Meloxin; Mobic; Moxen; Neoxicam; Newsicam; Osteolax; Rafree; ***Pol.***: Aglan; Aspicam; Celomix; Lormed; Melobax; Meloksam; Melokssia†; Melotev; Meloxic; MeloxiLek; Meloxistad; Mexan; Movalis; Movmax; Opokan; ***Port.***: Dortex; Lador; Marlex; Meipor; Movalis; ***Rus.***: Amelotex (Амелотекс); *Artrozan (Артрозан); Lem (Лем); Mataren (Матарен);* Melbek (Мелбек); Meloflam (Мелофлам); Melokan (Мелокан)†; Melox (Мелокс); Mesipol (Месипол); Mirlox (Мирлокс); Mixol (Миксол); Movalis (Мовалис); Movasin (Мовасин); Movix (Мовикс); ***S.Afr.***: Arthrocox; Coxflam; Flamaryx; Flexocam; Loxiflam; M-Cam; Meliflam; Mobic; ***Singapore***: Melox; Mobic; ***Spain***: Aliviodol; Movalis; Parocin; Uticox†; ***Swed.***: Mobic†; ***Switz.***: Mobicox; ***Thai.***: Cambic; Mel-OD; Melcam; Melobic; Melox; Mobic; ***Turk.***: Exen; Meksun; Melcam; Melox; Meliurjin; Meskun; Mobic; Mone; Romacox; Runomex; Zeloxim; ***UK***: Mobic†; ***Ukr.***: Melbek (Мелбек); Meloksam (Мелоксам)†; Meloxic (Мелоксик)†; Movalis (Мовалис); Reumoxicam (Ревмоксикам); ***USA***: Mobic; ***Venez.***: Biomelox; Melonax; Melovax; Mobic; Taucaron.

Multi-ingredient Preparations. *Arg.*: Aldoron Flex; Aldoron M; Bronax Flex; Dolo Asotrex; Dolo Baliartrin; Flexidol Relax; Mextran Flex; Tenaron Flex; ***India***: Melodol; ***Mex.***: Dolocam Plus; Dolocartigen; Dorsal; Flexamol†; Nuro-B; Retoflam F; Tremecox.

Pharmacopoeial Preparations
BP 2014: Meloxicam Tablets;
USP 36: Meloxicam Oral Suspension; Meloxicam Tablets.

Meptazinol Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de meptazinol; IL-22811 (meptazinol); Meptazinol, Chlorhydrate de; Meptazinol, hidrocloruro de; Meptazinoli Hydrochloridum; Wy-22811 (meptazinol); Мептазинона Гидрохлорид.

3-(3-Ethyl-1-methylperhydroazepin-3-yl)phenol hydrochloride.

$C_{15}H_{23}NO.HCl$=269.8

CAS — 54340-58-8 (meptazinol); 59263-76-2 (meptazinol hydrochloride); 34154-59-1 (±-meptazinol hydrochloride).

ATC — N02AX05.

The symbol † denotes a preparation no longer actively marketed

ATC Vet — QN02AX05
UNII — T62FQ4ZCPA

Pharmacopoeias. In *Br.*

BP 2014: (Meptazinol Hydrochloride). A white or almost white powder. Very soluble in water and in methyl alcohol; freely soluble in alcohol; very slightly soluble in acetone; dissolves in dilute solutions of alkali hydroxides. Store at a temperature not exceeding 25 degrees.

Uses and Administration

Meptazinol is a mixed opioid agonist and antagonist with partial opioid agonist activity at the μ_1 opioid receptor (see p. 108.1); it also has cholinergic activity. Meptazinol is used in the treatment of moderate to severe pain. It has a shorter duration of action than morphine.

Meptazinol hydrochloride is given orally or by intramuscular or intravenous injection; doses are expressed in terms of the base. Meptazinol hydrochloride 115.6 mg is equivalent to about 100 mg of meptazinol. For the short-term treatment of moderate pain meptazinol is given in an oral dose of 200 mg every 3 to 6 hours, as required. The intramuscular dose is 75 to 100 mg given every 2 to 4 hours, as required; for obstetric pain a dose of 2 mg/kg (100 to 150 mg) may be used. Meptazinol is also given by slow intravenous injection in doses of 50 to 100 mg every 2 to 4 hours, as required.

Administration. *EPIDURAL ROUTE.* Epidural meptazinol 90 mg for postoperative pain was reported to be superior to an intramuscular dose of 90 mg.[1] However, in another study[2] a 30-mg dose was ineffective and associated with an unacceptable incidence of adverse effects. A 60-mg dose was also found to be ineffective because of its short duration of action.[3]

UK licensed product information states that the injectable formulation is not suitable for epidural or intrathecal use.

1. Verborgh C, *et al.* Meptazinol for postoperative pain relief in man: comparison of extradural and im administration. *Br J Anaesth* 1987; 59: 1134–9.
2. Francis RI, Lockhart AS. Epidural meptazinol. *Anaesthesia* 1986; 41: 88–9.
3. Birks RJS, Marsh DRG. Epidural meptazinol. *Anaesthesia* 1986; 41: 883.

Administration in hepatic impairment. See under Pharmacokinetics, below for a suggestion that doses may need to be reduced in patients with cirrhosis.

Dependence and Withdrawal

As for Opioid Analgesics, p. 109.1.

In assessing the dependence potential of meptazinol, a WHO expert committee[1] noted in 1989 that abrupt discontinuation of chronic meptazinol use precipitated only slight withdrawal signs in *animals* and that meptazinol did not suppress opioid withdrawal signs and symptoms in humans dependent on morphine. Abuse had not been reported. They considered that the likelihood of abuse was moderate and that international control was not warranted at that time.

1. WHO. WHO expert committee on drug dependence: twenty-fifth report. *WHO Tech Rep Ser 775* 1989. Also available at: http://libdoc.who.int/trs/WHO_TRS_775.pdf (accessed 26/06/08)

Adverse Effects, Treatment, and Precautions

As for Opioid Analgesics in general, p. 110.1.

Gastrointestinal adverse effects are commonly reported with meptazinol and include abdominal pain, constipation, dyspepsia, diarrhoea, and nausea and vomiting. Meptazinol is claimed to have a low incidence of respiratory depression; nonetheless, UK licensed product information states that it should not be used in patients with acute respiratory depression. There have been occasional reports of psychiatric disorders such as hallucinations, confusion, and depression. As meptazinol has both antagonist and agonist properties its effects may be only partially reversed by naloxone, but use of the latter is still recommended in overdosage.

Meptazinol has the potential to precipitate withdrawal symptoms if given to patients who are physically dependent on opioids.

Abuse. See under Dependence and Withdrawal, above.

Effects on the respiratory system. Meptazinol is said to have a relatively low potential for respiratory depression and in healthy subjects was reported to produce substantially less respiratory depression than morphine or pentazocine at usual analgesic doses.[1] However, respiratory depression does occur in anaesthetised patients given meptazinol[2] and the effects on respiration may be similar to those of morphine[3,4] or pethidine.[5,6] Compensatory mechanisms may come into play after repeated doses of meptazinol but the intravenous use of meptazinol during anaesthesia should be viewed with as much caution as with any other opioid.[6]

Respiratory arrest occurred after an *overdose* of 50 meptazinol 200-mg tablets and a quarter of a bottle of whisky.[7] Full recovery eventually followed supportive measures although spontaneous respiration was not re-established by naloxone intravenously to a cumulative total dose of 10 mg.

1. Jordan C, *et al.* A comparison of the respiratory effects of meptazinol, pentazocine and morphine. *Br J Anaesth* 1979; 51: 497–502.
2. Hardy PAJ. Meptazinol and respiratory depression. *Lancet* 1983; ii: 576.
3. Frater RAS, *et al.* Analgesia-induced respiratory depression: comparison of meptazinol and morphine in the postoperative period. *Br J Anaesth* 1989; 63: 260–5.
4. Verborgh C, Camu F. Post-surgical pain relief with zero-order intravenous infusions of meptazinol and morphine: a double-blind placebo-controlled evaluation of their effects on ventilation. *Eur J Clin Pharmacol* 1990; 38: 437–42.
5. Wilkinson DJ, *et al.* Meptazinol—a cause of respiratory depression in general anaesthesia. *Br J Anaesth* 1985; 57: 1077–84.
6. Lee A, Drummond GB. Ventilatory effects of meptazinol and pethidine in anaesthetised patients. *Br J Anaesth* 1987; 59: 1127–33.
7. Davison AG, *et al.* Meptazinol overdose producing near fatal respiratory depression. *Hum Toxicol* 1987; 6: 331.

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

Plasma concentrations of meptazinol may be increased by ritonavir and use together should be avoided (see also p. 111.2).

Pharmacokinetics

After oral doses of meptazinol peak plasma concentrations have occurred within 0.5 to 2 hours, but bioavailability is low since it undergoes extensive first-pass metabolism. Systemic availability is improved after rectal doses. Peak plasma concentrations have occurred 30 minutes after rectal or intramuscular use. Plasma protein binding has averaged only about 27%. Elimination half-lives of about 2 hours have been reported. Meptazinol is extensively metabolised in the liver and is excreted mainly in the urine as the glucuronide conjugate. Less than 10% of a dose has been recovered from the faeces. Meptazinol crosses the placenta.

References.

1. Franklin RA, *et al.* Studies on the metabolism of meptazinol, a new analgesic drug. *Br J Clin Pharmacol* 1976; 3: 497–502.
2. Franklin RA, *et al.* Studies on the absorption and disposition of meptazinol following rectal administration. *Br J Clin Pharmacol* 1977; 4: 163–7.
3. Davies G, *et al.* Pharmacokinetics of meptazinol in man following repeated intramuscular administration. *Eur J Clin Pharmacol* 1982; 23: 535–8.
4. Norbury HM, *et al.* Pharmacokinetics of the new analgesic, meptazinol, after oral and intravenous administration to volunteers. *Eur J Clin Pharmacol* 1983; 25: 77–80.
5. Murray GR, *et al.* The systemic availability of meptazinol in man after oral and rectal doses. *Eur J Clin Pharmacol* 1989; 36: 279–82.

The elderly. A lower clearance and longer elimination half-life have been reported for meptazinol in elderly patients, but dosage reduction was not considered warranted on pharmacokinetic grounds. Mean half-lives in elderly and young subjects were 3.39 and 1.94 hours, respectively after single oral doses[1] and 2.93 and 2.06 hours, respectively after intravenous doses.[2]

1. Norbury HM, *et al.* Pharmacokinetics of meptazinol after single and multiple oral administration to elderly patients. *Eur J Clin Pharmacol* 1984; 27: 223–6.
2. Murray GR, *et al.* Pharmacokinetics of meptazinol after parenteral administration in the elderly. *Eur J Clin Pharmacol* 1987; 31: 733–6.

Hepatic impairment. Oral bioavailability of meptazinol appeared to be enhanced in patients with liver disease. After a single oral dose of meptazinol mean peak plasma concentrations were 184 nanograms/mL, 131 nanograms/mL, and 53 nanograms/mL in cirrhotic patients, patients with non-cirrhotic liver disease, and patients with normal liver function, respectively, although there was no evidence of accumulation after chronic dosing.[1] There were no significant differences in plasma clearance after an intravenous dose. Reduced oral doses of meptazinol might be advisable in cirrhotic patients.

1. Birnie GG, *et al.* Enhanced oral bioavailability of meptazinol in cirrhosis. *Gut* 1987; 28: 248–54.

Pregnancy. In women given an intramuscular injection of 100 to 150 mg during labour, meptazinol was found to cross the placenta readily but was rapidly eliminated from the neonate.[1] This contrasted with pethidine which was known to be excreted very slowly from neonates. As in the adult, elimination of meptazinol by the neonate appeared to take place mainly by conjugation with glucuronic acid.[2] A half-life of 3.4 hours, similar to that in adults, has been reported in the neonate,[3] in contrast to 22.7 hours for pethidine in neonates.

Disposition of meptazinol appears not to be significantly affected by pregnancy. Mean half-lives of 1.36 and 1.68 hours were reported in pregnant and non-pregnant women respectively,[4] compared with 2.06 hours in men.

1. Franklin RA, *et al.* Preliminary studies on the disposition of meptazino in the neonate. *Br J Clin Pharmacol* 1981; 12: 88–90.
2. Dowell PS, *et al.* Routes of meptazinol conjugation in the neonate. *Br J Clin Pharmacol* 1982; 14: 748–9.
3. Jackson MBA, Robson PJ. Preliminary clinical and pharmacokinetic experiences in the newborn when meptazinol is compared with pethidine as an obstetric analgesic. *Postgrad Med J* 1983; 59 (suppl 1): 47–51.
4. Murray GR, *et al.* The disposition of meptazinol after single and multiple intravenous administration to pregnant and non-pregnant women. *Eur J Clin Pharmacol* 1989; 36: 273–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Meptid; *Gr.*: Nestan; *Irl.*: Meptid; *UK*: Meptid.

Pharmacopoeial Preparations
BP 2014: Meptazinol Injection; Meptazinol Tablets.

Methadone Hydrochloride

(BANM, pINNM) ⊗

Amidine Hydrochloride; Amidone Hydrochloride; Hidrocloruro de amidina; Hidrocloruro de metadona; Metadon Hidroklorür; Metadona, hidrocloruro de; Metadon-hidroklorid; Metadonhydroklorid; Metadonihydrokloridi; Metadono hidrochloridas; Metadonu chlorowodorek; Methadon hydrochlorid; Méthadone, chlorhydrate de; Methadonhydrochlorid; Methadoni Hydrochloridum; Phenadone; Метадона Гидрохлорид; (±)-Methadone Hydrochloride.

(±)-6-Dimethylamino-4,4-diphenylheptan-3-one hydrochloride.

$C_{21}H_{27}NO,HCl$=345.9

CAS — 76-99-3 (methadone); 297-88-1 (±methadone); 1095-90-5 (methadone hydrochloride); 125-56-4 (±methadone hydrochloride).

ATC — N07BC02.

ATC Vet — QN07BC02.

UNII — 2298099358.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of methadone:

Amidone; Balloons; Breeze; Burdock; Buzz bomb; Dollies; Dolls; Done; Doses; Fizzies; Juice; Jungle juice; Junk; Meta; Mud; Phy; Physamps; Tootsie roll.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Methadone Hydrochloride). A white or almost white, crystalline powder. Soluble in water; freely soluble in alcohol. Protect from light.

USP 36: (Methadone Hydrochloride). Odourless colourless crystals or white crystalline powder. Soluble in water; freely soluble in alcohol and in chloroform; practically insoluble in ether and in glycerol. pH of a 1% solution in water is between 4.5 and 6.5. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Incompatibility. There appears to be adequate evidence that stable solutions containing methadone hydrochloride and hydroxybenzoate esters can be formulated but the risk of precipitation exists if syrup preserved with hydroxybenzoates is used to extemporaneously prepare a methadone mixture 1 mg/mL to the DTF formula.[1] An oral formulation of methadone hydrochloride 5 mg/mL containing methyl hydroxybenzoate 0.1% as preservative rather than chloroform has been reported stable for at least 4 months at room temperature.[2]

1. *PSGB Lab Report P/80/1* 1980.
2. Ching MS, *et al.* Stability of methadone mixture with methyl hydroxybenzoate as a preservative. *Aust J Hosp Pharm* 1989; 19: 159–61.

Uses and Administration

Methadone hydrochloride, a diphenylheptane derivative, is an opioid analgesic (p. 108.1) that is mainly a μ-opioid agonist. Single doses of methadone have a less marked sedative action than single doses of morphine. Methadone is a racemic mixture and levomethadone (p. 83.1) is the active isomer.

Methadone hydrochloride is used in the treatment of moderate to severe pain; it may be of use for those patients who have excitation or exacerbation of pain with morphine. Methadone is also used in the management of opioid dependence. It has a depressant action on the cough centre and has been used as a cough suppressant in terminal illness, although the *BNF* discourages this use because of the risks of accumulation.

For **pain relief** starting oral doses of methadone hydrochloride may range from 2.5 to 10 mg given every 6 to 8 hours or longer and thereafter adjusted as necessary. Methadone may also be given parenterally. In the UK, the

subcutaneous and intramuscular routes are licensed with the intramuscular route being recommended for prolonged use; US licensed product information states that the intravenous, intramuscular, and subcutaneous routes may be used although it gives doses for the intravenous route only. Initial dose ranges for parenteral routes are similar to those used orally; however, if transferring between oral and parenteral methadone, US product information states that the initial conversion dose should be based on the guide that 10 mg of oral methadone is equivalent to about 5 mg of parenteral methadone. The analgesic effect of methadone begins about 10 to 20 minutes after parenteral injection and about 30 to 60 minutes after oral doses, the effect of a single dose usually lasting about 4 hours. As accumulation occurs with repeated doses, the effects become more prolonged. Consequently, to avoid the risk of opioid overdose, it is recommended that in prolonged use methadone should not be given more than twice daily.

Methadone is used as part of the treatment of **opioid dependence**, although prolonged use of methadone itself may result in dependence. Initially, methadone hydrochloride is given in doses sufficient to suppress signs of opioid withdrawal but avoid toxicity; the *BNF* and US licensed product information recommended a starting dose of 10 to 40 mg daily. Subsequent dose adjustments should be made cautiously because of the risks of accumulation; the *BNF* suggests adjusting the dose in steps of up to 10 mg to a maximum weekly increase of 30 mg. Once the dose has been stabilised, patients may choose to receive prolonged therapy with a carefully selected methadone dose for each individual; most patients in such maintenance programmes are stabilised on once-daily doses of 60 to 120 mg. Alternatively, detoxification may be appropriate with the dose of methadone being gradually decreased until total withdrawal is achieved. Methadone is usually given orally for the treatment of dependence although parenteral routes may be used, particularly when oral therapy is not possible; the doses stated above may be given orally or parenterally. In the UK, oral treatment is commonly given as a mixture containing 1 mg/mL of methadone hydrochloride.

For details of doses in children, see below.

For the control of intractable **cough** associated with terminal lung cancer, methadone hydrochloride is usually given in the form of a linctus in a dose of 1 to 2 mg every 4 to 6 hours, but reduced to twice daily on prolonged use.

Administration. Although duration of action after single doses of methadone is similar to that of morphine, it increases considerably with multiple dosing of methadone because of the long elimination half-life (see under Pharmacokinetics, p. 91.1). The minimum effective dose of methadone can be difficult to titrate for the individual patient. A fixed 10-mg oral dose with a flexible patient-controlled dosage interval has been used in patients with chronic cancer pain.[1] Dosage not more frequently than every 4 hours during the first 3 to 5 days, followed by a fixed dose every 8 to 12 hours depending on the patient's requirements, was advised.

A suggested initial dose for patients who need to switch from oral morphine to methadone because of poor pain control is one tenth of the total daily dose of morphine, but not greater than 100 mg, given at intervals determined by the patient, typically every 8 hours.[2]

When switching from oral to parenteral use it was suggested[3] that the dose of methadone should be halved and adjusted thereafter as necessary.

Evidence of the prolonged effect of methadone was seen when a single intravenous bolus dose of 20 mg resulted in postoperative analgesia lasting about 25 hours.[4] An initial 2-hour loading intravenous infusion of methadone 100 to 200 micrograms/kg per hour to provide rapid analgesia followed by infusion at a lower maintenance rate of 10 to 20 micrograms/kg per hour for continuous pain relief has been used in burn patients.[5] Methadone has also been given by continuous subcutaneous infusion for severe cancer pain[6,7] although this route has been associated with local tissue irritation and induration. Epidural methadone has been used successfully in doses of up to 5 mg for analgesia with bupivacaine.[8,9] Intermittent and continuous epidural infusion of methadone has also been tried[10] in postoperative analgesia.

A small case series[11] found topical methadone powder to be effective for pain relief of open, exudative wounds.

1. Säwe J, *et al.* Patient-controlled dose regimen of methadone for chronic cancer pain. *BMJ* 1981; **282**: 771–3.
2. Morley JS, *et al.* Methadone in pain uncontrolled by morphine. *Lancet* 1993; **342**: 1243.
3. Säwe J. High-dose morphine and methadone in cancer patients: clinical pharmacokinetic considerations of oral treatment. *Clin Pharmacokinet* 1986; **11**: 87–106.
4. Gourlay GK, *et al.* Methadone produces prolonged postoperative analgesia. *BMJ* 1982; **284**: 630–1.
5. Denson DD, *et al.* Pharmacokinetics of continuous intravenous infusion of methadone in the early post-burn period. *J Clin Pharmacol* 1990; **30**: 70–5.
6. Mathew P, Storey P. Subcutaneous methadone in terminally ill patients: manageable local toxicity. *J Pain Symptom Manage* 1999; **18**: 49–52.
7. Makin MK, Morley JS. Subcutaneous methadone in terminally-ill patients. *J Pain Symptom Manage* 2000; **19**: 237–8.
8. Drenger B, *et al.* Extradural bupivacaine and methadone for extracorporeal shock-wave lithotripsy. *Br J Anaesth* 1989; **62**: 82–6.
9. Martin CS, *et al.* Extradural methadone and bupivacaine in labour. *Br J Anaesth* 1990; **65**: 330–2.
10. Prieto-Alvarez P, *et al.* Continuous epidural infusion of racemic methadone results in effective postoperative analgesia and low plasma concentrations. *Can J Anaesth* 2002; **49**: 25–31.
11. Gallagher RE, *et al.* Analgesic effects of topical methadone: a report of four cases. *Clin J Pain* 2005; **21**: 190–2.

Administration in children. Methadone is not licensed for use in children. However, it has been tried[1] intravenously in children aged 3 to 7 years to prevent postoperative pain; a dose of 200 micrograms/kg was given perioperatively followed postoperatively by 50 micrograms/kg every 10 minutes until the patient was both comfortable and adequately alert. Methadone has also been tried[2] orally for the treatment of severe pain in hospitalised children; daily doses ranged from 200 to 600 micrograms/kg for up to 6 weeks.

Methadone is used for the management of **neonatal abstinence syndrome** (p. 110.1). The *BNFC* suggests an initial oral dose of 100 micrograms/kg increased by 50 micrograms/kg every 6 hours until symptoms are controlled; once stabilised, the total daily dose is given in 2 divided doses for maintenance. When withdrawing methadone, the dose should be reduced over 7 to 10 days.

1. Berde CB, *et al.* Comparison of morphine and methadone for prevention of postoperative pain in 3- to 7-year-old children. *J Pediatr* 1991; **119**: 136–41.
2. Shir Y, *et al.* Oral methadone for the treatment of severe pain in hospitalized children: a report of five cases. *Clin J Pain* 1998; **14**: 350–3.

Cancer pain. Methadone is used as an alternative to morphine in the treatment of severe cancer pain (p. 7.1). A better understanding of its pharmacokinetics and of equianalgesic doses may address early concerns about the risk of cumulative toxicity associated with prolonged use. However, its long terminal half-life makes it less suitable for the treatment of breakthrough pain.

Methadone has been given by the oral, rectal, and parenteral routes.

References.

1. Ayonrinde OT, Bridge DT. The rediscovery of methadone for cancer pain management. *Med J Aust* 2000; **173**: 536–40.
2. Bruera E, Sweeney C. Methadone use in cancer patients with pain: a review. *J Palliat Med* 2002; **5**: 127–38.
3. Bruera E, *et al.* Methadone versus morphine as a first-line strong opioid for cancer pain: a randomized, double-blind study. *J Clin Oncol* 2004; **22**: 185–92.
4. Moryl N, *et al.* Methadone in the treatment of pain and terminal delirium [sic] in advanced cancer patients. *Palliat Support Care* 2005; **3**: 311–17.
5. Mannino R, *et al.* Methadone for cancer-related neuropathic pain: a review of the literature. *J Opioid Manag* 2006; **2**: 269–76.
6. Nicholson AB. Methadone for cancer pain. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 26/06/08).

Opioid dependence. The treatment of opioid dependence is discussed on p. 109.2. In the UK, oral liquid preparations of methadone hydrochloride 1 mg/mL are widely used for this purpose. It is important to note that these preparations are 2.5 times stronger than Methadone Linctus (BP 2014), and although some are licensed for analgesia in severe pain, many are licensed for the treatment of opioid dependence only. Methadone Oral Solution (1 mg/mL) (BP 2014) is available as a ready-to-use solution or may be prepared from Methadone Hydrochloride Oral Concentrate. However, most commercially available preparations in the UK still follow an earlier formula formerly listed in the Drug Tariff Formulary (DTF):

Methadone Mixture 1 mg/mL
methadone hydrochloride 10 mg
Green S and Tartrazine Solution (BP 1980) 0.02 mL
Compound Tartrazine Solution (BP 1980) 0.08 mL
syrup, unpreserved 5 mL
chloroform water, double-strength to 10 mL.

Some commercially available forms of DTF Methadone Mixture 1 mg/mL use a preservative system based on hydroxybenzoate esters rather than chloroform; however, syrup preserved with hydroxybenzoate esters may be unsuitable for extemporaneous dispensing (see Incompatibility, p. 88.3).

References.

1. Ghodse AH, *et al.* Comparison of oral preparations of heroin and methadone to stabilise opiate misusers as inpatients. *BMJ* 1990; **300**: 719–20.
2. Wolff K, *et al.* Measuring compliance in methadone maintenance patients: use of a pharmacologic indicator to "estimate" methadone plasma levels. *Clin Pharmacol Ther* 1991; **50**: 199–207.
3. Wilson P, *et al.* Methadone maintenance in general practice: patients, workload, and outcomes. *BMJ* 1994; **309**: 641–4.
4. Farrell M, *et al.* Methadone maintenance treatment in opiate dependence: a review. *BMJ* 1994; **309**: 997–1001.
5. Henry JA. Methadone: where are we now? *Hosp Med* 1999; **60**: 161–4.
6. Faggiano F, *et al.* Methadone maintenance at different dosages for opioid dependence. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 28/08/08).
7. Amato L, *et al.* Methadone at tapered doses for the management of opioid withdrawal. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 26/06/08).
8. NICE. Methadone and buprenorphine for the management of opioid dependence: Technology Appraisal Guidance 114 (issued January 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/TA114Niceguidance.pdf (accessed 26/06/08)
9. Mattick RP, *et al.* Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2009 (accessed 11/11/09).

Dependence and Withdrawal

As for Opioid Analgesics, p. 109.1.

Methadone withdrawal symptoms are similar to, but more prolonged than, those produced by morphine or diamorphine. They develop more slowly and do not usually appear until 3 to 4 days after the last dose.

Methadone is used for substitution therapy in the management of opioid dependence (see Uses and Administration, p. 88.3) including neonatal abstinence syndrome (see Administration in Children, above).

Adverse Effects and Treatment

As for Opioid Analgesics in general, p. 110.1.

Methadone has a more prolonged effect than morphine and readily accumulates with repeated doses. It may have a relatively greater respiratory depressant effect than morphine and, although reported to be less sedating, repeated doses of methadone may result in marked sedation. QT prolongation and torsade de pointes have been reported rarely with methadone use, particularly at doses above 100 mg daily. After gross overdosage symptoms are similar to those of morphine poisoning. Pulmonary oedema after overdosage is a common cause of fatalities among addicts.

Methadone causes pain at injection sites; subcutaneous injection causes local tissue irritation and induration.

Effects on the cardiovascular system. Methadone prolongs the QT interval and has rarely been associated with torsade de pointes. In a retrospective case series,[1] 17 patients on high-dose methadone (mean daily dose of 397 mg) developed torsade de pointes; of these, 14 had potential risk factors for arrhythmia and 6 had had their dose increased within the last month. In another study[2] torsade de pointes developed in 5 patients taking methadone (mean daily dose 268 mg); however, they all had other contributing risk factors. Other studies[3,4] did not find instances of torsade de pointes and the increase in QT interval was considered clinically insignificant; in one study,[4] the mean daily dose of methadone was 110 mg and some patients also had risk factors for arrhythmia.

For a report of QT interval prolongation in an infant born to a mother on maintenance methadone therapy for opioid addiction, see Pregnancy, p. 90.2.

In a small case-controlled study of sudden cardiac deaths,[5] the prevalence of underlying cardiac disease or structural abnormalities was lower in the 22 cases with evidence of therapeutic methadone levels when compared with the 106 cases without evidence of methadone use. The authors considered that the low prevalence of cardiac risk factors in the methadone group suggested a role for methadone itself in the pathogenesis of sudden death in this group.

1. Krantz MJ, *et al.* Torsade de pointes associated with very-high-dose methadone. *Ann Intern Med* 2002; **137**: 501–4.
2. Sticherling C, *et al.* Methadone-induced torsade de pointes tachycardias. *Swiss Med Wkly* 2005; **135**: 282–5.
3. Martell BA, *et al.* The impact of methadone induction on cardiac conduction in opiate users. *Ann Intern Med* 2003; **139**: 154–5.
4. Cruciani RA, *et al.* Measurement of QTc in patients receiving chronic methadone therapy. *J Pain Symptom Manage* 2005; **29**: 385–91.
5. Chugh SS, *et al.* A community-based evaluation of sudden death associated with therapeutic levels of methadone. *Am J Med* 2008; **121**: 66–71.

Effects on the endocrine system. Hypoadrenalism has been found in chronic methadone addicts. Findings consistent with deficient ACTH production and subsequent secondary hypoadrenalism have been reported[1] although there is also evidence[2] of methadone-induced primary adrenal cortical hypofunction.

Hyperprolactinaemia and galactorrhoea have also been reported.[3] See also Effects on Sexual Function, p. 90.1.

1. Dackis CA, *et al.* Methadone induced hypoadrenalism. *Lancet* 1982; **ii**: 1167.
2. Pullan PT, *et al.* Methadone-induced hypoadrenalism. *Lancet* 1983; **i**: 714.
3. Bennett J, Whale R. Galactorrhoea may be associated with methadone use. *BMJ* 2006; **332**: 1071.

Effects on the nervous system. Choreic movements occurred in a 25-year-old man on long-term methadone maintenance treatment of 45 to 60 mg daily for diamorphine addiction.[1] Similar adverse effects were seen in a 41-year-old woman taking 5 mg methadone four times daily for complex regional pain syndrome.[2] In both cases, symptoms resolved when methadone was stopped.

1. Wasserman S, Yahr MD. Choreic movements induced by the use of methadone. *Arch Neurol* 1980; **37**: 727–8.
2. Clark JD, Elliott J. A case of a methadone-induced movement disorder. *Clin J Pain* 2001; **17**: 375–7.

Effects on the respiratory system. Sleep apnoea has been reported[1,2] in patients on stable methadone maintenance treatment.

1. Teichtahl H, *et al.* Sleep-disordered breathing in stable methadone programme patients: a pilot study. *Addiction* 2001; 96: 395–403.
2. Wang D, *et al.* Central sleep apnea in stable methadone maintenance treatment patients. *Chest* 2005; 128: 1348–56.

Effects on sexual function. Sexual performance was impaired in 29 male diamorphine addicts receiving methadone maintenance therapy.[1] The function of secondary sex organs was markedly suppressed when compared with untreated diamorphine addicts or controls and serum-testosterone concentrations were 43% lower in those on methadone. However, in a more recent study[2] in 92 opioid addicts also receiving methadone maintenance, rates of sexual dysfunction (erectile, libido, and orgasm dysfunction) were found to be similar to that of the general population. Rates of dysfunction between patients just started on methadone and those on methadone for at least 60 days were not significantly different although new patients generally had lower rates. Mean plasma concentrations of testosterone and prolactin were within normal ranges and although 8 individuals had low testosterone concentrations, only 1 case of dysfunction was reported in this group.

1. Cicero TJ, *et al.* Function of the male sex organs in heroin and methadone users. *N Engl J Med* 1975; 292: 882–7.
2. Brown R, *et al.* Methadone maintenance and male sexual dysfunction. *J Addict Dis* 2005; 24: 91–106.

Overdosage. Most cases of methadone poisoning occur in persons not on maintenance,[1-4] particularly children or family members of maintenance patients.[2] Methadone is highly toxic to anyone who is not tolerant to opioids; 50 to 100 mg can be life-threatening in non-tolerant adults and 10 mg can be fatal in a young child.[2] Furthermore, life-threatening toxicity from oral doses as low as 5 mg has been reported in children.[1,4]

Various groups[5,6] have found that the risk of death from methadone toxicity is greatest during the first 2 weeks of maintenance therapy. This has been attributed to the difficulty in determining a safe and effective starting dose of methadone and unreliable accounts of a patient's recent drug use.

1. Aronow R, *et al.* Childhood poisoning: an unfortunate consequence of methadone availability. *JAMA* 1972; 219: 321–4.
2. Harding-Pink D. Opioid toxicity: methadone: one person's maintenance dose is another's poison. *Lancet* 1993; 341: 665–6.
3. Zador DA, Sunjic SD. Methadone-related deaths and mortality rate during induction into methadone maintenance, New South Wales, 1996. *Drug Alcohol Rev* 2002; 21: 131–6.
4. Sachdeva DK, Stadnyk JM. Are one or two dangerous? Opioid exposure in toddlers. *J Emerg Med* 2005; 29: 77–84.
5. Caplehorn JRM, Drummer OH. Mortality associated with New South Wales methadone programs in 1994: lives lost and saved. *Med J Aust* 1999; 170: 104–9.
6. Buster MCA, *et al.* An increase in overdose mortality during the first 2 weeks after entering or re-entering methadone treatment in Amsterdam. *Addiction* 2002; 97: 993–1001.

Precautions

As for Opioid Analgesics in general, p. 110.3.

Methadone should be given with caution to patients at risk of developing prolongation of the QT interval including those with cardiac or hepatic disease, with hypokalaemia or other electrolyte imbalance, or with a family history of sudden death. It should also be used with caution in patients who are taking other potentially arrhythmogenic drugs, drugs likely to cause electrolyte imbalance, or drugs that inhibit the cytochrome P450 isoenzyme CYP3A4 (see under Interactions, below). ECG monitoring is recommended before starting methadone treatment in these patients, with a further test at dose stabilisation. ECG monitoring is also recommended before and at 7 days after dose titration above 100 mg daily in patients without recognised risk factors.

Administration. Methadone has a long half-life and accumulation may occur with repeated doses, especially in elderly or debilitated patients. An 81-year-old woman given methadone 5 mg three times daily orally for 2 days became deeply unconscious but awoke immediately when given naloxone 400 micrograms intravenously.[1]

Sudden death in 10 diamorphine addicts occurred between 2 and 6 days after starting a methadone maintenance programme.[2] The mean prescribed dose of methadone at the time of death had been about 60 mg. There was evidence of chronic persistent hepatitis in all cases and liver disease could have reduced methadone clearance resulting in higher than expected blood concentrations. Liver function tests and urine testing for the presence of drugs before entry into methadone maintenance programmes, and lower starting doses, might decrease the likelihood of such deaths. Like dextropropoxyphene, methadone has membrane stabilising activity and can block nerve conduction, and it was suggested[3] that the sudden deaths were mainly due to accumulation of methadone over several days resulting in complications such as cardiac arrhythmias or cardiovascular collapse (see Effects on the Cardiovascular System, p. 89.3). See also Overdosage, above.

For the effects of hepatic and renal impairment on the disposition of methadone, see under Pharmacokinetics, p. 91.2.

1. Symonds P. Methadone and the elderly. *BMJ* 1977; i: 512.
2. Drummer OH, *et al.* Deaths of heroin addicts starting on a methadone maintenance programme. *Lancet* 1990; 335: 108.
3. Wu C, Henry JA. Deaths of heroin addicts starting on methadone maintenance. *Lancet* 1990; 335: 424.

Breast feeding. The American Academy of Pediatrics considers that the use of methadone in breast-feeding mothers is usually compatible with breast feeding.[1] The *BNF* also permits breast feeding by mothers on methadone maintenance although the dose should be as low as possible and the infant monitored to avoid sedation. Others have suggested that the amount of methadone in breast milk is unlikely to have any pharmacological effect on the infant.[2-8] However, there has been a report of the death of a 5-week-old breast-fed infant whose mother was on methadone maintenance.[9]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction, *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/06/08)
2. Blinick G, *et al.* Methadone assays in pregnant women and progeny. *Am J Obstet Gynecol* 1975; 121: 617–21.
3. Wojnar-Horton RE, *et al.* Methadone distribution and excretion into breast milk of clients in a methadone maintenance programme. *Br J Clin Pharmacol* 1997; 44: 543–7.
4. Geraghty B, *et al.* Methadone levels in breast milk. *J Hum Lact* 1997; 13: 227–30.
5. McCarthy JJ, Posey BL. Methadone levels in human milk. *J Hum Lact* 2000; 16: 115–20.
6. Begg EJ, *et al.* Distribution of R- and S-methadone into human milk during multiple, medium to high oral dosing. *Br J Clin Pharmacol* 2001; 52: 681–5.
7. Jansson LM, *et al.* Methadone maintenance and breastfeeding in the neonatal period. *Pediatrics* 2008; 121: 106–14.
8. Jansson LM, *et al.* Methadone maintenance and long-term lactation. *Breastfeed Med* 2008; 3: 34–7.
9. Smialek JE, *et al.* Methadone deaths in children. *JAMA* 1977; 238: 2516–17.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies methadone as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/10/11)

Pregnancy. Methadone is not recommended for use in labour because its prolonged duration of action increases the risk of neonatal respiratory depression.

Neonatal abstinence syndrome and low birth-weight are immediate problems in infants born to women receiving methadone for the management of opioid addiction; increased still-birth rates have also been noted.[1-3] In the neonatal period moderate to severe opioid abstinence syndrome occurred in 75% of infants in a study,[2] as well as reduced head circumference and raised systolic blood pressure. At follow-up over 18 months these children had a higher incidence of otitis media, of reduced head circumference, and of abnormal eye findings when compared with drug-free controls. Neurobehavioural abnormalities and lower scores on mental and motor developmental indices were thought to be possible predictors of later learning and behavioural problems. In a later study,[4] the use of methadone alone during pregnancy as part of a maintenance program was claimed to increase the risk of prematurity twofold, of intra-uterine growth retardation fourfold, and of microcephaly threefold when compared with a normal population. In addition, in those mothers who continued to abuse other drugs, as well as receive methadone, the risks of these events were further increased. However, an earlier study[5] has reported that methadone or diamorphine had no specific effect on intra-uterine and postnatal growth.

The relationship between maternal methadone dose and the incidence and severity of neonatal abstinence syndrome is unclear. Although a retrospective study[6] found a correlation in some pregnancies, others[7,8] did not and there was no evidence of an increased incidence of neonatal withdrawal symptoms even with high maternal doses of 100 mg or more daily.[8]

A small retrospective study[9] comparing the use of methadone during pregnancy for the treatment of chronic pain with use in maintenance therapy for opioid addiction found a lower incidence of neonatal abstinence syndrome and better growth parameters in infants born to the former group of mothers; however, a higher rate of slight prematurity was also found in this group of infants. The authors suggested that lower maternal doses and shorter durations of treatment may account for the favourable findings, in addition to better maternal health, nutrition, and socio-economic status.

Clinically significant prolongation of the QT interval has been reported[10] in an infant born to a mother taking methadone 50 mg daily for maintenance therapy; the infant had mild withdrawal symptoms and follow-up at 2 months of age was normal.

1. Blinick G, *et al.* Methadone maintenance, pregnancy, and progeny. *JAMA* 1973; 225: 477–9.
2. Rosen TS, Johnson HL. Children of methadone-maintained mothers: follow-up to 18 months of age. *J Pediatr* 1982; 101: 192–6.
3. Kaltenbach K, Berkowitz J. Congenital malformations. *N Engl J Med* 1983; 308: 491–7.
4. Arlettaz R, *et al.* Methadone maintenance program in pregnancy in a Swiss perinatal center (II): neonatal outcome and social resources. *Acta Obstet Gynecol Scand* 2005; 84: 145–50.
5. Lifschitz MH, *et al.* Fetal and postnatal growth of children born to narcotic-dependent women. *J Pediatr* 1983; 102: 686–91.
6. Dashe JS *et al.* Relationship between maternal methadone dosage and neonatal withdrawal. *Obstet Gynecol* 2002; 100: 1244–9.
7. Berghella V, *et al.* Maternal methadone dose and neonatal withdrawal. *Am J Obstet Gynecol* 2003; 189: 312–17.
8. McCarthy JJ, *et al.* High-dose methadone maintenance in pregnancy: maternal and neonatal outcomes. *Am J Obstet Gynecol* 2005; 193: 606–10
9. Sharpe C, Kuschel C. Outcomes of infants born to mothers receiving methadone for pain management in pregnancy. *Arch Dis Child Fetal Neonatal Ed* 2004; 89: F33–F36.
10. Hussain T, Ewer AK. Maternal methadone may cause arrhythmias in neonates. *Acta Paediatr* 2007; 96: 768–9.

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

Methadone is metabolised in the liver mainly via the cytochrome P450 isoenzyme CYP3A4; the isoenzymes CYP2B6, CYP2D6, CYP2C9, CYP2C19, and CYP1A2 are also thought to be involved. Consequently, use with other drugs that induce or inhibit these isoenzymes may result in changes in plasma concentrations of methadone and, possibly adverse effects. There is a risk of cardiac events in patients receiving methadone who are also taking drugs that affect cardiac conduction or electrolyte balance.

Drugs that *acidify* or *alkalinise* the urine may have an effect on methadone pharmacokinetics since body clearance is increased at acidic pH and decreased at alkaline pH.[1]

1. Nilsson M-I, *et al.* Effect of urinary pH on the disposition of methadone in man. *Eur J Clin Pharmacol* 1982; 22: 337–42.

Antibacterials. Withdrawal symptoms have been reported in patients maintained on methadone when they were given the enzyme inducer *rifampicin*.[1-3] Conversely, the use of *ciprofloxacin*, which inhibits CYP1A2 and CYP3A4, has resulted in signs of methadone toxicity.[4]

1. Kreek MJ, *et al.* Rifampin-induced methadone withdrawal. *N Engl J Med* 1976; 294: 1104–6.
2. Bending MR, Skacel PO. Rifampicin and methadone withdrawal. *Lancet* 1977; i: 1211.
3. Raistrick D, *et al.* Methadone maintenance and tuberculosis treatment. *BMJ* 1996; 313: 925–6.
4. Herrlin K, *et al.* Methadone, ciprofloxacin, and adverse drug reactions. *Lancet* 2000; 356: 2069–70.

Antidepressants. *SSRIs* such as fluoxetine[1] and fluvoxamine[1,2] may enhance the effects of some opioid analgesics; such interactions may lead to methadone toxicity. *St John's wort* reduced the plasma-methadone concentration to dose ratios by 47% in 4 patients on methadone maintenance therapy for opioid addiction; 2 patients reported symptoms suggestive of a withdrawal syndrome.[3]

1. Eap CB, *et al.* Fluvoxamine and fluoxetine do not interact in the same way with the metabolism of the enantiomers of methadone. *J Clin Psychopharmacol* 1997; 17: 113–17.
2. Bertschy G, *et al.* Probable metabolic interaction between methadone and fluvoxamine in addict patients. *Ther Drug Monit* 1994; 16: 42–5.
3. Eich-Höchli D, *et al.* Methadone maintenance treatment and St. John's Wort: a case report. *Pharmacopsychiatry* 2003; 36: 35–7.

Antiepileptics. Opioid withdrawal symptoms have been reported in patients maintained on methadone when they were given *carbamazepine*,[1,2] *phenobarbital*,[3] or *phenytoin*.[4,5] Conversely, methadone-induced respiratory depression developed in a patient on carbamazepine, gabapentin, and methadone for neuropathic pain, after carbamazepine was stopped.[6]

1. Bell J, *et al.* The use of serum methadone levels in patients receiving methadone maintenance. *Clin Pharmacol Ther* 1988; 43: 623–9.
2. Saxon AJ, *et al.* Valproic acid, unlike other anticonvulsants, has no effects on methadone metabolism: two cases. *J Clin Psychiatry* 1989; 50: 228–9.
3. Liu S-J, Wang RIH. Case report of barbiturate-induced enhancement of methadone metabolism and withdrawal syndrome. *Am J Psychiatry* 1984; 141: 1287–8.
4. Finelli PF. Phenytoin and methadone tolerance. *N Engl J Med* 1976; 294: 227.
5. Tong TG, *et al.* Phenytoin-induced methadone withdrawal. *Ann Intern Med* 1981; 94: 349–51.
6. Benítez-Rosario MA, *et al.* Methadone-induced respiratory depression after discontinuing carbamazepine administration. *J Pain Symptom Manage* 2006; 32: 99–100.

Antifungals. Use of methadone with *fluconazole* has been reported[1] to increase serum concentrations of methadone although the authors considered that for patients being treated for opioid dependence the interaction was unlikely

to require adjustment of the methadone dose. However, respiratory depression has been reported[2] after intravenous doses of fluconazole were given to a 60-year-old man also taking oral methadone for pain relief in advanced gastric cancer. Although a randomised placebo-controlled study[3] found that giving *voriconazole* to patients on methadone maintenance therapy for opioid addiction was generally safe and well tolerated, the authors recommended monitoring and possible dose reduction of methadone when the 2 drugs are used together. Similar recommendations are also given in the licensed product information for voriconazole.

1. Cobb MN, *et al.* The effect of fluconazole on the clinical pharmacokinetics of methadone. *Clin Pharmacol Ther* 1998; 63: 655–62.
2. Tarumi Y, *et al.* Methadone and fluconazole: respiratory depression by drug interaction. *J Pain Symptom Manage* 2002; 23: 148–53.
3. Liu P, *et al.* Pharmacokinetic interaction between voriconazole and methadone at steady state in patients on methadone therapy. *Antimicrob Agents Chemother* 2007; 51: 110–18.

Antivirals. The potential for interaction between antiretrovirals and methadone has been reviewed.[1] Available evidence for HIV-protease inhibitors suggests that *atazanavir, indinavir,* and, possibly, *saquinavir* alone have no effect on plasma concentrations of methadone; *amprenavir, nelfinavir, ritonavir,* and *ritonavir-boosted saquinavir* may reduce plasma-methadone concentrations but the effect is unlikely to be clinically significant. *Lopinavir-ritonavir* may also reduce methadone concentrations and, although most studies found the interaction to be insignificant, one study reported opioid withdrawal symptoms in some patients. Unpublished data [also referred to in the licensed product information] on *tipranavir* (boosted with ritonavir) in healthy, opioid-naive subjects suggest that it may decrease plasma-methadone; licensed product information for tipranavir recommends that patients are monitored for symptoms of opioid withdrawal.

The NNRTIs *nevirapine* and *efavirenz* have both been reported to reduce plasma-methadone levels and withdrawal symptoms have occurred when they were given to patients receiving methadone. Conversely, *delavirdine* may increase methadone concentrations although the effect is unlikely to be clinically significant. Methadone possibly increases plasma concentrations of the NRTI *zidovudine* (see p. 1026.2).

1. Bruce RD, *et al.* Pharmacokinetic drug interactions between opioid agonist therapy and antiretroviral medications: implications and management for clinical practice. *J Acquir Immune Defic Syndr* 2006; 41: 563–72.

Gastrointestinal drugs. Histamine H_2-antagonists such as *cimetidine* (see p. 111.3) may enhance the effects of some opioid analgesics; such interactions may lead to methadone toxicity.

Grapefruit juice. Grapefruit juice, an inhibitor of the cytochrome P450 isoenzyme CYP3A4, has been shown to modestly increase the bioavailability of methadone;[1] although no symptoms of methadone toxicity were seen in the studied patients, the authors commented that such effects may occur in patients with reduced opioid tolerance, particularly when starting methadone treatment.

1. Benmebarek M, *et al.* Effects of grapefruit juice on the pharmacokinetics of the enantiomers of methadone. *Clin Pharmacol Ther* 2004; 76: 55–63.

Pharmacokinetics

Methadone hydrochloride is readily absorbed from the gastrointestinal tract and after subcutaneous or intramuscular injections. It is widely distributed in the tissues, diffuses across the placenta, and is distributed into breast milk. It is extensively protein bound. Methadone is metabolised in the liver, mainly by *N*-demethylation and cyclisation, and the metabolites are excreted in the bile and urine. Metabolism is mainly catalysed by CYP3A4, although other cytochrome P450 isoenzymes also play a role (see Interactions, p. 90.3). It has a prolonged half-life and is subject to accumulation.

In reviews of the pharmacokinetics of methadone[1-5] particular reference has been made to its long elimination half-life, accumulation after repeated doses, and wide interindividual variations.

Methadone is rapidly absorbed after oral doses and has high oral bioavailability; peak plasma concentrations have been reported 1 to 5 hours after a single tablet. It undergoes considerable tissue distribution and protein binding is reported to be 60 to 90% with α_1-acid glycoprotein being the main binding protein in plasma. Metabolism to the major metabolite 2-ethylidine-1,5-dimethyl-3,3-diphenylpyrrolidine and the minor metabolite 2-ethyl-3,3-diphenyl-5-methylpyrrolidine, both of them inactive, occurs in the liver. These metabolites are excreted in the faeces and urine with unchanged methadone. Other metabolites, including methadol and normethadol, have also been described. The liver may also serve as a major storage site of unchanged methadone which is taken up, bound non-specifically by the liver, and released again mainly unchanged. Urinary excretion of methadone is pH-dependent, the lower the pH the greater the clearance.

In addition to marked interindividual variations there are differences in the pharmacokinetics of methadone after single or multiple doses. Elimination half-lives vary considerably (a range of 15 to 60 hours has been quoted) and may be much longer than the 18 hours reported following a single dose. Careful adjustment of dosage is necessary with repeated doses.

Most studies have been in addicts. Plasma concentrations have been found to vary widely during methadone maintenance therapy with large differences between patients and wide fluctuations in individual patients. These variations in kinetics have also been seen in cancer patients.

1. Säwe J. High-dose morphine and methadone in cancer patients: clinical pharmacokinetic considerations of oral treatment. *Clin Pharmacokinet* 1986; 11: 87–106.
2. Moore RA, *et al.* Opiate metabolism and excretion. *Baillieres Clin Anaesthesiol* 1987; 1: 829–58.
3. Eap CB, *et al.* Interindividual variability of the clinical pharmacokinetics of methadone: implications for the treatment of opioid dependence. *Clin Pharmacokinet* 2002; 41: 1153–93.
4. Ferrari A, *et al.* Methadone—metabolism, pharmacokinetics and interactions. *Pharmacol Res* 2004; 50: 551–9.
5. Lugo RA, *et al.* Pharmacokinetics of methadone. *J Pain Palliat Care Pharmacother* 2005; 19: 13–24.

Administration. Methadone is considerably more lipid-soluble than morphine. A study of plasma concentrations and analgesia after intramuscular injection indicated that more rapid and greater relief of pain might be achieved if lipid-soluble opioid analgesics were injected into the deltoid rather than the gluteal muscle; there was no significant difference in absorption of morphine from the two sites.[1]

Other routes investigated in pharmacokinetic studies include continuous intravenous infusion[2] and continuous epidural infusion.[3] Rectal administration[4] has also been studied.

1. Grabinski PY, *et al.* Plasma levels and analgesia following deltoid and gluteal injections of methadone and morphine. *J Clin Pharmacol* 1983; 23: 48–55.
2. Denson DD, *et al.* Pharmacokinetics of continuous intravenous infusion of methadone in the early post-burn period. *J Clin Pharmacol* 1990; 30: 70–5.
3. Shir Y, *et al.* Plasma concentrations of methadone during postoperative patient-controlled extradural analgesia. *Br J Anaesth* 1990; 65: 204–9.
4. Dale O, *et al.* Bioavailabilities of rectal and oral methadone in healthy subjects. *Br J Clin Pharmacol* 2004; 58: 156–62.

Hepatic impairment. Overall hepatic dysfunction does not seem unduly to disrupt methadone metabolism[1] and it has been suggested[2] that maintenance dosage of methadone need not be changed in stable chronic liver disease, although abrupt changes in hepatic status might result in substantial alterations in methadone disposition requiring dosage adjustments.

In a study of patients on methadone maintenance therapy[2] apparent terminal half-life of methadone was prolonged from a mean of 18.8 hours in those with healthy livers to 35.5 hours in patients with severe chronic liver disease. However, plasma concentrations were not increased in such patients.

1. Moore RA, *et al.* Opiate metabolism and excretion. *Baillieres Clin Anaesthesiol* 1987; 1: 829–58.
2. Novick DM, *et al.* Methadone disposition in patients with chronic liver disease. *Clin Pharmacol Ther* 1981; 30: 353–62.

Pregnancy. Plasma concentrations of methadone were reduced in methadone-maintained pregnant women, probably due to enhanced metabolism.[1,2] It was suggested that the dose of methadone might need to be increased in such patients.

1. Pond SM, *et al.* Altered methadone pharmacokinetics in methadone-maintained pregnant women. *J Pharmacol Exp Ther* 1985; 233: 1–6.
2. Wolff K, *et al.* Changes to methadone clearance during pregnancy. *Eur J Clin Pharmacol* 2005; 61: 763–8.

Renal impairment. The urinary excretion of methadone was reduced in renal failure,[1] but plasma concentrations were within the usual range and faecal excretion accounted for the majority of the dose. Very little methadone was removed by peritoneal dialysis or haemodialysis.

1. Kreek MJ, *et al.* Methadone use in patients with chronic renal disease. *Drug Alcohol Depend* 1980; 5: 197–205.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Gobbidona; Metacalmans; *Austral.*: Biodone; Physeptone; *Austria*: Heptadon; *Belg.*: Mephenon; *Braz.*: Metadon; Mytedom; *Canad.*: Metadol; *Fin.*: Dolmed; Metadon; *Ger.*: Eptadone; Methaddict†; *Hung.*: Depridol; Metadon; *Irl.*: Phymet DTF; Pinadone DTF; *Israel*: Adolan; *Ital.*: Eptadone; *Jpn*: Methapain; *Malaysia*: Aseptone; Bennaston; *Mex.*: Rubidexol; *Neth.*: Eptadone; Pinadone†; Symoron; *NZ*: Biodone; Methatabs; Pallidone; *S.Afr.*: Physeptone; *Spain*: Eptadone; Metasedin; *Switz.*: Ketalgine; *UK*: Eptadone; Martindale Methadone Mixture DTF; Methadose; Physeptone; Synastone; *USA*: Diskets; Dolophine; Methadose.

Pharmacopoeial Preparations
BP 2014: Methadone Injection; Methadone Linctus; Methadone Oral Solution (1 mg per mL); Methadone Tablets;
USP 36: Methadone Hydrochloride Injection; Methadone Hydrochloride Oral Concentrate; Methadone Hydrochloride Oral Solution; Methadone Hydrochloride Tablets for Oral Suspension; Methadone Hydrochloride Tablets.

Methyl Butetisalicylate

Butetisalicilato de metilo; Methyl Diethylacetylsalicylate. Methyl *O*-(2-ethylbutyryl)salicylate.
$C_{14}H_{18}O_4$=250.3

Profile

Methyl butetisalicylate is a salicylic acid derivative that has been used similarly to methyl salicylate (p. 92.1) as a rubefacient for the relief of musculoskeletal, joint, and soft-tissue pain.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Doloderm.

Methyl Gentisate

Gentisato de metilo; Метилгентисат.
2,5-Dihydroxybenzoic acid methyl ester.
$C_8H_8O_4$=168.1
CAS — 2150-46-1.

Profile

Methyl gentisate has been used topically for the relief of musculoskeletal and joint pain. It is also used as a skin lightening agent.

References.
1. Gallo R, Baldari M. Allergic contact dermatitis from methyl gentisate in a bleaching cream. *Contact Dermatitis* 2006; 54: 220–1.
2. Serra-Baldrich E, *et al.* Allergic contact dermatitis to methyl gentisate. *Contact Dermatitis* 2009; 60: 225–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Ital.*: Reumacort.

Methyl Nicotinate *(USAN)*

Methyle, nicotinate de; Methyli Nicotinas; Methylis nicotinas; Methylnicotinat; Methyl-nikotinát; Metilo nikotinatas; Metyl-nikotinat; Metyylinikotinaatti; Nicotinato de metilo; Метилникотинат.
Methyl pyridine-3-carboxylate.
$C_7H_7NO_2$=137.1
CAS — 93-60-7.
UNII — 7B1AVU9DJN.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Methyl Nicotinate). A white or almost white powder. M.p. 40 degrees to 42 degrees. Very soluble in water, in alcohol, and in dichloromethane. Protect from light.

Profile

Methyl nicotinate is used in topical preparations as a rubefacient.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *UK*: Pickles Chilblain Cream.

Multi-ingredient Preparations. *Arg.*: Medex Rub; *Austral.*: Deep Heat; *Austria*: Berggeist; *Belg.*: Algipan; Emerxil; Percutalgine; *Canad.*: Le Baume Ehrlich†; *Chile*: Calorub Sport; Frixio†; Konirub†; Mentobalsam†; *Fr.*: Algipan†; Capsic†; Decontractyl; Gel Rubefiant; Percutalgine; *Ger.*: Kytta-Balsam f; Rheuma Bad†; *Gr.*: Faragel-Forte; Heet; *Hung.*: Deep Heat Spray; *India*: Algipan; Diclowin; Flamar†; Heelcare; Medicreme; Neurophen; Relaxyl; *Indon.*: Remakrim†; *Irl.*: Deep Heat; Ralgex Heat Spray; Ralgex; Ralgex; *Israel*: Deep Heat Spray; *Ital.*: Balsamo Sifcamina; Relaxar; Sedalpan; *Neth.*: Capsicum comp; Cremor Capsici Compositus; Kruidvat Spierbalsem; *Pol.*: Deep Heat; *S. Afr.*: Deep Heat Spray†; Infrarub†; Sloan's Heat Rub; *Spain*: Doctofril Antiinflamat†; Radio Salil; *Switz.*: Kytta Baume†; Midalgan Nouvelle Formule†; Radalgin†; *UK*: Cremalgin†; Deep Heat Spray; Dubam; Fiery Jack; Radian-B Red Oils; Ralgex Heat Spray (low-odour)†; Ralgex†; Red Oil; Transvasin Heat Spray; *Ukr.*: Deep Heat (Дип Хит); *USA*: Musterole.

Methyl Salicylate

Methyl Sal.; Méthyle, salicylate de; Methylii Salicylas; Methylis Salicylas; Methylsalicylat; Methyl-salicylát; Metilsalicilatas; Metilsalisilat; Metil-szalicilát; Metylosalicylat; Metylu salicylan; Metyylisalisylaatti; Salicilato de metilo; Метилсалицилат.
Methyl 2-hydroxybenzoate.
$C_8H_8O_3$=152.1.
CAS — 119-36-8.
ATC Herb — HM02AW5005 (Gaultheria procumbens: essential oil); HM02AW5001 (Betula lenta: essential oil).
UNII — LAV5US022Y.

NOTE. Methyl salicylate and methyl salicylate liniment have been known previously as oil of wintergreen, wintergreen, and wintergreen oil. Wintergreen oil has also been known as sweet birch oil.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *Viet*. Also in *USNF*.

Ph. Eur. 8: (Methyl Salicylate). A colourless or slightly yellow liquid. Very slightly soluble in water; miscible with alcohol, and with fatty and essential oils. Protect from light.

USNF 31: (Methyl Salicylate). It is produced synthetically or is obtained from the leaves of *Gaultheria procumbens* (Ericaceae) [wintergreen] or from the bark of *Betula lenta* (Betulaceae) [sweet or black birch]. The source of the methyl salicylate must be indicated on the label.

A colourless, yellowish, or reddish liquid having the characteristic odour of wintergreen. Slightly soluble in water; soluble in alcohol and in glacial acetic acid. Store in airtight containers.

Storage. Certain plastic containers, such as those made from polystyrene, are unsuitable for liniments or ointments containing methyl salicylate.

Uses and Administration

Methyl salicylate is a salicylic acid derivative that is irritant to the skin and is used topically in rubefacient preparations for the relief of pain in musculoskeletal, joint, and soft-tissue disorders. It is also used for minor peripheral vascular disorders such as chilblains and as an ingredient in inhalations for the symptomatic relief of upper respiratory-tract disorders.

Wintergreen oil is also used in aromatherapy.

Adverse Effects, Treatment, and Precautions

Salicylate intoxication can occur after ingestion or topical application of methyl salicylate (see Overdosage, below).

Overdosage. Ingestion of methyl salicylate poses the threat of severe, rapid-onset salicylate poisoning because of its liquid concentrated form and lipid solubility.[1] It is readily absorbed from the gastrointestinal tract and most is rapidly hydrolysed to free salicylate. The symptoms, which may appear within 2 hours of ingestion, are similar to those of salicylate poisoning in general (see Adverse Effects of Aspirin, p. 24.2), although methyl salicylate is expected to be more toxic because of its lipid solubility. There have been reports of fatalities after ingestion of as little as 4 mL in a child and 6 mL in an adult, although the adult lethal dose is estimated to be 30 mL.[1] Topical Chinese herbal medicinal preparations may contain methyl salicylate in variable amounts, and salicylate poisoning has been reported in a 40-year-old man after a total body application of such a preparation.[2] Salicylate poisoning has also been reported in a woman who had attempted suicide by ingesting Red Flower Oil, a topical Chinese herbal oil.[3] The authors also noted that some patients took small amounts of this preparation orally in an attempt to enhance its analgesic effects.

1. Chan TYK. Potential dangers from topical preparations containing methyl salicylate. *Hum Exp Toxicol* 1996; 15: 747–50.
2. Bell AJ, Duggin G. Acute methyl salicylate toxicity complicating herbal skin treatment for psoriasis. *Emerg Med (Fremantle)* 2002; 14: 188–90.
3. Chan TH, *et al.* Severe salicylate poisoning associated with the intake of Chinese medicinal oil ('Red Flower Oil'). *Aust N Z J Med* 1995; 25: 57.

Percutaneous absorption. Like other salicylates, methyl salicylate may be absorbed through intact skin.[1] Percutaneous absorption is enhanced by exercise, heat, occlusion, or disruption of the integrity of the skin. The amount absorbed will also be increased by application to large areas of skin.

Results from a study in healthy subjects showed that a considerable amount of salicylic acid may be absorbed through the skin after topical application of products containing methyl salicylate.[2] Both the rate and extent of absorption increased after repeated application; the bioavailability of the ointment preparation used in the study increased from 15% after the second dose to 22% after the third to eighth dose. The authors recommend that topical analgesic preparations containing methyl salicylate or other salicylates should be used with caution in patients at increased risk of developing salicylate adverse effects (see Precautions of Aspirin, p. 25.3).

Results from another study[3] showing high tissue to plasma ratios after topical application of a methyl salicylate formulation suggest that direct penetration and not recirculation in the blood is responsible for the salicylate concentrations found. The results also showed that methyl salicylate is extensively metabolised to salicylic acid in the dermal and subcutaneous tissues after topical application.

However, for a study suggesting limited absorption from a patch preparation containing camphor, menthol, and methyl salicylate, see Menthol, p. 2554.1.

1. Chan TYK. Potential dangers from topical preparations containing methyl salicylate. *Hum Exp Toxicol* 1996; 15: 747–50.
2. Morra P, *et al.* Serum concentrations of salicylic acid following topical applied salicylate derivatives. *Ann Pharmacother* 1996; 30: 935–40.
3. Cross SE, *et al.* Is there tissue penetration after application of topical salicylate formulations? *Lancet* 1997; 350: 636.

Interactions

Absorption of methyl salicylate through the skin can occur after excessive topical application (see Percutaneous Absorption, above), and interactions would be expected to be as for other salicylates (see Interactions of Aspirin, p. 26.3).

Anticoagulants. Potentiation of *warfarin* anticoagulation has been reported[1-3] after topical application of methyl salicylate preparations.

1. Littleton F. Warfarin and topical salicylates. *JAMA* 1990; 263: 2888.
2. Tam LS, *et al.* Warfarin interactions with Chinese traditional medicines: danshen and methyl salicylate medicated oil. *Aust N Z J Med* 1995; 25: 258.
3. Joss JD, LeBlond RF. Potentiation of warfarin anticoagulation associated with topical methyl salicylate. *Ann Pharmacother* 2000; 34: 729–33.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Rati Salil Gel; *Canad.*: Deep Heating; *Chile*: Mentholatum Calorub Parche; *China*: Qing Feng (清风); *Ger.*: Dolo Roll-On; *India*: Capsigyl-D; Dolocide Plus; *Mex.*: Balsamo Nordin; Friccion Don Juan†; Tolan†; *S. Afr.*: Thermo-Rub; *Thai.*: Filup; Mygesal; *UK*: Numark Muscle Rub; *USA*: Gordogesic.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Homoeopathic Preparations. *Canad.*: Stress L72†; *Fr.*: L 72.

Pharmacopoeial Preparations
BP 2014: Kaolin Poultice; Methyl Salicylate Liniment; Methyl Salicylate Ointment; Surgical Spirit.

Mofezolac *(rINN)*

Mofézolac; Mofezolaco; Mofezolacum; N-22; Мофезолак.
3,4-Bis(*p*-methoxyphenyl)-5-isoxazoleacetic acid.
$C_{19}H_{17}NO_5$=339.3
CAS — 78967-07-4.
UNII — RVJ0BV3H3Y.

Profile

Mofezolac is an NSAID (p. 102.3) given orally in the management of pain and musculoskeletal and joint disorders. A usual dose is 75 mg three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Disopain.

Morniflumate *(USAN, rINN)*

Morniflumato; Morniflumatum; UP-164; Морнифлумат.
2-Morpholinoethyl 2-(α,α,α-trifluoro-*m*-toluidino)nicotinate.
$C_{19}H_{20}F_3N_3O_3$=395.4
CAS — 65847-85-0.
ATC — M01AX22.
ATC Vet — QM01AX22.
UNII — R133MWH7X1.

Profile

Morniflumate, the morpholinoethyl ester of niflumic acid (p. 101.2), is an NSAID (p. 102.3). It has been used in inflammatory conditions in doses of 700 mg given twice daily orally or rectally as suppositories.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Nifluril; *Gr.*: Niflamol; *Ital.*: Flomax; Flumarin; Morniflu; Niflam; *Spain*: Niflactol.

Morphine *(BAN)* ⊗

Morfiini; Morfin; Morfina; Morphinum; Морфин.
7,8-Didehydro-4,5-epoxy-17-methylmorphinan-3,6-diol.
$C_{17}H_{19}NO_3$=285.3
CAS — 57-27-2 (anhydrous morphine); 6009-81-0 (morphine monohydrate).
ATC — N02AA01.
ATC Vet — QN02AA01.
UNII — 76I7G6D29C (morphine); 41TQ665R1X (morphine monohydrate).

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of morphine:

Adolf; Block; China White; Cube; Dreamer; Drug store dope; Drugstore dope; Emsel; First line; German boy; God's drug; Goma; Hard stuff; Hospital Heroin; Hows; Hydrogen Bomb; M; Miss Emma; Mister blue; Mojo; Monf; Monker; Morf; Morfa; Morfs; Morphia; Morphina; Morpho; Morph'; Mr. Blue; M.S.; MS; Mud; Murphy; Nasty; Nazi; Sweet Jesus; Sweet Morpheus; Tar; Unkie; White Stuff.

Morphine Hydrochloride *(BANM)* ⊗

Morfiinihydrokloridi; Morfin Hidroklorür; Morfina, hidrocloruro de; Morfin-hidroklorid; Morfin-hydrochlorid trihydrát; Morfinhydroklorid; Morfino hidrochloridas; Morfiny chlorowodorek; Morphine, chlorhydrate de; Morphinhydrochlorid; Morphini hydrochloridum; Morphini Hydrochloridum Trihydricum; Morphinii Chloridum; Morphinum Chloratum; Морфина Гидрохлорид.
$C_{17}H_{19}NO_3$,HCl,3H_2O=375.8
CAS — 52-26-6 (anhydrous morphine hydrochloride); 6055-06-7 (morphine hydrochloride trihydrate).
UNII — J28GE0ROVX.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *Viet*.

Ph. Eur. 8: (Morphine Hydrochloride). Colourless, silky needles, cubical masses or a white or almost white crystalline powder. It is efflorescent in a dry atmosphere Soluble in water; slightly soluble in alcohol; practically insoluble in toluene. Protect from light.

Incompatibility. See under Morphine Sulfate, below.

Morphine Sulfate *(BANM)* ⊗

Morfiinisulfaatti; Morfin Sülfat; Morfina, sulfato de; Morfino sulfatas; Morfinsulfat; Morfin-sulfát pentahydrát; Morfinszulfát; Morfiny siarczan; Morphine, sulfate de; Morphine Sulphate; Morphini sulfas; Morphini Sulfas Pentahydricus; Morphinsulfat; Морфина Сульфат.
($C_{17}H_{19}NO_3$)$_2$,H_2SO_4,5H_2O=758.8
CAS — 64-31-3 (anhydrous morphine sulfate); 6211-15-0 (morphine sulfate pentahydrate).
UNII — X3P646A2J0.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US*.

Ph. Eur. 8: (Morphine Sulfate). A white or almost white, crystalline powder. Soluble in water; very slightly soluble in alcohol; practically insoluble in toluene. Protect from light.

USP 36: (Morphine Sulfate). White, feathery, silky crystals, cubical masses of crystals, or a white crystalline powder. Is odourless and when exposed to air it gradually loses water of hydration. It darkens on prolonged exposure to light. Soluble 1 in 16 of water and 1 in 1 of water at 80 degrees; soluble 1 in 570 of alcohol and 1 in 240 of alcohol at 60 degrees; insoluble in chloroform and in ether. Store in airtight containers at a temperature up to 40 degrees as permitted by the manufacturer. Protect from light.

Incompatibility. Incompatibility data for morphine have been extensively studied[1,2] and may depend on many factors such as the formulation used, and order and ratio of mixing; however, most studies are usually only short term and contain few details on mixing the same drugs in a variety of different situations.

Morphine salts are sensitive to changes in pH and morphine is liable to be precipitated out of solution in an alkaline environment. Compounds incompatible with morphine salts include aminophylline and sodium salts of barbiturates and phenytoin. Other incompatibilities, sometimes attributed to particular formulations, have included:

- Aciclovir sodium—precipitate noted 2 hours after admixture with morphine sulfate solution[3]
- Chlorpromazine hydrochloride injection—precipitation was considered to be due to chlorocresol present in the morphine sulfate injection[4]
- Doxorubicin—addition of morphine sulfate 1 mg/mL to doxorubicin hydrochloride liposomal injection 400 micrograms/mL in dextrose 5% resulted in turbidity changes[5]

- Fluorouracil—immediate precipitate formed after admixture of fluorouracil 1 or 16 mg/mL with morphine sulfate 1 mg/mL in dextrose 5% or sodium chloride 0.9%[6]
- Furosemide—precipitate noted 1 hour after admixture with morphine sulfate solution[5]
- Haloperidol—immediate precipitation seen after admixture of haloperidol and morphine sulfate solution[7]
- Heparin sodium—incompatibility has been reported from straightforward additive studies.[1] Another study[8] indicated that morphine sulfate and heparin sodium were only incompatible at morphine sulfate concentrations greater than 5 mg/mL and that this incompatibility could be prevented by using 0.9% sodium chloride solution as the admixture diluent rather than water
- Pethidine hydrochloride—incompatibility has been noted after admixture with morphine sulfate[1,9]
- Prochlorperazine edisilate—immediate precipitation was attributed to phenol in the morphine sulfate injection formulation[10,11]
- Promethazine hydrochloride—cloudiness was reported to develop when 12.5 mg of promethazine hydrochloride was drawn into a syringe containing morphine sulfate 8 mg.[12] Others[9] have noted no incompatibility
- Ranitidine hydrochloride—crystal needles and/or sticky spots seen in admixtures of morphine hydrochloride and ranitidine hydrochloride in various ratios stored at different temperatures[13]
- Tetracyclines—colour change from pale yellow to light green occurred when solutions of minocycline hydrochloride or tetracycline hydrochloride were mixed with morphine sulfate in 5% glucose injection[14]

1. Patel JA, Phillips GL. A guide to physical compatibility of intravenous drug admixtures. *Am J Hosp Pharm* 1966; 23: 409–11.
2. Vermeire A, Remon JP. Stability and compatibility of morphine. *Int J Pharm* 1999; 187: 17–51.
3. Pugh CB, *et al.* Visual compatibility of morphine sulphate and meperidine hydrochloride with other injectable drugs during simulated Y-site injection. *Am J Hosp Pharm* 1991; 48: 123–5.
4. Crapper JB. Mixing chlorpromazine and morphine. *BMJ* 1975; i: 33.
5. Trissel LA, *et al.* Compatibility of doxorubicin hydrochloride liposome injection with selected other drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; 54: 2708–13.
6. Xu QA, *et al.* Stability and compatibility of fluorouracil with morphine sulfate and hydromorphone hydrochloride. *Ann Pharmacother* 1996; 30: 756–61.
7. LeBelle MJ, *et al.* Compatibility of morphine and midazolam or haloperidol in parenteral admixtures. *Can J Hosp Pharm* 1995; 48: 155–60.
8. Baker DE, *et al.* Compatibility of heparin sodium and morphine sulfate. *Am J Hosp Pharm* 1985; 42: 1352–5.
9. Parker WA. Physical compatibilities of preanesthetic medications. *Can J Hosp Pharm* 1976; 29: 91–2.
10. Stevenson JG, Patriarca C. Incompatibility of morphine sulfate and prochlorperazine edisylate in syringes. *Am J Hosp Pharm* 1985; 42: 2651.
11. Zuber DEL. Compatibility of morphine sulfate injection and prochlorperazine edisylate injection. *Am J Hosp Pharm* 1987; 44: 67.
12. Fleischer NM. Promethazine hydrochloride—morphine sulfate incompatibility. *Am J Hosp Pharm* 1973; 30: 665.
13. Vermeire A, *et al.* A new method to obtain and present complete information on the compatibility: study of its validity for eight binary mixtures of morphine with drugs frequently used in palliative care. *Palliat Med* 2002; 16: 417–24.
14. Nieves-Cordero AL, *et al.* Compatibility of narcotic analgesic solutions with various antibiotics during simulated Y-site injection. *Am J Hosp Pharm* 1985; 42: 1108–9.

Stability. *INTRAVENOUS PREPARATIONS.* Solutions of morphine sulfate for intravenous infusion appear to be relatively stable. In a study[1] solutions containing 40 micrograms/mL or 400 micrograms/mL retained more than 90% of their initial concentration of morphine sulfate when stored at 4 degrees or 23 degrees for 7 days, whether or not they were protected from light. Solutions prepared from commercially available injection or from powder, in 0.9% sodium chloride or 5% glucose, and stored in PVC bags or glass bottles did not differ in stability from one another. In a further study[2] 10 mg/mL or 5 mg/mL solutions of morphine sulfate in glucose or sodium chloride and stored in portable infusion pump cassettes retained more than 95% of their initial concentration when kept at 23 degrees for 30 days. A 0.9% solution of sodium chloride containing morphine sulfate 2 mg/mL was stable for 6 weeks when stored in polypropylene syringes at ambient temperatures in the light or dark but a similar solution that also contained 0.1% sodium metabisulfite lost 15% of its potency during the same period.[3] Stability of such a solution with or without sodium metabisulfite was considered to be unacceptable when stored in glass syringes in the dark.[4]

A later review[5] (which included some of the above studies) has concluded that the degradation of morphine solutions is not affected by oxygen, light, diluent type, salt form, or morphine concentration when stored under normal conditions; it was considered that morphine solutions could be stored for at least 3 months without stability problems.

1. Vecchio M, *et al.* The stability of morphine intravenous infusion solutions. *Can J Hosp Pharm* 1988; 41: 5–9, 43.
2. Walker SE, *et al.* Hydromorphone and morphine stability in portable infusion pump cassettes and minibags. *Can J Hosp Pharm* 1988; 41: 177–82.
3. Grassby PF. The stability of morphine sulphate in 0.9 per cent sodium chloride stored in plastic syringes. *Pharm J* 1991; 248: HS24–HS25.
4. Grassby PF, Hutchings L. Factors affecting the physical and chemical stability of morphine sulphate solutions stored in syringes. *Int J Pharm Pract* 1993; 2: 39–43.
5. Vermeire A, Remon JP. Stability and compatibility of morphine. *Int J Pharm* 1999; 187: 17–51.

ORAL PREPARATIONS. Studies[1,2] have shown that for optimum stability of morphine content, Kaolin and Morphine Mixture (BP) needed to be stored in well-filled glass containers.

1. Helliwell K. Game P. Stability of morphine in kaolin and morphine mixture BP. *Pharm J* 1981; 227: 128–9.
2. Helliwell K, Jennings P. Kaolin and morphine mixture BP: effects of containers on the stability of morphine. *Pharm J* 1984; 232: 682.

TOPICAL PREPARATIONS. When mixed with about 8 g of *Intrasite* gel (*Smith & Nephew Healthcare, UK*) morphine sulfate, in a concentration of 1.25 mg/mL, remained chemically stable over a 28-day period stored at 4 degrees or at room temperature, irrespective of light exposure.[1] However, unless prepared under sterile conditions, the mixture should be used within 7 days because of the risk of microbial contamination once the gel has been opened.

1. Zeppetella G, *et al.* Stability of morphine sulphate and diamorphine hydrochloride in Intrasite gel®. *Palliat Med* 2005; 19: 131–6.

Morphine Tartrate *(BANM)* ⊗

Morfina, tartrato de; Морфина Тартрат.

$(C_{17}H_{19}NO_3)_2C_4H_6O_6.3H_2O$=774.8

CAS — 302-31-8 (anhydrous morphine tartrate); 6032-59-3 (morphine tartrate trihydrate).

UNII — U3NSU23LHD.

Incompatibility. See under Morphine Sulfate, p. 92.3.

Uses and Administration

Morphine, a phenanthrene derivative, is the main alkaloid of opium (p. 111.3). It is now commonly obtained from whole opium poppies (*Papaver somniferum*) which are harvested as poppy straw; a concentrate of poppy straw is known as CPS.

Morphine is an opioid analgesic (p. 108.1) with agonist activity mainly at μ opioid receptors and perhaps at κ and δ receptors. It acts mainly on the CNS and smooth muscle. Although morphine is mainly a CNS depressant it has some central stimulant actions which result in nausea and vomiting and miosis. Morphine generally increases smooth muscle tone, especially the sphincters of the gastrointestinal and biliary tracts.

Morphine may produce both physical and psychological dependence (see p. 109.1) and should therefore be used with discrimination. Tolerance may also develop.

Morphine is used for the relief of moderate to severe pain, especially that associated with cancer, myocardial infarction, and surgery. In addition to relieving pain, morphine also alleviates the anxiety associated with severe pain and it is useful as a hypnotic where sleeplessness is due to pain. It is also used in the management of neonatal abstinence syndrome (see Administration in Children, p. 94.1).

Morphine reduces intestinal motility but its role, if any, in the symptomatic treatment of diarrhoea is very limited. It also relieves dyspnoea associated with various conditions, including that due to pulmonary oedema resulting from left ventricular failure. It is an effective cough suppressant, but codeine is usually preferred as there is less risk of dependence; morphine may however be necessary to control intractable cough associated with terminal lung cancer. Morphine has been used pre-operatively as an adjunct to anaesthesia for pain relief and to allay anxiety. It has also been used in high doses as a general anaesthetic in specialised procedures such as open-heart surgery.

Morphine is usually **administered** as the sulfate, although the hydrochloride and the tartrate are used in similar doses. Doses are expressed as the salts. Dosage routes include the oral, subcutaneous, intramuscular, intravenous, intraspinal, and rectal routes. Subcutaneous injections are considered unsuitable for oedematous patients. Parenteral doses may be intermittent injections or continuous or intermittent infusions adjusted according to individual analgesic requirements.

Doses should generally be reduced in the elderly or debilitated, or in patients with hepatic or renal impairment (see also under Precautions, p. 95.1 and p. 95.2).

For **pain:**

- *Oral* doses are usually equivalent to 5 to 20 mg every 4 hours and may be given as an aqueous solution of the hydrochloride or sulfate, as modified-release granules or tablets, or as immediate-release tablets. With modified-release preparations the 24-hour dose is usually given as a single dose or in 2 divided doses; in the USA, a modified-release preparation (*MS Contin, Purdue*) that allows dosing every 8 or 12 hours is also available. With all modified-release preparations, additional doses of a conventional formulation may be needed if breakthrough pain occurs. As with the other routes, high oral doses may be required for effective analgesia in palliative care.
- Morphine is sometimes given *rectally* generally as suppositories in doses of 10 to 30 mg every 4 hours. Oral modified-release preparations have also been used rectally although such use is unlicensed in the UK and is generally not recommended except, possibly, in some emergency situations.
- The usual dose by *subcutaneous* or *intramuscular* injection is 10 mg every 4 hours but may range from 5 to 20 mg.
- For premedication, the *BNF* recommends that up to 10 mg may be given by subcutaneous or intramuscular injection 60 to 90 minutes before surgery.
- Doses of up to 15 mg have been given by slow *intravenous* injection, sometimes as a loading dose for continuous or patient-controlled infusion. For continuous intravenous administration maintenance doses have generally ranged from 0.8 to 80 mg/hour, although some patients have required and been given much higher doses. Similar doses have been given by continuous subcutaneous infusion.
- For myocardial infarction, the *BNF* recommends that 5 to 10 mg may be given by intravenous injection at a rate of 1 to 2 mg/minute followed by a further 5 to 10 mg if necessary; half this dose should be used in elderly or debilitated patients.
- Intraspinal doses are in the region of 5 mg for an initial *epidural* injection; if pain relief is unsatisfactory after one hour, further doses of 1 to 2 mg may be given up to a total dose of 10 mg per 24 hours. The recommended initial dose for continuous epidural infusion in opioid-naive patients ranges from 3.5 to 7.5 mg daily; those who have some degree of opioid tolerance may be given 4.5 to 10 mg daily. However, dosage requirements may increase significantly during treatment and up to 20 to 30 mg daily may be required in some patients. A modified-release formulation of liposomal morphine sulfate for lumbar epidural use is also available for the treatment of pain after major surgery; doses range from 10 to 20 mg, depending on the type of surgery, and should be given before the operation, or after clamping of the umbilical cord if used during caesarean section. It is intended for single-use only and no other drugs should be administered into the epidural space for at least the next 48 hours.
- *Intrathecal* use of morphine and its salts has tended to be less common than epidural. A single dose of 0.2 to 1 mg given by intrathecal injection may provide satisfactory pain relief for up to 24 hours. The recommended initial dose for continuous intrathecal infusion in opioid-naive patients ranges from 0.2 to 1 mg daily; those who have some degree of opioid tolerance may be given 1 to 10 mg daily. However, dosage requirements may increase during treatment and up to 20 mg daily may be required in some patients.

For details of doses in children, see p. 94.1.

In **acute pulmonary oedema** 5 to 10 mg may be given by intravenous injection at a rate of 2 mg/minute; half this dose should be used in elderly or debilitated patients.

For the control of intractable **cough** associated with terminal lung cancer, morphine oral solution is given in an initial dose of 5 mg every 4 hours.

As a deterrent to abuse a combined oral preparation of morphine sulfate and naltrexone hydrochloride is available in some countries.

Administration. *CONTINUOUS INFUSION.* Both acute and chronic pain have been controlled satisfactorily by continuous intravenous or subcutaneous infusions of morphine sulfate[1-3] but diamorphine hydrochloride or hydromorphone hydrochloride may be preferred for subcutaneous infusion because their greater solubility in water allows a smaller dose volume. Continuous subcutaneous infusions may be preferred to continuous intravenous infusions.[4] Continuous subcutaneous infusion may be less effective than epidural morphine for relief of postoperative pain;[5] however, it was still considered to provide simple and relatively effective analgesia with a low rate of adverse effects.

See also Patient-controlled Analgesia, p. 94.1.

1. Waldmann CS, *et al.* Serum morphine levels: a comparison between continuous subcutaneous infusion and continuous intravenous infusion in postoperative patients. *Anaesthesia* 1984; 39: 768–71.
2. Goudie TA, *et al.* Continuous subcutaneous infusion of morphine for postoperative pain relief. *Anaesthesia* 1985; 40: 1086–92.
3. Stuart GJ, *et al.* Continuous intravenous morphine infusions for terminal pain control: a retrospective review. *Drug Intell Clin Pharm* 1986; 20: 968–72.
4. Drexel H. Long-term continuous subcutaneous and intravenous opioid infusions. *Lancet* 1991; 337: 979.
5. Hindsholm KB, *et al.* Continuous subcutaneous infusion of morphine—an alternative to extradural morphine for postoperative pain relief. *Br J Anaesth* 1993; 71: 580–2.

INTRA-ARTICULAR ROUTE. Intra-articular injection of morphine into the knee at the end of arthroscopy has been reported to provide some degree of postoperative pain relief;[1,2] such pain relief may be more pronounced than that produced

by the same dose given intravenously[1] or intramuscularly.[2] The effect appears to be due to the action of morphine on peripheral opioid receptors[2] although a systemic effect has not been completely excluded.[1]

There have been conflicting results on whether addition of morphine to intra-articular bupivacaine improves analgesia[3,4] and a systematic review[5] concluded that from the few well-controlled studies there was no evidence of an added analgesic effect of morphine compared with saline alone.

Doses of morphine reported to have been injected intra-articularly have ranged from 1 to 10 mg.

1. Gupta A, *et al.* A systematic review of the peripheral analgesic effects of intraarticular morphine. *Anesth Analg* 2001; 93: 761–70.
2. Raj N, *et al.* Comparison of the analgesic efficacy and plasma concentrations of high-dose intra-articular and intramuscular morphine for knee arthroscopy. *Eur J Anaesthesiol* 2004; 21: 932–7.
3. Laurent SC, *et al.* Addition of morphine to intra-articular bupivacaine does not improve analgesia after day-case arthroscopy. *Br J Anaesth* 1994; 72: 170–3.
4. Heine MF, *et al.* Intra-articular morphine after arthroscopic knee operation. *Br J Anaesth* 1994; 73: 413–15.
5. Rosseland LA. No evidence for analgesic effect of intra-articular morphine after knee arthroscopy: a qualitative systematic review. *Reg Anesth Pain Med* 2005; 30: 83–98.

INTRANASAL ROUTE. An intranasal formulation of morphine has been investigated for the relief of acute pain.

INTRASPINAL ROUTE. Morphine is given epidurally and intrathecally to relieve both acute and chronic pain. However, reviews on the role of spinal opioids have generally concluded that they should be reserved for pain not controlled by more conventional routes.[1-3] When converting from conventional routes it has been suggested that 1% of the total daily dose could be tried as the daily intrathecal dose and 10% as the epidural dose.[3] Conversion from intrathecal to oral dosage has also been investigated.[4]

Intrathecal morphine may be delivered continuously via an implanted programmable infusion pump for the long-term management of chronic non-malignant and cancer pain.

See also Patient-controlled Analgesia, below.

1. Anonymous. Spinal opiates revisited. *Lancet* 1986; i: 655–6.
2. Gustafsson LL, Wiesenfeld-Hallin Z. Spinal opioid analgesia: a critical update. *Drugs* 1988; 35: 597–603.
3. McQuay HJ. Opioids in chronic pain. *Br J Anaesth* 1989; 63: 213–26.
4. Sylvester RK, *et al.* The conversion challenge: from intrathecal to oral morphine. *Am J Hosp Palliat Care* 2004; 21: 143–7.

PATIENT-CONTROLLED ANALGESIA. Morphine is one of the most frequently used opioid analgesics for patient-controlled analgesia (see p. 5.3). Most experience has been with the intravenous route, but the intramuscular, subcutaneous, oral, pulmonary, and epidural[1] routes have also been used. Reasonable initial settings recommended for intravenous use have been a demand dose of 1 to 2 mg of morphine sulfate (or its equivalent) and a lockout interval of 5 to 10 minutes.[2]

1. Sjöström S, *et al.* Patient-controlled analgesia with extradural morphine or pethidine. *Br J Anaesth* 1988; 60: 358–66.
2. Grass JA. Patient-controlled analgesia. *Anesth Analg* 2005; 101 (suppl): S44–S61.

PULMONARY ROUTE. For reference to the use of nebulised morphine see Dyspnoea, below.

TOPICAL ROUTE. Morphine has been applied topically for local analgesia in oral mucositis[1,2] and cutaneous ulceration[3-6] including epidermolysis bullosa.[7]

1. Cerchietti LC, *et al.* Effect of topical morphine for mucositis-associated pain following concomitant chemoradiotherapy for head and neck carcinoma. *Cancer* 2000; 95: 2230–6. Correction, *ibid.* 2003; 97: 1137.
2. Cerchietti L. Morphine mouthwashes for painful mucositis. *Support Care Cancer* 2007; 15: 115–16.
3. Twillman RK, *et al.* Treatment of painful skin ulcers with topical opioids. *J Pain Symptom Manage* 1999; 17: 288–92.
4. Krajnik M, *et al.* Potential uses of topical opioids in palliative care–report of 6 cases. *Pain* 1999; 80: 121–5.
5. Zeppetella G, *et al.* Analgesic efficacy of morphine applied topically to painful ulcers. *J Pain Symptom Manage* 2003; 25: 555–8.
6. Zeppetella G, Ribeiro MDC. Morphine in Intrasite gel applied topically to painful ulcers. *J Pain Symptom Manage* 2005; 29: 118–19.
7. Watterson G, *et al.* Peripheral opioids in inflammatory pain. *Arch Dis Child* 2004; 89: 679–81.

Administration in children. Opioid analgesics are used in children in the management of moderate to severe pain (see p. 5.2); morphine is the most widely used opioid for severe pain in children and is the standard against which other opioids are compared. Morphine may be given to children requiring acute analgesia as a result of surgery or invasive procedures. It may also be given for chronic non-malignant pain and is the opioid of choice for the oral treatment of severe pain in palliative care. Its analgesic and sedative properties are useful in the management of children in intensive care (see p. 1033.1); morphine is considered to be a more rational choice than fentanyl in settings where long-term infusions are required. Respiratory depression with morphine treatment is a risk in all children; however, neonates (and particularly those who are breathing spontaneously) may have an enhanced susceptibility because of the pharmacokinetic differences of morphine in this age group (see p. 96.2).

The following initial doses are recommended by the *BNFC* according to age; doses should thereafter be adjusted according to response:

By subcutaneous injection:
- neonates: 100 micrograms/kg every 6 hours
- 1 to 6 months: 100 to 200 micrograms/kg every 6 hours
- 6 months to 2 years: 100 to 200 micrograms/kg every 4 hours
- 2 to 12 years: 200 micrograms/kg every 4 hours
- 12 to 18 years: 2.5 to 10 mg every 4 hours

By intravenous injection over at least 5 minutes:
- neonates: 50 micrograms/kg every 6 hours
- 1 to 6 months: 100 micrograms/kg every 6 hours
- 6 months to 12 years: 100 micrograms/kg every 4 hours
- 12 to 18 years: 5 mg every 4 hours

The following doses given by slow intravenous injection are suggested as loading doses for *continuous intravenous infusion*:
- neonates: 50 micrograms/kg
- 1 month to 12 years: 100 micrograms/kg
- 12 to 18 years: 5 mg

The loading dose may be followed by an infusion given as follows:
- neonates: 5 to 20 micrograms/kg per hour
- 1 to 6 months: 10 to 30 micrograms/kg per hour
- 6 months to 18 years: 20 to 30 micrograms/kg per hour

By mouth or rectum:
- 1 to 3 months: 50 to 100 micrograms/kg every 4 hours
- 3 to 6 months: 100 to 150 micrograms/kg every 4 hours
- 6 to 12 months: 200 micrograms/kg every 4 hours
- 1 to 12 years: 200 to 300 micrograms/kg every 4 hours
- 12 to 18 years: 5 to 10 mg every 4 hours

In *palliative care*, modified-release oral preparations may be used; they are given as a single daily dose or in 2 divided doses.

By continuous subcutaneous infusion:
- 1 to 3 months: 10 micrograms/kg per hour
- 3 months to 18 years: 20 micrograms/kg per hour

Intraspinal doses of morphine that have been tried[1] in children are as follows:
- caudal epidural block, 100 micrograms/kg
- thoracic or lumbar epidural block, 50 micrograms/kg
- intrathecal doses of 20 or 30 micrograms/kg have provided satisfactory postoperative pain relief, but respiratory depression occurred in 10 and 25%, respectively

Guidelines[2] for analgesia in children in Accident and Emergency departments in the UK recommend the use of intravenous morphine as an alternative to, or after initial treatment with, intranasal diamorphine for *severe pain* such as that associated with large burns, long bone fracture or dislocation, appendicitis, or sickle-cell crisis, but it should be used with caution if there is risk of depression of airway, breathing, or circulation.

In the UK, morphine is also used in the management of **neonatal abstinence syndrome** (p. 110.1) under specialist supervision. The *BNFC* recommends an initial oral dose of 40 micrograms/kg (increase dose if necessary) every 4 hours until symptoms are controlled; the dosage frequency should be reduced gradually over 6 to 10 days until a dose of 40 micrograms/kg once daily is achieved after which the drug should be stopped.

1. Lloyd-Thomas AR. Pain management in paediatric patients. *Br J Anaesth* 1990; 64: 85–104.
2. The College of Emergency Medicine. Best practice guideline: management of pain in children (issued July 2013). Available at: http://secure.collemergencymed.ac.uk/asp/document.asp?ID=4682 (accessed 11/12/13)

Cancer pain. Morphine is the opioid of choice for moderate to severe cancer pain (p. 7.1); guidelines for its use issued by the European Association for Palliative Care[1] include:
- the optimal route for use is orally. For best effect, both immediate-release (for dose titration) and modified-release (for maintenance) dosage forms are required
- the simplest method of dose titration is with immediate-release morphine dosage every 4 hours, and the same dose for breakthrough pain. This 'rescue dose' may be given as often as required, up to hourly. The total daily dose of morphine should be reviewed each day and the regular dose adjusted to take into account the amount needed for breakthrough pain
- if pain returns consistently before the next dose is due the regular dose should be increased. Immediate-release formulations do not generally need to be given more often than every 4 hours, and modified-release products should be given according to the intended duration of the preparation (usually every 12 or 24 hours). Patients stabilised on regular oral morphine require continued access to a rescue dose for breakthrough pain
- if an immediate-release formulation of morphine is not available and treatment is started with modified-release morphine, changes to the regular dose should not be made more often than every 48 hours, which means that dose titration will be prolonged
- for patients taking immediate-release morphine preparations every 4 hours, a double dose at bedtime is effective to prevent pain disturbing sleep
- if patients are unable to take morphine orally the preferred alternative route is subcutaneous. There is no indication for intramuscular morphine for cancer pain since subcutaneous dosage is simpler and less painful
- when converting dosage, the relative potency of oral to subcutaneous morphine is between about 1:2 and 1:3, so 20 to 30 mg of oral morphine is equianalgesic to 10 mg by subcutaneous injection
- in patients who need continuous parenteral morphine the preferred route is by subcutaneous infusion. However, intravenous infusion may be preferred:
  in patients who already have an indwelling intravenous line
  in those with generalised oedema
  if erythema, soreness, or sterile abscess develop during subcutaneous dosage
  in patients with coagulation disorders
  where peripheral circulation is poor
- when converting dosage, the relative potency of oral to intravenous morphine is also between about 1:2 and 1:3
- the buccal, sublingual, and nebulised routes of administration are not recommended in the absence of evidence for clinical advantage over more usual routes
- a small proportion of patients develop intolerable adverse effects with oral morphine (with adjuvant non-opioid analgesics as appropriate) before achieving adequate pain relief. In such patients a change to an alternative opioid, or a change in the route should be considered. Although switching between opioids complicates pain management, adequate pain relief for some may depend on the use of alternative drugs, the use of intraspinal routes, or non-drug methods of pain control

Similar recommendations are given in guidelines issued by the US National Comprehensive Cancer Network.[2]

1. Hanks GW, *et al.* Expert Working Group of the Research Network of the European Association for Palliative Care. Morphine and alternative opioids in cancer pain: the EAPC recommendations. *Br J Cancer* 2001; 84: 587–93.
2. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: adult cancer pain (version 1.2010). Available at: http://www.nccn.org/professionals/physician_gls/PDF/pain.pdf (accessed 02/08/10)

Dyspnoea. In the treatment of dyspnoea (p. 108.3), doses of morphine tend to be smaller than those used for pain relief. Morphine hydrochloride or sulfate may be given as an oral solution in carefully titrated doses, starting at a dose of 5 mg every 4 hours; as little as 2.5 mg every 4 hours may be sufficient for opioid-naive patients.[1] In acute pulmonary oedema, 5 to 10 mg may be given by slow intravenous injection. In patients already receiving morphine for pain relief the following doses have been suggested:[2]
- mild dyspnoea: 25 to 50% of usual analgesic dose
- moderate dyspnoea: 50 to 100% of usual analgesic dose
- severe dyspnoea: 100% or more of usual analgesic dose

Patients have also obtained relief from subcutaneous injection.[3]

Although it has been reported that a low dose of nebulised morphine (mean dose 1.7 mg) improved exercise endurance in patients with dyspnoea due to advanced chronic lung disease,[4] several subsequent studies[5-7] have failed to obtain significant improvements with doses up to 40 mg. It is considered that current evidence does not support the use of nebulised morphine for breathlessness.[1,8-10] Furthermore, bronchospasm can be a problem, particularly at high doses, and there is no consensus on the optimal dose, schedule, or method of dose titration.

1. Davis C, Percy G. Breathlessness, cough, and other respiratory problems. In: Fallon M, Hanks G, eds. *ABC of palliative care*. 2nd ed. London: BMJ Publishing Group, 2006: 13–16.
2. Twycross R, Wilcock A. *Palliative Care Formulary*. 3rd ed. Nottingham, Palliativedrugs.com Ltd, 2007: 280.
3. Bruera E, *et al.* Subcutaneous morphine for dyspnea in cancer patients. *Ann Intern Med* 1993; 119: 906–7.
4. Young IH, *et al.* Effect of low dose nebulised morphine on exercise endurance in patients with chronic lung disease. *Thorax* 1989; 44: 387–90.
5. Beauford W, *et al.* Effects of nebulized morphine sulfate on the exercise tolerance of the ventilatory limited COPD patients. *Chest* 1993; 104: 175–8.
6. Noseda A, *et al.* Disabling dyspnoea in patients with advanced disease: lack of effect of nebulized morphine. *Eur Respir J* 1997; 10: 1079–83.
7. Jankelson D, *et al.* Lack of effect of high doses of inhaled morphine on exercise endurance in chronic obstructive pulmonary disease. *Eur Respir J* 1997; 10: 2270–4.
8. Polosa R, *et al.* Nebulised morphine for severe interstitial lung disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 26/06/08).
9. Foral PA, *et al.* Nebulized opioids use in COPD. *Chest* 2004; 125: 691–4.
10. Brown SJ, *et al.* Nebulized morphine for relief of dyspnea due to chronic lung disease. *Ann Pharmacother* 2005; 39: 1088–92.

Dependence and Withdrawal

As for Opioid Analgesics, p. 109.1.

Dependence associated with morphine and closely related μ-agonists appears to result in more severe withdrawal symptoms than that associated with κ-receptor agonists. With morphine, withdrawal symptoms usually begin within a few hours, reach a peak within 36 to 72 hours, and then gradually subside.

Morphine is used for substitution therapy in the management of neonatal abstinence syndrome (see Administration in Children, p. 94.1).

Adverse Effects and Treatment

As for Opioid Analgesics in general, p. 110.1.

References.
1. Cherny N, *et al.* Strategies to manage the adverse effects of oral morphine: an evidence-based report. *J Clin Oncol* 2001; 19: 2542–54.

Effects on the cardiovascular system. For a reference to the effects of morphine on histamine release compared with some other opioids, see under Pethidine, p. 122.3.

Effects on the muscles. Severe rectovaginal spasms that occurred in a patient given intrathecal morphine[1] were successfully controlled with midazolam.

1. Littrell RA, *et al.* Muscle spasms associated with intrathecal morphine therapy: treatment with midazolam. *Clin Pharm* 1992; 11: 57–9.

Effects on the nervous system. Myoclonus, often associated with hyperalgesia, has been reported in patients with advanced malignant disease treated with morphine.[1-5] It appears to be uncommon with typical oral doses of morphine and is more often associated with high intravenous and spinal doses. Neuroexcitatory metabolites of morphine are often implicated in the development of myoclonus;[2,4,5] however, other possible mechanisms such as drug interactions cannot be ruled out.[4-6]

It has been reported that myoclonus induced by morphine can be successfully controlled using a benzodiazepine such as midazolam.[7] Indeed, some researchers[8] consider benzodiazepines to be the drugs of choice: clonazepam, diazepam, and lorazepam were most frequently used. Dantrolene[5,8] and gabapentin[9] have also been tried.

1. Potter JM, *et al.* Myoclonus associated with treatment with high doses of morphine: the role of supplemental drugs. *BMJ* 1989; 299: 150–3.
2. Glare PA, *et al.* Normorphine, a neurotoxic metabolite? *Lancet* 1990; 335: 725–6.
3. De Conno F, *et al.* Hyperalgesia and myoclonus with intrathecal infusion of high-dose morphine. *Pain* 1992; 47: 337–9.
4. Sjøgren P, *et al.* Hyperalgesia and myoclonus in terminal cancer patients treated with continuous intravenous morphine. *Pain* 1993; 55: 93–7.
5. Mercadante S. Pathophysiology and treatment of opioid-related myoclonus in cancer patients. *Pain* 1998; 74: 5–9.
6. Quinn N. Myoclonus associated with high doses of morphine. *BMJ* 1989; 299: 683–4.
7. Holdsworth MT, *et al.* Continuous midazolam infusion for the management of morphine-induced myoclonus. *Ann Pharmacother* 1995; 29: 25–9.
8. Ferris DJ. Controlling myoclonus after high-dosage morphine infusions. *Am J Health-Syst Pharm* 1999; 56: 1009–10.
9. Mercadante S, *et al.* Gabapentin for opioid-related myoclonus in cancer patients. *Support Care Cancer* 2001; 9: 205–6.

Precautions

As for Opioid Analgesics in general, p. 110.3.

Biliary-tract disorders. See under Precautions of Opioid Analgesics, p. 111.1.

Breast feeding. Measurable blood concentrations of morphine have been detected in 2 breast-fed infants whose mothers received oral or intrathecal morphine during and after their pregnancies; however, no adverse effects were reported in either of these infants.[1,2] In a group of 7 women given patient-controlled analgesia with intravenous morphine after caesarean delivery, the concentrations of morphine and its metabolite morphine-6 glucuronide in the colostrum were found to be very small.[3] Although no infants were breast fed during the study, it was considered that the effects of maternal morphine on breast-fed infants would be negligible.[3] The American Academy of Pediatrics[4] also states that the use of morphine is usually compatible with breast feeding.

1. Robieux I, *et al.* Morphine excretion in breast milk and resultant exposure of a nursing infant. *J Toxicol Clin Toxicol* 1990; 28: 363–70.
2. Oberlander TF, *et al.* Prenatal and breast milk morphine exposure following maternal intrathecal morphine treatment. *J Hum Lact* 2000; 16: 137–42.
3. Baka N-E, *et al.* Colostrum morphine concentrations during postcesarean intravenous patient-controlled analgesia. *Anesth Analg* 2002; 94: 184–7.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/06/08)

Hepatic impairment. In view of its hepatic metabolism, caution is generally advised when giving morphine to patients with hepatic impairment (but see under Pharmacokinetics, p. 96.3). The *BNF* advises that use should be avoided or the dose reduced because of the risk of precipitating a coma. However, it has also been noted that many patients with hepatic impairment tolerate morphine well. Others have considered that severe hepatic impairment may affect morphine metabolism but less severe impairment does not.[1]

The mean elimination half-life of morphine in 12 patients with cirrhosis was almost twice that in 10 healthy subjects after administration of a modified-release oral morphine preparation (*MST-Continus; Napp, UK*) and peak serum concentrations were almost three times as high.[2] Patients with cirrhosis had a greater degree of sedation but none developed encephalopathy. It was recommended that the dose for modified-release preparations should be reduced and that it be given less often when patients have cirrhosis.

In a later study[3] 15 patients with liver cancer were given the same oral morphine preparation and compared with 10 healthy subjects from the previous study; the area under the serum concentration-time curve of morphine was increased three- to fourfold in those with cancer. The elimination half-life of morphine was also prolonged in patients with primary cancer when compared with healthy subjects and those with secondary metastatic disease. Adverse effects were more frequent in the primary cancer group and included 2 cases of respiratory depression; the authors commented that altered blood-brain transportation may have been partly responsible for such effects.

1. Twycross R, Wilcock A. *Palliative Care Formulary*. 3rd ed. Nottingham, Palliativedrugs.com Ltd, 2007: 274.
2. Kotb HIM, *et al.* Pharmacokinetics of controlled release morphine (MST) in patients with liver cirrhosis. *Br J Anaesth* 1997; 79: 804–6.
3. Kotb HIM, *et al.* Pharmacokinetics of controlled release morphine (MST) in patients with liver carcinoma. *Br J Anaesth* 2005; 94: 95–9.

Phaeochromocytoma. Morphine and some other opioids can induce the release of endogenous histamine and thereby stimulate catecholamine release making them unsuitable for use in patients with phaeochromocytoma. For further details, see p. 111.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies morphine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/10/11)

Renal impairment. Severe and prolonged respiratory depression has occurred in patients with renal impairment given morphine. Toxicity in 3 such patients was attributed to the accumulation of the active metabolite morphine-6-glucuronide.[1] Plasma concentrations of this metabolite were found[2] to be ten times higher than normal in a 7-year-old girl with haemolytic uraemic syndrome given morphine intravenously although the half-life of morphine was also prolonged. Plasma concentrations of morphine-6-glucuronide were also reported[3] to be persistently increased 19 days after stopping morphine by intravenous infusion in a 17-year-old girl with normal renal function. The authors of the report suggested that alterations in bowel flora after antibacterial therapy or inhibition of morphine-3-glucuronide glucuronidation by lorazepam might be responsible. It has also been reported[4] that accumulation of morphine can occur in renal failure, although to a lesser extent than accumulation of metabolites (see also under Pharmacokinetics, p. 96.3).

1. Osborne RJ, *et al.* Morphine intoxication in renal failure: the role of morphine-6-glucuronide. *BMJ* 1986; 292: 1548–9.
2. Hasselström J, *et al.* Long lasting respiratory depression induced by morphine-6-glucuronide? *Br J Clin Pharmacol* 1989; 27: 515–18.
3. Calleja MA, *et al.* Persistently increased morphine-6-glucuronide concentrations. *Br J Anaesth* 1990; 64: 649.
4. Osborne R, *et al.* The pharmacokinetics of morphine and morphine glucuronides in kidney failure. *Clin Pharmacol Ther* 1993; 54: 158–67.

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

US licensed product information for some once-daily modified-release preparations of morphine sulfate states that patients must not ingest alcohol, including alcohol-containing medicines, at the same time due to the risk of rapid release and absorption of a potentially fatal dose of morphine; *in-vitro* studies showed that alcohol accelerated the release of morphine.

For references to myoclonus associated with morphine and the concurrent use of other drugs, see Effects on the Nervous System under Adverse Effects, above.

Antibacterials. Potent enzyme inducer *rifampicin* can reduce the serum concentration of morphine and decrease its analgesic effect;[1] induction of the enzymes responsible for conversion of morphine to the active glucuronide metabolite did not seem to occur.

1. Fromm MF, *et al.* Loss of analgesic effect of morphine due to coadministration of rifampin. *Pain* 1997; 72: 261–7.

Benzodiazepines. An additive sedative effect is to be expected between opioid analgesics and benzodiazepines and has been reported with morphine and *midazolam*.[1]

For reference to a suggestion that *lorazepam* may inhibit morphine-3-glucuronide glucuronidation, see Renal Impairment under Precautions, above.

1. Tverskoy M, *et al.* Midazolam-morphine sedative interaction in patients. *Anesth Analg* 1989; 68: 282–5.

Cisapride. Plasma concentrations of morphine have been increased by oral cisapride.[1]

1. Rowbotham DJ, *et al.* Effect of cisapride on morphine absorption after oral administration of sustained-release morphine. *Br J Anaesth* 1991; 67: 421–5.

Histamine H_2-antagonists. See under Opioid Analgesics, p. 111.3.

Local anaesthetics. Prior use of epidural *chloroprocaine*, when compared with lidocaine, has been reported to reduce the duration[1] and efficacy[2] of epidural morphine analgesia. However, a later study[3] found no such effects; the authors suggested that findings from the previous 2 studies were due to breakthrough pain caused by the early resolution of chloroprocaine anaesthesia occurring before the maximum onset of morphine analgesia.

1. Eisenach JC, *et al.* Effect of prior anesthetic solution on epidural morphine analgesia. *Anesth Analg* 1991; 73: 119–23.
2. Karambelkar DJ, Ramanathan S. 2-Chloroprocaine antagonism of epidural morphine analgesia. *Acta Anaesthesiol Scand* 1997; 41: 774–8.
3. Hess PE, *et al.* Chloroprocaine may not affect epidural morphine for postcesarean delivery analgesia. *J Clin Anesth* 2006; 18: 29–33.

Metoclopramide. The effects of metoclopramide on morphine have included an increased rate of onset and degree of sedation when oral metoclopramide was given with modified-release morphine[1] and antagonism of the effects of morphine on gastric emptying by intravenous metoclopramide.[2]

1. Manara AR, *et al.* The effect of metoclopramide on the absorption of oral controlled release morphine. *Br J Clin Pharmacol* 1988; 25: 518–21.
2. McNeill MJ, *et al.* Effect of iv metoclopramide on gastric emptying after opioid premedication. *Br J Anaesth* 1990; 64: 450–2.

Tricyclic antidepressants. Both *clomipramine* and *amitriptyline* significantly increased the plasma availability of morphine when given to cancer patients taking oral morphine solution.[1] It was noted however that the potentiation of the analgesic effects of morphine by these drugs might not be confined to increased bioavailability of morphine; the dose of tricyclic to use with morphine in the treatment of cancer pain should be decided by clinical evaluation rather than by pharmacokinetic data.

1. Ventafridda V, *et al.* Antidepressants increase bioavailability of morphine in cancer patients. *Lancet* 1987; i: 1204.

Pharmacokinetics

Morphine salts are well absorbed from the gastrointestinal tract but have poor oral bioavailability since they undergo extensive first-pass metabolism in the liver and gut. After subcutaneous or intramuscular injection morphine is readily absorbed into the blood. The majority of a dose of morphine is conjugated with glucuronic acid in the liver and gut to produce morphine-3-glucuronide and morphine-6-glucuronide. The latter is considered to contribute to the analgesic effect of morphine, especially with repeated oral doses. Morphine-3-glucuronide on the other hand can antagonise the analgesic action and might be responsible for the paradoxical pain seen in some patients given morphine. Other active metabolites include normorphine, codeine, and morphine ethereal sulfate. Enterohepatic circulation probably occurs. Morphine is distributed throughout the body but mainly in the kidneys, liver, lungs, and spleen, with lower concentrations in the brain and muscles. Morphine crosses the blood-brain barrier less readily than more lipid-soluble opioids such as diamorphine, but it has been detected in the CSF as have its highly polar metabolites morphine-3-glucuronide and morphine-6-glucuronide. Morphine diffuses across the placenta and traces also appear in breast milk and sweat. About 35% is protein bound. Mean plasma elimination half-lives of about 2 hours for morphine and 2.4 to 6.7 hours for morphine-3-glucuronide have been reported.

Up to 10% of a dose of morphine may eventually be excreted, as conjugates, through the bile into the faeces. The remainder is excreted in the urine, mainly as conjugates. About 90% of total morphine is excreted in 24 hours with traces in urine for 48 hours or more.

Much has been published on the metabolism and disposition of morphine and its relevance to the clinical use of morphine, in particular the analgesic effect of repeated oral doses and the relative potency of oral to parenteral

doses. There has been uncertainty as to the contributions in man of first-pass metabolism in the liver and gut,[1-4] the possible role of renal metabolism,[2,4-6] the analgesic activity and clinical importance of the metabolite morphine-6-glucuronide,[2,7-21] and enterohepatic circulation.[2,9] There has also been interest in the effects of the metabolite morphine-3-glucuronide.[19,22-24]

1. Hanks GW, Aherne GW. Morphine metabolism: does the renal hypothesis hold water? *Lancet* 1985; i: 221–2.
2. Hanks GW, *et al.* Explanation for potency of repeated oral doses of morphine? *Lancet* 1987; ii: 723–5.
3. Moore RA, *et al.* Opiate metabolism and excretion. *Baillieres Clin Anaesthesiol* 1987; 1: 829–58.
4. Bodenham A, *et al.* Extrahepatic morphine metabolism in man during the anhepatic phase of orthotopic liver transplantation. *Br J Anaesth* 1989; 63: 380–4.
5. McQuay H, Moore A. Metabolism of narcotics. *BMJ* 1984; 288: 237.
6. Moore A, *et al.* Morphine kinetics during and after renal transplantation. *Clin Pharmacol Ther* 1984; 35: 641–5.
7. McQuay HJ, *et al.* Potency of oral morphine. *Lancet* 1987; ii: 1458–9.
8. Hanks GW, *et al.* Enterohepatic circulation of morphine. *Lancet* 1988; i: 469.
9. Osborne R, *et al.* Analgesic activity of morphine-6-glucuronide. *Lancet* 1988; i: 828.
10. Hanks GW, Wand PJ. Enterohepatic circulation of opioid drugs: is it clinically relevant in the treatment of cancer patients? *Clin Pharmacokinet* 1989; 17: 65–8.
11. Paul D, *et al.* Pharmacological characterization of morphine-6 β-glucuronide, a very potent morphine metabolite. *J Pharmacol Exp Ther* 1989; 251: 477–83.
12. Hanna MH, *et al.* Analgesic efficacy and CSF pharmacokinetics of intrathecal morphine-6-glucuronide: comparison with morphine. *Br J Anaesth* 1990; 64: 547–50.
13. Osborne R, *et al.* Morphine and metabolite behavior after different routes of morphine administration: demonstration of the importance of the active metabolite morphine-6-glucuronide. *Clin Pharmacol Ther* 1990; 47: 12–19.
14. McQuay HJ, *et al.* Oral morphine in cancer pain: influences on morphine and metabolite concentration. *Clin Pharmacol Ther* 1990; 48: 236–44.
15. Hanna MH, *et al.* Disposition of morphine-6-glucuronide and morphine in healthy volunteers. *Br J Anaesth* 1991; 66: 103–7.
16. Portenoy RK, *et al.* The metabolite morphine-6-glucuronide contributes to the analgesia produced by morphine infusion in patients with pain and normal renal function. *Clin Pharmacol Ther* 1992; 51: 422–31.
17. Thompson PI, *et al.* Respiratory depression following morphine and morphine-6-glucuronide in normal subjects. *Br J Clin Pharmacol* 1995; 40: 145–52.
18. Lötsch J, Geisslinger G. Morphine-6-glucuronide: an analgesic of the future? *Clin Pharmacokinet* 2001; 40: 485–99.
19. Lugo RA, Kern SE. Clinical pharmacokinetics of morphine. *J Pain Palliat Care Pharmacother* 2003; 16 (4): 5–18.
20. Wittwer E, Kern SE. Role of morphine's metabolites in analgesia: concepts and controversies. *AAPS J* 2006; 8: E348–E352.
21. van Dorp ELA, *et al.* Morphine-6-glucuronide: morphine's successor for postoperative pain relief? *Anesth Analg* 2006; 102: 1789–97.
22. Smith MT, *et al.* Morphine-3-glucuronide—a potent antagonist of morphine analgesia. *Life Sci* 1990; 47: 579–85.
23. Morley JS, *et al.* Paradoxical pain. *Lancet* 1992; 340: 1045.
24. Morley JS, *et al.* Methadone in pain uncontrolled by morphine. *Lancet* 1993; 342: 1243.

Administration. There have been many studies on the pharmacokinetics of morphine given by various routes and methods. These include the buccal route (see below), modified-release oral preparations,[1,2] the rectal route,[3,4] the topical route,[5] the pulmonary route,[6,7] continuous subcutaneous compared with intravenous infusion,[8] and the intraspinal route.[9-13]

Slow dural transfer of morphine and its prolonged presence in the CSF appear to correlate with its slow onset and long duration of action by epidural and intrathecal injection.[14] Modified release epidural preparations have further extended the duration of morphine.[15] More lipid-soluble opioids, such as diamorphine and pethidine, enter and leave the CSF more rapidly than morphine.

The pharmacokinetics of morphine given by 5 different routes—intravenous bolus injection and oral, sublingual, buccal, and modified-release buccal tablets—were studied[16] with particular reference to morphine-6-glucuronide, the active metabolite. This metabolite occurred in large quantities after intravenous doses and plasma concentrations rapidly exceeded those of morphine. After oral doses morphine-6-glucuronide and morphine-3-glucuronide were present in quantities similar to those seen after intravenous morphine; morphine concentrations in plasma were very low and the mean morphine-6-glucuronide to morphine area under the concentration-time curve ratio was 9.7 to 1. There was delayed absorption with attenuation and delay of peak morphine and metabolite plasma concentrations after sublingual or buccal dosage.

Compared with oral doses, concentrations of morphine were higher and those of its glucuronides lower when morphine was given rectally,[17] suggesting avoidance of first-pass metabolism.

Morphine was not absorbed systemically when applied topically to ulcers although some absorption may occur when a large surface area is involved.[5]

1. Pinnock CA, *et al.* Absorption of controlled release morphine sulphate in the immediate postoperative period. *Br J Anaesth* 1986; 58: 868–71.
2. Savarese JJ, *et al.* Steady-state pharmacokinetics of controlled release oral morphine sulphate in healthy subjects. *Clin Pharmacokinet* 1986; 11: 505–10.
3. Moolenaar F, *et al.* Drastic improvement in the rectal absorption profile of morphine in man. *Eur J Clin Pharmacol* 1985; 29: 119–21.
4. Cole L, *et al.* Further development of a morphine hydrogel suppository. *Br J Clin Pharmacol* 1990; 30: 781–6.
5. Ribeiro MDC, *et al.* The bioavailability of morphine applied topically to cutaneous ulcers. *J Pain Symptom Manage* 2004; 27: 434–9.
6. Masood AR, Thomas SHL. Systemic absorption of nebulized morphine compared with oral morphine in healthy subjects. *Br J Clin Pharmacol* 1996; 41: 250–2.
7. Ward ME, *et al.* Morphine pharmacokinetics after pulmonary administration from a novel aerosol delivery system. *Clin Pharmacol Ther* 1997; 62: 596–609.
8. Waldmann CS, *et al.* Serum morphine levels: a comparison between continuous subcutaneous infusion and continuous intravenous infusion in postoperative patients. *Anaesthesia* 1984; 39: 768–71.
9. Gustafsson LL, *et al.* Disposition of morphine in cerebrospinal fluid after epidural administration. *Lancet* 1982; i: 796.
10. Moore A, *et al.* Spinal fluid kinetics of morphine and heroin. *Clin Pharmacol Ther* 1984; 35: 40–5.
11. Max MB, *et al.* Epidural and intrathecal opiates: cerebrospinal fluid and plasma profiles in patients with chronic cancer pain. *Clin Pharmacol Ther* 1985; 38: 631–41.
12. Nordberg G, *et al.* Extradural morphine: influence of adrenaline admixture. *Br J Anaesth* 1986; 58: 598–604.
13. Ionescu TI, *et al.* The pharmacokinetics of intradural morphine in major abdominal surgery. *Clin Pharmacokinet* 1988; 14: 178–86.
14. Morgan M. The rational use of intrathecal and extradural opioids. *Br J Anaesth* 1989; 63: 165–88.
15. Viscusi ER, *et al.* Pharmacokinetics of extended-release epidural morphine sulfate: pooled analysis of six clinical studies. *Am J Health-Syst Pharm* 2009; 66: 1020–30.
16. Osborne R, *et al.* Morphine and metabolite behavior after different routes of morphine administration: demonstration of the importance of the active metabolite morphine-6-glucuronide. *Clin Pharmacol Ther* 1990; 47: 12–19.
17. Babul N, Darke AC. Disposition of morphine and its glucuronide metabolites after oral and rectal administration: evidence of route specificity. *Clin Pharmacol Ther* 1993; 54: 286–92.

BUCCAL ROUTE. Conflicting results from studies on buccal morphine may reflect differences in formulation[1] and hence absorption. Some[2] reported equivalent analgesia with buccal and intramuscular morphine although others[3] found marked interindividual variability with mean peak serum concentrations of morphine some eight times lower after a buccal tablet than after an intramuscular injection and occurring a mean of 4 hours later. Morphine sulfate in aqueous solution has been reported to be moderately well absorbed from the buccal mucosa.[4] Absolute bioavailability for morphine was estimated to be 23.8% after an oral solution, 22.4% after a modified-release oral tablet (*MST Continus; Napp, UK*), and 20.2% after a modified-release buccal tablet, with peak plasma-morphine concentrations at 45 minutes, 2.5 hours, and 6 hours, respectively; mean ratios of area under the plasma concentration-time curve for morphine-6-glucuronide to morphine in plasma were 11:1 after buccal and oral morphine compared with 2:1 for intravenous morphine.[5] There was considerable inter-subject variation in plasma concentrations of the morphine metabolites, morphine-3-glucuronide and morphine-6-glucuronide after buccal doses of morphine as a modified-release formulation,[6] and lack of pain relief was subsequently reported with this buccal formulation.[7] Poor absorption of morphine from modified-release buccal tablets when compared with intramuscular injection was also reported;[8] bitterness of the tablets, leading to their premature removal, and poor dissolution may have contributed.

1. Calvey TN, Williams NE. Pharmacokinetics of buccal morphine. *Br J Anaesth* 1990; 64: 256.
2. Bell MDD, *et al.* Buccal morphine—a new route for analgesia? *Lancet* 1985; i: 71–3.
3. Fisher AP, *et al.* Serum morphine concentrations after buccal and intramuscular morphine administration. *Br J Clin Pharmacol* 1987; 24: 685–7.
4. Al-Sayed-Omar O, *et al.* Influence of pH on the buccal absorption of morphine sulphate and its major metabolite, morphine-3-glucuronide. *J Pharm Pharmacol* 1987; 39: 934–5.
5. Hoskin PJ, *et al.* The bioavailability and pharmacokinetics of morphine after intravenous, oral and buccal administration in healthy volunteers. *Br J Clin Pharmacol* 1989; 27: 499–505.
6. Manara AR, *et al.* Pharmacokinetics of morphine following administration by the buccal route. *Br J Anaesth* 1989; 62: 498–502.
7. Manara AR, *et al.* Analgesic efficacy of perioperative buccal morphine. *Br J Anaesth* 1990; 64: 551–5.
8. Simpson KH, *et al.* An investigation of premedication with morphine given by the buccal or intramuscular route. *Br J Clin Pharmacol* 1989; 27: 377–80.

Children. The pharmacokinetics of morphine in *children* are generally considered similar to those in adults;[1-3] in both an elimination half-life of about 2 hours has been reported after intravenous administration of morphine. In *neonates*, however, clearance is generally reduced[4-7] and pharmacokinetics are more variable.[8-10] Studies[7,11] have found significantly higher plasma concentrations of morphine and a significantly lower morphine-6-glucuronide to morphine ratio in neonates when compared with older infants and children; however, the morphine-6-glucuronide to morphine-3-glucuronide ratio remains constant irrespective of age.[7] Elimination half-lives of 6.7 and 10 hours have been reported in term and preterm infants, respectively after a single intravenous dose of morphine, with nearly 80% of the dose remaining unbound.[8] The reduced clearance, which is dependent on gestational age and birth weight,[12,13] and higher morphine concentrations are probably due to reduced metabolism in neonates as well as immature renal function: the capacity to conjugate morphine by glucuronidation is reduced in preterm infants,[6,9,10] and some premature neonates may lack the capacity entirely.[9]

1. Stanski DR, *et al.* Kinetics of high-dose intravenous morphine in cardiac surgery patients. *Clin Pharmacol Ther* 1976; 19: 752–6.
2. Dahlström B, *et al.* Morphine kinetics in children. *Clin Pharmacol Ther* 1979; 26: 354–65.
3. Olkkola KT, *et al.* Clinical pharmacokinetics and pharmacodynamics of opioid analgesics in infants and children. *Clin Pharmacokinet* 1995; 8: 385–404.
4. Koren G, *et al.* Postoperative morphine infusion in newborn infants: assessment of disposition characteristics and safety. *J Pediatr* 1985; 107: 963–7.
5. Lynn AM, Slattery JT. Morphine pharmacokinetics in early infancy. *Anesthesiology* 1987; 66: 136–9.
6. Choonara IA, *et al.* Morphine metabolism in children. *Br J Clin Pharmacol* 1989; 28: 599–604.
7. Bouwmeester NJ, *et al.* Age- and therapy-related effects on morphine requirements and plasma concentrations of morphine and its metabolites in postoperative infants. *Br J Anaesth* 2003; 90: 642–52.
8. Bhat R, *et al.* Pharmacokinetics of a single dose of morphine in preterm infants during the first week of life. *J Pediatr* 1990; 117: 477–81.
9. Bhat R, *et al.* Morphine metabolism in acutely ill preterm newborn infants. *J Pediatr* 1992; 120: 795–9.
10. Hartley R, *et al.* Pharmacokinetics of morphine infusion in premature neonates. *Arch Dis Child* 1993; 69: 55–8.
11. Bouwmeester NJ, *et al.* Postoperative pain in the neonate: age-related differences in morphine requirements and metabolism. *Intensive Care Med* 2003; 29: 2009–15.
12. Scott CS, *et al.* Morphine pharmacokinetics and pain assessment in premature newborns. *J Pediatr* 1999; 135: 423–9.
13. Saarenmaa E, *et al.* Morphine clearance and effects in newborn infants in relation to gestational age. *Clin Pharmacol Ther* 2000; 68: 160–6.

The elderly. The pharmacokinetics of morphine were compared[1] in 7 healthy elderly (60 to 69 years) and 13 healthy young (24 to 28 years) subjects, after a single intravenous injection of morphine sulfate 10 mg per 70 kg. Although the terminal rate of drug disappearance from plasma was faster in the elderly group, apparent volume of distribution at steady state was about half that of the young group and plasma clearance was reduced.

1. Owen JA, *et al.* Age-related morphine kinetics. *Clin Pharmacol Ther* 1983; 34: 364–8.

Hepatic impairment. The liver is a major site of morphine metabolism and therefore hepatic impairment could be expected to affect elimination (see under Precautions, p. 95.1). There is some evidence that in cirrhosis glucuronidation might be relatively spared compared with other metabolic processes and that some extrahepatic metabolism may occur. Several studies have served to illustrate these points:

- Hepatic extraction of morphine was impaired in cirrhotic patients, but less than expected[1]
- Morphine metabolism was minimal during the anhepatic phase of liver transplantation, but increased markedly when the new liver was reperfused[2]
- Morphine metabolism was virtually complete after liver transplantation with only 4.5% unchanged morphine being excreted in the urine 24 hours after administration[3]
- Morphine elimination was reduced when hepatic blood flow was impaired[4]

1. Crotty B, *et al.* Hepatic extraction of morphine is impaired in cirrhosis. *Eur J Clin Pharmacol* 1989; 36: 501–6.
2. Bodenham A, *et al.* Extrahepatic morphine metabolism in man during the anhepatic phase of orthotopic liver transplantation. *Br J Anaesth* 1989; 63: 380–4.
3. Shelly MP, *et al.* Pharmacokinetics of morphine in patients following orthotopic liver transplantation. *Br J Anaesth* 1989; 63: 375–9.
4. Manara AR, *et al.* Morphine elimination and liver blood flow: a study in patients undergoing distal splenorenal shunt. *Br J Hosp Med* 1989; 42: 148 (abstract).

Renal impairment. Only a small amount of morphine is excreted unchanged in the urine. There are conflicting reports of morphine accumulation in patients with renal impairment; some for,[1,2] others against.[3-5] It does seem clear though that morphine metabolites accumulate in such patients[5-9] including those on peritoneal dialysis;[10] the half-life of the active metabolite morphine-6-glucuronide was reported to be prolonged and its clearance reduced when morphine-6-glucuronide was given to patients with renal impairment.[11] Opioid intoxication[12] and a prolonged opioid effect[13] in patients with renal failure has been associated with morphine-6-glucuronide (see also under Precautions, p. 95.2).

1. Ball M, *et al.* Renal failure and the use of morphine in intensive care. *Lancet* 1985; i: 784–6.
2. Osborne R, *et al.* The pharmacokinetics of morphine and morphine glucuronides in kidney failure. *Clin Pharmacol Ther* 1993; 54: 158–67.
3. Säwe J, *et al.* Kinetics of morphine in patients with renal failure. *Lancet* 1985; ii: 211.
4. Woolner DP, *et al.* Renal failure does not impair the metabolism of morphine. *Br J Clin Pharmacol* 1986; 22: 55–9.
5. Chauvin M, *et al.* Morphine pharmacokinetics in renal failure. *Anesthesiology* 1987; 66: 327–31.
6. Säwe J, Odar-Cederlöf I. Kinetics of morphine in patients with renal failure. *Eur J Clin Pharmacol* 1987; 32: 377–82.
7. Wolff J, *et al.* Influence of renal function on the elimination of morphine and morphine glucuronides. *Eur J Clin Pharmacol* 1988; 34: 353–7.
8. Sear JW, *et al.* Studies on morphine disposition: influence of renal failure on the kinetics of morphine and its metabolites. *Br J Anaesth* 1989; 62: 28–32.
9. Peterson GM, *et al.* Plasma levels of morphine and morphine glucuronides in the treatment of cancer pain: relationship to renal

function and route of administration. *Eur J Clin Pharmacol* 1990; 38: 121–4.
10. Pauli-Magnus C, *et al.* Pharmacokinetics of morphine and its glucuronides following intravenous administration of morphine in patients undergoing continuous ambulatory peritoneal dialysis. *Nephrol Dial Transplant* 1999; 14: 903–9.
11. Hanna MH, *et al.* Morphine-6-glucuronide disposition in renal impairment. *Br J Anaesth* 1993; 70: 511–14.
12. Osborne RJ, *et al.* Morphine intoxication in renal failure: the role of morphine-6-glucuronide. *BMJ* 1986; 292: 1548–9.
13. Bodd E, *et al.* Morphine-6-glucuronide might mediate the prolonged opioid effect of morphine in acute renal failure. *Hum Exp Toxicol* 1990; 9: 317–21.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Algedol; Amidiaz; Analmorph; Duramorph; GNO; MST Continus; Neocalmans; ***Austral.***: Anamorph; DepoDur; Kapanol; Momex; MS Contin; MS Mono; Ordine; Sevredol; ***Austria***: Compensan; Kapanol; M-Dolor; Morapid; Mundidol; Oramorph; Substitol; Vendal; ***Belg.***: Docmorfine†; Kapanol†; MS Contin; MS Direct; Oramorph; Stellorphine; ***Braz.***: Dimorf; Dolo Moff; Morfenil; ***Canad.***: Doloral; Kadian; M-Eslon; MOS; MS Contin; MSIR; Statex; ***Chile***: M-Eslon; ***China***: Meifeikang (美菲康); MS Contin (美施康定); Shi Ni Kang (史尼康); ***Cz.***: Efemorf; M-Eslon†; MSI; MST Continus†; Sevredol; Slovalgin†; Vendal; ***Denm.***: Contalgin; Depolan; Doltard; Malfin; Oramorph; ***Fin.***: Depolan; Dolcontin; Oramorph; ***Fr.***: Actiskenan; Kapanol†; Moscontin; Oramorph; Sevredol; Skenan; ***Ger.***: Capros; Kapanol†; M-beta; M-long; M-Stada; Morixon†; Morph†; Morphanton†; MSI; MSR; MST; Oramorph; Painbreak; Sevredol; ***Gr.***: Mongol; Morficontin; MXL; Oramorph; ***Hong Kong***: M-Eslon†; MST Continus; ***Hung.***: M-Eslon; MST Continus; Sevredol; ***India***: Duramor; Morcontin; Morf; Morphitroy; ***Indon.***: MST Continus; ***Irl.***: Ethirfin†; MST Continus; MXL†; Oramorph; Sevredol; ***Israel***: MCR; MIR; MSP†; ***Ital.***: MS Contin; Oramorph; Ticinan†; Twice; ***Jpn***: MS Contin; ***Malaysia***: MST Continus; ***Mex.***: Analfin; Graten; ***Neth.***: Kapanol; MS Contin; Oramorph; Sevredol†; Skenan†; ***Norw.***: Dolcontin; Oramorph; ***NZ***: Kapanol†; LA Morph†; M-Eslon; RA Morph; Sevredol; ***Philipp.***: M-Dolor†; Morin; MST Continus; Relimal; ***Pol.***: Doltard; MST Continus; Oramorph; Sevredol; Vendal†; ***Port.***: Ethirfin†; Grumorph; MST; Oramorph; Sevredol; Skenan†; ***S.Afr.***: MST Continus; SRM-Rhotard; ***Singapore***: MST Continus; SRM-Rhotard; Statex; ***Spain***: Dolq; MST Continus; Oramorph; Sevredol; Skenan†; Zomorph; ***Swed.***: Depolan; Dolcontin; Oramorph; ***Switz.***: Kapanol; M-retard; MST Continus; Oramorph; Sevre-Long; Sevredol; ***Thai.***: Kapanol; MST Continus; ***Turk.***: M-Eslon; Vendal; ***UK***: DepoDur; Filnarine; Morphgesic; MST Continus; MXL; Oramorph; Rhotard; Sevredol; Zomorph; ***USA***: Astramorph; Avinza; DepoDur; Duramorph; Embeda; Infumorph; Kadian; MS Contin; MSIR; Oramorph; RMS; Roxanol; ***Venez.***: MS Contin.

Multi-ingredient Preparations. ***China***: Gan Han (甘含); ***Irl.***: Cyclimorph; ***Ital.***: Cardiostenol; ***S.Afr.***: Chloropect; Cyclimorph; Enterodyne†; Pectrolyte; ***Swed.***: Spasmofen; ***Switz.***: Spasmosol†; ***UK***: Collis Browne's; Collis Browne's; Cyclimorph; Diocalm Dual Action; Opazimes.

Pharmacopoeial Preparations
BP 2014: Chloroform and Morphine Tincture; Morphine and Atropine Injection; Morphine Sulphate Injection; Morphine Suppositories; Morphine Tablets; Prolonged-release Morphine Tablets;
USP 36: Morphine Sulfate Extended-Release Capsules; Morphine Sulfate Injection; Morphine Sulfate Suppositories.

Morpholine Salicylate

Morfoliinisalisylaatti; Morfolinsalicylat; Morpholini Salicylas; Salicilato de morfolinio; Морфолин Салицилат.

2-Hydroxybenzoic acid compounded with morpholine (1:1).

$C_{11}H_{15}NO_4$=225.2

CAS — 147-90-0.

ATC — N02BA08.

ATC Vet — QN02BA08.

Profile

Morpholine salicylate is a salicylic acid derivative (see Aspirin, p. 22.2) that has been used for musculoskeletal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Israel***: Dolical†.

Nabumetone *(BAN, USAN, rINN)*

BRL-14777; Nabumeton; Nabumetona; Nabumetonas; Nabumétone; Nabumetoni; Nabumetonum; Набуметон.

4-(6-Methoxy-2-naphthyl)butan-2-one.

$C_{15}H_{16}O_2$=228.3

CAS — 42924-53-8.

ATC — M01AX01.

ATC Vet — QM01AX01.

UNII — LW0TW155Z.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Nabumetone). A white or almost white crystalline powder. Practically insoluble in water; freely soluble in acetone; slightly soluble in methyl alcohol. Protect from light.

USP 36: (Nabumetone). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol and in methyl alcohol; freely soluble in acetone. Store in airtight containers. Protect from light.

Uses and Administration

Nabumetone is a non-active prodrug whose major metabolite is an NSAID (p. 102.3) structurally similar to naproxen (p. 98.2). It is used for the relief of pain and inflammation associated with osteoarthritis and rheumatoid arthritis in a usual oral dose of 1 g taken as a single dose in the evening; if necessary 0.5 to 1 g may be given additionally in the morning. It has been recommended that a dose of 1 g daily should not be exceeded in elderly patients and that 500 mg daily may be satisfactory in some cases.

References.
1. Friedel HA, *et al.* Nabumetone: a reappraisal of its pharmacology and therapeutic use in rheumatic diseases. *Drugs* 1993; 45: 131–56.
2. Proceedings of a symposium: continuing developments with nabumetone: an investigators' update. *Am J Med* 1993; 95 (suppl 2A): 1S–45S.
3. Dahl SL. Nabumetone: a "nonacidic" nonsteroidal antiinflammatory drug. *Ann Pharmacother* 1993; 27: 456–63.
4. Hedner T, *et al.* Nabumetone: therapeutic use and safety profile in the management of osteoarthritis and rheumatoid arthritis. *Drugs* 2004; 64: 2315–43.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3. Nabumetone is contra-indicated in patients with severe hepatic impairment.

Effects on the gastrointestinal tract. Like other NSAIDs nabumetone can produce adverse effects on the gastrointestinal tract, although some studies have produced favourable comparisons with ibuprofen[1] or naproxen.[2] A recent review[3] noted that limited comparative data suggest that nabumetone has a similar gastrointestinal adverse effect profile to that of selective cyclo-oxygenase-2 (COX-2) inhibitors. It has been suggested[4] that nabumetone may be a preferential inhibitor of COX-2 but the significance of this in determining its adverse effects is uncertain.

1. Roth SH, *et al.* A controlled study comparing the effects of nabumetone, ibuprofen, and ibuprofen plus misoprostol on the upper gastrointestinal tract mucosa. *Arch Intern Med* 1993; 153: 2565–71.
2. Roth SH, *et al.* A longterm endoscopic evaluation of patients with arthritis treated with nabumetone vs naproxen. *J Rheumatol* 1994; 21: 1118–23.
3. Bannwarth B. Safety of the nonselective NSAID nabumetone: focus on gastrointestinal tolerability. *Drug Safety* 2008; 31: 485–503.
4. Davies NM. Clinical pharmacokinetics of nabumetone: the dawn of selective cyclo-oxygenase-2 inhibition? *Clin Pharmacokinet* 1997; 33: 403–16.

Effects on the lungs. Pulmonary fibrosis developed in a 68-year-old woman taking nabumetone 1.5 g daily; symptoms appeared after 2 weeks of therapy and worsened during the next 6 weeks.[1] There was rapid resolution on stopping nabumetone and starting treatment with oral corticosteroids.

1. Morice A, *et al.* Pulmonary fibrosis associated with nabumetone. *Postgrad Med J* 1991; 67: 1021–2.

Effects on the skin. Pseudoporphyria characterised by blistering on the neck and hands developed in a 36-year-old woman taking nabumetone and auranofin for rheumatoid arthritis.[1] Stopping auranofin had no effect on the blistering, which only resolved once nabumetone was withdrawn. The authors of the report stated that the UK CSM had received 3 additional reports of pseudoporphyria suspected to be caused by nabumetone.

1. Varma S, Lanigan SW. Pseudoporphyria caused by nabumetone. *Br J Dermatol* 1998; 138: 549–50. Correction. *ibid.* 139: 759. [dose]

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nabumetone as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 23/10/11)

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Pharmacokinetics

Nabumetone is well absorbed from the gastrointestinal tract. Plasma concentrations after oral doses are too small to be measured, as it undergoes rapid and extensive first-pass metabolism in the liver to the principal active compound 6-methoxy-2-naphthylacetic acid (6-MNA) and other inactive metabolites. 6-MNA is more than 99% bound to plasma proteins. It diffuses into synovial fluid, crosses the placenta, and is distributed into breast milk. There is considerable interindividual variation in the plasma elimination half-life of 6-MNA, especially in the elderly; some reported mean values at steady state include 22 to about 27 hours for young adults and about 25 and 34 hours in elderly patients. 6-MNA eventually undergoes further metabolism by *O*-methylation and conjugation. About 80% of a dose is excreted in the urine as inactive or conjugated metabolites and less than 1% as unchanged 6-MNA.

References.
1. Brier ME, *et al.* Population pharmacokinetics of the active metabolite of nabumetone in renal dysfunction. *Clin Pharmacol Ther* 1995; 57: 622–7.
2. Davies NM. Clinical pharmacokinetics of nabumetone: the dawn of selective cyclo-oxygenase-2 inhibition? *Clin Pharmacokinet* 1997; 33: 403–16.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Gambaran; ***China***: Angtaifen (昂泰芬); Ao Sai Jing (奥赛金); Hong Xu Lai (弘旭来); Kefenting; Li Dao (力道); Nai Pu Tong (萘普酮); Relafen (瑞力芬); Si Rui Ke (司瑞克); Tong Shu Tong (彤舒通); Yifangtong (易方彤); ***Cz.***: Relifex†; ***Denm.***: Relifex; ***Fin.***: Relifex; ***Fr.***: Nabucox; ***Ger.***: Relifex; ***Gr.***: Akratol; Ameinon; Anfer; Ethyfen; Flogmed; Mevedal; Nabuton; Naditone; Relifex; ***Hung.***: Relifex; ***India***: Nabuflam; Nilitis; ***Indon.***: Goflex; ***Irl.***: Relifex; Religer†; ***Israel***: Nabuco; Relifex†; ***Ital.***: Artaxan; Nabuser; Relifex; ***Jpn***: Relifen; ***Mex.***: Naflam; Relifex; ***Neth.***: Mebutan; ***Norw.***: Relifex; ***Philipp.***: Relifex; ***Pol.***: Coxalgan; Coxeton†; Nabuton; Relifex†; Rodanol S; ***Port.***: Balmox; Elitar; ***Rus.***: Rodanol (Роданол)†; ***S.Afr.***: Relifen†; Relisan†; Relitone†; ***Spain***: Listran†; Relif; ***Swed.***: Relifex; ***Switz.***: Balmox; ***Thai.***: Aflex; Bumetone; Ensaid†; Fafex; Nabone; Nabonet†; Naflex; Nametone; Relifex†; Rheumetone; ***Turk.***: Relifex; ***UK***: Relifex; ***Ukr.***: Synmeton (Синметон).

Pharmacopoeial Preparations
BP 2014: Nabumetone Oral Suspension; Nabumetone Tablets;
USP 36: Nabumetone Tablets.

Nalbuphine Hydrochloride

(BANM, USAN, rINNM)

EN-2234A; Hidrocloruro de nalbufina; Nalbufina, hidrocloruro de; Nalbufine Hydrochloride; Nalbuphine, Chlorhydrate de; Nalbuphini Hydrochloridum; Налбуфина Гидрохлорид.

17-Cyclobutylmethyl-7,8-dihydro-14-hydroxy-17-normorphine hydrochloride; (-)-(5*R*,6*S*,14*S*)-9a-Cyclobutylmethyl-4,5-epoxymorphinan-3,6,14-triol hydrochloride.

$C_{21}H_{27}NO_4$,HCl=393.9

CAS — 20594-83-6 (nalbuphine); 23277-43-2 (nalbuphine hydrochloride).

ATC — N02AF02.

ATC Vet — QN02AF02.

UNII — ZU4275277R.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of nalbuphine hydrochloride:
Nubian.

Incompatibility. Incompatibility has been reported between injections of nalbuphine hydrochloride and nafcillin sodium,[1] diazepam,[2] pentobarbital sodium,[2] or thiethylperazine maleate.[2] US licensed product information states that nalbuphine is also physically incompatible with ketorolac.

1. Jeglum EL, *et al.* Nafcillin sodium incompatibility with acidic solutions. *Am J Hosp Pharm* 1981; 38: 462–4.
2. Jump WG, *et al.* Compatibility of nalbuphine hydrochloride with other preoperative medications. *Am J Hosp Pharm* 1982; 39: 841–3.

Uses and Administration

Nalbuphine hydrochloride, a phenanthrene derivative, is an opioid analgesic (p. 108.1). It has mixed opioid agonist and antagonist activity. It is used for the relief of moderate to severe pain and as an adjunct to anaesthesia. Nalbuphine hydrochloride is reported to act within 15 minutes of subcutaneous or intramuscular injection or within 2 to 3 minutes of intravenous injection and generally to produce analgesia for 3 to 6 hours. It is given subcutaneously, intramuscularly, or intravenously. Intravenous infusion as part of a patient-controlled analgesia system has also been used.

The usual dose of nalbuphine hydrochloride for pain relief is 10 to 20 mg every 3 to 6 hours as required.

As an adjunct in balanced **anaesthesia** a usual dose is 0.3 to 3 mg/kg given intravenously over 10 to 15 minutes at induction. Maintenance doses of 250 to 500 micrograms/kg may be given as intravenous boluses if required.

Action. Nalbuphine is generally described as a mixed agonist and antagonist acting mainly as an agonist at κ opioid receptors and as an antagonist or partial agonist at μ receptors. It has shown antagonist activity similar to that seen with naloxone in opioid-dependent subjects.[1] Nalbuphine is structurally related to naloxone and oxymorphone. Pharmacologically nalbuphine is qualitatively similar to pentazocine, but nalbuphine is a more potent antagonist at μ opioid receptors, is less likely to produce psychotomimetic effects such as hallucinations, and is reported to produce no significant cardiovascular effects in patients with ischaemic heart disease. It differs from pure μ agonists such as morphine in that its analgesic, sedative, and respiratory depressant actions are subject to a 'ceiling' effect and may not increase proportionately with dose.

1. Preston KL, *et al.* Antagonist effects of nalbuphine in opioid-dependent human volunteers. *J Pharmacol Exp Ther* 1989; **248**: 929–37.

Administration. References to alternative routes or dosage schedules.

1. Krenn H, *et al.* Nalbuphine by PCA-pump for analgesia following hysterectomy: bolus application versus continuous infusion with bolus application. *Eur J Pain* 2001; **5**: 219–26.
2. Woollard M, *et al.* Hitting them where it hurts? Low dose nalbuphine therapy. *Emerg Med J* 2002; **19**: 565–70.
3. Sung KC, *et al.* Transdermal delivery of nalbuphine and its prodrugs by electroporation. *Eur J Pharm Sci* 2003; **18**: 63–70.
4. Gear RW, *et al.* Dose ratio is important in maximizing naloxone enhancement of nalbuphine analgesia in humans. *Neurosci Lett* 2003; **351**: 5–8.
5. Liu KS, *et al.* Antinociceptive effect of a novel long-acting nalbuphine preparation. *Br J Anaesth* 2004; **92**: 712–15.
6. Woollard M, *et al.* Less IS less: a randomised controlled trial comparing cautious and rapid nalbuphine dosing regimens. *Emerg Med J* 2004; **21**: 362–4.
7. Gordon AT, *et al.* Open-label exploration of an intravenous nalbuphine and naloxone mixture as an analgesic agent following gynecologic surgery. *Pain Med* 2007; **8**: 525–30.

Dependence and Withdrawal

As for Opioid Analgesics, p. 109.1.

A WHO expert committee considered in 1989 that the likelihood of nalbuphine abuse was low to moderate and was not great enough to warrant international control.[1] Abuse had been reported infrequently and the withdrawal syndrome produced when naloxone was given after continuous nalbuphine dosage was less severe than that in morphine dependence. Subsequently, there have been occasional reports of abuse[2,3] including misuse among athletes.[4,5]

1. WHO. WHO expert committee on drug dependence: twenty-fifth report. *WHO Tech Rep Ser 775* 1989. Also available at: http://libdoc.who.int/trs/WHO_TRS_775.pdf (accessed 26/06/08)
2. Spadari M, *et al.* Pharmacodépendance à la nalbuphine (Nubain): à propos de 2 cas. *Therapie* 2002; **57**: 504–5.
3. Klinzig F, *et al.* Hair analysis by LC-MS as evidence of nalbuphine abuse by a nurse. *J Anal Toxicol* 2007; **31**: 62–5.
4. McBride AJ, *et al.* Three cases of nalbuphine hydrochloride dependence associated with anabolic steroid use. *Br J Sports Med* 1996; **30**: 69–70.
5. Wines JD, *et al.* Nalbuphine hydrochloride dependence in anabolic steroid users. *Am J Addict* 1999; **8**: 161–4.

Adverse Effects and Treatment

As for Opioid Analgesics in general, p. 110.1.

Headache may occur. Nausea and vomiting occur less than with other opioids. Hallucinations and other psychotomimetic effects are rare and have been reported less frequently than with pentazocine. As nalbuphine has both antagonist and agonist activity its effects may be only partially reversed by naloxone, but use of the latter is still recommended in nalbuphine overdose.

Effects on the respiratory system. Nalbuphine produces similar respiratory depression to morphine at equianalgesic doses, but there is a ceiling effect with nalbuphine and, unlike morphine, respiratory depression does not increase appreciably with higher doses.[1] In a cumulative-dose study[2] a plateau effect was seen with nalbuphine above a total dose of 30 mg per 70 kg intravenously. Similar ventilatory depression has been noted[3] with single intravenous doses of nalbuphine of 15, 30, or 60 mg per 70 kg; naloxone failed to reverse the depression at the highest dose.

1. Klepper ID, *et al.* Respiratory function following nalbuphine and morphine in anaesthetized man. *Br J Anaesth* 1986; **58**: 625–9.
2. Romagnoli A, Keats AS. Ceiling effect for respiratory depression by nalbuphine. *Clin Pharmacol Ther* 1980; **27**: 478–85.
3. Pugh GC, *et al.* Effect of nalbuphine hydrochloride on the ventilatory and occlusion pressure responses to carbon dioxide in volunteers. *Br J Anaesth* 1989; **62**: 601–9.

Precautions

As for Opioid Analgesics in general, p. 110.3.

Nalbuphine may precipitate withdrawal symptoms if given to patients physically dependent on opioids.

The dose of nalbuphine should be reduced in patients with hepatic or renal impairment.

Abuse. See under Dependence and Withdrawal, above.

Pregnancy. When nalbuphine is used for analgesia during labour there is more placental transfer and sedation in mothers and their infants than with pethidine.[1] There have also been reports of bradycardia and respiratory depression in neonates whose mothers received nalbuphine during labour.[2,3] It was considered that nalbuphine should be given with caution during labour, especially by the intravenous route. Some[2] have recommended subcutaneous dosage and advised that nalbuphine should not be given around the expected time of delivery.

Further references on the transplacental transfer of nalbuphine are given under Pharmacokinetics, below.

1. Wilson CM, *et al.* Transplacental gradient of pethidine and nalbuphine in labour. *Br J Clin Pharmacol* 1986; **21**: 571P–572P.
2. Guillonneau M, *et al.* Perinatal adverse effects of nalbuphine given during parturition. *Lancet* 1990; **335**: 1588.
3. Sgro C, *et al.* Perinatal adverse effects of nalbuphine given during labour. *Lancet* 1990; **336**: 1070.

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

Pharmacokinetics

There appears to be considerable first-pass metabolism of nalbuphine after oral doses. On intramuscular injection nalbuphine has been reported to produce peak plasma concentrations after 30 minutes. It is metabolised in the liver and is excreted in the urine and faeces as unchanged drug and conjugates. Nalbuphine crosses the placenta and small amounts are distributed into breast milk.

References.

1. Sear JW, *et al.* Disposition of nalbuphine in patients undergoing general anaesthesia. *Br J Anaesth* 1987; **59**: 572–5.
2. Kay B, *et al.* Pharmacokinetics of oral nalbuphine in postoperative patients. *Br J Anaesth* 1987; **59**: 1327P.
3. Aitkenhead AR, *et al.* The pharmacokinetics of oral and intravenous nalbuphine in healthy volunteers. *Br J Clin Pharmacol* 1988; **25**: 264–8.
4. Jaillon P, *et al.* Pharmacokinetics of nalbuphine in infants, young healthy volunteers, and elderly patients. *Clin Pharmacol Ther* 1989; **46**: 226–33.

Pregnancy. References.

1. Wilson CM, *et al.* Transplacental gradient of pethidine and nalbuphine in labour. *Br J Clin Pharmacol* 1986; **21**: 571P–572P.
2. Dadabhoy ZP, *et al.* Transplacental transfer of nalbuphine in patients undergoing cesarean section: a pilot study. *Acta Anaesthesiol Ital* 1988; **39**: 227–32.
3. Nicolle E, *et al.* Therapeutic monitoring of nalbuphine: transplacental transfer and estimated pharmacokinetics in the neonate. *Eur J Clin Pharmacol* 1996; **49**: 485–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Gobbinal; Naltrox†; Nubaina; Onfor; *Braz.*: Nalfina; Nubain; *Canad.*: Nubain; *Cz.*: Nubain†; *Denm.*: Nalpain; *Fin.*: Nalpain; *Ger.*: Nalpain; *Gr.*: Mexifen; Nubain; *Hong Kong*: Intapan†; *Hung.*: Bufimorf; Nubain†; *Irl.*: Lapainol; *Malaysia*: Intapan; *Mex.*: Bufigen; Bufilem; Fabitec; Nalcryn; *Philipp.*: Nubain; Nukaine; *Port.*: Nalpain; *Singapore*: Intapan; Nubain; *Swed.*: Nalpain; *Thai.*: Nubain; *USA*: Nubain†; *Venez.*: Bufidol.

Naproxen *(BAN, USAN, rINN)*

Naprokseeni; Naproksen; Naproksenas; Naproxén; Naproxène; Naproxeno; Naproxenum; RS-3540; Напроксен.

(+)-2-(6-Methoxy-2-naphthyl)propionic acid.

$C_{14}H_{14}O_3$=230.3

CAS — 22204-53-1.

ATC — G02CC02; M01AE02; M02AA12.

ATC Vet — QG02CC02; QM01AE02; QM02AA12.

UNII — 57Y76R9ATQ.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Naproxen). A white or almost white, crystalline powder. Practically insoluble in water; soluble in alcohol and in methyl alcohol. Protect from light.

USP 36: (Naproxen). A white to off-white, practically odourless, crystalline powder. Practically insoluble in water; soluble in alcohol, in dehydrated alcohol, and in chloroform; sparingly soluble in ether. Store in airtight containers.

Naproxen Sodium *(BANM, USAN, rINNM)*

Naproksen Sodyum; Naproxen-Natrium; Naproxène Sodique; Naproxeno sódico; Naproxenum natricum; Natrii Naproxenum; RS-3650; Натрий Напроксен.

$C_{14}H_{13}NaO_3$=252.2

CAS — 26159-34-2.

UNII — 9TN87S3A3C.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Naproxen Sodium). A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; sparingly soluble in alcohol; freely soluble or soluble in methyl alcohol. A 2% solution in water has a pH of 7.0 to 9.8. Store in airtight containers. Protect from light.

USP 36: (Naproxen Sodium). A white to creamy crystalline powder. Soluble in water and in methyl alcohol; sparingly soluble in alcohol; very slightly soluble in acetone; practically insoluble in chloroform and in toluene. Store in airtight containers.

Uses and Administration

Naproxen, a propionic acid derivative, is an NSAID (p. 102.3).

Naproxen is used in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis including juvenile idiopathic arthritis. It is also used in dysmenorrhoea, headache including migraine, postoperative pain, soft-tissue disorders, acute gout, and to reduce fever. Naproxen is usually given *orally* as the free acid or as the sodium salt. The doses in the licensed product information are expressed in terms of the free acid or the sodium salt as appropriate for an individual preparation; however, the doses given below are expressed in terms of the equivalent amount of free acid only. Each 550 mg of naproxen sodium is equivalent to about 500 mg of naproxen.

In the treatment of **rheumatic disorders**, the usual dose of naproxen or naproxen sodium is the equivalent of 500 mg to 1 g of naproxen daily either as a single dose or in 2 divided doses. US licensed product information states that patients who tolerate lower doses may have their dosage increased to 1.5 g daily for a period of up to 6 months, if required. For dosage in children, see below.

In **other painful conditions** such as dysmenorrhoea and acute musculoskeletal disorders the usual regimen is the equivalent of 500 mg of naproxen initially, followed by 250 mg every 6 to 8 hours, up to a maximum daily dose of 1.25 g on the first day and 1 g thereafter.

In **acute gout** an initial dose equivalent to 750 mg of naproxen followed by 250 mg every 8 hours is used.

For the treatment of **migraine**, the equivalent of 750 mg of naproxen can be given at the first symptom of an impending attack and, if necessary, this may be followed after at least half an hour by further doses of 250 to 500 mg throughout the day to a total maximum daily dose of 1250 mg. See Headache, below for a suggested dose for the prophylaxis of migraine.

Naproxen has been given *rectally* in similar doses to those used orally.

Naproxen has also been used as the piperazine, aminobutanol, choline, and lysine salts, and as naproxen cetrimonium. Naproxen has been given as part of a combination pack with misoprostol (p. 2140.3) or lansoprazole (p. 1854.3), or as a modified-release combination preparation with esomeprazole (p. 1844.1) for patients at risk of NSAID-induced peptic ulceration.

Reviews.

1. Todd PA, Clissold SP. Naproxen: a reappraisal of its pharmacology, and therapeutic use in rheumatic diseases and pain states. *Drugs* 1990; **40**: 91–137.
2. Curran MP, Wellington K. Delayed-release lansoprazole plus naproxen. *Drugs* 2004; **64**: 1915–19.
3. Derry C, *et al.* Single dose oral naproxen and naproxen sodium for acute postoperative pain in adults. Available in The Cochrane Database of Systematic Reviews; Issue 9. Chichester: John Wiley; 2009 (accessed 18/09/09).

Administration in children. In the treatment of juvenile idiopathic arthritis, US licensed product information recommends an oral dose of about 10 mg/kg daily of naproxen in 2 divided doses for children aged 2 years and over; in the UK, this dose is licensed for those aged over 5 years. In addition, higher doses may also be used: the *BNFC* suggests a dose of up to 15 mg/kg daily (maximum of 1 g daily) in children aged 2 to 18 years.

For pain and inflammation in musculoskeletal disorders and dysmenorrhoea, the *BNFC* suggests that those aged 1 month to 18 years may be given an oral dose of 5 mg/kg twice daily (maximum of 1 g daily).

Headache. An NSAID such as naproxen is among the drugs tried first for the symptomatic treatment of various types of headache including migraine (p. 670.3) and tension-type headache (p. 671.3). An NSAID given at the onset of symptoms can successfully treat an acute attack of migraine.[1,2] Co-treatment with a triptan may provide additional benefit and a preparation containing both sumatriptan succinate and naproxen sodium (*Treximet; GlaxoSmithKline, USA*) is available.[3-6]

NSAIDs also appear to be effective for the prophylaxis of migraine, although propranolol is generally preferred. Studies have indicated that naproxen sodium 550 mg [equivalent to 500 mg of naproxen] given twice daily may be useful for reducing the number of attacks suffered.[7-9]

Naproxen can be used to manage the aggravation of symptoms associated with the withdrawal of analgesics in medication-overuse headache (p. 670.2). An oral dose of 250 mg three times daily or 500 mg twice daily should be

taken regularly; some suggest a single course of 3 to 4 weeks, others a 6-week course with the dose of naproxen being reduced gradually.[10]

1. Treves TA, *et al.* Naproxen sodium versus ergotamine tartrate in the treatment of acute migraine attacks. *Headache* 1992; 32: 280–2.
2. Suthisisang CC, *et al.* Meta-analysis of the efficacy and safety of naproxen sodium in the acute treatment of migraine. *Headache* 2010; 50: 808–18.
3. Winner P, *et al.* Twelve-month tolerability and safety of sumatriptan-naproxen sodium for the treatment of acute migraine. *Mayo Clin Proc* 2007; 82: 61–8.
4. Brandes JL, *et al.* Sumatriptan-naproxen for acute treatment of migraine: a randomized trial. *JAMA* 2007; 297: 1443–54.
5. Mathew NT, *et al.* Fixed-dose sumatriptan and naproxen in poor responders to triptans with a short half-life. *Headache* 2009; 49: 971–82.
6. Khoury CK, Couch JR. Sumatriptan-naproxen fixed combination for acute treatment of migraine: a critical appraisal. *Drug Des Devel Ther* 2010; 4: 9–17.
7. Sargent J, *et al.* A comparison of naproxen sodium to propranolol hydrochloride and a placebo control for the prophylaxis of migraine headache. *Headache* 1985; 25: 320–4.
8. Welch KMA, *et al.* Successful migraine prophylaxis with naproxen sodium. *Neurology* 1985; 35: 1304–10.
9. Sances G, *et al.* Naproxen sodium in menstrual migraine prophylaxis: a double-blind placebo controlled study. *Headache* 1990; 30: 705–9.
10. British Association for the Study of Headache. Guidelines for all healthcare professionals in the diagnosis and management of migraine, tension-type, cluster and medication-overuse headache. 3rd edn. (Issued 18th January, 2007; 1st revision, September 2010). Available at: http://217.174.249.183/upload/NS_BASH/2010_BASH_Guidelines.pdf (accessed 21/06/11)

Malignant neoplasms. Some NSAIDs such as naproxen may be of value both for the differential diagnosis and the management of neoplastic fever[1-4] as they appear to be more effective in reducing this type of fever than against fever associated with infections. However, the reliability of naproxen in the diagnosis of neoplastic fever has been questioned.[5] In a group of 72 patients, naproxen decreased body temperature in 55% of patients with neoplastic disorders and 38% of patients with other conditions. Thus, the sensitivity of the test was calculated as 55% and its specificity as 62%, which the authors considered to be too low to be reliable.

1. Chang JC, Gross HM. Neoplastic fever responds to the treatment of an adequate dose of naproxen. *J Clin Oncol* 1985; 3: 552–8.
2. Azeemuddin SK, *et al.* The effect of naproxen on fever in children with malignancies. *Cancer* 1987; 59: 1966–8.
3. Economos K, *et al.* The effect of naproxen on fever in patients with advanced gynecologic malignancies. *Gynecol Oncol* 1995; 56: 250–4.
4. Cunha BA, *et al.* Fever of unknown origin (FUO) caused by multiple myeloma: the diagnostic value of the Naprosyn test. *Heart Lung* 2006; 35: 358–62.
5. Vanderschueren S, *et al.* Lack of value of the naproxen test in the differential diagnosis of prolonged febrile illnesses. *Am J Med* 2003; 115: 572–5.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3.

Suppositories containing naproxen may cause rectal irritation and occasional bleeding.

Naproxen should be used with caution in renal impairment, and use is not recommended in patients whose creatinine clearance is less than 20 mL/min.

Reviews.

1. Bansal V, *et al.* A look at the safety profile of over-the-counter naproxen sodium: a meta-analysis. *J Clin Pharmacol* 2001; 41: 127–38.

Breast feeding. The American Academy of Pediatrics[1] states that there have been no reports of any clinical effect on the infant associated with the use of naproxen by breast-feeding mothers, and that therefore it may be considered to be usually compatible with breast feeding. The *BNF* also considers that the amount of naproxen distributed into breast milk is too small to be harmful to a breast-fed infant; however, some licensed product information recommends that breast feeding should be avoided during naproxen therapy.

In a study[2] of a breast-fed infant only 0.26% of the mother's dose was recovered from the infant.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/11/07)
2. Jamali F, Stevens DRS. Naproxen excretion in milk and its uptake by the infant. *Drug Intell Clin Pharm* 1983; 17: 910–11.

Effects on the blood. Haematological adverse effects reported in patients given naproxen include haemolytic anaemia,[1,2] aplastic anaemia,[3] agranulocytosis,[4] and immune thrombocytopenia.[5]

1. Hughes JA, Sudell W. Hemolytic anemia associated with naproxen. *Arthritis Rheum* 1983; 26: 1054.
2. Lo TCN, Martin MA. Autoimmune haemolytic anaemia associated with naproxen suppositories. *BMJ* 1986; 292: 1430.
3. McNeil P, *et al.* Naproxen-associated aplastic anaemia. *Med J Aust* 1986; 145: 53–4.
4. Nygard N, Starkebaum G. Naproxen and agranulocytosis. *JAMA* 1987; 257: 1732.
5. Bougie D, Aster R. Immune thrombocytopenia resulting from sensitivity to metabolites of naproxen and acetaminophen. *Blood* 2001; 97: 3846–50.

Effects on the cardiovascular system. For a discussion of the possible cardiovascular effects of naproxen, see p. 105.1.

Effects on the CNS. Aseptic meningitis has been associated with naproxen therapy;[1,2] attacks may be recurrent and cross-sensitivity with other NSAIDs has occurred.[2]

There has been a report[3] of a patient with Parkinson's disease whose symptoms had previously been well controlled but who deteriorated when she was given naproxen. She improved on withdrawal of naproxen and the effect was confirmed by rechallenge. It was noted that the UK CSM had recorded a case of parkinsonism associated with a combined preparation of naproxen and misoprostol and 12 other reports of tremor or ataxia precipitated by naproxen.

1. Weksler BB, Lehany AM. Naproxen-induced recurrent aseptic meningitis. *DICP Ann Pharmacother* 1991; 25: 1183–4.
2. Seaton RA, France AJ. Recurrent aseptic meningitis following non-steroidal anti-inflammatory drugs – a reminder. *Postgrad Med J* 1999; 75: 771–2.
3. Shaunak S, *et al.* Exacerbation of idiopathic Parkinson's disease by naproxen. *BMJ* 1995; 311: 422.

Effects on the eyes. Keratopathy, characterised by whorl-like corneal opacities, occurred in a woman taking naproxen; complete regression occurred after stopping the drug.[1] There has also been a report of exacerbation of glaucoma in a 65-year-old woman given naproxen.[2]

For reference to effects on the optic nerve associated with naproxen, see p. 105.3.

1. Szmyd L, Perry HD. Keratopathy associated with the use of naproxen. *Am J Ophthalmol* 1985; 99: 598.
2. Fincham JE. Exacerbation of glaucoma in an elderly female taking naproxen sodium: a case report. *J Geriatr Drug Ther* 1989; 3: 139–43.

Effects on the gastrointestinal tract. Gastrointestinal adverse effects are among the most frequently reported during short- and long-term treatment with naproxen. Acute proctocolitis associated with the use of naproxen has been reported.[1] Oesophageal ulceration reported in 7 patients[2] may have arisen due to incorrect consumption (such as taking the dosage without fluids or lying down after a dose) but other causes could not be dismissed.

1. Ravi S, *et al.* Colitis caused by non-steroidal anti-inflammatory drugs. *Postgrad Med J* 1986; 62: 773–6.
2. Kahn LH, *et al.* Over-the-counter naproxen sodium and esophageal injury. *Ann Intern Med* 1997; 126: 1006.

Effects on the kidneys. Acute renal failure,[1] renal papillary necrosis,[2,3] interstitial nephritis,[4] and hyperkalaemia[1] have been reported in patients receiving naproxen. As with other NSAIDs, renal adverse effects occur more frequently in patients with certain risk factors such as volume depletion, diuretic therapy, heart failure, and pre-existing renal dysfunction.[1]

1. Todd PA, Clissold SP. Naproxen: a reappraisal of its pharmacology, and therapeutic use in rheumatic diseases and pain states. *Drugs* 1990; 40: 91–137.
2. Caruana RJ, Semble EL. Renal papillary necrosis due to naproxen. *J Rheumatol* 1984; 11: 90–1.
3. Kovacevic L, *et al.* Renal papillary necrosis induced by naproxen. *Pediatr Nephrol* 2003; 18: 826–9.
4. Quigley MR, *et al.* Concurrent naproxen- and penicillamine-induced renal disease in rheumatoid arthritis. *Arthritis Rheum* 1982; 25: 1016–19.

Effects on the liver. There have been a few reports[1,2] of moderate to severe jaundice attributed to naproxen including one in which the patient also had a similar reaction with fenoprofen.[2]

1. Victorino RMM, *et al.* Jaundice associated with naproxen. *Postgrad Med J* 1980; 56: 368–70.
2. Andrejak M, *et al.* Cross hepatotoxicity between non-steroidal anti-inflammatory drugs. *BMJ* 1987; 295: 180–1.

Effects on the lungs. See Hypersensitivity, below.

Effects on the salivary glands. For reference to salivary gland swelling associated with naproxen therapy, see Hypersensitivity, below.

Effects on the skin. Cutaneous reactions reported in patients receiving naproxen include erythema nodosum,[1] lichen planus,[2] toxic pustular skin eruption,[3] bullous dermatosis,[4] and fixed drug eruption.[5] Photodermatitis, characterised by vesicle formation or increased skin fragility on sun-exposed skin, has been reported in adults[6-8] and children.[9,10]

A relapse of subacute cutaneous lupus erythematosus was reported to be possibly associated with naproxen.[11]

For reference to facial scars of unknown origin developing in children receiving NSAIDs, and in particular naproxen, see under NSAIDs, p. 107.1.

1. Grattan CEH, Kennedy CTC. Naproxen induced erythema nodosum. *BMJ* 1984; 288: 114.
2. Heymann WR, *et al.* Naproxen-induced lichen planus. *J Am Acad Dermatol* 1984; 10: 299–301.
3. Page SR, Grattan CEH. Pustular reaction to naproxen with cholestatic jaundice. *BMJ* 1986; 293: 510.
4. Bouldin MB, *et al.* Naproxen-associated linear IgA bullous dermatosis: case report and review. *Mayo Clin Proc* 2000; 75: 967–70.
5. Leivo T, Heikkilä H. Naproxen-induced generalized bullous fixed drug eruption. *Br J Dermatol* 2004; 151: 232.
6. Howard AM, *et al.* Pseudoporphyria due to naproxen. *Lancet* 1985; i: 819–20.
7. Rivers JK, Barrisetson RS. Naproxen-induced bullous photodermatitis. *Med J Aust* 1989; 151: 167–8.
8. Levy ML, *et al.* Naproxen-induced pseudoporphyria: a distinctive photodermatitis. *J Pediatr* 1990; 117: 660–4.
9. Parodi A, *et al.* Possible naproxen-induced relapse of subacute cutaneous lupus erythematosus. *JAMA* 1992; 268: 51–2.
10. Lang BA, Finlayson LA. Naproxen-induced pseudoporphyria in patients with juvenile rheumatoid arthritis. *J Pediatr* 1994; 124: 639–42.
11. Cox NH, Wilkinson DS. Dermatitis artefacta as the presenting feature of auto-erythrocyte sensitization syndrome and naproxen-induced pseudoporphyria in a single patient. *Br J Dermatol* 1992; 126: 86–9.

Hypersensitivity. In an early case-report in 11 aspirin-sensitive asthmatic patients, all developed reactions (rhinorrhoea, tightness of chest, wheezing, dyspnoea) after taking naproxen in low doses of 80 mg or less.[1] More recently, angioedema occurred after a single dose of naproxen in a patient known to be aspirin-sensitive.[2] Hypersensitivity to individual NSAIDs is believed to be closely linked to the extent to which these drugs inhibit prostaglandin synthesis (see under Aspirin, p. 25.2). There may therefore be a dose threshold below which no detectable symptoms occur. Such an effect has been reported[3] in a patient previously stabilised on naproxen for about one year who had a hypersensitivity reaction after a dosage increase.

A hypersensitivity reaction characterised by pulmonary infiltrates with eosinophilia[4,5] has been reported in patients taking naproxen. There has also been a report of a generalised hypersensitivity reaction with acute eosinophilic colitis in a 57-year-old woman treated with naproxen for osteoarthritis.[6] Bilateral swelling of the major salivary glands, a generalised rash, and eosinophilia suggestive of a hypersensitivity response was reported in another patient after use of naproxen.[7] Leucocytoclastic vasculitis with peripheral neuropathy and nephritis has also been noted in a 62-year-old woman after naproxen treatment.[8]

1. Szczeklik A, *et al.* Asthmatic attacks induced in aspirin-sensitive patients by diclofenac and naproxen. *BMJ* 1977; 2: 231–2.
2. Ghislain P-D, Ghislain E. Oedème de Quincke de la nuque induit par l'acide acétylsalicylique, avec réaction croisée pour le naproxène sodique. *Ann Med Interne (Paris)* 2000; 151: 227–9.
3. Briscoe-Dwyer L, Etzel JV. Dyspnea and periorbital edema following an increase in naproxen dose. *Ann Pharmacother* 1994; 28: 1110.
4. Nader DA, Schillaci RF. Pulmonary infiltrates with eosinophilia due to naproxen. *Chest* 1983; 83: 280–2.
5. Buscaglia AJ, *et al.* Pulmonary infiltrates associated with naproxen. *JAMA* 1984; 251: 65–6.
6. Bridges AJ, *et al.* Acute eosinophilic colitis and hypersensitivity reaction associated with naproxen therapy. *Am J Med* 1990; 89: 526–7.
7. Knuls AC, *et al.* Salivary gland swelling following naproxen therapy. *Br J Dermatol* 1995; 133: 647–9.
8. Schapira D, *et al.* Naproxen-induced leukocytoclastic vasculitis. *Clin Rheumatol* 2000; 19: 242–4.

Parkinsonism. For a report of a patient whose symptoms of Parkinson's disease were exacerbated by naproxen, see Effects on the CNS, above.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies naproxen as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 23/10/11)

Interactions

For interactions associated with NSAIDs, see p. 107.3.

The excretion of naproxen is delayed by probenecid resulting in raised plasma concentrations of naproxen.

Antiepileptics. For the effect of naproxen on the protein binding of *valproic acid*, see p. 557.2.

Pharmacokinetics

Naproxen and naproxen sodium are readily absorbed from the gastrointestinal tract. Peak plasma concentrations occur about 1 to 2 hours after ingestion of naproxen sodium and about 2 to 4 hours after ingestion of naproxen. Food reduces the rate but not the extent of absorption. Naproxen and naproxen sodium are also well absorbed rectally. At therapeutic concentrations naproxen is more than 99% bound to plasma proteins. Plasma concentrations of naproxen increase proportionally with dose up to about 500 mg daily; at higher doses there is an increase in clearance caused by saturation of plasma proteins. Naproxen diffuses into synovial fluid; it crosses the placenta and is distributed into breast milk in small amounts. Naproxen has a plasma elimination half-life of about 12 to 17 hours. About 95% of a dose is excreted in urine as naproxen and 6-*O*-desmethylnaproxen and their conjugates. Less than 5% of a dose appears in the faeces.

References.

1. Bruno R, *et al.* Naproxen kinetics in synovial fluid of patients with osteoarthritis. *Br J Clin Pharmacol* 1988; 26: 41–4.

2. Bertin P, *et al.* Sodium naproxen: concentration and effect on inflammatory response mediators in human rheumatoid synovial fluid. *Eur J Clin Pharmacol* 1994; 46: 3–7.
3. Davies NM, Anderson KE. Clinical pharmacokinetics of naproxen. *Clin Pharmacokinet* 1997; 32: 268–93.
4. Bowalgaha K, *et al.* S-Naproxen and desmethylnaproxen glucuronidation by human liver microsomes and recombinant human UDP-glucuronosyltransferases (UGT): role of UGT2B7 in the elimination of naproxen. *Br J Clin Pharmacol* 2005; 60: 423–33.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Aleve; Alidase; Bumaflex N; Congex; Debril; Fabralgina; Fadalivio; Flaxvan; Keldor; Melgar; Monarit; Mox; Naprofidex; Naprogen; Naprontag; Naprux; Neuralprona†; Tundra; *Austral.*: Anaprox; Chemists Own Period Pain; Crysanal; Femme Free; Inza; Naprogesic; Naprosyn; Proxen; Vimovo; *Austria*: Aleve; Miranax; Naprobene; Proxen; *Belg.*: Aleve; Apranax; Naproflam; Naprosyne; Vimovo; *Braz.*: Flanax; Napronax; Naprosyn; Naprox; Naxotec; *Canad.*: Aleve; Anaprox; Apo-Napro-Na; Maxidol; Naprelan; Naprosyn; Novo-Naprox†; Nu-Naprox; Vimovo; *Chile*: Atac; Deucoval; Eurogesic; Flogotone; Naprogesic; Triox NF; *China*: An Li; Ao Pu Li (澳普利); Bai Tong (柏通); Bei Li (倍利); Hui Ke (惠可); Jia Dan (佳丹); Jie Jie (杰潔); Jinkangpuli (金康普力); Na Pu Xing (那普星); Napton (那普洛); Qi Gu Ke (奇谷克); Shi Luo Te (适洛特); Tai Ze (泰泽); YuanQi (元奇); *Cz.*: Aleve; Emoxen; Nalgesin; Vimovo; *Denm.*: Bonyl; Vimovo; *Fin.*: Alpoxen; Miranax; Naprometin; Napromex; Naxopren; Pronaxen; Vimovo; *Fr.*: Alevetabs; Antalnox; Apranax; Naprosyne; *Ger.*: Alacetan NNA†; Aleve; Dolormin mit Naproxen; Dysmenalgit; Mobilat Schmerztabletten mit Naproxen†; Proxen; *Gr.*: Anaprox; Anexopen; Momendol; Naprosyn; Nopron; Nycopren; *Hong Kong*: Inza; Naprorex; Naprosyn†; Napxen†; Noflam-N; Soden; *Hung.*: Aleve; Apranax; Napmel; Naprosyn; *India*: Antesvel; Artagen; Easy Dayz; Movibon; Napexar; Napris; Naprosyn; Napryn; Naxen; Xenobid; *Indon.*: Naxen†; Synflex†; Xenifar; *Irl.*: Gerinap; Naprosyn; Synflex†; Vimovo; *Israel*: Naproxi; Narocin; Naxyn; Point; Vimovo; *Ital.*: Akudol; Aleve; Dropsen; Floginax; Gynestrel; Laser; Momendol; Napreben; Naprius; Naprocet; Naprossene; Naprosyn; Neo Eblimon; Nitens; Prexan; Provindol; Proxagol; Synalgo†; Synflex; Uninapro; Vimovo; Xenar; *Malaysia*: Apo-Napro-Na; Safrosyn S; Seladin; Sunprox; Synflex; *Mex.*: Actiquim; Analgen; Anapsyl†; Arsenal; Arxen; Atiflan†; Bioxan; Bixen; Dafloxen; Deflamox; Diferbest; Dolxen; Donaprox; Edem; Fagofen†; Faraxen; Flanax; Flavoxen; Flaxendol; Flogen; Fuxen†; Inflanox; Iqfasol; Luzapren; Messelxen; Naflapen†; Napoxol; Naprodil†; Navixen†; Naxen†; Naxopaar; Neonaxil; Novaxen; Pactens; Praxedol; Profaxen; Pronat†; Pronaxil; Pronoxen; Propional; Proxalin; Sertrixen; Sodixen; Tandax; Tanizona†; Unirelaxed†; Vantin; Velsay; *Neth.*: Aleve; Momendol; Naprelan†; Naprovite†; Vimovo; *Norw.*: Ledox†; Napren; Naprosyn†; Vimovo; *NZ*: Naprogesic; Naprosyn; Naxen; Noflam; Sonaflam; Synflex; Vimovo; *Philipp.*: Alpron; Flacidon; Flanax; Naflax; Napoxen; Naprelan†; Naprosyn; Sanomed; Skelan Protect; Skelan; *Pol.*: Aleve; Anapran; Apo-Napro; Boloxen†; DiFortan†; Natrax; Naxil; Tarproxen†; *Port.*: Momendol; Naprocet; Naprosyn; Reuxen; *Rus.*: Algezir (Алгезир); Nalgesin (Налгезин); *S.Afr.*: Acusprain†; Aleve; Nafasol; Napflam; Naproscript; Synflex; Traumox†; *Singapore*: Aleve; Apo-Napro-Na; Inza; Naprosyn; Nuprafen; Seladin; Soden; Soproxen; SP-Anflam; Sunprox; Synflex; Vimovo; *Spain*: Aleve; Aliviomast; Antalgin; Denaxpren†; Lundiran; Momen; Naprosyn; Tacron†; Vimovo; *Swed.*: Alpoxen†; Eox†; Naprosyn; Pronaxen; Vimovo; *Switz.*: Aleve; Apranax; Proxen; Vimovo; *Thai.*: Annoxen; Buproxen; Naproflex; Naprosian; Naprosyn; Napsen†; Nasin; Naxene; Polyxen; Prodaril-N; Proxen; Serviproxan†; Sonap; Soproxen; Synflex; Synogin; U-Proxyn†; Vinsen; *Turk.*: A-Nox; Aleve; Anaprotab; Apraljin†; Apranax; Aprodent; Aprol; Apromed; Aprowell; Armanaks; Atren; Bonmin; Exvile; Femidolor; Floneks; Inaprol; Kapnax; Karoksen; Mednap; Naponal; Napradol; Napren; Napro-Pac; Naprodev; Naprodex; Naprosyn; Naprotab; Opraks; Relokap; Romaksen; Rumazolidin†; Seroksen; Synax; Syndol†; *UK*: Arthroxen; Feminax Ultra; Napratec; Naprosyn; Period Pain Relief; Syndol Period Pain Relief; Synflex†; Vimovo; *Ukr.*: Cefecon N (Цефекон Н); Nalgesin (Налгезин); Promax (Промакс); *USA*: Aleve; Anaprox; Naprelan; Naprosyn; Prevacid NapraPAC†; Vimovo.

Multi-ingredient Preparations. *Arg.*: Naprontag Flex; Naprux Disten; Papasine; *China*: Gao Di (高迪); Pu Sen Ou Ke (普森欧克); Xi Tai Meng (西泰孟); *India*: Naprodom; Naxdom; Pacinac-NP; *Ital.*: Momendol; *Mex.*: Analgen Forte; Arsenal Compuesto; Arxen Compositum; Bifardol; Blocacid†; Brax; Bremol; Caridoxen; Caxidol; Contraxen; Dafloxen-F; Decosil; Deflamox Plus; Dolotandax; Drunen; Farxen; Febrax; Fiverdol; Flaxenol; Flucol†; Grifed; Kensedal; Movex; Naprodil Plus†; Naxodol†; Nedoxal; Neorpan Plus; Onexmol; Pensodil; Polet; Profenlax†; Proxalin Plus; Raxenol; Reucortil; Somalgesic; Taxenan†; Ulpafle-N; Velsay-S Compuesto; Viplus; Xenorac's; *Rus.*: Cefecon N (Цефекон Н); Pentalgin (Пенталгин); Pentalgin-N (Пенталгин-Н); Pyralgin (Пиралгин); *USA*: Treximet.

Pharmacopoeial Preparations

BP 2014: Gastro-resistant Naproxen Tablets; Naproxen Oral Suspension; Naproxen Suppositories; Naproxen Tablets;
USP 36: Naproxen Delayed-Release Tablets; Naproxen Oral Suspension; Naproxen Sodium Tablets; Naproxen Tablets.

Nefopam Hydrochloride

(BANM, USAN, rINNM)

Benzoxazocine; Fenazoxine; Hidrocloruro de nefopam; Nefopam, Chlorhydrate de; Nefopam, hidrocloruro de; Nefopami Hydrochloridum; R-738; Нефопама Гидрохлорид; 3,4,5,6-Tetrahydro-5-methyl-1-phenyl-1*H*-2,5-benzoxazocine hydrochloride.

$C_{17}H_{19}NO.HCl = 289.8$

CAS — 13669-70-0 (nefopam); 23327-57-3 (nefopam hydrochloride).

ATC — N02BG06.

ATC Vet — QN02BG06.

UNII — 685J48E13W.

Pharmacopoeias. In *Chin.*

Uses and Administration

Nefopam hydrochloride is a non-opioid analgesic considered to act centrally, although its mechanism of action is unclear. It also has some antimuscarinic and sympathomimetic actions. Nefopam hydrochloride is used for the relief of moderate acute and chronic pain. The usual oral dose range is 30 to 90 mg three times daily; the recommended initial dose is 60 mg (or 30 mg in elderly patients) three times daily. Nefopam hydrochloride may also be given in doses of 20 mg by intramuscular injection, repeated every 6 hours if necessary; it has been recommended that the patient should always be lying down when receiving the injection and should remain so for 15 to 20 minutes afterwards. It has also been given by slow intravenous injection in doses of 20 mg every 4 hours up to a maximum of 120 mg daily.

Hiccup. In three case series[1-3] involving 12 patients in total, hiccups refractory to standard therapy stopped after treatment with intravenous nefopam. For the management of intractable hiccups see under Chlorpromazine, p. 1046.3.

1. Bilotta P, Rosa G. Nefopam for severe hiccups. *N Engl J Med* 2000; 343: 1973–4.
2. Bilotta F, *et al.* Nefopam for refractory postoperative hiccups. *Anesth Analg* 2001; 93: 1358–60.
3. Pajot S, *et al.* Hiccup during weaning from mechanical ventilation: the use of nefopam. *Br J Anaesth* 2007; 99: 748–9.

Pain. Systematic reviews considered that there was little or no evidence to justify the use of nefopam as an analgesic for the management of postoperative pain.[1,2]

1. Evans MS, *et al.* Nefopam for the prevention of postoperative pain: quantitative systematic review. *Br J Anaesth* 2008; 101: 610–17.
2. Kakkar M, *et al.* Single dose oral nefopam for acute postoperative pain in adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2009 (accessed 28/07/10).

Shivering. Nefopam is one of several drugs tried[1-3] in the prevention of postoperative shivering (p. 1900.2).

1. Bilotta F, *et al.* Nefopam and tramadol for the prevention of shivering during neuraxial anesthesia. *Reg Anesth Pain Med* 2002; 27: 380–4.
2. Piper SN, *et al.* A comparison of nefopam and clonidine for the prevention of postanaesthetic shivering: a comparative, double-blind and placebo-controlled dose-ranging study. *Anaesthesia* 2004; 59: 559–64.
3. Bilotta F, *et al.* Nefopam or clonidine in the pharmacologic prevention of shivering in patients undergoing conscious sedation for interventional neuroradiology. *Anaesthesia* 2005; 60: 124–8.

Adverse Effects and Treatment

Adverse effects occurring with nefopam include gastrointestinal disturbances, such as nausea and vomiting, sweating, drowsiness, insomnia, urinary retention, dizziness, hypotension, tremor, paraesthesia, palpitations, lightheadedness, nervousness, confusion, blurred vision, headache, dry mouth, syncope, angioedema, allergic reactions, and tachycardia. Euphoria, hallucinations, and convulsions have occasionally been reported, as has temporary pink discoloration of the urine. Symptoms of overdosage have included CNS and cardiovascular toxicity.

Incidence of adverse effects. The French Pharmacovigilance System has reported[1] that, from January 1995 to December 2004, it had received 324 reports of adverse reactions associated with the use of nefopam. The most frequently reported reactions were sweating (15 cases), nausea (10 cases), tachycardia (8 cases), malaise (6 reports), and vomiting (5 cases). Unexpected reactions included hallucinations (11 cases), confusion (11 cases), cutaneous reactions such as erythema (7 cases), pruritus (4 cases), and urticaria (3 cases), and anaphylactic reactions including anaphylactic shock (4 cases) and angioedema (2 cases). The anaphylactic reactions were reported to have occurred shortly after nefopam was given during the postoperative period. There was a single case of fatal convulsion and no cases of overdosage had been reported (but see below).

1. Durrieu G, *et al.* French Network of Pharmacovigilance Centers. Overview of adverse reactions to nefopam: an analysis of the French Pharmacovigilance database. *Fundam Clin Pharmacol* 2007; 21: 555–8.

Effects on the urinary tract. In January 1989, the UK CSM[1] reported that it had received 53 reports in which nefopam was associated with the development of urinary retention or symptoms of hesitancy, poor stream, or dribbling. In one case there was a history of prostatism.

1. *CSM. Nefopam hydrochloride (Acupan). Current Problems 24* 1989. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024431&RevisionSelectionMethod=LatestReleased (accessed 14/07/08)

Overdosage. There have been reports of fatal overdoses with nefopam.[1-4] One report[1] also provided details of 9 other patients who recovered with routine supportive treatment.

1. Piercy DM, *et al.* Death due to overdose of nefopam. *BMJ* 1981; 283: 1508–9.
2. Urwin SC, Smith HS. Fatal nefopam overdose. *Br J Anaesth* 1999; 83: 501–2.
3. Tracqui A, *et al.* Fatal overdosage with nefopam (Acupan). *J Anal Toxicol* 2002; 26: 239–43.
4. Kerr DE, Fletcher AK. Fatal nefopam overdose. *Emerg Med J* 2010; 27: 407–8.

Precautions

Nefopam is contra-indicated in patients with a history of convulsive disorders. It should be used with caution in the elderly and in patients with glaucoma, urinary retention, or impaired hepatic or renal function.

Abuse. Abuse of parenteral nefopam has been reported in 3 patients with a history of chronic pain.[1] Psychostimulant-like symptoms such as agitation, impatience, and violence, were noted in 2 of the patients; antimuscarinic effects were also seen. All 3 patients were found to be psychologically dependent; in 2 who attempted to stop nefopam, withdrawal symptoms were noted.

1. Villier C, Mallaret MP. Nefopam abuse. *Ann Pharmacother* 2002; 36: 1564–6.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving nefopam, and the last available guidance from the American Academy of Pediatrics considered[1] that it is therefore usually compatible with breast feeding.

Studies in 5 healthy nursing mothers given nefopam for post-episiotomy pain indicated that nefopam was present in human milk in an equivalent concentration to that in plasma.[2] It was calculated that on a body-weight basis a breast-fed infant would receive less than 3% of the maternal dose.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/10/06)
2. Liu DTY, *et al.* Nefopam excretion in human milk. *Br J Clin Pharmacol* 1987; 23: 99–101.

Renal impairment. Following a single dose of nefopam 20 mg, given as an intravenous infusion, the clearance of nefopam was found to be reduced in 12 patients with end-stage renal disease (ESRD) when compared with aged-matched healthy subjects;[1] peak plasma concentrations of nefopam were also significantly higher in those with ESRD. The authors recommended that a 50% dosage reduction should be considered in those with severe renal impairment.

1. Mimoz O, *et al.* Nefopam pharmacokinetics in patients with end-stage renal disease. *Anesth Analg* 2010; 111: 1146–53.

Interactions

It has been recommended that nefopam should not be given to patients receiving MAOIs and should be used cautiously in those receiving tricyclic antidepressants. The adverse effects of nefopam may be additive to those of other drugs with antimuscarinic or sympathomimetic activity.

Pharmacokinetics

Nefopam is absorbed from the gastrointestinal tract. Peak plasma concentrations occur 1 to 3 hours after an oral dose and up to 1 hour after intramuscular injection. About 73% is bound to plasma proteins. Nefopam is distributed into breast milk. It has an elimination half-life of about 4 hours. It is extensively metabolised and excreted mainly in urine, in which less than 5% of a dose is excreted unchanged. About 8% of a dose is excreted via the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Acupan; *China*: Fu Lu Ke (福卢可); Fu Lu Na (福卢纳); Hong Kang Wei Si (弘康威司); Shengfu (圣福); *Fr.*: Acupan; *Gr.*: Leoplexamin; Pallopikeron; *Irl.*: Acupan; *NZ*: Acupan; *Rus.*: Oxadol (Оксадол); *UK*: Acupan; *Ukr.*: Acupan (Акупан).

Nepafenac *(BAN, USAN, rINN)*

AHR-9434; AL-6515; Népafénac; Nepafenaco; Nepafenacum; Непафенак.

2-(2-Amino-3-benzoylphenyl)acetamide.

$C_{15}H_{14}N_2O_2$=254.3

CAS — 78281-72-8.

ATC — S01BC10.

ATC Vet — QS01BC10.

UNII — 0J9L7J6V8C.

Profile

Nepafenac, an NSAID (p. 102.3), is a prodrug of amfenac (p. 20.3). It is used in the treatment of pain and inflammation following cataract surgery. An ophthalmic suspension containing nepafenac 0.1% is instilled 3 times daily starting on the day before surgery and continuing for 2 weeks after surgery, to a maximum of 3 weeks if necessary. An additional drop should be instilled 30 to 120 minutes before surgery.

References.

1. Colin J, Paquette B. Comparison of the analgesic efficacy and safety of nepafenac ophthalmic suspension compared with diclofenac ophthalmic solution for ocular pain and photophobia after excimer laser surgery: a phase II, randomized, double-masked trial. *Clin Ther* 2006; **28**: 527–36.
2. Lane SS. Nepafenac: a unique nonsteroidal prodrug. *Int Ophthalmol Clin* 2006; **46**: 13–20.
3. Lane SS, *et al.* Nepafenac ophthalmic suspension 0.1% for the prevention and treatment of ocular inflammation associated with cataract surgery. *J Cataract Refract Surg* 2007; **33**: 53–8. Correction. *ibid.*: 564.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Nevanac; *Braz.*: Nevanac; *Canad.*: Nevanac; *Chile*: Nevanac; *Cz.*: Nevanac; *Denm.*: Nevanac; *Gr.*: Nevanac; *India*: Nevanac; *Irl.*: Nevanac; *Israel*: Nevanac; *Jpn*: Nevanac; *Malaysia*: Nevanac; *Mex.*: Nevanac; *Neth.*: Nevanac; *Norw.*: Nevanac; *NZ*: Nevanac; *Philipp.*: Nevanac; *Pol.*: Nevanac; *Port.*: Nevanac; *Singapore*: Nevanac; *Spain*: Nevanac; *Swed.*: Nevanac; *Switz.*: Nevanac; *Thai.*: Nevanac; *Turk.*: Nevanac; *UK*: Nevanac; *USA*: Ilevro; Nevanac.

Nicoboxil *(rINN)*

Butoxyethyl Nicotinate; Nicoboxilo; Nicoboxilum; Никобоксил.

2-Butoxyethyl nicotinate.

$C_{12}H_{17}NO_3$=223.3

CAS — 13912-80-6.

UNII — GSD589US0W.

Profile

Nicoboxil is a nicotinate used in topical preparations as a rubefacient. It is also included in some topical preparations used for the treatment of acne vulgaris.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Finalgon; *Austria*: Finalgon; *Ger.*: Finalgon; *Gr.*: Finalgon; *Ital.*: Anti-Acne; *Port.*: Finalgon; *Rus.*: Betalgon (Беталгон); Betanicomylon (Бетаникомилон); Finalgon (Финалгон); *UK*: Actinact†; *Ukr.*: Finalgon (Финалгон).

Nicomorphine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de nicomorfina; Nicomorfina, hidrocloruro de; Nicomorphine, Chlorhydrate de; Nicomorphini Hydrochloridum; Никоморфина Гидрохлорид.

3,6-Di-O-nicotinoylmorphine hydrochloride; (-)-(5*R*,6*S*)-4,5-Epoxy-9a-methylmorphin-7-en-3,6-diyl dinicotinate hydrochloride.

$C_{29}H_{25}N_3O_5$,HCl=532.0

CAS — 639-48-5 (nicomorphine); 12040-41-4 (nicomorphine hydrochloride); 35055-78-8 (nicomorphine xHCl).

ATC — N02AA04.

ATC Vet — QN02AA04.

Profile

Nicomorphine hydrochloride is an opioid analgesic (p. 108.1) used in the treatment of moderate to severe pain. It is given in oral doses of 5 to 10 mg daily or by intramuscular, slow intravenous, or subcutaneous injection in doses of 10 to 20 mg; higher doses have also been used. It may also be given rectally in usual doses of 10 to 20 mg daily.

References.

1. Koopman-Kimenai PM, *et al.* Pharmacokinetics of intravenously administered nicomorphine and its metabolites in man. *Eur J Anaesthesiol* 1993; **10**: 125–32.
2. Koopman-Kimenai PM, *et al.* Rectal administration of nicomorphine in patients improves biological availability of morphine and its glucuronide conjugates. *Pharm World Sci* 1994; **16**: 248–53.
3. Koopman-Kimenai PM, *et al.* The bioavailability of intramuscularly administered nicomorphine (Vilan) with its metabolites and their glucuronide conjugates in surgical patients. *Int J Clin Pharmacol Ther* 1995; **33**: 442–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Vilan; *Denm.*: Vilan; *Neth.*: MorZet; *Switz.*: Vilan.

Niflumic Acid *(BAN, rINN)*

Acide Niflumique; Ácido niflúmico; Acidum niflumicum; Niflúmico, ácido; Niflumińsäure; UP-83; Нифлумовая Кислота.

2-(aαα-Trifluoro-*m*-toluidino)nicotinic acid.

$C_{13}H_9F_3N_2O_2$=282.2

CAS — 4394-00-7.

ATC — M01AX02; M02AA17.

ATC Vet — QM01AX02; QM02AA17.

UNII — 4U5MP5IUD8.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Niflumic Acid). A pale yellow, crystalline powder. Practically insoluble in water; soluble in alcohol and in methyl alcohol; freely soluble in acetone.

Uses and Administration

Niflumic acid, a nicotinic acid derivative, is an NSAID (p. 102.3). It has been used in inflammatory and musculoskeletal and joint disorders in usual oral doses of about 250 mg three or four times daily; up to 1500 mg daily has been used in severe disorders. It has also been used topically as a 3% ointment or 2.5% gel. The morpholinoethyl ester, morniflumate (p. 92.2), has similar uses.

Niflumic acid glycinamide has been used topically in inflammatory mouth disorders.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3.

Fluoride-associated osteosis has been reported with prolonged use. Niflumic acid should be stopped if hypersensitivity skin reactions appear.

Effects on the skin. From a case-control study[1] of children admitted to a hospital emergency department in Italy it was calculated that the odds-ratio of users of niflumic acid, or its derivative morniflumate, developing serious cutaneous reactions was 4.9. Given this figure and the fact that safer drugs were available the authors considered that there was no indication for which niflumic acid was required in children. However, a large cohort study[2] involving 193 727 children aged between 0 and 14 years found that niflumic acid was not associated with a higher risk of mucocutaneous reactions when compared with other NSAIDs or paracetamol. The authors of the later study suggested that the conclusions of the original study may have been confounded because there was no adjustment for age or indication.

1. Menniti-Ippolito F, *et al.* Niflumic acid and cutaneous reactions in children. *Arch Dis Child* 2001; **84**: 430–1.
2. Sturkenboom M, *et al.* Incidence of mucocutaneous reactions in children treated with niflumic acid, other nonsteroidal antiinflammatory drugs, or nonopioid analgesics. Abstract: *Pediatrics* 2005; **116**: 212. Full version: http://pediatrics.aappublications.org/cgi/content/full/116/1/e26 (accessed 08/11/07)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Flogovital; *Belg.*: Niflugel; *Cz.*: Niflugel†; Nifluril†; *Fr.*: Niflugel; Nifluril; *Gr.*: Chrispapon; Livornex; Myoskelet; Niflamol; Novopone; Radiogen; Sariu; *Hung.*: Donalgin; *Ital.*: Niflam; *Port.*: Nifluril; *Rus.*: Donalgin (Доналгин); *Spain*: Niflactol.

Multi-ingredient Preparations. *Arg.*: Flogodisten.

Nimesulide *(BAN, rINN)*

Nimesulid; Nimesulida; Nimesulidas; Nimésulide; Nimesulidi; Nimesulidinum; Nimesulidum; Nimeszulid; R-805; Нимесулид.

4'-Nitro-2'-phenoxymethanesulphonanilide.

$C_{13}H_{12}N_2O_5S$=308.3

CAS — 51803-78-2.

ATC — M01AX17; M02AA26.

ATC Vet — QM01AX17; QM02AA26.

UNII — V4TKW1454M.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Nimesulide). A yellowish crystalline powder. It exhibits polymorphism. Practically insoluble in water; slightly soluble in dehydrated alcohol; freely soluble in acetone.

Profile

Nimesulide is an NSAID (p. 102.3) reported to be a selective inhibitor of cyclo-oxygenase-2 (COX-2). It is used to treat acute pain and dysmenorrhoea in oral doses of up to 100 mg twice daily; use in the EU is limited to second-line treatment for a maximum of 15 days due to reports of hepatotoxicity (see Adverse Effects, below). It has also been given rectally in a dose of 200 mg twice daily. In the symptomatic treatment of sprains and tendinitis nimesulide has been applied topically as a 3% gel.

Nimesulide betadex (nimesulide betacyclodextrin complex) has been used similarly.

References.

1. Bennett A, *et al.* Nimesulide: a multifactorial therapeutic approach to the inflammatory process? A 7-year clinical experience. *Drugs* 1993; **46**: (suppl 1): 1–283.
2. Senna GE, *et al.* Nimesulide in the treatment of patients intolerant of aspirin and other NSAIDs. *Drug Safety* 1996; **14**: 94–103.
3. Vizzardi M, *et al.* Nimesulide beta cyclodextrin (nimesulide-betadex) versus nimesulide in the treatment of pain after arthroscopic surgery. *Curr Ther Res* 1998; **59**: 162–71.
4. Bernareggi A. Clinical pharmacokinetics of nimesulide. *Clin Pharmacokinet* 1998; **35**: 247–74.
5. Shah AA, *et al.* Selective inhibition of COX-2 in humans is associated with less gastrointestinal injury: a comparison of nimesulide and naproxen. *Gut* 2001; **48**: 339–46.
6. Nüling RM, *et al.* Pathogenetic role of cyclooxygenase-2 in hyperprostaglandin E syndrome/antenatal Bartter syndrome: therapeutic use of the cyclooxygenase-2 inhibitor nimesulide. *Clin Pharmacol Ther* 2001; **70**: 384–90.

Adverse effects. Although *thrombocytopenia* is a common feature in patients infected with HIV, a group of workers considered that thrombocytopenia in one of their patients was related to the use of nimesulide.[1]

There have been reports[2-4] of *hepatotoxicity* after treatment with nimesulide. Data from spontaneous reports have also suggested that nimesulide may be associated with a higher risk of hepatotoxicity than other NSAIDs.[4] A cohort study[5] involving about 400 000 users of NSAIDs in one region of Italy between 1997 and 2001 found that those taking nimesulide were 1.3 times more likely to develop hepatotoxicity than users of other NSAIDs and 1.9 times more likely to suffer severe liver injury. Reports of serious hepatotoxicity had led to the suspension of marketing authorisations of nimesulide in Finland and Spain in 2002. This issue was also reviewed by the EMEA[6] and in 2004 they reported that the risk/benefit ratio for nimesulide remained favourable; however, they recommended that its indications be restricted to acute pain, dysmenorrhoea, and osteoarthritis for systemic formulations, and to the relief of sprains and tendinitis for topical formulations. It was also recommended that the oral dose be reduced to a maximum of 100 mg twice daily. Subsequently, in May 2007 the Irish regulatory authority withdrew systemic formulations of nimesulide from the Irish market after concerns about hepatotoxicity.[7] Since being licensed in 1995, nimesulide had generated 53 adverse reaction reports involving liver toxicity, including 9 cases of liver failure, 3 of which resulted in death and 6 in liver transplantation; there had also been 1 other liver-related fatality. The withdrawal prompted another review by the EMEA[8] which concluded that the risk/benefit ratio of systemic formulations of nimesulide was still favourable; however, since most hepatic reactions were noted after 2 weeks of treatment, it was recommended that treatment with nimesulide should be limited to 15 days. After a full assessment of the risks and benefits of nimesulide, in 2011, the EMEA[9] further restricted the indications of systemic formulations to second-line treatment of acute pain and dysmenorrhoea only; use in osteoarthritis was no longer recommended.

There have been reports[10,11] of *toxic pustuloderma* (acute generalised exanthematous pustulosis) with oral nimesulide. *Fixed drug eruptions* have also been seen.[12]

An infant developed hypotension and hypothermia after inadvertently taking an *overdose* of 8 times the recommended daily dose of nimesulide.[13] The patient recovered

after gastric lavage with activated charcoal and supportive therapy.

1. Pastieci MB, *et al.* Nimesulide, thrombocytopenic purpura, and human immunodeficiency virus (HIV) infection. *Ann Intern Med* 1990; 112: 233–4.
2. McCormick PA, *et al.* COX 2 inhibitor and fulminant hepatic failure. *Lancet* 1999; 353: 40–1.
3. Sheit W, *et al.* Nimesulide-induced acute hepatitis. *Ann Pharmacother* 2001; 39: 1049–52.
4. Maciá MA, *et al.* Hepatotoxicity associated with nimesulide: data from the Spanish pharmacovigilance system. *Clin Pharmacol Ther* 2002; 72: 596–7.
5. Traversa G, *et al.* Cohort study of hepatotoxicity associated with nimesulide and other non-steroidal anti-inflammatory drugs. *BMJ* 2003; 327: 18–22.
6. EMEA. CPMP opinion following an article 31 referral: nimesulide containing medicinal products (issued 7th May, 2004). Available at: http://www.ema.europa.eu/pdfs/human/referral/nimesulide/172404en.pdf (accessed 08/04/10)
7. Irish Medicines Board. Immediate suspension of the marketing of medicines containing nimesulide (issued 15th May, 2007). Available at: http://www.imb.ie/EN/Safety-Quality/Advisory-Warning-Recall-Notices/Human-Medicines/Nimesulide-Suspension.aspx?page=1&noticetypeid=-1&year=2007 (accessed 08/11/07)
8. EMEA. Questions and answers on the CHMP recommendation on nimesulide-containing medicines (issued 21st September, 2007). Available at: http://www.emea.europa.eu/pdfs/human/opinion/43098807en.pdf (accessed 08/11/07)
9. EMEA. Questions and answers on the review of systemic medicines containing nimesulide (issued 20th January, 2012). Available at: http://www.emea.europa.eu/docs/en_GB/document_library/Referrals_document/Nimesulide_31/WC500107957.pdf (accessed 23/08/12)
10. Lateo S, Boffa MJ. Localized toxic pustuloderma associated with nimesulide therapy confirmed by patch testing. *Br J Dermatol* 2002; 147: 624–5.
11. Teixeira M, *et al.* Acute generalized exanthematous pustulosis induced by nimesulide. *Dermatol Online J* 2006; 12: 20. Available at: http://dermatology.cdlib.org/126/case_presentations/agep/teixeira.html (accessed 08/11/07)
12. Malheiro D, *et al.* Nimesulide-induced fixed drug eruption. *Allergol Immunopathol (Madr)* 2005; 33: 285–7.
13. Yapakci E, *et al.* Hypoglycaemia and hypothermia due to nimesulide overdose. *Arch Dis Child* 2001; 85: 510.

Pregnancy. Irreversible *end-stage renal failure* has been reported in a neonate born to a mother given nimesulide as a tocolytic from the 26th to the 32nd week of pregnancy.[1] Others have reported neonatal renal failure associated with nimesulide.[2] *Premature closure of the ductus arteriosus* leading, in some cases, to *persistent pulmonary hypertension* has also been seen in 10 neonates whose mothers self-medicated with nimesulide during the third trimester of pregnancy.[3]

1. Peruzzi L, *et al.* Neonatal end-stage renal failure associated with maternal ingestion of cyclo-oxygenase-type-2 selective inhibitor nimesulide as tocolytic. *Lancet* 1999; 354: 1615. Correction. *ibid.* 2000; 355: 238.
2. Balasubramaniam J. Nimesulide and neonatal renal failure. *Lancet* 1999; 355: 575.
3. Paladini D, *et al.* Severe ductal constriction in the third-trimester fetus following maternal self-medication with nimesulide. *Ultrasound Obstet Gynecol* 2005; 25: 357–61.

Premature labour. Nimesulide has been tried as an alternative to indometacin to delay labour in patients with a history of preterm delivery (p. 2131.1). Nimesulide was given from 16 to 34 weeks of gestation and a successful delivery started 6 days after withdrawal.[1] There appeared to be no adverse effect on fetal renal function or the ductus arteriosus. The authors suggested that fetal prostaglandin synthesis might be mainly mediated through cyclo-oxygenase-1 (COX-1) and that a relatively selective COX-2 inhibitor such as nimesulide might produce fewer adverse effects on the fetus than other non-selective NSAIDs. However, in a small study short-term effects on the fetus were similar for nimesulide, indometacin, and sulindac.[2]

Adverse effects have been reported in some neonates whose mothers received nimesulide during their pregnancies, see above.

1. Sawdy R, *et al.* Use of a cyclo-oxygenase type-2-selective non-steroidal anti-inflammatory agent to prevent preterm delivery. *Lancet* 1997; 350: 265–6.
2. Sawdy RJ, *et al.* A double-blind randomized study of fetal side effects during and after the short-term maternal administration of indomethacin, sulindac, and nimesulide for the treatment of preterm labor. *Am J Obstet Gynecol* 2003; 188: 1046–51.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Aldoron; Flogovital NF; Virobron; *Austria*: Aulin†; *Belg.*: Mesulid; *Braz.*: Arflex; Cimelide; Deflogen; Deltaflan; Fasulide; Inflalid; Maxsulid; Mesalgin; Neosulida; Nimalgex; Nimesilam; Nimesubal; Nimesulin; Nimesulix; Nimesulon; Nisalgen; Nisoflan; Nisufar; Nisuflex; Nisulid; Nizuil; Prexulid; Scaflam; Scalid; Sintalgin; Sulonil; *Chile*: Ainext; Doloc; Nimepast; Nimesyl; Nisulid; Nisural; *China*: Anjielishu (安洁力舒); BangNi (邦尼); Fu Mei Shu (孚美舒); Hua Shuang Jie (化双节); Huang Xing Yun Shu (皇星云舒); Li Nuo Ke (利诺刻); Li Shu Tong (力舒同); Nuo Zheng (诺正); Pu Fei Te (普菲特); Pu Wei (普威); Rui Li (锐丽); Rui Pu Le (瑞普乐); Rui Zhi Li (瑞芝利); Rui Zhi Qing (瑞芝清); Sai Pu Da (赛扑达); Shan Yi Ting (山易亭); Si Rui (斯瑞); Surong (苏榕); Tengke (腾克); Xianleke (先乐克); Yi Mei Li (怡美力); Yi Ya Xuan (益雅轩); *Cz.*: Aulin; Coxtral; Mesulid; Nimed; Nimesil; *Fr.*: Nexen; *Gr.*: Aflogen; Alencast; Algosulid; Algover; Amocetin; Aulin; Auromelid; Bioxidol; Chemisulide; Cliovyl; Discorid; Dolostop; Edrigyl; Elinap; Erlecit; Erreflog; Fladalgin; Flogostop; G-Revm; Kartal; Lalide; Lasazin; Lemesil†; Lizepat; Londopon; Lovirem; Melicate; Melimont; Mesilex; Mesulid; Mesupon; Min-A-Pon; Mosuolit; Multiformil; Myxina; Naofid; Neo-Lemesil; Niberan; Nimegel; Nimelide; Nimesul; Omnibus; Rhemid; Ristolzit; Ritamine; Rolaket; Scaflam; Specilid; Sudinet; Tranzicalm; Ventor; Volonten; *Hong Kong*: Mesulid; Nidol; Nimm; *Hung.*: Mesulid; Nidol; Nimelid; Xilox; *India*: Actinim; Adenim; Aglonim; Anafebrin; Anim; Antipen; Arinox-MD; Arsulide; Arthorid; Asilid; Auronim; Avinim; Benice-DT; Benim; Bestonim; Beta Nicip; Bio-Nim; Blisulide; Boflam; Brinimo; C-Nim; Canmet; Caslide; Ceralide-MD; Colide; Cunim; Dardnil; Delnim MD; Denim MD; Denim; Dolide; Dolonim; E-Nim-MD; Elide; Elnim-MD; Emsulide; Fenim; Fonim MD; Genlide; Gesnim; Hilyte; Kind-MD; Ladex; Lupisulide; Mangolide; Maxiflam; Maxulide; Mesulid; Milenim; Monogesic; Movinim-MD; Myonal; N-Lid; N-Side; Nam; Namosid; Nap; Nayanim; Neem-MD; Neet; Nelsid; Nemeriv; Nemil; Nemon; Neulab; Neulide; New Nicip; Ni-MD; Nicip; Nikee; Nile; Nilide; Nilup; Nimace-MD; Nimact; Nimagyl; Nimaid; Nimat; Nimbid; Nimbu; Nimbus; Nimcet; Nimdal; Nimdard; Nimeb; Nimegesic; Nimel; Nimeril; Nimesel; Nimesis-MD; Nimfast; Nimi; Nimica; Nimind CT; Nimiz; Nimkair; Nimkul; Nimlak-MD; Nimley-MD; Nimlid-MD; Nimlodi; Nimobid; Nimodol; Nimofen; Nimogem; Nimoril; Nimotas-CD; Nimpain-MD; Nimpic; Nimpure-MD; Nimras-MD; Nimriz; Nimsaid; Nimsutech; Nimtop; Nimucare; Nimuda; Nimulex-FD; Nimulid; Nimupain; Nimupet; Nimustar; Nimusym; Nimusyp; Nimutab; Nimutal; Nimvar-MD; Nimven-MD; Nimvista; Nisba; Nise; Nisulid; Nizapas-MD; Nizer; NMD; Nobel; Nodard; Nom; Novigan-M; Novolid; Nugesic; Nuleb; Nulide; Numel; Onalide-MD; Onim-MD; Orthobid; Osonim; Panim; Pansulide RD; Willgo; *Indon.*: Arnid†; Aulin†; Nicox†; Nimed; Nimost†; Sohoflam†; Ximede; *Irl.*: Aulin; Mesulid†; *Israel*: Mesulid; *Ital.*: Actalide; Algimesil; Algolider; Antalor; Areuma; Aulin; Delfos; Dimesul; Domes; Efridol; Erreflog; Eudolene†; Fansulide; Flolid; Isodol; Ledoren; Mesulid; Nerelid; Nimedex; Nimenol†; Nimesulene; Nims; Oronime; Pantames; Remov; Solving; Sulidamor; Sulide; *Malaysia*: Precoxi; *Mex.*: Apolide; Cargespril; Defam; Degorflan; Dexlin; Eskaflam; Fenoxil; Flamide; Flamozin; Igrexa; Inim; Lesiden; Lusemin; Medani; Meliden; Mesulid; Minus; Nidolin; Nilden; Nilid; Nimepis; Nizurin; Quidofril; Redaflam; Severin; Sidel†; Sindel; Sulidek; Sulidol-GB; Sundir; Ul-Flam; *Philipp.*: Aulin†; Flamesul†; Mesulid†; Nidolid; Sorinil†; Sulidin; *Pol.*: Aulin; Coxtral; Minesulin; Nimesil; *Port.*: Aulin; Donulide; Gerilide; Jabasulide; Nilmide; Nimalge†; Nimartin†; Nimed; Nimesulene; Reumolide; Sulidor; Sulimed†; Vitolide†; *Rus.*: Actasulid (Актасулид); Aponil (Апонил); Auronim (Ауроним); Coxtral (Кокстрал); Flolid (Фолид); Nimesil (Нимесил); Nimica (Нимика); Nimulid (Нимулид); Nise (Найз); Prolid (Пролид); *Switz.*: Aulin; Nisulid; *Thai.*: Emdon; Nemil-Os†; Neptide; Nidol; Nilide; Nimill; Nimind†; Nimlide; Nimo†; Nimulid; Veedol; *Turk.*: Coxulid; Mesulid†; Motival; Nimelid; Nimes; Romasulid; Sulidin; *Ukr.*: Nimegesic (Нимегезик); Nimesil (Нимесил); Nise (Найз); Remesulid (Ремесулид)†; Remisid (Ремисид); *Venez.*: Ainex; Aulin; Drexel; Nimecox; Nimelid; Reduben; Scaflan.

Multi-ingredient Preparations. *Arg.*: Mio Aldoron; Mio-Virobron; *India*: Adenim Plus; Adenim-MR; Adnim-P; Aldee-P; Alsolide Plus; Alsolide-MR; Amidase-N; Anafortan-N; Anim-P; Anm-P; Antipen-T; Arinox Plus; Arnim-P; Arsulide-D; Arsulide-P; Arsulide-S; Arthorid; Artifen; Asilid Relief; Avinim Plus; Avinim-MR; Axinim; Baselide; Benim-P; Bestogesic MR; Bestogesic; Bestonim P; Biozobid-N; C-Nim Plus; Cadiflam-NP; Cadpo-N; Canmet-MR; Canmet-P; Canmet-SN; Carnil MR; Carnil Plus; Caslide-P; Ceralide-P; Cipzen N; Citanz; Cofev; Comspa; Cranim-P; Cunim Plus; Cuzen-NM; Cyclozed-N; Cyclozobid; Dacnis N; Dardnil-P; Delnim-P; Delnim-SP; Denim P; Denim Plus; Densera-N; Diplonim-MR; Diplonim; Dizer-N; Dolamide; Dolide Plus; Doloflam Plus; Doloflam-MR; Dolospan; Drolid; DS-15 Plus; Dyspas; E-Nim Plus; Edase-N; Elnim-D; Emanzen-N; Emsulide-Fen; Emsulide-P; Etiza; Fedol; Fevni-P; Flamar-P; Flozen-NS; Flupara-N; Flupara-SN; Fonim-P; Fonim-S; Genlide Plus; Gesnim-MR; Gesnim-P; Gesnim-S; Gonim; GSNim-P; Hilyte-P; Hitz-NP; Imosan; Imsimol; Indlide; Ingesic-MR; Ingesic-P; Inslide; Itzgon; Jumo; Jumocip; Kaylid-P; Khalli; Kind Plus; Ladex-P; Lebec-NP; Leebec-NP; Litnim; Lupisulide MR; Lupisulide-D; Lupisulide-P; Maxiflam-SP; Maxonim-P; Meriflam; Mesu-P; Minipar-P; Minipar-SP; Minipar-TZ; Minsu-P; Molide; Molulid; Mortrin-T; Movinim-P; Movinim-S; N-Plus; N-S-Plus; Nam Cold-L; Nam Cold-SR; Nam Cold; Nam-P; Nam; Namplus; Namsafe; Nap Plus; Need; Neet Plus; Neet-S; Nefter; Nelsid Fort; Nelsid Plus; Nelsid-MR; Nelsid-S; Nelsid; Nemeriv-P; Nency-P; Neomol-MR; Neomol-XP; Neosulide Plus; Nepar; Neulab Active; Neulab D; Neulab-MR; Neurophen-Compound; Nevis-P; Niap; Nicet; Niciflex-T; Nicip Cold; Nicip D; Nicip MR; Nicip Plus; Nicip Supergel; Nicip T; Nicispas; Nidic; Nifen MR; Nifen Plus; Nifen; Nile Plus; Nile-CZ; Nile-P; Nile-S; Nile-SP; Nile-TZ; Nilup-P; Nim-MR; Nimace-P; Nimace-SP; Nimagyl-PC; Nimaid-P; Nimat-MR; Nimat-Plus; Nimbra Plus; Nimbus Plus; Nimcare-A; Nimcet Plus; Nimcin-P; Nimdard Plus; Nimdase-P; Nimdase; Nimdin; Nimeb-P; Nimegesic-P; Nimelide Fen; Nimeril-T; Nimesel-P; Nimesis-P; Nimeter-A; Nimetiz; Nimi-LB; Nimica Plus; Nimitiz; Nimiz-Plus; Nimkair-P; Nimkul DCM; Nimkul Para; Nimkul SP; Nimkul-CZ; Nimkul-MR; Nimlak-Plus; Nimley-P; Nimley-S; Nimli-P; Nimlid-P; Nimnil-P; Nimodex; Nimodia-P; Nimofen-P; Nimofen-T; Nimopace; Nimotas-P; Nimotiz MR; Nimoven; Nimpa; Nimpain P; Nimpain PS; Nimpain T; Nimpar; Nimpara; Nimpep; Nimpure-P; Nimpure-PS; Nimriz Plus; Nims-P; Nimsaid-P; Nimsaid-S; Nimsaid-T; Nimsol Plus; Nimspa; Nimspas; Nimtech; Nimtiz-MR; Nimucare-P; Nimucetfen; Nimucet-MR; Nimucet; Nimucold; Nimudin; Nimuflex-MR; Nimuflex-P; Nimulid MR; Nimulid Nugel; Nimulid SP; Nimumol-P; Nimupain Plus; Nimuris-Plus; Nimuspas; Nimustar-P; Nimustar-S; Nimusym-Plus; Nimutal-Plus; Nimvar Plus; Nimvar-MR; Nimven Plus; Nimven-S; Nimven-T; Nimvista Plus; Nimvista-D; Nimvista-MR; Nimvon-S; Nisba Plus; Nise Gel; Nise-MR; Niser; Niza-Spas; Nizapas-MR; Nizapas-P; Nizapas-SP; Nizi; Nobel Plus; Nobel Spas; Nobel-MR; Nodard Plus; Noflam P; Nom-P; Normal; Norpy; Novolid-MR; Novolid-S; Nozy Cold; NP.Com; NPM; Nugesia; Nupar; Onalide-MR; Opel Plus; Opel-MR; Orthobid Plus; Orthobid-MR; Orthodex-MR; Osnip; Osonim-P; Ospas; Oxin Plus; Oxyprem; Pacimol Plus; Panum-P; Panum-SP; Paralide; Paratel-NP; Parazolandin; *Mex.*: Amoxiclide; Zitroflam; *Ukr.*: Inflarax (Инфлараис); Nizer (Найзер)†.

Nonivamide *(rINN)*

Nonivamida; Nonivamidum; Noniwamid; Nonylvanillamide; PAVA; Pelargonyl Vanillylamide; Pseudocapsaicin; Нониваид.

N-Vanillylnonamide; *N*-[(4-Hydroxy-3-methoxyphenyl)methyl]nonanamide.

$C_{17}H_{27}NO_3$=293.4

CAS — 2444-46-4.

UNII — S846B891OR.

NOTE. Use of the term 'synthetic capsaicin' to describe nonivamide has arisen from the use of nonivamide as an adulterant for capsaicin and capsicum oleoresin.

Profile

Nonivamide is a synthetic analogue of capsaicin (p. 35.1) that is used in topical preparations for the relief of muscular and rheumatic pain.

Nonivamide has also been used as a food flavour and in 'pepper sprays' for law enforcement and self defence.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: ABC Hydrogel-Warmepflaster†; *Ger.*: Capsi-med; Gothaplast Capsicum-Warmepflaster.

Multi-ingredient Preparations. *Austral.*: Finalgon; *Austria*: Finalgon; Rubriment; *Cz.*: Capsicolle; *Ger.*: Finalgon; Rubriment†; *Gr.*: Finalgon; *Port.*: Finalgon; *Rus.*: Betalgon (Бегалгон); Betanicomylon (Бетаникомилон); Capsicam (Капсикам); Finalgon (Финалгон); *Switz.*: Histalgane; Radalgin†; *Thai.*: Ammeltz; *UK*: Pain Relief Balm†; *Ukr.*: Capsicam (Капсикам); Finalgon (Финалгон).

Nonsteroidal Anti-inflammatory Drugs

AINE; AINS; Fármacos antiinflamatorios no esteroideos; NSAIDs; NSAIl'ler; НСПВП; НПВП; НПВС; Нестероидные Противовоспалительные Препараты.

Uses and Administration

Given as single doses or in short-term intermittent therapy NSAIDs can relieve mild to moderate pain. However, it may take up to 3 weeks of use before their anti-inflammatory effects become evident. The combined analgesic and anti-inflammatory effects make them particularly useful for the symptomatic relief of painful and/or inflammatory conditions including rheumatic disorders such as rheumatoid arthritis, osteoarthritis, and the spondyloarthropathies, and also in peri-articular disorders, and soft-tissue rheumatism. Some NSAIDs are used in the management of dental or postoperative pain. Some NSAIDs, but not aspirin or other salicylates, are also used to treat acute gouty arthritis.

Generally, it is considered that there are only small differences in anti-inflammatory activity between the various NSAIDs and choice is largely empirical. Responses of individual patients vary widely. Thus, if a patient fails to respond to one NSAID, another drug may be successful. However, it has been recommended that NSAIDs associated with a low risk of gastrointestinal toxicity should generally be preferred and the lowest effective dose used. Treatment with NSAIDs that are selective inhibitors of cyclo-oxygenase-2 (COX-2), such as celecoxib, is limited in the UK to those patients with a history of serious gastrointestinal problems or considered to be at high risk of developing such problems if given a non-selective NSAID (see Effects on the Gastrointestinal Tract, p. 105.3).

NSAIDs are usually given orally, with or after food, although some such as diclofenac, ketoprofen, ketorolac, parecoxib, piroxicam, and tenoxicam can be given intramuscularly; diclofenac, ketorolac, parecoxib, and tenoxicam can also be given intravenously. Some NSAIDs are applied topically or given rectally as suppositories.

Several NSAIDs are used in ophthalmic preparations for the inhibition of intra-operative miosis, control of postoperative ocular inflammation, and prevention of cystoid macular oedema.

Action. Cyclo-oxygenases play an important role in the biosynthesis of prostaglandins (p. 2598.1). Non-selective NSAIDs inhibit both cyclo-oxygenase-1 (COX-1) and cyclo-oxygenase-2 (COX-2); the idea that inhibition of COX-1 is associated with adverse gastrointestinal effects while inhibition of COX-2 is associated with anti-inflammatory activity,[1-6] led to the development[7] of preferential or selective inhibitors of COX-2. Meloxicam and nimesulide are preferential inhibitors of COX-2, (i.e. they have a higher selectivity for COX-2 than COX-1 but are not exclusive COX-2 inhibitors); etodolac and nabumetone are also claimed to have preference for COX-2 although there is less evidence for this. Drugs with a very high selectivity for COX-2 are also available; celecoxib and parecoxib are two examples. Although the selective inhibition of COX-2 may be associated with reduced gastrointestinal toxicity, adverse effects associated with such inhibition have been noted in other body systems, see Thrombotic Events under Effects on the Cardiovascular System p. 105.1, and Effects on the Kidneys, p. 106.2.

There is evidence that NSAIDs may also have a central mechanism of action that augments the peripheral mechanism.[6]

Many NSAIDs possess centres of chirality within their molecular structure, with different chiral forms (enantiomers) having different degrees of pharmacological activity.[8,9] For example, indometacin, its analogues, and some arylpropionic acids are chiral drugs with the *S*(+)-enantiomer in most cases showing the dominant pharmacological activity. However, the ratio of *S*/*R* activity varies between drugs and between *animal* species. NSAIDs are generally used clinically as the racemate with only a few currently being given as the *S*-enantiomer (for example, dexibuprofen and dexketoprofen). The chirality of a drug may have subtle effects on its toxicity and interactions, and it may be more desirable to use a drug as its active enantiomer.[9]

1. Hayllar J, Bjarnason I. NSAIDs, Cox-2 inhibitors, and the gut. *Lancet* 1995; 346: 521–2.
2. Bennett A, Tavares IA. NSAIDs, Cox-2 inhibitors, and the gut. *Lancet* 1995; 346: 1105.
3. Vane JR. NSAIDs, Cox-2 inhibitors, and the gut. *Lancet* 1995; 346: 1105–6.
4. Jouzeau J-Y, *et al.* Cyclo-oxygenase isoenzymes: how recent findings affect thinking about nonsteroidal anti-inflammatory drugs. *Drugs* 1997; 53: 563–82.
5. Richardson C, Emery P. The clinical implications of inhibition of the inducible form of cyclo-oxygenase. *Drug Safety* 1996; 15: 249–60.
6. Cashman JN. The mechanisms of action of NSAIDs in analgesia. *Drugs* 1996; 52 (suppl 5): 13–23.
7. Hawkey CJ. COX-2 inhibitors. *Lancet* 1999; 353: 307–14. Correction. *ibid.*; 1440. [dose]
8. Kean WF, *et al.* Chirality in antirheumatic drugs. *Lancet* 1991; 338: 1565–8.
9. Hayball PJ. Chirality and nonsteroidal anti-inflammatory drugs. *Drugs* 1996; 52 (suppl 5): 47–58.

Colic pain. Prostaglandins have been implicated in the aetiology of biliary colic (p. 6.3), and some NSAIDs such as diclofenac, indometacin, and ketoprofen have been used to relieve such pain.

Dementia. Although NSAIDs have been associated with memory impairment and attention deficits in the elderly (see Effects on the CNS, p. 105.2), some studies have shown that long-term use may reduce the rate of cognitive decline[1,2] or the risk of developing Alzheimer's disease[3-5] (see Dementia, p. 390.1). A systematic review[6] of observational studies, which included some of these studies, also suggested that the risk of developing dementia is lower in patients who are taking NSAIDs. However, a randomised study[7] found no benefit from treatment with naproxen or rofecoxib in patients with existing mild to moderate Alzheimer's disease. Another systematic review[8] has suggested that the beneficial effects of NSAIDs seen in some studies are likely to be due to biases such as recall introduced by the study's design; the benefit of NSAIDs in preventing dementia or cognitive impairment was 50% in studies with prevalent (pre-existing) dementia cases, which decreased to 20% in studies of incident dementia cases (those developing during the study period), and was absent in those which used cognitive decline as an endpoint. Furthermore, a more recent randomised primary prevention study[9] concluded that neither naproxen nor celecoxib had a protective effect and there was some evidence that naproxen had a detrimental effect when compared with placebo. A large population-based cohort study[10] of the elderly also did not find a reduction in the risk of dementia or Alzheimer's disease among NSAID users. Instead, previous sustained use of NSAIDs was found to be associated with an increased incidence of dementia and Alzheimer's disease; the authors suggested that NSAIDs might only delay the onset of dementia. Further studies are needed to determine the role of NSAIDs in dementia.[10]

1. Karplus TM, Saag KG. Nonsteroidal anti-inflammatory drugs and cognitive function—do they have a beneficial or deleterious effect? *Drug Safety* 1998; 19: 427–33.
2. Rozzini R, *et al.* Protective effect of chronic NSAID use on cognitive decline in older persons. *J Am Geriatr Soc* 1996; 44: 1025–9.
3. Stewart WF, *et al.* Risk of Alzheimer's disease and duration of NSAID use. *Neurology* 1997; 48: 626–32.
4. in 't Veld BA, *et al.* Nonsteroidal antiinflammatory drugs and the risk of Alzheimer's disease. *N Engl J Med* 2001; 345: 1515–21.
5. Vlad SC, *et al.* Protective effects of NSAIDs on the development of Alzheimer disease. *Neurology* 2008; 70: 1672–7.
6. Etminan M, *et al.* Effect of non-steroidal anti-inflammatory drugs on risk of Alzheimer's disease: systematic review and meta-analysis of observational studies. *BMJ* 2003; 327: 128–31.
7. Aisen PS, *et al.* Effects of rofecoxib or naproxen vs placebo on Alzheimer disease progression: a randomized controlled trial. *JAMA* 2003; 289: 2819–26.
8. de Craen AJM, *et al.* Meta-analysis of nonsteroidal antiinflammatory drug use and risk of dementia. *Am J Epidemiol* 2005; 161: 114–20.
9. ADAPT Research Group. Cognitive function over time in the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT): results of a randomized, controlled trial of naproxen and celecoxib. *Arch Neurol* 2008; 65: 896–905.
10. Breitner JCS, *et al.* Risk of dementia and AD with prior exposure to NSAIDs in an elderly community-based cohort. *Neurology* 2009; 72: 1899–1905.

Diabetes insipidus. NSAIDs such as indometacin have been used in the treatment of diabetes insipidus; for some references, see p. 72.1.

Ectopic ossification. Ectopic ossification (heterotopic ossification) is a condition in which mature bone develops in non-skeletal tissues, commonly the connective tissue of muscles. It occurs after local trauma, for example after joint dislocation or surgery such as total hip replacement, and also after neurological damage such as severe head or spinal cord injuries.[1,2] Ectopic bone formation usually starts about 2 weeks after the injury, though symptoms, which include localised pain, fever, swelling, erythema, and restriction of movement, may not appear for 8 to 12 weeks.[1,3] Neurogenic ectopic ossification may develop even several years after spinal cord injury.[3] A congenital form of ectopic ossification, myositis ossificans progressiva (fibrodysplasia ossificans progressiva), also occurs but is rare. The principal complications of ectopic ossification are loss of joint mobility and function.[1,2]

Ectopic ossification should be distinguished from the calcification of soft tissue which may occur in connective tissue disorders or in parathyroid disorders as a result of high circulating concentrations of calcium and or phosphate; in these conditions calcification occurs without bone formation.

Surgical resection can improve joint motion[1,3] in patients with ectopic ossification, but may be associated with severe complications and poor outcome, and ossification may recur postoperatively.[3] Delaying surgery as long as possible until bone formation has decreased may lessen the likelihood of these complications,[1] although earlier surgery may prevent fibrous ankylosis and muscle contracture.[3] Although there is no consensus on treatment, early, regular and cautious physiotherapy is recommended to mobilise joints;[1-3] aggressive manipulation may cause further ossification.

Prophylactic measures include radiotherapy or drug therapy. While prophylaxis does not always prevent the development of ectopic ossification, it can decrease its occurrence and severity. Prophylactic measures should be begun as early as possible and with regard to orthopaedic surgery may be started before the operation. Prophylaxis is also required if mature ectopic bone is to be surgically excised in order to minimise the rate of recurrence. Low-dose radiotherapy is as effective as high-dose, and pre-operative irradiation is as effective as postoperative.[4] Studies suggest that NSAID prophylaxis is of similar efficacy to radiotherapy.[4] NSAIDs appear to significantly reduce the incidence of ectopic bone formation,[2-5] possibly by inhibiting inflammation and suppressing mesenchymal cell proliferation.[3] While controversy exists as to duration and doses, indometacin is considered the NSAID of choice by some; naproxen, tenoxicam, and diclofenac may also be of benefit.[4] Ibuprofen has been tried; however, a study[6] has found that, although it significantly reduced the rate of ectopic bone formation, there were no clinical benefits 6 to 12 months after surgery. Bisphosphonates that inhibit the mineralisation of the deposited bone, such as etidronate, have also been used but they do not prevent the formation of the osteoid matrix. Also when etidronate is stopped, some mineralisation can occur, resulting in delayed ectopic or rebound ossification, though it is usually less severe. Prolonged treatment may be needed.[2,3] A systematic review,[7] however, found insufficient evidence to recommend the use of etidronate for the treatment of acute ectopic ossification.

1. Shehab D, *et al.* Heterotopic ossification. *J Nucl Med* 2002; 43: 346–53.
2. Vanden Bossche L, Vanderstraeten G. Heterotopic ossification: a review. *J Rehabil Med* 2005; 37: 129–36.
3. van Kuijk AA, *et al.* Neurogenic heterotopic ossification in spinal cord injury. *Spinal Cord* 2002; 40: 313–26.
4. Fijn R, *et al.* Prevention of heterotopic ossification after total hip replacement with NSAIDs. *Pharm World Sci* 2003; 25: 138–45.
5. Fransen M, Neal B. Non-steroidal anti-inflammatory drugs for preventing heterotopic bone formation after hip arthroplasty. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 08/11/07).
6. Fransen M, *et al.* Safety and efficacy of routine postoperative ibuprofen for pain and disability related to ectopic bone formation after hip replacement surgery (HIPAID): randomised controlled trial. *BMJ* 2006; 333: 519–21.
7. Haran M, *et al.* Pharmacological interventions for treating acute heterotopic ossification. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 08/11/07).

Eye disorders. Miosis resistant to conventional mydriatics often develops during ocular surgery, possibly due to release of prostaglandins and other substances associated with trauma. NSAIDs, which are prostaglandin synthetase inhibitors, are therefore used prophylactically as eye drops before ocular surgery to ameliorate intra-operative miosis but there has been some doubt that the effect they produce is of clinical significance. Those commonly used include diclofenac, indometacin, and flurbiprofen. These drugs do not possess intrinsic mydriatic properties.

Some NSAIDs are used topically or systemically in inflammatory ocular disorders, including inflammation and cystoid macular oedema following ocular surgery (see below). Topical NSAIDs are also effective analgesics when used in the management of corneal abrasions. However, their role in the treatment of macular oedema associated with uveitis (p. 1615.1) is less clear. NSAIDs are also used in the treatment of scleritis (see p. 1612.3). Diclofenac and ketorolac have also both been used in the management of seasonal allergic conjunctivitis (see p. 611.1).

References.

1. Flach AJ. Cyclo-oxygenase inhibitors in ophthalmology. *Surv Ophthalmol* 1992; 36: 259–84.
2. Koay P. The emerging roles of topical non-steroidal anti-inflammatory agents in ophthalmology. *Br J Ophthalmol* 1996; 80: 480–5.
3. Schalnus R. Topical nonsteroidal anti-inflammatory therapy in ophthalmology. *Ophthalmologica* 2003; 217: 89–98.
4. Calder LA, *et al.* Topical nonsteroidal anti-inflammatory drugs for corneal abrasions: meta-analysis of randomized trials. *Acad Emerg Med* 2005; 12: 467–73.

POSTOPERATIVE INFLAMMATORY OCULAR DISORDERS. Corticosteroids are used topically for the control of **postoperative ocular inflammation** but caution is required as they can delay wound healing and mask postoperative infection. They should only be used for short periods as they can cause glaucoma in susceptible individuals. Topical NSAIDs have also been tried and appear to be as effective as corticosteroids in controlling signs of inflammation after ocular surgery,[1] but there has been some concern about reports of corneal toxicity (see p. 50.1).

Cystoid macular oedema may follow cataract or retinal detachment surgery due to a disturbance of the blood-retinal barrier. NSAIDs[1-6] such as diclofenac, flurbiprofen, indometacin, and ketorolac are used topically with or without corticosteroids to prevent or relieve cystoid macular oedema. NSAIDs including indometacin are also used systemically in its management. However, a systematic review[6] has found insufficient evidence for the efficacy of NSAIDs (topical and oral) in acute or chronic cystoid macular oedema after cataract surgery although topical ketorolac may have a positive effect in chronic disease.

1. Colin J. The role of NSAIDs in the management of postoperative ophthalmic inflammation. *Drugs* 2007; 67: 1291–1308.
2. Jampol LM. Pharmacologic therapy of aphakic and pseudophakic cystoid macular edema. *Ophthalmology* 1985; 92: 807–10.
3. Flach AJ, *et al.* Effectiveness of ketorolac tromethamine 0.5% ophthalmic solution for chronic aphakic and pseudophakic cystoid macular edema. *Am J Ophthalmol* 1987; 103: 479–86.
4. Jampol LM, *et al.* Nonsteroidal anti-inflammatory drugs and cataract surgery. *Arch Ophthalmol* 1994; 112: 891–4.
5. *Italian Diclofenac Study Group. Efficacy of diclofenac eyedrops in* preventing postoperative inflammation and long-term cystoid macular edema. *J Cataract Refract Surg* 1997; 23: 1183–9.
6. Sivaprasad S, *et al.* Non-steroidal anti-inflammatory agents for treating cystoid macular oedema following cataract surgery. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 25/09/09).

Fever. Paracetamol, salicylates, and some other NSAIDs are the main antipyretics used to control fever (p. 11.3). Paracetamol is usually the antipyretic of choice in infants and children but ibuprofen is an effective alternative; alternation of the two may be better than either alone, although this is controversial. Salicylates are generally contra-indicated in these patients because of the possible link between their use and the development of Reye's syndrome (see under Adverse Effects of Aspirin, p. 25.3).

Gout. NSAIDs are the drugs usually used first for the treatment of acute attacks of gout (p. 600.1). Since the drug treatment of chronic gout can lead to the mobilisation of urate crystals from established tophi to produce acute attacks, NSAIDs may also be used for the prophylaxis of acute gout during the first few months of urate-lowering therapy.

Headache. An NSAID is often tried first for the symptomatic treatment of various types of headache including migraine (p. 670.3) and tension-type headache (p. 671.3). NSAIDs may also be effective prophylactic drugs for migraine, although propranolol is generally preferred. Paroxysmal hemicrania, a rare variant of cluster headache (p. 670.1), responds to indometacin.

Kidney disorders. Although NSAIDs can produce adverse effects on the kidney (see p. 106.2) they may have a role in the management of some types of glomerular kidney disease (p. 1604.3). They may be of use for the control of proteinuria due to nephrotic syndrome except when there is overt renal failure.

Malignant neoplasms. An early study by the American Cancer Society[1] suggested that regular use of aspirin might reduce the risk of developing fatal cancer of the oesophagus, stomach, colon, or rectum. Death rates due to other gastrointestinal cancers did not appear to be affected. Some studies[2-12] appear to support this reduced risk of colorectal cancer (see Prophylaxis, under Malignant Neoplasms of the Gastrointestinal Tract, p. 707.2) in regular users of aspirin or other NSAIDs, particularly in high-risk patients, conclusions that were cautiously endorsed by a systematic review.[13] Furthermore, a pooled analysis[14] of data from 2 randomised studies concluded that taking 300 mg, or more, of aspirin daily for at least 5 years is effective in reducing the risk of colorectal cancer, with a latency of 10 years. However, other studies[15,16] have found no evidence of an association between the use of aspirin or NSAIDs and the incidence of colorectal cancer; the authors suggest that these results may be explained by the short treatment period and the low dose of aspirin used. More recent reviews[17,18] prepared for the US Preventive Services Task Force (USPSTF) indicated that aspirin and NSAIDs, including selective cyclo-oxygenase-2 (COX-2) inhibitors, reduce the incidence of colonic adenomas, and that aspirin and NSAIDs also reduce the incidence of colorectal cancer; however, the USPSTF issued a statement[19] that, because of the adverse cardiovascular and gastrointestinal effects associated with these agents, their use to prevent colorectal cancer could not be recommended in those at average risk of colorectal cancer.

The potential role that inhibition of COX-2 may play in the management of cancer has been discussed[20,21] and a study[22] has found that regular use of aspirin appears to reduce the risk of colorectal cancers that overexpress COX-2 but not those with weak or absent expression of COX-2.

A large case-control study,[23] using data held on the UK General Practice Research Database, has examined information on NSAID use and the development of common cancers. This study also found that the use of NSAIDs (including aspirin) may protect against cancer of the oesophagus, stomach, colon, and rectum. However, the study failed to show any decrease in risk of non-gastrointestinal cancers. Subsequently, 2 meta-analyses[24,25] have also suggested that aspirin and NSAID use reduce the risk of other gastrointestinal cancers such as oesophageal or stomach cancer. In addition, one analysis[24] considered the effect of NSAID and aspirin use on non-gastrointestinal cancers: aspirin use showed a chemoprotective effect in pancreatic cancer although this was not significant statistically; there was also a slight, but nonetheless significant, reduction in the risk of breast cancer associated with both aspirin and NSAID use. The results for other sites, namely ovary, lung, bladder, and prostate, suggested no effect or possibly a slight reduced risk. The authors considered that it was unclear if any potential benefit in non-gastrointestinal cancers may be offset by the known adverse effects associated with the long-term use of these drugs particularly in those cancers with a low incidence.

Treatment with sulindac (see Gastrointestinal Disorders, p. 134.2) has been found to reduce the number of polyps in patients with familial adenomatous polyposis, a condition which predisposes to development of colorectal cancer. Celecoxib has similar effects (see p. 37.1).

1. Thun MJ, *et al.* Aspirin use and the risk of fatal cancer. *Cancer Res* 1993; 53: 1322–7.
2. Rosenberg L, *et al.* A hypothesis: nonsteroidal anti-inflammatory drugs reduce the incidence of large-bowel cancer. *J Natl Cancer Inst* 1991; 83: 355–8.
3. Logan RFA, *et al.* Effect of aspirin and non-steroidal anti-inflammatory drugs on colorectal adenomas: case-control study of subjects participating in the Nottingham faecal occult blood screening programme. *BMJ* 1993; 307: 285–9.
4. Giovannucci E, *et al.* Aspirin use and the risk for colorectal cancer and adenoma in male health professionals. *Ann Intern Med* 1994; 121: 241–6.
5. Giovannucci E, *et al.* Aspirin and the risk of colorectal cancer in women. *N Engl J Med* 1995; 333: 609–14.
6. Sandler RS, *et al.* Aspirin and nonsteroidal anti-inflammatory agents and risk for colorectal adenomas. *Gastroenterology* 1998; 114: 441–7.
7. Smalley W, *et al.* Use of nonsteroidal anti-inflammatory drugs and incidence of colorectal cancer: a population-based study. *Arch Intern Med* 1999; 159: 161–6.
8. Jolly K, *et al.* NSAIDs and gastrointestinal cancer prevention. *Drugs* 2002; 62: 945–56.
9. Sandler RS, *et al.* A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. *N Engl J Med* 2003; 348: 883–90.
10. Baron JA, *et al.* A randomized trial of aspirin to prevent colorectal adenomas. *N Engl J Med* 2003; 348: 891–9.
11. Chan AT, *et al.* Long-term use of aspirin and nonsteroidal anti-inflammatory drugs and risk of colorectal cancer. *JAMA* 2005; 294: 914–23.
12. Chan AT, *et al.* Aspirin dose and duration of use and risk of colorectal cancer in men. *Gastroenterology* 2008; 134: 21–8.
13. Asano TK, McLeod RS. Non steroidal anti-inflammatory drugs (NSAID) and aspirin for preventing colorectal adenomas and carcinomas. Available in The Cochrane Database of Systematic Reviews: Issue 1. Chichester: John Wiley; 2004 (accessed 08/11/07).
14. Flossmann E, Rothwell PM. British Doctors Aspirin Trial and the UK-TIA Aspirin Trial. Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies. *Lancet* 2007; 369: 1603–13.
15. Stürmer T, *et al.* Aspirin use and colorectal cancer: post-trial follow-up data from the Physicians' Health Study. *Ann Intern Med* 1998; 128: 713–20.
16. Stürmer T, *et al.* Colorectal cancer after start of nonsteroidal anti-inflammatory drug use. *Am J Med* 2006; 119: 494–502.
17. Rostom A, *et al.* U.S. Preventive Services Task Force. Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors for primary prevention of colorectal cancer: a systematic review prepared for the U. S. Preventive Services Task Force. *Ann Intern Med* 2007; 146: 376–89.
18. Dubé C, *et al.* U.S. Preventive Services Task Force. The use of aspirin for primary prevention of colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force. *Ann Intern Med* 2007; 146: 365–75.
19. U. S. Preventive Services Task Force. Routine aspirin or nonsteroidal anti-inflammatory drugs for the primary prevention of colorectal cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2007; 146: 361–4.
20. Liao Z, *et al.* Cyclo-oxygenase-2 and its inhibition in cancer: is there a role? *Drugs* 2007; 67: 821–45.
21. Markowitz SD. Aspirin and colon cancer—targeting prevention? *N Engl J Med* 2007; 356: 2195–8.
22. Chan AT, *et al.* Aspirin and the risk of colorectal cancer in relation to the expression of COX-2. *N Engl J Med* 2007; 356: 2131–42.
23. Langman MJS, *et al.* Effect of anti-inflammatory drugs on overall risk of common cancer: case-control study in general practice research database. *BMJ* 2000; 320: 1642–6.
24. González-Pérez A, *et al.* Effects of non-steroidal anti-inflammatory drugs on cancer sites other than the colon and rectum: a meta-analysis. *BMC Cancer* 2003; 3: 28. Available at: http://www.biomedcentral.com/1471-2407/3/28 (accessed 08/11/07)
25. Wang WH, *et al.* Non-steroidal anti-inflammatory drug use and the risk of gastric cancer: a systematic review and meta-analysis. *J Natl Cancer Inst* 2003; 95: 1784–91.

Menstrual disorders. Menorrhagia (p. 2300.3) is thought to be associated with abnormalities of prostaglandin production. Treatment with NSAIDs such as ibuprofen, mefenamic acid, or naproxen during menstruation, can reduce uterine blood loss by an average of 30% in women with menorrhagia. There does not appear to be any evidence that one NSAID is more effective than another.

NSAIDs are usually the first choice for the pain of dysmenorrhoea (p. 8.2). Mefenamic acid may have a theoretical advantage over other NSAIDs in being able to inhibit both the synthesis and the peripheral action of prostaglandins, but clinical studies have not shown fenamates to be more effective, and systematic review has suggested that ibuprofen may have the best risk/benefit ratio.

Migraine. See Headache, above.

Orthostatic hypotension. Fludrocortisone is usually the first drug tried in the treatment of orthostatic hypotension (p. 1634.3) when nonpharmacological treatment has failed. NSAIDs such as flurbiprofen, ibuprofen, or indometacin may be used alone or added to treatment if the response is inadequate.

Pain. NSAIDs have a similar analgesic effect to aspirin and paracetamol in single doses but, in regular full dosage, they have both a lasting analgesic and an anti-inflammatory effect. They are used in the management of mild to moderate pain (see Choice of Analgesic, p. 4.2) and are of particular value in pain due to inflammation. NSAIDs may be of benefit for inflammatory pain in infants and children (p. 5.2), although paracetamol is generally the preferred non-opioid analgesic in this age group. NSAIDs may be used in the treatment of acute low back pain (p. 9.2) if paracetamol fails to provide adequate pain relief. NSAIDs may also be used as an adjunct to opioids in the management of severe pain such as cancer pain (p. 7.1) and are particularly effective in bone pain of malignant origin. NSAIDs may be used for postoperative analgesia (p. 6.1), and are of particular value after day-case surgery because of their lack of sedative effects. They are not usually considered to be strong enough as the sole analgesic after major surgery, but may be used with stronger analgesics and may allow dosage reduction of opioids. The pain of mild sickle-cell crises (p. 11.1) may be controlled by analgesics such as NSAIDs or less potent opioids, for example codeine or dihydrocodeine; NSAIDs may be used with more potent opioids such as morphine for severe crises.

Dependence and tolerance are not a problem with non-opioid analgesics such as NSAIDs, but there is a ceiling of efficacy, above which, increasing the dose has no further therapeutic effect.

Rheumatic disorders. NSAIDs provide symptomatic relief for rheumatic disorders such as rheumatoid arthritis (p. 13.2) and spondyloarthropathies (p. 14.3), but they do not alter the course of the disease and additional antirheumatic drugs may need to be given to prevent irreversible joint damage. NSAIDs may also be used as an alternative to paracetamol for osteoarthritis (p. 12.3). Short-term use of oral NSAIDs may help to relieve pain and reduce inflammation of soft-tissue rheumatism (p. 14.2); topical formulations of some NSAIDs are also used.

Scleroderma. NSAIDs should be used with caution in scleroderma (p. 1942.3) because of the risk of exacerbating renal and other problems.

Adverse Effects and Treatment

The commonest adverse effects of NSAIDs are generally gastrointestinal disturbances, such as gastrointestinal discomfort, nausea, and diarrhoea; these are usually mild and reversible but in some patients peptic ulceration and severe gastrointestinal bleeding may occur. It is generally agreed that inhibition of cyclo-oxygenase-1 (COX-1) plays an important role in the gastrointestinal effects of NSAIDs the selective inhibition of COX-2 improves gastrointestinal tolerance.

CNS-related adverse effects include headache, vertigo, dizziness, nervousness, tinnitus, depression, drowsiness, and insomnia. Hypersensitivity reactions may occur occasionally and include fever, angioedema, bronchospasm, and rashes. Hepatotoxicity and aseptic meningitis, which occur rarely, may also be hypersensitivity reactions. Patients with connective-tissue disorders such as SLE may be particularly susceptible to aseptic meningitis. Some patients may have visual disturbances.

Haematological adverse effects of NSAIDs include anaemias, thrombocytopenia, neutropenia, eosinophilia, and agranulocytosis. Unlike aspirin, inhibition of platelet aggregation is reversible with other NSAIDs.

Some NSAIDs have been associated with nephrotoxicity such as interstitial nephritis and nephrotic syndrome; renal failure may be provoked by NSAIDs especially in patients with pre-existing renal impairment. Haematuria has also occurred. Long-term use or abuse of analgesics, including NSAIDs, has been associated with nephropathy.

Fluid retention may occur, rarely precipitating heart failure in susceptible patients. Other cardiovascular adverse effects of NSAIDs, including those selective for COX-2 inhibition, are discussed in detail on p. 105.1.

Other adverse effects include photosensitivity. Alveolitis, pulmonary eosinophilia, pancreatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis are other rare adverse effects. Induction or exacerbation of colitis or Crohn's disease has also been reported. Long-term use of some NSAIDs has been associated with reduced female fertility that was reversible on stopping treatment.

Further details concerning the adverse effects of the individual NSAIDs may be found under their respective monographs.

Incidence of adverse effects. The relative toxicity of NSAIDs is a subject of debate.[1] Attempts have been made to rank these drugs according to their toxicity on various body systems.[2] The toxicity of selective cyclo-oxygenase-2 (COX-2) inhibitors has also been reviewed.[3] For further details see below under individual headings.

1. Skeith KJ, *et al.* Differences in NSAID tolerability profiles: fact or fiction? *Drug Safety* 1994; 10: 183–95.
2. CSM/MCA. Relative safety of oral non-aspirin NSAIDs. *Current Problems* 1994; 20: 9–11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015615&RevisionSelectionMethod=LatestReleased (accessed 08/11/07)
3. Chaiamnuay S, *et al.* Risks versus benefits of cyclooxygenase-2-selective nonsteroidal antiinflammatory drugs. *Am J Health-Syst Pharm* 2006; 63: 1837–51.

Effects on the blood. The UK CSM has provided data on the reports it had received between July 1963 and January 1993 on agranulocytosis and neutropenia.[1] Several groups of drugs were commonly implicated, among them NSAIDs for which there were 133 reports of agranulocytosis (45 fatal) and 187 of neutropenia (15 fatal). The most frequently implicated NSAID was phenylbutazone with 74 reports of agranulocytosis (39 fatal) and 40 of neutropenia (4 fatal).

1. CSM/MCA. Drug-induced neutropenia and agranulocytosis. *Current Problems* 1993; 19: 10–11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024456&RevisionSelectionMethod=LatestReleased (accessed 08/11/07)

Effects on bone. Prostaglandins have been shown to play an important role in the bone-healing process and, consequently, the decrease in prostaglandin levels produced by NSAID use may impair the healing process.[1] Under experimental conditions, many NSAIDs including the cyclo-oxy-

genase-2 (COX-2) inhibitors have been shown to reduce healing.[1] However, clinical evidence of such an effect is rare.[2] There is also concern that some NSAIDs such as indometacin may accelerate the rate of cartilage destruction in patients with osteoarthritis.[3,4]

1. Harder AT, An YH. The mechanisms of the inhibitory effects of nonsteroidal anti-inflammatory drugs on bone healing: a concise review. *J Clin Pharmacol* 2003; **43**: 807–15.
2. Glassman SD, *et al.* The effect of postoperative nonsteroidal anti-inflammatory drug administration on spinal fusion. *Spine* 1998; **23**: 834–8.
3. Rashad S, *et al.* Effect of non-steroidal anti-inflammatory drugs on the course of osteoarthritis. *Lancet* 1989; **II**: 519–22.
4. Huskisson EC, *et al.* Effects of antiinflammatory drugs on the progression of osteoarthritis of the knee. *J Rheumatol* 1995; **22**: 1941–6.

Effects on the cardiovascular system. *BLOOD PRESSURE.* A meta-analysis[1] of 50 randomised studies of the effects of NSAIDs on blood pressure in a total of 771 patients found that NSAIDs had elevated mean supine blood pressure by 5 mmHg. Piroxicam, indometacin, and ibuprofen had produced the greatest increase but the effect was only found to be statistically significant for piroxicam. Aspirin, sulindac, and flurbiprofen produced the smallest elevation in blood pressure while the effect of tiaprofenic acid, diclofenac, and naproxen was intermediate. The increase was more marked in studies in which patients had received antihypertensive therapy than in those where such treatment had not been used. NSAIDs had antagonised all antihypertensive therapy but the effect had been greater against beta blockers and vasodilators than against diuretics. An earlier meta-analysis of intervention studies had produced similar results.[2] Of the 1324 patients who had received NSAIDs, increases in mean arterial pressure were greatest in hypertensive patients who had taken either indometacin, naproxen, or piroxicam, although results were only significant for indometacin and naproxen. Sulindac and aspirin had minimal effects on mean arterial pressure.

It has been suggested that the use of NSAIDs in the elderly may increase the risk of the need for antihypertensive therapy.[3] A study[3] of 9411 patients aged 65 years or older who had just started treatment with antihypertensives found that 41% had used NSAIDs in the previous year compared with 26% of 9629 control patients not being treated with antihypertensives.

1. Johnson AG, *et al.* Do nonsteroidal anti-inflammatory drugs affect blood pressure? *Ann Intern Med* 1994; **121**: 289–300.
2. Pope JE, *et al.* A meta-analysis of the effects of nonsteroidal anti-inflammatory drugs on blood pressure. *Arch Intern Med* 1993; **153**: 477–84.
3. Gurwitz JH, *et al.* Initiation of antihypertensive treatment during nonsteroidal anti-inflammatory drug therapy. *JAMA* 1994; **272**: 781–6.

HEART FAILURE. The recent use of NSAIDs has been associated with an increased risk of developing heart failure in elderly patients.[1] A case-control study[2] found that the use of an NSAID in the previous week doubled the odds of being admitted to hospital with heart failure; this risk was increased tenfold in those with a history of heart disease. The study also suggested an association between both high-dose and long drug plasma half-life and an increased risk of heart failure.

1. Bleumink GS, *et al.* Nonsteroidal anti-inflammatory drugs and heart failure. *Drugs* 2003; **63**: 525–34.
2. Page J, Henry D. Consumption of NSAIDs and the development of congestive heart failure in elderly patients: an underrecognised public health problem. *Arch Intern Med* 2000; **160**: 777–84.

THROMBOTIC EVENTS. After the introduction of the selective cyclo-oxygenase-2 (COX-2) inhibitors, concerns arose that the risk of thrombotic events such as myocardial infarction and stroke might be increased in patients treated with these selective NSAIDs, and their safety was continuously reviewed by some regulatory bodies. Subsequently, clinical study data confirmed that there was a small increased risk of these events with the COX-2 inhibitors which prompted the general world-wide withdrawal of rofecoxib (see p. 128.3) and valdecoxib (see p. 141.3). For those selective NSAIDs that remained, prescribing restrictions were imposed (for further details, see under Celecoxib, p. 37.3).

Concerns have also been raised that the increased risk of thrombotic events seen with the selective COX-2 inhibitors may also apply to the non-selective NSAIDs. After a review of data available at the time, the FDA[1] reported in April 2005 that the use of non-selective NSAIDs may potentially increase cardiovascular risk. In August 2005, the UK CSM advised that any cardiovascular risk with the non-selective NSAIDs was likely to be small and associated with continuous long-term treatment and higher doses;[2] no changes to current prescribing practices were recommended. This advice was endorsed a few months later by the EMEA in Europe.[3] However, new information has since become available and, in October 2006, the EMEA updated its advice.[4] Based on data which included the MEDAL programme[5] and reviews of several important epidemiological studies[6-8] the following points were made:

- the results from the MEDAL programme suggest that *diclofenac* (150 mg daily) has a risk of thrombotic events similar to that of etoricoxib (60 mg or 90 mg daily); however, at the time, further issues needed to be considered before this could be considered conclusive (see also below)
- based on study and epidemiological evidence, diclofenac, particularly at a high dose (150 mg daily), may be associated with an increased risk of thrombotic events
- clinical study data suggest that high-dose *ibuprofen* (2.4 g daily) is associated with an increased risk of thrombotic events; however, overall, epidemiological studies do not support an increased risk with low-dose ibuprofen (1.2 g daily or less)
- *naproxen* (1 g daily) may be associated with a lower risk for thrombotic events than the COX-2 inhibitors, but a small risk cannot be excluded; overall, there is no evidence of a cardioprotective effect
- for all *other non-selective NSAIDs* there are insufficient data to assess the thrombotic risk and consequently an increased risk cannot be excluded; a small increase in absolute risk seems most likely when used in high doses and for long-term treatment

In February 2009, the UK CHM[9] reported that results from 2 more recent epidemiological studies[10,11] support the view that an increase in thrombotic risk is associated with *all NSAIDs* and is independent of a patient's baseline cardiovascular risk factors or duration of NSAID use; however, the absolute risk for healthy users is very low.

After a Europe-wide review, the European Pharmacovigilance Risk Assessment Committee (PRAC)[12] concluded in June 2013 that the thrombotic risk of systemic diclofenac, particularly at high doses (150 mg daily) and in long-term treatment, is similar to that of the selective COX-2 inhibitors. This review included a meta-analysis[13] of more than 600 randomised studies which found that of 1000 patients allocated a COX-2 inhibitor or diclofenac for a year, 3 more had major cardiovascular events (1 of which was fatal) when compared with placebo; this finding was independent of baseline characteristics, including cardiovascular risk factors.

The American Heart Association[14] has also issued a statement about the cardiovascular effects of NSAIDs.

It has been suggested that NSAIDs may reduce the cardioprotective effect of aspirin, but see under Interactions of Aspirin, p. 27.1.

1. FDA. FDA announces series of changes to the class of marketed non-steroidal anti-inflammatory drugs (NSAIDs) (issued 7th April, 2005). Available at: http://www.fda.gov/bbs/topics/news/2005/NEW01171.html (accessed 08/11/07)
2. CSM. Cardiovascular safety of NSAIDs: review of evidence. Message from Professor G Duff, Chairman of CSM (issued August 2005). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=con1004303&RevisionSelectionMethod=Latest (accessed 08/11/07)
3. EMEA. European Medicines Agency update on non-selective NSAIDs (issued 17th October, 2005). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/29896405en.pdf (accessed 29/08/08)
4. EMEA. Opinion of the Committee for Medicinal Products for Human Use pursuant to article 5(3) of regulation (EC) no 726/2004, for non-selective non steroidal anti-inflammatory drugs (NSAIDs) (issued 18th October, 2006). Available at: http://www.emea.europa.eu/pdfs/human/opinion/nsaids.pdf (accessed 08/11/07)
5. Cannon CP, *et al.* Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. *Lancet* 2006; **368**: 1771–81.
6. Kearney PM, *et al.* Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ* 2006; **332**: 1302–8.
7. Hernández-Díaz S, *et al.* Non-steroidal antiinflammatory drugs and the risk of acute myocardial infarction. *Basic Clin Pharmacol Toxicol* 2006; **98**: 266–74.
8. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. *JAMA* 2006; **296**: 1633–44.
9. MHRA/CHM. Non-steroidal anti-inflammatory drugs: cardiovascular risk. *Drug Safety Update* 2009; **2** (7): 3–4. Available at: http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON038625 (accessed 24/09/09)
10. García Rodríguez LA, *et al.* Role of dose potency in the prediction of risk of myocardial infarction associated with nonsteroidal anti-inflammatory drugs in the general population. *J Am Coll Cardiol* 2008; **52**: 1628–36.
11. Fosbøl EL, *et al.* Risk of myocardial infarction and death associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) among healthy individuals: a nationwide cohort study. *Clin Pharmacol Ther* 2009; **85**: 190–7.
12. EMEA. PRAC recommends the same cardiovascular precautions for diclofenac as for selective COX-2 inhibitors (issued 14th June, 2013). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Diclofenac-containing_medicinal_products/Recommendation_provided_by_Pharmacovigilance_Risk_Assessment_Committee/WC500144452.pdf (accessed 07/01/14)
13. Bhala N, *et al.* Coxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet* 2013; **382**: 769–79.
14. Antman EM, *et al.* Use of nonsteroidal antiinflammatory drugs: an update for clinicians—a scientific statement from the American Heart Association. *Circulation* 2007; **115**: 1634–42.

Effects on the CNS. A literature review[1] revealed that headache, hearing loss, and tinnitus are the most frequent CNS adverse effects in patients taking NSAIDs. Aseptic meningitis had occurred rarely in patients using NSAIDs such as naproxen, sulindac, or tolmetin, but the most common reports were in patients with SLE who were receiving ibuprofen (see also p. 69.2).

Reports of psychosis appear to be rare[1,2] and have involved indometacin or sulindac, but in some reviewers' experience it was probably under-reported and was typically seen in elderly patients given indometacin.[1]

Adverse CNS effects have also been reported with the selective cyclo-oxygenase-2 (COX-2) inhibitors.[2]

The role of NSAIDs in the development of cognitive decline in the elderly is unclear. They have been associated with memory impairment and attention deficits in elderly patients,[1,3] especially when given in high doses;[4] however, NSAIDs have been reported to reduce the rate of cognitive decline or the risk of developing Alzheimer's disease (see Dementia, under Uses and Administration, p. 103.1).

1. Hoppmann RA, *et al.* Central nervous system side effects of nonsteroidal anti-inflammatory drugs: aseptic meningitis, psychosis, and cognitive dysfunction. *Arch Intern Med* 1991; **151**: 1309–13.
2. Onder G, *et al.* NSAID-related psychiatric adverse events: who is at risk? *Drugs* 2004; **64**: 2619–27.
3. Saag KG, *et al.* Nonsteroidal antiinflammatory drugs and cognitive decline in the elderly. *J Rheumatol* 1995; **22**: 2142–7.
4. Karpius TM, Saag KG. Nonsteroidal anti-inflammatory drugs and cognitive function—do they have a beneficial or deleterious effect? *Drug Safety* 1998; **19**: 427–33.

Effects on electrolytes. See Effects on the Kidneys, p. 106.2.

Effects on the eyes. Ocular effects such as blurred vision occur rarely in patients taking NSAIDs. Other more serious effects on the eyes associated with NSAIDs also appear to be rare. In the USA the National Registry of Drug-Induced Ocular Side Effects analysed 144 reports they received of possible adverse optic nerve reactions associated with the use of NSAIDs.[1] Of the 24 cases of papilloedema with or without pseudotumor cerebri more than half were associated with propionic acid derivatives, but it was considered that the data indicated that, on rare occasions, most NSAIDs could cause this effect; the number of reports for individual drugs was: 7 for ibuprofen, 5 each for indometacin and naproxen, 3 for meclofenamate, and 1 each for diflunisal, ketoprofen, sulindac, and tolmetin. Almost two-thirds of the 120 cases of optic or retrobulbar neuritis were also associated with propionic acid derivatives; the number of reports for individual drugs was: ibuprofen 43, naproxen 17, indometacin 9, benoxaprofen 8, phenylbutazone 8, piroxicam 8, zomepirac 7, sulindac 6, fenoprofen 5, oxyphenbutazone 3, meclofenamate 2, tolmetin 2, diflunisal 1, and ketoprofen 1.

Ocular adverse effects have also been reported with the selective cyclo-oxygenase-2 (COX-2) inhibitors.[2]

There have been reports of severe corneal toxicity associated with the use of some topical NSAIDs, such as diclofenac and ketorolac, in the eye (see p. 50.1).

1. Fraunfelder FT, *et al.* Possible optic nerve side effects associated with nonsteroidal anti-inflammatory drugs. *J Toxicol Cutan Ocul Toxicol* 1994; **13**: 311–16.
2. Coulter DM, *et al.* Celecoxib, rofecoxib, and acute temporary visual impairment. *BMJ* 2003; **327**: 1214–15.

Effects on fertility. Reversible infertility has been reported in women on long-term NSAIDs.[1-3] Prostaglandins are considered to be involved in the processes of ovulation and it is thought that NSAIDs may compromise ovulation via inhibition of cyclo-oxygenase-2 (COX-2). Women trying to become pregnant may need to avoid treatment with NSAIDs.

1. Mendonça LLF, *et al.* Non-steroidal anti-inflammatory drugs as a possible cause for reversible infertility. *Rheumatology (Oxford)* 2000; **39**: 880–2.
2. Norman RJ. Reproductive consequences of COX-2 inhibition. *Lancet* 2001; **358**: 1287–8.
3. Stone S, *et al.* Nonsteroidal anti-inflammatory drugs and reversible female infertility: is there a link? *Drug Safety* 2002; **25**: 545–51.

Effects on the gastrointestinal tract. NSAIDs can cause clinically important damage of the gastrointestinal tract, increasing the incidence of bleeding in the upper gastrointestinal tract and of perforation, although serious complications and death are relatively infrequent. They have also been associated with damage to the distal small intestine and colon.[1-3]

The complex **mechanisms** involved are not fully understood, although it is generally accepted that the inhibition of cyclo-oxygenase-1 (COX-1) plays a role in gastrointestinal toxicity and that the selective COX-2 inhibitors are less gastrotoxic than the traditional NSAIDs (see below).[4-8] The gastric mucosa is damaged both by local and systemic effects of NSAIDs.[5] The local effect is pH-dependent and varies between individual drugs. The systemic effect is pH-independent, can occur with any route of administration, and is less drug specific; it is this effect that is thought to involve COX-1 inhibition.

Risk factors continue to be studied and so far the most important patient-related factors for upper gastrointestinal toxicity are old age, a history of peptic ulcers or bleeding of the gastrointestinal tract, and concomitant use of corticosteroids.[9] It has also been suggested that risk is

increased in children.[10] *Helicobacter pylori* infection exacerbates the risk of ulceration, but patients remain at increased risk even if infection is eradicated.[11] Duration of therapy is not thought to influence the risk for serious events; a cohort study[12] found that the risk of gastrointestinal bleeding or perforation with NSAIDs was constant throughout treatment, and risk quickly declines after NSAID withdrawal.[13]

Several studies[14-17] have been conducted on the **relative toxicity** of oral NSAIDs on the upper gastrointestinal tract and various rankings of these drugs have been discussed.[18-22] The UK CSM[20] examined 10 epidemiological studies for 7 oral non-aspirin NSAIDs and also examined the spontaneous reports they had received of gastrointestinal effects associated with NSAIDs. The CSM concluded that:

- azapropazone was associated with the *highest* risk of gastrointestinal reactions
- ibuprofen carried the *lowest* risk (but this may be related to dose, see below)
- piroxicam, ketoprofen, indometacin, naproxen, and diclofenac had an *intermediate* risk; it was considered that the risk for piroxicam might be higher than for the other NSAIDs with intermediate toxicity

A later update[23] by the CSM confirmed these findings.

The relative gastrointestinal toxicity of NSAIDs has also been reviewed by the EMEA[22] using data from epidemiological studies and spontaneous adverse drug reaction reports. Available evidence suggested that piroxicam and ketoprofen, particularly in high doses, were associated with the greatest risk of gastrointestinal toxicity when compared with diclofenac, etodolac, ibuprofen, indometacin, meloxicam, nabumetone, naproxen, and nimesulide. No firm conclusions were made for the other NSAIDs although there was weak evidence to suggest that the risk of toxicity was slightly higher for indometacin and naproxen than for diclofenac and ibuprofen. As a result of this review the EMEA carried out a full benefit-risk assessment for piroxicam and subsequently placed restrictions on its systemic usage (see p. 126.1).

In a systematic review[24] of controlled epidemiological studies that found a relation between NSAID use and hospital admission for gastric haemorrhage or perforation, the low risk of serious gastric toxicity with ibuprofen appeared to be attributable mainly to the low doses used clinically; higher doses of ibuprofen were associated with a similar risk to indometacin and naproxen. For reference to an association between aspirin and the most severe gastric lesions compared with other NSAIDs, see p. 24.3.

Results from controlled studies have confirmed that the **selective COX-2 inhibitors** are associated with a lower incidence of serious gastrointestinal effects, such as bleeding, perforation, and obstruction, than the traditional NSAIDs[25] (see also Celecoxib, p. 38.1 for further details). However, since the risk of such effects is inherently low in those with no history of peptic ulcer disease, the general prescribing of selective COX-2 inhibitors to all patients requiring an NSAID is questioned, particularly in the light of concerns about their cardiovascular effects (see Thrombotic Events, p. 105.1). In the UK, the use of selective COX-2 inhibitors is limited to patients with good cardiovascular health and at high risk of developing serious gastrointestinal problems if given a non-selective NSAID. High-risk patients include the elderly, those already receiving gastrotoxic drugs, and those with existing gastrointestinal disorders.

There has been concern that **topical** use of NSAIDs may also be associated with gastrointestinal toxicity but a case-controlled study[26] concluded that this route was not associated with significant upper gastrointestinal bleeding or perforation.

Apart from the selection of an NSAID with a lower risk for gastrointestinal toxicity, other methods used for the **prevention or treatment** of NSAID-associated ulceration are discussed under the treatment of peptic ulcer disease on p. 1816.2.

1. Kwo PY, Tremaine WJ. Nonsteroidal anti-inflammatory drug-induced enteropathy: case discussion and review of the literature. *Mayo Clin Proc* 1995; **70:** 55–61.
2. Gleeson MH, *et al.* Non-steroidal anti-inflammatory drugs, salicylates, and colitis. *Lancet* 1996; **347:** 904–5.
3. Evans JMM, *et al.* Non-steroidal anti-inflammatory drugs are associated with emergency admission to hospital for colitis due to inflammatory bowel disease. *Gut* 1997; **40:** 619–22.
4. Hayllar J, Bjarnason I. NSAIDs, Cox-2 inhibitors, and the gut. *Lancet* 1995; **346:** 521–2.
5. Bjorkman DJ. Nonsteroidal anti-inflammatory drug-induced gastrointestinal injury. *Am J Med* 1996; **101** (suppl 1A): 25S–32S.
6. Soll A. Pathogenesis of nonsteroidal anti-inflammatory drug-related upper gastrointestinal toxicity. *Am J Med* 1998; **105** (suppl 5A): 10S–16S.
7. Hawkey CJ. COX-2 inhibitors. *Lancet* 1999; **353:** 307–14. Correction. *ibid.*; 1440. [dose]
8. Wolfe MM, *et al.* Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N Engl J Med* 1999; **340:** 1888–99.
9. Seager JM, Hawkey CJ. ABC of the upper gastrointestinal tract: indigestion and non-steroidal anti-inflammatory drugs. *BMJ* 2001; **323:** 1236–9.
10. Mulberg AE, *et al.* Identification of nonsteroidal antiinflammatory drug-induced gastroduodenal injury in children with juvenile rheumatoid arthritis. *J Pediatr* 1993; **122:** 647–9.
11. Pounder RE. Helicobacter pylori and NSAIDs—the end of the debate? *Lancet* 2002; **358:** 3–4.
12. MacDonald TM, *et al.* Association of upper gastrointestinal toxicity of non-steroidal anti-inflammatory drugs with continued exposure: cohort study. *BMJ* 1997; **315:** 1333–7.
13. Mellemkjaer L, *et al.* Upper gastrointestinal bleeding among users of NSAIDs: a population-based cohort study in Denmark. *Br J Clin Pharmacol* 2002; **53:** 173–81.
14. Kaufman DW, *et al.* Nonsteroidal anti-inflammatory drug use in relation to major upper gastrointestinal bleeding. *Clin Pharmacol Ther* 1993; **53:** 485–94.
15. García Rodríguez LA, Jick H. Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. *Lancet* 1994; **343:** 769–72.
16. Langman MJS, *et al.* Risks of bleeding peptic ulcer associated with individual non-steroidal anti-inflammatory drugs. *Lancet* 1994; **343:** 1075–8.
17. Lewis SC, *et al.* Dose–response relationships between individual nonaspirin nonsteroidal anti-inflammatory drugs (NANSAIDs) and serious upper gastrointestinal bleeding: a meta-analysis based on individual patient data. *Br J Clin Pharmacol* 2002; **54:** 320–6.
18. Bateman DN. NSAIDs: time to re-evaluate gut toxicity. *Lancet* 1994; **343:** 1051–2.
19. Smith CC, *et al.* NSAIDs and gut toxicity. *Lancet* 1994; **344:** 56–7.
20. CSM/MCA. Relative safety of oral non-aspirin NSAIDs. *Current Problems* 1994; **20:** 9–11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015615&RevisionSelectionMethod=LatestReleased (accessed 08/11/07)
21. Laporte J-R, *et al.* Upper gastrointestinal bleeding associated with the use of NSAIDs: newer versus older agents. *Drug Safety* 2004; **27:** 411–20.
22. EMEA. Public CHMP assessment report of medicinal products containing non-selective non steroidal anti-inflammatory drugs (NSAIDs) (issued 7th November, 2006). Available at: http://www.emea.europa.eu/pdfs/human/opiniongen/44213006en.pdf (accessed 08/11/07)
23. CSM/MCA. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and gastrointestinal (GI) safety. *Current Problems* 2002; **28:** 5. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007454&RevisionSelectionMethod=LatestReleased (accessed 08/11/07)
24. Henry D, *et al.* Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. *BMJ* 1996; **312:** 1563–6.
25. Fitzgerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. *N Engl J Med* 2001; **345:** 433–42.
26. Evans JMM, *et al.* Topical non-steroidal anti-inflammatory drugs and admission to hospital for upper gastrointestinal bleeding and perforation: a record linkage case-control study. *BMJ* 1995; **311:** 22–6.

Effects on the kidneys. NSAIDs can produce renal disorders on systemic or topical use,[1] some of which are due to their inhibition of prostaglandin synthesis.[2,3] In the presence of renal vasoconstriction the vasodilator action of prostaglandins increases renal blood flow and thereby helps to maintain renal function.[4,5] Patients whose renal function is being maintained by prostaglandins are therefore at risk from NSAIDs. Such patients include those with impaired circulation, the elderly, those on diuretics, and those with heart failure or renal vascular disease.[2,4] Other risk factors for renal impairment with NSAIDs include dehydration, cirrhosis, surgery, sepsis,[6] and a history of gout or hyperuricaemia.[6,7] The half-life of an NSAID may be a more important determinant of the risk of developing functional renal impairment than the ingested dose.[7] Evidence of renal toxicity due to cyclo-oxygenase-2 (COX-2) selective inhibitors is less extensive; however, such NSAIDS appear to have effects on renal function similar to those of the non-selective NSAIDs.[8,9] A large pharmacoepidemiological analysis[10] of elderly patients taking non-selective NSAIDs or selective COX-2 inhibitors found that about 1 in 200 patients aged over 65 years developed acute kidney injury within 45 days of starting therapy. Most NSAIDs were found to have a similar risk when compared with celecoxib; however, rofecoxib, ibuprofen, and indometacin (listed in increasing order of risk) all showed a higher risk.

ACE inhibitors and angiotensin receptor antagonists can also produce renal impairment and combined use with NSAIDs should be undertaken with great care.[11,12] The Australian Adverse Drug Reactions Advisory Committee[11] stated in August 2003 that over 50% of cases of renal failure reported to the committee were associated with use of NSAIDs, ACE inhibitors, or diuretics (alone or together); where all these were taken together the fatality rate for reported cases of renal failure was 10%.

Prostaglandin inhibition may also lead to salt and water retention particularly when there is pre-existing hypertension or sodium depletion.[4] NSAIDs, therefore, tend to counteract the action of diuretics and antihypertensives.[2,4] There have been isolated reports of severe hyponatraemia and other symptoms resembling the syndrome of inappropriate antidiuretic hormone secretion in patients taking NSAIDs.[13,14]

Potassium homoeostasis is less dependent on prostaglandins and hyperkalaemia occurs infrequently with NSAIDs.[3] It is more likely to occur in patients with specific risk factors such as those receiving potassium supplements or potassium-sparing diuretics.[3] Indometacin appears to be the main NSAID implicated.

NSAIDs may cause acute interstitial nephritis, perhaps involving an allergic response,[2,3,15] and it may progress to interstitial fibrosis or papillary necrosis.[3,16]

Analgesic abuse or prolonged excessive use can produce nephropathy, a condition characterised by renal papillary necrosis and chronic interstitial nephritis, and, eventually, renal failure.[17] Phenacetin, a para-aminophenol derivative, has long been recognised as being one of the main drugs responsible for analgesic nephropathy,[18,19] but nephropathy has also been associated with the long-term use of NSAIDs and paracetamol without phenacetin.[20]

1. O'Callaghan CA, *et al.* Renal disease and use of topical non-steroida anti-inflammatory drugs. *BMJ* 1994; **308:** 110–11.
2. Kendall MJ, Horton RC. Clinical pharmacology and therapeutics *Postgrad Med J* 1990; **66:** 166–85.
3. Whelton A, Hamilton CW. Nonsteroidal anti-inflammatory drugs effects on kidney function. *J Clin Pharmacol* 1991; **31:** 588–98.
4. Harris K. The role of prostaglandins in the control of renal function. *Br J Anaesth* 1992; **69:** 233–5.
5. Kenny GNC. Potential renal, haematological and allergic adverse effects associated with nonsteroidal anti-inflammatory drugs. *Drugs* 1992; **44** (suppl 5): 31–7.
6. MacDonald TM. Selected side-effects: 14. non-steroidal anti-inflammatory drugs and renal damage. *Prescribers' J* 1994; **34:** 77–80.
7. Henry D, *et al.* Consumption of non-steroidal anti-inflammatory drugs and the development of functional renal impairment in elderly subjects: results of a case-control study. *Br J Clin Pharmacol* 1997; **44:** 85–90.
8. Perazella MA, Tray K. Selective cyclooxygenase-2 inhibitors: a pattern of nephrotoxicity similar to traditional nonsteroidal anti-inflammatory drugs. *Am J Med* 2001; **111:** 64–7.
9. Noroian G, Clive D. Cyclo-oxygenase-2 inhibitors and the kidney: a case for caution. *Drug Safety* 2002; **25:** 165–72.
10. Winkelmayer WC, *et al.* Nonselective and cyclooxygenase-2-selective NSAIDs and acute kidney injury. *Am J Med* 2005; **118:** 1092–8.
11. Adverse Drug Reactions Advisory Committee (ADRAC). ACE inhibitor, diuretic and NSAID: a dangerous combination. *Aust Adverse Drug React Bull* 2003; **22:** 14–15. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0308.htm (accessed 08/11/07)
12. Loboz KK, Shenfield GM. Drug combinations and impaired renal function—the 'triple whammy'. *Br J Clin Pharmacol* 2005; **59:** 239–43.
13. Petersson L, *et al.* Water intoxication associated with non-steroidal anti-inflammatory drug therapy. *Acta Med Scand* 1987; **221:** 221–3.
14. Cheung NT, *et al.* Syndrome of inappropriate secretion of antidiuretic hormone induced by diclofenac. *BMJ* 1993; **306:** 186.
15. Ravnskov U. Glomerular, tubular and interstitial nephritis associated with non-steroidal antiinflammatory drugs. Evidence of a common mechanism. *Br J Clin Pharmacol* 1999; **47:** 203–10.
16. Sandler DP, *et al.* Nonsteroidal anti-inflammatory drugs and the risk for chronic renal disease. *Ann Intern Med* 1991; **115:** 165–72.
17. De Broe ME, Elseviers MM. Analgesic nephropathy. *N Engl J Med* 1998; **338:** 446–52.
18. Sandler DP, *et al.* Analgesic use and chronic renal disease. *N Engl J Med* 1989; **320:** 1238–43.
19. Dubach UC, *et al.* An epidemiologic study of abuse of analgesic drugs: effects of phenacetin and salicylate on mortality and cardiovascular morbidity (1968 to 1987). *N Engl J Med* 1991; **324:** 155–60.
20. Perneger TV, *et al.* Risk of kidney failure associated with the use of acetaminophen, aspirin, and nonsteroidal antiinflammatory drugs. *N Engl J Med* 1994; **331:** 1675–9.

Effects on the liver. A retrospective study involving over 220 000 adults who were either using, or had used, NSAIDs identified a small excess risk of serious, acute non-infectious liver injury; in current users there was a twofold increase in risk and there was a predominance of the cholestatic type of liver injury among such patients. Nonetheless, admissions to hospital for liver injury had been rare.[1] In a review[2] of cohort and case-control studies describing an association between NSAIDs and liver disease, the strongest evidence emerged for sulindac. There were also a significant number of reports of hepatotoxicity on rechallenge with diclofenac. Evidence of hepatotoxicity for other NSAIDs was weak, although the risk appeared to be high when they were used with other hepatotoxic drugs. However, the overall incidence of liver disease with NSAIDs was very low.

A later review has also concluded that NSAID-induced hepatotoxicity is an uncommon event.[3] Nevertheless, an increased risk of hepatotoxicity has been associated with the selective cyclo-oxygenase-2 (COX-2) inhibitor lumiracoxib which led to its subsequent withdrawal in many countries (see p. 84.2). For similar reasons, nimesulide has been withdrawn in some countries and its use is limited in others (see p. 101.3).

1. García Rodríguez LA, *et al.* The role of non-steroidal anti-inflammatory drugs in acute liver injury. *BMJ* 1992; **305:** 865–8. Correction. *ibid.*; 920.
2. Manoukian AV, Carson JL. Nonsteroidal anti-inflammatory drug-induced hepatic disorders. *Drug Safety* 1996; **15:** 64–71.
3. O'Connor N, *et al.* Hepatocellular damage from non-steroidal anti-inflammatory drugs. *Q J Med* 2003; **96:** 787–91.

Effects on the lungs. Adverse pulmonary effects such as pneumonitis, alveolitis, pulmonary infiltrates, and pulmonary fibrosis, often suggestive of an allergic or immune reaction, have been reported with several NSAIDs. For references, see under individual monographs.

Effects on the pancreas. A review[1] of drug-induced pancreatitis considered that sulindac was amongst the drugs for which a definite association with pancreatitis had been established. There had been isolated reports of pancreatitis with ketoprofen, mefenamic acid, and piroxicam but any association was considered to be questionable. A more recent population-based, case-controlled study found a substantial variation in the risk of pancreatitis between individual NSAIDs.[2] The increase in risk was highest for diclofenac and ketoprofen (adjusted odds ratios of 5.0 and 4.8, respectively), with indometacin and ibuprofen showing smaller but nonetheless significant increases (odds ratios of 3.6 and 1.5, respectively). Of the other NSAIDs studied (celecoxib, etodolac, naproxen, and rofecoxib), all

showed a small but non-significant increase in risk of pancreatitis in current NSAID users.

For further references see under individual monographs.

1. Underwood TW, Prye CB. Drug-induced pancreatitis. *Clin Pharm* 1993; 12: 440–8.
2. Sørensen HT, *et al.* Newer cyclo-oxygenase-2 selective inhibitors, other non-steroidal anti-inflammatory drugs and the risk of acute pancreatitis. *Aliment Pharmacol Ther* 2006; 24: 111–16.

Effects on the skin. The diverse cutaneous reactions to NSAIDs including those selective for cyclo-oxygenase-2 (COX-2) inhibition have been reviewed.[1-3]

Of 250 children attending a rheumatology clinic 34 (13.6%) were found to have 4 or more facial scars of unknown origin.[4] This number of scars was found in 22.2% of the 116 children who had received naproxen and in 9.2% of the 87 who had received other NSAIDs. Children affected were more likely to have light skin and blue or green eyes. It was unknown whether this was a form of phototoxic reaction but pseudoporphyria-like eruptions associated with NSAIDs, and naproxen in particular (see p. 99.2), have been reported.[5,6]

Concern by the EMEA over the serious nature of skin reactions associated with piroxicam has led to restrictions on the systemic use of piroxicam in the EU (see p. 126.2).

See also Hypersensitivity, below.

1. Bigby M, Stern R. Cutaneous reactions to nonsteroidal anti-inflammatory drugs. *J Am Acad Dermatol* 1985; 12: 866–76.
2. La Grenade L, *et al.* Comparison of reporting of Stevens-Johnson syndrome and toxic epidermal necrolysis in association with selective COX-2 inhibitors. *Drug Safety* 2005; 28: 917–24.
3. Layton D, *et al.* Serious skin reactions and selective COX-2 inhibitors: a case series from prescription-event monitoring in England. *Drug Safety* 2006; 29: 687–96.
4. Wallace CA, *et al.* Increased risk of facial scars in children taking nonsteroidal antiinflammatory drugs. *J Pediatr* 1994; 125: 819–22.
5. Checketts SR, *et al.* Nonsteroidal anti-inflammatory-induced pseudoporphyria: is there an alternative drug? *Cutis* 1999; 63: 223–5.
6. Al-Khenaizan S, *et al.* Pseudoporphyria induced by propionic acid derivatives. *J Cutan Med Surg* 1999; 3: 162–6.

Hypersensitivity. NSAIDs have produced various hypersensitivity reactions in susceptible individuals: the most common include skin rashes, urticaria, rhinitis, angioedema, bronchoconstriction, and anaphylactic shock. Hypersensitivity to NSAIDs appears to occur more frequently in patients with asthma or allergic disorders but other risk factors have been identified (for further details, see under Aspirin, p. 25.2). The occurrence of aspirin sensitivity in patients with asthma and nasal polyps has been referred to as the 'aspirin triad'. There is considerable cross-reactivity between aspirin and other NSAIDs and it is generally recommended that patients who have had a hypersensitivity reaction to aspirin or any other NSAID should avoid all NSAIDs. For references to hypersensitivity reactions associated with NSAIDs, see under individual monographs. See also Effects on the Skin (p. 79.2) for a report suggesting that ketoprofen is more allergenic than other topical NSAIDs.

The selective cyclo-oxygenase-2 (COX-2) inhibitors contain the sulfa moiety ($-SO_2NH_2$) and the licensed product information for some products states that their use is contra-indicated in patients with a sulfonamide (sulfa) allergy. For further information on cross-reactivity between sulfa-containing drugs see Hypersensitivity, under Sulfamethoxazole, p. 367.3.

Overdosage. In general, symptoms of NSAID poisoning are mild, and usually include nausea and vomiting, epigastric pain, tinnitus, headache, drowsiness, blurred vision, and dizziness. Gastrointestinal bleeding may also occur. There have been isolated case reports of more serious toxicity, including seizures, hypotension, apnoea, coma, and renal failure, although usually after ingestion of substantial quantities. Exacerbation of asthma may occur in asthmatics. Seizures are a particular problem with mefenamic acid overdosage.

Treatment of NSAID overdosage is entirely supportive. The benefit of gastric decontamination is uncertain although activated charcoal may be of benefit within 1 hour of ingestion of a potentially toxic amount. Multiple doses of activated charcoal may be useful in enhancing elimination of NSAIDs with long half-lives such as piroxicam and sulindac. Forced diuresis, haemodialysis, or haemoperfusion are unlikely to be of benefit for NSAID overdosage, although haemodialysis may be required if oliguric renal failure develops.

Precautions

All NSAIDs are contra-indicated in patients with active peptic ulceration or gastrointestinal bleeding; in addition, the non-selective NSAIDs should be used with caution, if at all, in patients with a history of such disorders. To reduce the risk of gastrointestinal effects, NSAIDs may be taken with or after food or milk. Histamine H_2-antagonists, proton pump inhibitors such as omeprazole, or misoprostol may be used for a similar purpose in high-risk patients taking non-selective NSAIDs (see Peptic Ulcer Disease, p. 1816.2). The use of proton pump inhibitors with selective inhibitors of cyclo-oxygenase-2 (COX-2) may be appropriate for those with a history of bleeding or with several risk factors for ulceration. However, food, milk, and such measures may reduce the rate and extent of drug absorption. The UK CSM recommends that NSAIDs associated with the lowest risk of gastrointestinal toxicity (see Effects on the Gastrointestinal Tract, under Adverse Effects, p. 105.3) should be tried first in the lowest recommended dose, and not more than one oral NSAID should be used at a time; selective COX-2 inhibitors should be reserved for patients at highest risk of ulcer, perforation, or bleeding, and after assessment of cardiovascular risk. NSAIDs should be used with caution in patients with Crohn's disease or ulcerative colitis as these conditions may be exacerbated.

All NSAIDs are contra-indicated in severe heart failure. Furthermore, diclofenac and selective COX-2 inhibitors should not be used in patients with moderate to severe heart failure, ischaemic heart disease, peripheral arterial disease, or cerebrovascular disease; these NSAIDs should also be used with caution in patients with hypertension, left ventricular dysfunction, oedema, or a history of cardiac failure, and in those with other risk factors for developing 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 patients with risk factors for cardiovascular events.

NSAIDs should be used with caution in patients with infections, since symptoms such as fever and inflammation may be masked (for the suggestion that they should not be used in children with varicella see below). They should also be used with caution in patients with asthma or allergic disorders. NSAIDs (including topical NSAIDs) are contra-indicated in patients with a history of hypersensitivity reactions to such drugs, including those in whom attacks of asthma, angioedema, urticaria, or rhinitis have been precipitated by aspirin or any other NSAID.

Other general precautions to be observed include use in patients with haemorrhagic disorders, connective-tissue disorders, or impaired renal or hepatic function. Patients undergoing therapy with some NSAIDs may need to be monitored for the development of blood, kidney, liver, or eye disorders. NSAIDs should be used with caution in the elderly and may need to be given in reduced doses.

Some NSAIDs can interfere with thyroid function tests by lowering serum-thyroid hormone concentrations.

Further details concerning the precautions of the individual NSAIDs may be found under their respective monographs.

Pregnancy. Most licensed product information recommends avoidance of NSAIDs during pregnancy, unless the proposed benefit outweighs the risks, but in many cases published data on use of the drugs in pregnancy are scanty or absent, making an informed decision difficult. Use of NSAIDs during pregnancy may delay the onset of labour and increase its duration.

Use of NSAIDs during the third trimester of pregnancy may result in the *premature closure of fetal ductus arteriosus*. A recent meta-analysis[1] suggested that the short-term use of NSAIDs was associated with a fifteenfold increase in the risk of premature closure when compared with either placebo or other non-NSAIDs. There were insufficient data to predict the outcome of long-term NSAID treatment in late pregnancy; however, it seemed likely that the risk of premature closure would be even greater with such treatment.

Results from a case-control interview study[2] suggested that prenatal ingestion of aspirin or other NSAIDs might be implicated in *persistent pulmonary hypertension* of the newborn. The authors suggested that these drugs may be responsible for gestational structural or functional alterations of the pulmonary vasculature. However, the primary cause might also have been the underlying disorder for which the NSAIDs or aspirin were ingested. They were unable to pinpoint in which trimester the drugs might have their proposed action. Another study[3] has found that persistent pulmonary hypertension of the newborn is significantly associated with *in-utero* NSAID exposure, particularly to aspirin, ibuprofen, and naproxen. Fetal exposure to an NSAID was confirmed by meconium analysis.

More recently, the findings of a prospective cohort study have suggested that intrauterine exposure to simple analgesics such as aspirin, ibuprofen, and paracetamol may be a risk factor for developing congenital *cryptorchidism*.[4] In 491 Danish mothers directly questioned about analgesic use during pregnancy, there was a non-significant increase in the prevalence of cryptorchidism in boys whose mothers had used simple analgesics during pregnancy; the increase was significant for those mothers reporting the use of more than one analgesic and for those who had taken analgesics for more than 2 weeks. Use during the second trimester also significantly increased the risk. Similar results were noted from a self-administered questionnaire in 834 Danish women; however, in a group of 1463 Finnish women given the same questionnaire, there was generally no association between analgesic use and cryptorchidism. The authors did note that analgesic use appeared to have been under-reported in the questionnaire data.

The risk of *miscarriage* may be increased with NSAID use;[5,6] however, this observation remains to be confirmed. One study[5] also found no association between NSAID use and congenital abnormalities, low birth weight, or preterm birth.

1. Koren G, *et al.* Nonsteroidal antiinflammatory drugs during third trimester and the risk of premature closure of the ductus arteriosus: a meta-analysis. *Ann Pharmacother* 2006; 40: 824–9.
2. Van Marter LJ, *et al.* Persistent pulmonary hypertension of the newborn and smoking and aspirin and nonsteroidal antiinflammatory drug consumption during pregnancy. *Pediatrics* 1996; 97: 658–63.
3. Alano MA, *et al.* Analysis of nonsteroidal antiinflammatory drugs in meconium and its relation to persistent pulmonary hypertension of the newborn. *Pediatrics* 2001; 107: 519–23.
4. Kristensen DM, *et al.* Intrauterine exposure to mild analgesics is a risk factor for development of male reproductive disorders in human and rat. *Hum Reprod* 2010. Available at: http://humrep.oxfordjournals.org/content/early/2010/11/08/humrep.deq323.full.pdf+html (accessed 16/11/10)
5. Nielsen GL, *et al.* Risk of adverse birth outcome and miscarriage in pregnant users of non-steroidal anti-inflammatory drugs: population based observational study and case-control study. *BMJ* 2001; 322: 266–70.
6. Li D-K, *et al.* Exposure to non-steroidal anti-inflammatory drugs during pregnancy and risk of miscarriage: population based cohort study. *BMJ* 2003; 327: 368–71.

Renal impairment. The *BNF* recommends that NSAIDs in general should be avoided if possible, or given at the lowest effective dose for the shortest possible duration to patients with renal impairment and that renal function, and sodium and water retention, should be carefully monitored.

See also under individual monographs.

Thyroid function tests. References[1,2] to the interference with thyroid function tests by some NSAIDs.

1. Bishnoi A, *et al.* Effect of commonly prescribed nonsteroidal anti-inflammatory drugs on thyroid hormone measurements. *Am J Med* 1994; 96: 235–8.
2. Samuels MH, *et al.* Variable effects of nonsteroidal antiinflammatory agents on thyroid test results. *J Clin Endocrinol Metab* 2003; 88: 5710–16.

Varicella. The French regulatory authorities noted in July 2004 that after the report of 3 cases of septic shock, 1 fatal, in children treated with NSAIDs for fever and pain, pharmacovigilance studies had discovered several other cases of severe complications relating to infection of the skin lesions of chickenpox in NSAID-treated children.[1] Although these, and a few reports in the literature[2,3] could not establish a causal relation, it was considered prudent to avoid the use of NSAIDs in children with chickenpox, and licensed product information for the relevant drugs was to be modified appropriately.[1] More recently, a nested case-control study[4] of nearly 250 000 patients with chickenpox or shingles in the UK General Practice Research Database found an increased risk of severe skin and soft tissue complications associated with the use of NSAIDs, mostly in children with chickenpox.

1. Agence Française de Sécurité Sanitaire des Produits de Santé. L'utilisation d'anti-inflammatoires nonstéroïdiens (AINS), dans le traitement de la fièvre et/ou de la douleur, n'est pas recommandée chez l'enfant atteint de varicelle (issued 15th July, 2004). Available at: http://www.agmed.sante.gouv.fr/htm/10/fillrpsc/lp040701.htm (accessed 08/11/07)
2. Zerr DM, *et al.* A case-control study of necrotizing fasciitis during primary varicella. *Pediatrics* 1999; 103: 783–90.
3. Lesko SM, *et al.* Invasive group A streptococcal infection and nonsteroidal antiinflammatory drug use among children with primary varicella. *Pediatrics* 2001; 107: 1108–15.
4. Mikaeloff Y, *et al.* Nonsteroidal anti-inflammatory drug use and the risk of severe skin and soft tissue complications in patients with varicella or zoster disease. *Br J Clin Pharmacol* 2008; 65: 203–9.

Interactions

Interactions involving NSAIDs include enhancement of the effects of oral anticoagulants (especially by azapropazone and phenylbutazone) and increased plasma concentrations of lithium, methotrexate, and cardiac glycosides. The risk of nephrotoxicity may be increased if given with ACE inhibitors, ciclosporin, tacrolimus, or diuretics. Effects on renal function may lead to reduced excretion of some drugs. There may also be an increased risk of hyperkalaemia with ACE inhibitors and some diuretics, including potassium-sparing diuretics. The antihypertensive effects of some antihypertensives including ACE inhibitors, beta blockers, and diuretics may be reduced. Convulsions may occur due to an interaction with quinolones. NSAIDs may increase the effects of phenytoin and sulfonylurea antidiabetics.

Use of more than one NSAID together (including aspirin) should be avoided because of the increased risk of adverse effects. The risk of gastrointestinal bleeding and ulceration associated with NSAIDs is increased when used with corticosteroids, the SSRIs, the SNRI venlafaxine, the antiplatelets clopidogrel and ticlopidine, iloprost, erlotinib, sibutramine, or, possibly, alcohol, bisphosphonates, or

pentoxifylline. There may be an increased risk of haematotoxicity if zidovudine is used with NSAIDs. Ritonavir may increase the plasma concentrations of NSAIDs. Licensed product information for mifepristone advises of a theoretical risk that prostaglandin synthetase inhibition by NSAIDs or aspirin may alter the efficacy of mifepristone. There have been occasional reports of increased adverse effects when NSAIDs were given with misoprostol although such combinations have sometimes been used to *decrease* the gastrointestinal toxicity of NSAIDs.

Further details concerning the interactions of the individual NSAIDs may be found under their respective monographs.

References.
1. Brouwers JRBJ, de Smet PAGM. Pharmacokinetic-pharmacodynamic drug interactions with nonsteroidal anti-inflammatory drugs. *Clin Pharmacokinet* 1994; 27: 462–85.

Antihypertensives. For reference to the relative effects of NSAIDs in antagonising different types of antihypertensive drugs, see Effects on the Cardiovascular System and Effects on the Kidneys under Adverse Effects, p. 105.1 and p. 106.2, respectively.

Aspirin. It has been suggested that NSAIDS such as ibuprofen may reduce the cardioprotective effect of aspirin but see under Interactions of Aspirin, p. 27.1.

Pharmacokinetics

Details of the pharmacokinetics of individual NSAIDs may be found under their respective monographs.

General reviews.
1. Woodhouse KW, Wynne H. The pharmacokinetics of non-steroidal anti-inflammatory drugs in the elderly. *Clin Pharmacokinet* 1987; 12: 111–22.
2. Walson PD, Mortensen ME. Pharmacokinetics of common analgesics, anti-inflammatories and antipyretics in children. *Clin Pharmacokinet* 1989; 17 (suppl 1): 116–37.
3. Simkin PA, *et al.* Articular pharmacokinetics of protein-bound antirheumatic agents. *Clin Pharmacokinet* 1993; 25: 342–50.
4. Lapicque F, *et al.* Protein binding and stereoselectivity of nonsteroidal anti-inflammatory drugs. *Clin Pharmacokinet* 1993; 25: 115–25.
5. Day RO, *et al.* Pharmacokinetics of nonsteroidal anti-inflammatory drugs in synovial fluid. *Clin Pharmacokinet* 1999; 36: 191–210.

Opioid Analgesics

Analgésicos opioides u opiáceos; Analgésiques Opioïdes; Opioid-analgetika; Опиоидные Аналгетики.

Uses and Administration

Opioid analgesics possess some of the properties of naturally occurring or **endogenous opioid peptides**. Endogenous opioid peptides are widely distributed in the CNS and are also found in other parts of the body. They appear to function as neurotransmitters, modulators of neurotransmission, or neurohormones. Their presence in the hypothalamus suggests a role in the regulation of endocrine function. Opioids have been shown to stimulate the release of some pituitary hormones, including prolactin and growth hormone, and to inhibit the release of others, including corticotropin.

Endogenous peptides include the enkephalins, endorphins, and dynorphins; their polypeptide precursors may also be precursors for non-opioid peptides. Pro-enkephalin is the precursor of met- and leu-enkephalin; pro-opiomelanocortin is the precursor of beta-endorphin, beta-lipotrophin, melanocyte-stimulating hormone, and corticotropin; and prodynorphin is the precursor of dynorphins and neoendorphins.

Pharmacologically the opioid analgesics are broadly similar; qualitative and quantitative differences may be dependent on their interaction with **opioid receptors**. There are several types of opioid receptor and they are distributed in distinct patterns through the central and peripheral nervous systems. The three main types in the CNS were originally designated μ (mu), κ (kappa), and δ (delta) although they have been reclassified as OP_3, OP_2, and OP_1, respectively. Activities attributed to the stimulation of these receptors have been as follows:

- μ —analgesia (mainly at supraspinal sites), respiratory depression, miosis, reduced gastrointestinal motility, and euphoria; μ_1 (supraspinal analgesia) and μ_2 (respiratory depression and gastrointestinal activity) subtypes have been postulated
- κ —analgesia (mainly in the spinal cord); less intense miosis and respiratory depression, dysphoria and psychotomimetic effects
- δ —less certain in man, but probably analgesia; selective for enkephalins
- Other receptors include σ (sigma) and ε (epsilon) receptors. The psychotomimetic effects of agonist-antagonists such as pentazocine that are poorly antagonised by naloxone have been thought by some to be mediated by σ receptors

Opioids act at one or more of these receptors as full or partial agonists, or as antagonists. Morphine and similar opioid agonists (sometimes called μ agonists) are considered to act mainly at μ and perhaps at κ and δ receptors. Opioid agonist-antagonists such as pentazocine appear to act as κ agonists and μ antagonists whereas buprenorphine is a partial agonist at μ receptors with some antagonist activity at κ receptors. The opioid antagonist naloxone acts at μ, κ, and δ receptors.

In addition to differing affinities for particular receptors the degree of activation once bound also differs. The full agonist morphine produces maximum activation at the μ receptor and its effects increase with dose, whereas partial agonists and agonist-antagonists may show a 'ceiling effect' in that above a certain level their effects do not increase proportionately with dose.

Other differences between opioid analgesics may relate to their lipid solubility and pharmacokinetics; speed of onset and duration of action may influence the choice of analgesic.

Opioid analgesics have traditionally been classified as weak or strong opioids but use of such terms has the potential to mislead or lead to suboptimal care. An alternative classification is that used in the WHO three-step analgesic ladder (see Cancer Pain, p. 7.1). In this system opioids are divided into those that are used for **mild to moderate pain** and those that are used for **moderate to severe pain**. Examples of opioids in the first group include codeine, dextropropoxyphene, and dihydrocodeine; such opioids are distinguished by the existence of a ceiling effect and are often used with non-opioid analgesics. The principal opioid for the treatment of moderate to severe pain is morphine. Others include diamorphine, fentanyl, methadone, and pethidine.

In addition to the relief of pain, opioids are used in **anaesthesia** for premedication, induction, or maintenance; however, pre-operative use is generally limited to patients who require control of existing pain. In balanced anaesthesia they are used with an anaesthetic and a neuromuscular blocker. When used with an antipsychotic they can produce a state of mild sedation with analgesia called neuroleptanalgesia.

Some opioids are used for analgesia, sedation, and suppression of respiration in the management of mechanically ventilated patients under **intensive care** (p. 1033.1).

Opioids such as codeine, hydrocodone, and hydromorphone are used for the suppression of **cough**; for intractable cough in terminal illness morphine may be used.

Opioids may relieve some forms of **dyspnoea**; morphine and diamorphine are probably the most commonly used in the UK, but dihydrocodeine, hydrocodone, and oxymorphone have also been tried.

Methadone and buprenorphine are used in the treatment of opioid **dependence** (see p. 109.2).

References.
1. Cherny NI. Opioid analgesics: comparative features and prescribing guidelines. *Drugs* 1996; 51: 713–37.
2. Upton RN, *et al.* Pharmacokinetic optimisation of opioid treatment in acute pain therapy. *Clin Pharmacokinet* 1997; 33: 225–44.
3. Walsh D. Advances in opioid therapy and formulations. *Support Care Cancer* 2005; 13: 138–44.
4. Hanks GW, Reid C. Contribution to variability in response to opioids. *Support Care Cancer* 2005; 13: 145–52.
5. Smith HS. Opioid metabolism. *Mayo Clin Proc* 2009; 84: 613–24.

Action. Some references[1-6] to opioid receptors.

1. Pleuvry BJ. Opioid receptors and their ligands: natural and unnatural. *Br J Anaesth* 1991; 66: 370–80.
2. Pleuvry BJ. Opioid receptors and awareness of the Greek alphabet. *Br J Hosp Med* 1992; 48: 678–81.
3. Atcheson R, Lambert DG. Update on opioid receptors. *Br J Anaesth* 1994; 73: 132–4.
4. Dhawan BN, *et al.* International Union of Pharmacology. XII. Classification of opioid receptors. *Pharmacol Rev* 1996; 48: 567–86.
5. Inturrisi CE. Clinical pharmacology of opioids for pain. *Clin J Pain* 2002; 18 (4 suppl): S3–S13.
6. Gourlay GK. Advances in opioid pharmacology. *Support Care Cancer* 2005; 13: 153–9.

Administration in children. See under Precautions, p. 111.1.

Administration in the elderly. See under Precautions, p. 111.1.

Anaesthesia. Opioid analgesics have been given intravenously as supplements during general anaesthesia with inhalational or intravenous drugs. They have also been widely used as premedication before surgery to reduce anxiety, for smooth induction of anaesthesia, to reduce overall anaesthetic requirements, and to provide postoperative pain relief. Such use of opioids is now rare and is restricted to patients already in pain or to those who will be in pain before induction of anaesthesia. Very high doses of morphine have been infused intravenously to produce anaesthesia for cardiac surgery, but shorter acting drugs such as fentanyl and related opioids are generally used now; some may prefer agonist-antagonist opioids. Sedation and respiratory depression may be prolonged necessitating assisted ventilation; reversal of these effects can be achieved by opioid antagonists such as naloxone. For a discussion of the various drugs used to achieve and maintain conditions suitable for surgery, including the use of opioids in the induction and maintenance of anaesthesia, see p. 1899.1. Opioid analgesics, most commonly fentanyl, have been used with an antipsychotic to induce a state known as neuroleptanalgesia in which the patient is calm and indifferent to the surroundings yet is responsive to commands. For a brief discussion of neuroleptanalgesia and similar anaesthetic techniques, see p. 1899.3.

POSTOPERATIVE SHIVERING. Pethidine appears to be effective in the treatment of postoperative shivering (p. 1900.2) but not all opioids are necessarily effective.

Cough. Opioids are used to suppress cough (p. 1651.2). Pholcodine (p. 1675.1) and dextromethorphan (p. 1660.1), which lack classical analgesic activity and have fewer adverse effects, are the most commonly used opioids. Of the analgesic opioids, codeine is the most widely used as a cough suppressant. However, these opioids are seldom sufficiently potent to be effective in severe cough. Morphine and diamorphine are used for the relief of intractable cough in terminal illness, although morphine is now preferred. Methadone has also been used but should be avoided as it has a long duration of action and tends to accumulate.

Cough suppressants containing pholcodine or similar opioids (such as codeine) are generally not recommended for use in children, and should be avoided in those under 6 years of age.

Diarrhoea. Oral rehydration therapy, which is the treatment of choice for acute diarrhoea (p. 1808.2), prevents dehydration, but it does not necessarily shorten the duration of the diarrhoea. Preparations containing codeine, morphine, or other opioids have therefore been used for their antimotility action as adjuncts in the management of acute diarrhoea. However, the WHO considers that such antidiarrhoeal drug therapy is of limited value, and should never be given to children. Furthermore opioids should not be used in conditions where inhibition of peristalsis should be avoided, where abdominal distension develops or in diarrhoeal conditions such as severe ulcerative colitis or antibiotic-associated colitis.

Dyspnoea. Dyspnoea (a subjective feeling of abnormally uncomfortable, difficult, or laboured breathing) is associated with diseases that interfere with oxygenation of the blood. The course of dyspnoea should be established since it is often best relieved by treatment of the underlying disorder (the treatment of dyspnoea associated with asthma and chronic obstructive pulmonary disease (COPD) is discussed on p. 1195.2 and p. 1199.1, respectively). Where this is impossible or ineffective, symptomatic management is required.

Oxygen may reduce dyspnoea in some patients even if dyspnoea is not related to hypoxia. A flow of air directed across the face by a fan can also be effective. Despite the hazards of using benzodiazepines in patients with any form of respiratory depression or pulmonary insufficiency (see under Precautions of Diazepam, p. 1068.1), drugs such as diazepam, lorazepam, or midazolam may be helpful in patients with advanced cancer who have rapid shallow respiration, especially when this is associated with anxiety.[1] Levomepromazine is occasionally used as an alternative.

Opioids may relieve some forms of dyspnoea,[2-4] such as those due to acute left ventricular failure, pulmonary oedema, and malignant chest disease. Guidelines[5,6] (some based on the findings of systematic reviews[7]) and expert consensus statements[8] issued for the management of dyspnoea in palliative care recommend that opioids should be considered in patients with severe and unrelieved dyspnoea. Doses tend to be lower and increments smaller than those used for pain relief.[2] The use of opioids is generally not advised, or only with extreme caution, in patients with obstructive airways disease whose dyspnoea may be relieved by other means. However, they may be useful in patients with advanced COPD whose dyspnoea is resistant to conventional management.[9] Morphine and diamorphine are commonly used opioids for dyspnoea, but dihydrocodeine, hydrocodone, and oxymorphone have also been tried. It is unclear if all opioids are equally effective.[4]

Nebulised morphine, hydromorphone, or fentanyl have been tried for the management of dyspnoea, and there are anecdotal reports of benefit, especially in palliative care, but evidence from controlled studies to date does not support such use.[2,3,5,10-13] See also under Morphine, p. 94.3.

In patients with advanced cancer and intractable dyspnoea unresponsive to the above measures, chlorpromazine may be useful to relieve air hunger and sedate dying patients who have unrelieved distress;[1] midazolam may be used as an alternative. Promethazine has also been used.

High doses of a corticosteroid such as dexamethasone may help to relieve dyspnoea in patients with airways obstruction due to a tumour by reducing oedema around the tumour.

1. Walsh D. Dyspnoea in advanced cancer. *Lancet* 1993; **342**: 450–1.
2. Davis C, Percy G. Breathlessness, cough, and other respiratory problems. In: Fallon M, Hanks G, eds. *ABC of palliative care*. 2nd ed. London: BMJ Publishing Group, 2006: 13–16.
3. Jennings AL, *et al.* Opioids for the palliation of breathlessness in terminal illness. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2001 (accessed 26/06/08).
4. Kvale PA, *et al.* American College of Chest Physicians. Lung cancer: palliative care. *Chest* 2003; **123** (suppl): 284S–311S. Also available at: http://www.chestjournal.org/cgi/reprint/123/1_suppl/284S.pdf (accessed 26/06/08)
5. Lanken PN, *et al.* ATS End-of-Life Care Task Force. An official American Thoracic Society clinical policy statement: palliative care for patients with respiratory diseases and critical illnesses. *Am J Respir Crit Care Med* 2008; **177**: 912–27. Also available at: http://ajrccm.atsjournals.org/cgi/reprint/177/8/912.pdf (accessed 02/08/10)
6. Qaseem A, *et al.* Clinical Efficacy Assessment Subcommittee of the American College of Physicians. Evidence-based interventions to improve the palliative care of pain, dyspnea, and depression at the end of life: a clinical practice guideline from the American College of Physicians. *Ann Intern Med* 2008; **148**: 141–6. Also available at: http://www.annals.org/content/148/2/141.full (accessed 02/08/10)
7. Lorenz KA, *et al.* Evidence for improving palliative care at the end of life: a systematic review. *Ann Intern Med* 2008; **148**: 147–59. Correction. *ibid.* 2009; **151**: 674.
8. Mahler DA, *et al.* American College of Chest Physicians consensus statement on the management of dyspnea in patients with advanced lung or heart disease. *Chest* 2010; **137**: 674–91.
9. Rocker G, *et al.* Palliation of dyspnoea in advanced COPD: revisiting a role for opioids. *Thorax* 2009; **64**: 910–15.
10. Chandler S. Nebullzed opioids to treat dyspnea. *Am J Hosp Palliat Care* 1999; **16**: 418–22.
11. Foral PA, *et al.* Nebulized opioids use in COPD. *Chest* 2004; **125**: 691–4.
12. Brown SJ, *et al.* Nebulized morphine for relief of dyspnea due to chronic lung disease. *Ann Pharmacother* 2005; **39**: 1088–92.
13. Kallet RH. The role of inhaled opioids and furosemide for the treatment of dyspnea. *Respir Care* 2007; **52**: 900–10.

Pain. Opioid analgesics are used for the relief of acute and chronic pain (see Choice of Analgesic, p. 4.2). Not every type of pain responds; neuropathic pain, for example, may not be alleviated by opioid therapy. For further discussion of specific pain states and the role of opioid analgesics in their treatment see p. 6.3 onwards.

There has also been interest in the local analgesic effects of opioids themselves.[1,2]

The use of opioid analgesics in opioid-dependent patients receiving maintenance treatment with an opioid is the subject of much debate; however, some consider such use to be appropriate in the management of acute pain in these patients and recommendations have been issued.[3]

1. Thompson DF, Pierce DR. Local analgesia with opioid drugs. *Ann Pharmacother* 1995; **29**: 189–90.
2. Stein C. The control of pain in peripheral tissue by opioids. *N Engl J Med* 1995; **332**: 1685–90.
3. Alford DP, *et al.* Acute pain management for patients receiving maintenance methadone or buprenorphine therapy. *Ann Intern Med* 2006; **144**: 127–34.

HEADACHE. Opioid analgesics such as codeine are sometimes included in oral compound analgesic preparations used in the initial treatment of migraine (p. 670.3) or tension-type headache (p. 671.3), but are best avoided, especially in patients who have frequent attacks.

Restless legs syndrome. Some opioids may be beneficial in the treatment of restless legs syndrome (see Sleep-associated Movement Disorders, p. 1034.2), although evidence is scanty.

Sedation. In addition to their analgesic action opioids have been used for their sedative properties. Mention of this use of opioids can be found in the discussions of anaesthesia (p. 1899.1), endoscopy (p. 1032.3), and intensive care (p. 1033.1).

Tetanus. Opioid analgesics can be used to provide analgesia and additional sedation in patients undergoing treatment for tetanus (see p. 211.2 and p. 2029.2). Opioids such as fentanyl, morphine, and sufentanil have also been given to control the sympathetic overactivity in such patients.[1-3]

1. Rocke DA, *et al.* Morphine in tetanus—the management of sympathetic nervous system overactivity. *S Afr Med J* 1986; **70**: 666–8.
2. Moughabghab AV, *et al.* Management of autonomic dysfunction in severe tetanus: the use of fentanyl. *Can J Anaesth* 1995; **42**: 955.
3. Bhagwanjee S, *et al.* Management of sympathetic overactivity in tetanus with epidural bupivacaine and sufentanil: experience with 11 patients. *Crit Care Med* 1999; **27**: 1721–5.

Dependence and Withdrawal

Repeated use of opioids is associated with the development of psychological and physical dependence. Although this is less of a problem with legitimate therapeutic use, dependence may develop rapidly when opioids are regularly abused for their euphoriant effects. Drug dependence of the opioid type is characterised by an overwhelming need to keep taking the drug (or one with similar properties), by a physical requirement for the drug in order to avoid withdrawal symptoms, and by a tendency to increase the dose owing to the development of tolerance.

Abrupt withdrawal of opioids from persons physically dependent on them precipitates a withdrawal syndrome, the severity of which depends on the individual, the drug used, the size and frequency of the dose, and the duration of drug use. Withdrawal symptoms may also follow the use of an opioid antagonist such as naloxone or a mixed agonist and antagonist such as pentazocine in opioid-dependent persons. Neonatal abstinence syndrome may occur in the offspring of opioid-dependent mothers and these infants can suffer withdrawal symptoms at birth.

Opioid analgesics can be classified according to the receptors at which they act (see Uses and Administration, p. 108.1) and withdrawal syndromes are characteristic for a receptor type. Cross-tolerance and cross-dependence can be expected between opioids acting at the same receptors. Dependence associated with morphine and closely related μ-agonists appears to result in more severe withdrawal symptoms than those associated with κ-receptor agonists. Onset and duration of withdrawal symptoms also vary according to the duration of action of the specific drug. With morphine and diamorphine *withdrawal symptoms* usually begin within a few hours, reach a peak within 36 to 72 hours, and then gradually subside; they develop more slowly with methadone. Withdrawal symptoms include yawning, mydriasis, lachrymation, rhinorrhoea, sneezing, muscle tremor, weakness, sweating, anxiety, irritability, disturbed sleep or insomnia, restlessness, anorexia, nausea, vomiting, loss of weight, diarrhoea, dehydration, leucocytosis, bone pain, abdominal and muscle cramps, gooseflesh, vasomotor disturbances, and increases in heart rate, respiratory rate, blood pressure, and temperature. Some physiological values may not return to normal for several months after the acute withdrawal syndrome.

Withdrawal symptoms may be terminated by a suitable dose of the original or a related opioid. Tolerance diminishes rapidly after withdrawal so that a previously tolerated dose may prove fatal.

For a discussion of the treatment of opioid dependence and neonatal abstinence syndrome, see below and p. 110.1, respectively.

Review.

1. Van Ree JM, *et al.* Opioids, reward and addiction: an encounter of biology, psychology, and medicine. *Pharmacol Rev* 1999; **51**: 341–96.

Diagnosis. Naloxone (p. 1564.2) and other opioid antagonists have been used to diagnose opioid dependence.

Treatment of opioid dependence. The treatment of opioid dependence has been the subject of many reviews and discussions.[1-10]

Planned withdrawal (**detoxification**) may be effected slowly or rapidly. The usual method in many countries is to replace the drug of dependence with *methadone* (an opioid agonist) given as a liquid oral preparation, and then gradually withdraw the methadone if possible. Methadone is suitable for withdrawal therapy because it can be given orally and its long half-life allows once daily use. Oral *diamorphine* has been used similarly to methadone; reefers containing diamorphine have also been used in some centres. *Dihydrocodeine* tablets have been used successfully. The partial opioid agonist *buprenorphine*, given sublingually, is another alternative to methadone in the treatment of opioid dependence, and withdrawal symptoms may possibly resolve more quickly than with methadone.[11] However, it should only be given to patients with moderate dependence; those dependent on high doses of opioids may have withdrawal symptoms when given buprenorphine. The methadone derivative *levacetylmethadol* was a more recent introduction but its proarrhythmic effects have led to its use being suspended.

Iatrogenic opioid dependence may occur in patients receiving μ-agonists such as morphine, fentanyl, or pethidine for the management of acute pain or in an intensive care setting for more than 5 to 10 days. Methadone has been used successfully to manage opioid withdrawal in adult intensive care patients.[12] However, some[13] avoid using methadone to manage withdrawal in children because of the stigma of its associations with managing withdrawal in drug addicts. In physically dependent but non-addicted patients, gradual weaning using the same opioid that was used therapeutically is preferred where possible, although in some cases, it may be necessary to change to a different opioid because of ease of use, duration of action, and ability to taper the dose; virtually any opioid can be used.[13]

Other drugs used in the management of opioid withdrawal include alpha$_2$-adrenoceptor agonists such as *clonidine* and opioid antagonists such as *naltrexone* and *naloxone*. Clonidine may help to suppress symptoms of opioid withdrawal, such as anxiety, insomnia, and muscle aches. It appears to be more effective when used in the control of symptoms after abrupt withdrawal than when used during gradual withdrawal of methadone. Hypotension may limit its usefulness in some patients. The clonidine analogue *lofexidine* may produce similar results to those obtained with clonidine and appears to be less hypotensive.[14]

Naltrexone and naloxone block the euphoriant effects of opioids although their use as monotherapy in detoxification is limited by unacceptable opioid withdrawal effects. Naltrexone may be used with alpha$_2$-adrenoceptor agonists such as clonidine or lofexidine to ameliorate symptoms but there are insufficient data to determine whether such combinations reduce the duration of withdrawal treatment or increase the rate of transfer to maintenance therapy with an opioid antagonist.[15] Naloxone and naltrexone are also being used in the relatively new technique of rapid or ultra rapid opioid detoxification,[16-18] which is achieved while the patient is heavily sedated or under *general anaesthesia* and hence unaware of any unpleasant withdrawal symptoms. However, although detoxification may be achieved within 24 hours and has a high initial success rate, the technique itself is not without risks and it does not obviate the need for maintenance treatment (see below).

Concomitant counselling and other psychosocial services have been shown to be important in the outcome of withdrawal therapy.[19,20] Detoxification alone does not ensure long-term abstinence.

Several other drugs may be of use as **adjuncts** in the management of withdrawal symptoms. *Diphenoxylate* with atropine or *loperamide* may be used for the control of diarrhoea. *Promethazine* has been used for its antiemetic and sedative actions. Beta blockers such as *propranolol* may be of use for patients with pronounced somatic anxiety symptoms. *Benzodiazepines* or *clomethiazole* can be given to relieve anxiety and associated insomnia but only short courses should be used in order to minimise the risk of dependence and abuse.

Long-term **maintenance** treatment (stabilisation treatment) with an opioid may be tried, with psychosocial support, to enable the patient to acquire some form of social stability before, if possible, planned withdrawal. *Methadone* is most commonly used; the use of *diamorphine* although feasible[21,22] is controversial[23] and is advocated by only a few individual centres. *Buprenorphine* is another possibility.[24] The use of methadone for maintenance has been reviewed.[25-27] *Naltrexone* can be effective in maintaining abstinence in opioid addicts after detoxification, especially after rapid or ultra rapid detoxification. It is considered that naltrexone would probably be of most use in highly motivated addicts with good sociological and psychological support to discourage impulsive use of opioids.[1,28,29]

The problems associated with the management of the **pregnant** patient with opioid dependence have been discussed.[30] The aim should be to stabilise the patient first using *methadone* since acute withdrawal can result in fetal death. Drug withdrawal is best done slowly during the second trimester. It has been suggested that if patients present during the final trimester and cannot be detoxified, maintenance with *diamorphine* might be preferable to the use of methadone as it might produce less severe withdrawal symptoms in the neonate.[31] The management of neonatal abstinence syndrome is discussed on p. 110.1.

1. Herridge P, Gold MS. Pharmacological adjuncts in the treatment of opioid and cocaine addicts. *J Psychoactive Drugs* 1988; **20**: 233–42.
2. Guthrie SK. Pharmacologic interventions for the treatment of opioid dependence and withdrawal. *DICP Ann Pharmacother* 1990; **24**: 721–34.
3. Wodak A. Managing illicit drug use: a practical guide. *Drugs* 1994; **47**: 446–57.
4. Mattick RP, Hall W. Are detoxification programmes effective? *Lancet* 1996; **347**: 97–100.
5. Seivewright NA, Greenwood J. What is important in drug misuse treatment? *Lancet* 1996; **347**: 373–6.
6. National Concensus Development Panel on Effective Medical Treatment of Opiate Addiction. Effective medical treatment of opiate addiction. *JAMA* 1998; **280**: 1936–43.
7. O'Connor PG, Fiellin DA. Pharmacological treatment of heroin-dependent patients. *Ann Intern Med* 2000; **133**: 40–54.
8. Gonzalez G, *et al.* Treatment of heroin (diamorphine) addiction: current approaches and future prospects. *Drugs* 2002; **62**: 1331–43.
9. Raisch DW, *et al.* Opioid dependence treatment, including buprenorphine/naloxone. *Ann Pharmacother* 2002; **36**: 312–21.
10. DoH (England) and the devolved administrations (2007). *Drug misuse and dependence: UK guidelines on clinical management* (updated September 2007). London: Department of Health (England), the Scottish Government, Welsh Assembly Government and Northern Ireland Executive. Also available at: http://www.nta.nhs.uk/uploads/clinical_guidelines_2007.pdf (accessed 02/08/10)
11. Gowing L, *et al.* Buprenorphine for the management of opioid withdrawal. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2009 (accessed 02/08/10).
12. Böhrer H, *et al.* Methadone treatment of opioid withdrawal in intensive care patients. *Lancet* 1993; **341**: 636–7.
13. Yaster M, *et al.* The management of opioid and benzodiazepine dependence in infants, children, and adolescents. *Pediatrics* 1996; **98**: 135–40.
14. Gowing L, *et al.* Alpha$_2$-adrenergic agonists for the management of opioid withdrawal. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 02/08/10).
15. Gowing L, *et al.* Opioid antagonists with minimal sedation for opioid withdrawal. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 02/08/10).
16. Justins D. Rapid opioid detoxification under anaesthesia. *Hosp Med* 1998; **59**: 180.
17. Cook TM, Collins PD. Rapid opioid detoxification under anaesthesia. *Hosp Med* 1998; **59**: 245–7.

18. Gowing L, *et al.* Opioid antagonists under heavy sedation or anaesthesia for opioid withdrawal. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 02/08/10).
19. McLellan AT, *et al.* The effects of psychosocial services in substance abuse treatment. *JAMA* 1993; 269: 1953–9.
20. Amato L, *et al.* Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 02/08/10).
21. Perneger TV, *et al.* Randomised trial of heroin maintenance programme for addicts who fail in conventional drug treatments. *BMJ* 1998; 317: 13–18.
22. Rehm J, *et al.* Feasibility, safety, and efficacy of injectable heroin prescription for refractory opioid addicts: a follow-up study. *Lancet* 2001; 358: 1417–20.
23. Farrell M, Hall W. The Swiss heroin trials: testing alternative approaches. *BMJ* 1998; 316: 639.
24. Kakko J, *et al.* 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomised, placebo-controlled trial. *Lancet* 2003; 361: 662–8.
25. Farrell M, *et al.* Methadone maintenance treatment in opiate dependence: a review. *BMJ* 1994; 309: 997–1001.
26. Ward J, *et al.* Role of maintenance treatment in opioid dependence. *Lancet* 1999; 353: 221–6.
27. Bell J, Zador D. A risk-benefit analysis of methadone maintenance treatment. *Drug Safety* 2000; 22: 179–90.
28. Ginzburg HM, MacDonald MG. The role of naltrexone in the management of drug abuse. *Med Toxicol* 1987; 2: 83–92.
29. Gonzalez JP, Brogden RN. Naltrexone: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the management of opioid dependence. *Drugs* 1988; 35: 192–213.
30. Gerada C, *et al.* Management of the pregnant opiate user. *Br J Hosp Med* 1990; 43: 138–41.
31. Thomas CS, Osborn M. Inhaling heroin during pregnancy. *BMJ* 1988; 296: 1672.

NEONATAL ABSTINENCE SYNDROME. Infants born to opioid-dependent mothers may suffer withdrawal, with signs including CNS hyperirritability, gastrointestinal dysfunction, respiratory distress, yawning, sneezing, mottling, and fever. Onset of symptoms is partly dependent on the drug and varies from shortly after birth to 2 weeks of age, although most symptoms appear within 72 hours. Some symptoms may persist for 3 months or more. It is important to remember that many infants may have also been exposed to other licit and illicit substances, including alcohol

The American Academy of Pediatrics (AAP)[1] recommended that treatment of the neonate with abstinence syndrome should be mainly supportive and considered that many infants with signs of drug withdrawal could be managed in this way. They advised adoption of abstinence scoring methods to judge the need for drug therapy, although such systems do not appear to have been validated. Drugs that have been used for opioid withdrawal include paregoric (a USP 36 preparation containing opium), diluted tincture of opium, morphine, methadone, diazepam, chlorpromazine, phenobarbital, and clonidine. Naloxone should not routinely be given to infants of opioid-dependent mothers because of the risk of seizures with abrupt opioid withdrawal. The AAP[1] made no definite recommendations but considered that, when appropriate, specific drug therapy should be used for treatment of withdrawal symptoms. Thus for opioid withdrawal, tincture of opium was the preferred drug. Others favour treatment with oral morphine solution.[2,3] The *BNFC* also notes that morphine is widely used and the dose can be easily adjusted; however, it is stated that methadone may provide smoother control of symptoms.

Practice varies widely and evidence for the efficacy of particular drugs in the management of neonatal abstinence syndrome is scanty and difficult to compare.[4,5] It has been suggested that diazepam may be less useful than phenobarbital or paregoric but the use of paregoric (which contains both camphor and alcohol) has been questioned. In the UK, chlorpromazine has also been widely used[6] although a systematic review[7] found insufficient evidence to support such use. The authors[7] also found that phenobarbital may reduce the severity of withdrawal symptoms in those receiving an opioid; there was insufficient evidence to support the use of clonidine.

1. American Academy of Pediatrics, Committee on Drugs. Neonatal drug withdrawal. *Pediatrics* 1998; 101: 1079–88. Correction. *ibid.*; 102: 660 [dosage error].
2. Gregg JEM, *et al.* Maternal narcotic abuse and the newborn. *Arch Dis Child* 1988; 63: 684.
3. Jansson LM, *et al.* The opioid-exposed newborn: assessment and pharmacologic management. *J Opioid Manag* 2009; 5: 47–55.
4. Theis JGW, *et al.* Current management of the neonatal abstinence syndrome: a critical analysis of the evidence. *Biol Neonate* 1997; 71: 345–56.
5. Johnson K, *et al.* Treatment of neonatal abstinence syndrome. *Arch Dis Child Fetal Neonatal Ed* 2003; 88: F2–F5.
6. Morrison CL, Siney C. A survey of the management of neonatal opiate withdrawal in England and Wales. *Eur J Pediatr* 1996; 155: 323–6.
7. Osborn DA, *et al.* Sedatives for opiate withdrawal in newborn infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 26/06/08).

Adverse Effects

In usual doses the commonest adverse effects of opioid analgesics are nausea, vomiting, constipation, drowsiness, and confusion; tolerance to these (except constipation) generally develops with long-term use. Micturition may be difficult and there may be ureteric or biliary spasm; the latter may be associated with alterations in liver enzyme values. There is also an antidiuretic effect. Dry mouth, dizziness, sweating, facial flushing, headache, vertigo, bradycardia, tachycardia, palpitations, orthostatic hypotension, hypothermia, restlessness, changes of mood, decreased libido or potency, hallucinations, and miosis also occur. These effects tend to occur more commonly in ambulant patients than in those at rest in bed and in those without severe pain. Raised intracranial pressure occurs in some patients. Muscle rigidity has been reported after high doses. The euphoric activity of opioids has led to their abuse. For a discussion of opioid dependence, see p. 109.1.

Larger doses of opioids produce respiratory depression and hypotension, with circulatory failure and deepening coma. Convulsions may occur, especially in infants and children. Rhabdomyolysis progressing to renal failure has been reported in overdosage. Death may occur from respiratory failure. Toxic doses of specific opioids vary considerably with the individual and regular users may tolerate large doses. The triad of coma, pinpoint pupils, and respiratory depression is considered indicative of opioid overdosage; dilatation of the pupils occurs as hypoxia develops. Pulmonary oedema after overdosage is a common cause of fatalities among opioid addicts.

Morphine and some other opioids have a dose-related histamine-releasing effect which may be responsible in part for reactions such as urticaria and pruritus as well as hypotension and flushing. Contact dermatitis has been reported and pain and irritation may occur on injection. Anaphylactic reactions after intravenous injection have been reported rarely.

The adverse effects associated with individual opioid analgesics may reflect to some extent their activity at specific opioid receptors (see Uses and Administration, p. 108.1) or may result from a direct toxic effect.[1,2] Some adverse effects of pure opioid agonists, such as the respiratory depressant effect of morphine, are dose related, whereas agonist-antagonists such as buprenorphine, butorphanol, and nalbuphine exhibit a 'ceiling effect' as the dose increases.

The type and extent of adverse effects seen in practice may depend on whether or not opioid-sensitive pain is present, whether the opioid analgesic is being given for the control of chronic severe pain or acute pain, and the route used. In a review[3] of the use of opioids in *chronic pain* it was noted that, despite worries to the contrary, respiratory depression and dependence liability are not generally a problem when appropriate doses are used to treat opioid-sensitive pain. In fact the presence of opioid-sensitive pain appears to protect against the respiratory depressant effect, although it may occur if the source of opioid-sensitive pain is removed (e.g. by surgery) without adequate reduction in opioid dosage. The adverse effects of opioid analgesics when used in advanced cancer have also been discussed.[4] Constipation was considered to be the most troublesome adverse effect; significant respiratory depression was rarely seen with recommended regimens, since pain antagonises the central depressant effects of morphine.

In the context of *acute postoperative pain* opioid-induced respiratory depression is of concern but short-term postoperative use is unlikely to cause dependence (although see Treatment of Opioid Dependence, p. 109.2 for references to iatrogenic physical dependence).[5] It was hoped that giving opioids by the *spinal route* would result in fewer adverse effects, especially respiratory depression. In postoperative pain relief with spinal opioids, the incidence of adverse effects is said to be low when patients are properly monitored.[6] However, some[7] have reported pruritus, nausea and vomiting, and urinary retention to be common and respiratory depression to occur; more seriously the appearance of respiratory depression could be considerably delayed. These effects were more common with morphine, but all opioid analgesics had the propensity to produce respiratory depression when given spinally.[7] Delayed respiratory depression has been attributed to the poor lipid solubility of morphine, but does occur after other opioids. Some have considered that despite earlier worries, potentially fatal late respiratory depression was as rare with the spinal route as postoperative respiratory depression with the conventional route.[8,9] Disputes regarding the frequency of respiratory depression associated with even conventional use of opioid analgesics might be due to the methods used for measuring respiratory effects.[10] The incidence of ventilatory depression has been reported to be higher after intrathecal than epidural use of morphine.[11]

1. Duthie DJR, Nimmo WS. Adverse effects of opioid analgesic drugs. *Br J Anaesth* 1987; 59: 61–77.
2. Schug SA, *et al.* Adverse effects of systemic opioid analgesics. *Drug Safety* 1992; 7: 200–13.
3. McQuay HJ. Opioids in chronic pain. *Br J Anaesth* 1989; 63: 213–26.
4. Twycross RG, Lack SA. *Oral morphine in advanced cancer.* 2nd ed. Beaconsfield: Beaconsfield Publishers, 1989.
5. Mitchell RWD, Smith G. The control of acute postoperative pain. *Br J Anaesth* 1989; 63: 147–58.
6. Lutz LJ, Lamer TJ. Management of postoperative pain: review of current techniques and methods. *Mayo Clin Proc* 1990; 65: 584–96.
7. Morgan M. The rational use of intrathecal and extradural opioids. *Br J Anaesth* 1989; 63: 165–88.
8. Anonymous. Spinal opiates revisited. *Lancet* 1986; i: 655–6.
9. McQuay HJ. Spinal opiates. *Br J Hosp Med* 1987; 37: 354–5.
10. Wheatley RG, *et al.* Postoperative hypoxaemia: comparison of extradural, i.m. and patient-controlled opioid analgesia. *Br J Anaesth* 1990; 64: 267–75.
11. Gustafsson LL, *et al.* Adverse effects of extradural and intrathecal opiates: report of a nationwide survey in Sweden. *Br J Anaesth* 1982; 54: 479–85.

Effects on the cardiovascular system. For reference to histamine release and cardiovascular effects following the intravenous administration of some opioids see under Pethidine, p. 122.3.

Effects on the endocrine system. Endogenous opioid peptides may have a role in the regulation of endocrine function. Like endorphin and enkephalins, morphine has been found to stimulate prolactin release[1] and synthetic analogues of morphine are reported to have similar properties; long-term intrathecal opioids (morphine or hydromorphone) have been reported to produce hypogonadotrophic hypogonadism, adrenal insufficiency, and growth hormone deficiency, although tolerance to the effects on prolactin develops with long-term use.[2] Opioids such as morphine are also part of a large group of drugs implicated in causing hyperglycaemia.[3]

1. Heil K, Wernze H. Drug-induced changes in prolactin secretion: clinical implications. *Med Toxicol* 1988; 3: 463–98.
2. Abs R, *et al.* Endocrine consequences of long-term intrathecal administration of opioids. *J Clin Endocrinol Metab* 2000; 85: 2215–22.
3. O'Byrne S, Feely J. Effects of drugs on glucose tolerance in non-insulin-dependent diabetics (part II). *Drugs* 1990; 40: 203–19.

Treatment of Adverse Effects

Activated charcoal may be given orally in conscious patients if a substantial overdose has been ingested within 1 hour provided that the airway can be protected (see below) it should be considered in all patients if a substantial amount of a modified-release preparation has been ingested.

Intensive supportive therapy may be required to correct respiratory failure and shock. In addition, the specific antagonist naloxone is used for rapid reversal of the severe respiratory depression and coma produced by excessive doses of opioid analgesics (see p. 1563.1). Since naloxone has a shorter duration of action than many opioids patients who have already responded should be kept under close observation for signs of relapse and repeated injections given according to the respiratory rate and depth of coma. Alternatively, in situations where repeated administration is required, such as where a longer acting opioid is known or suspected to be the cause of symptoms, a continuous intravenous infusion of naloxone, adjusted according to response, may be used. All patients should be observed for at least 6 hours after the last dose of naloxone.

The use of opioid antagonists such as naloxone in persons physically dependent on opioids may induce withdrawal symptoms.

Activated charcoal. The National Poisons Information Service in the UK considers the benefit of gastric decontamination in the management of overdosage with opioid analgesics to be uncertain. However, it is suggested that oral activated charcoal may be considered if given within 1 hour of ingestion and the quantity of opioid analgesic is substantial or, for these specific drugs, exceeds the following amount:

- buprenorphine: 100 micrograms/kg (adults and children)
- codeine: 3 mg/kg (adults and children)
- dihydrocodeine: 3 mg/kg (adults and children)
- methadone: any amount in an opioid-naive patient or more than the prescribed daily dose if on methadone therapeutically
- tramadol: 500 mg (adult); 10 mg/kg (child)

See also under individual monographs.

Constipation. For reference to the use of opioid antagonists, particularly naloxone, to relieve opioid-induced constipation without compromising analgesic control in patients receiving long-term therapy with opioids, see Reversal of Opioid Effects under Uses and Administration of Naloxone, p. 1564.1.

References.
1. Kurz A, Sessler DI. Opioid-induced bowel dysfunction: pathophysiology and potential new therapies. *Drugs* 2003; 63: 649–71.

Precautions

Opioid analgesics are generally contra-indicated in acute respiratory depression and obstructive airways disease although opioids such as morphine are used in some forms of dyspnoea (see p. 108.3). They are also contra-indicated or should be used with great caution in acute alcoholism, convulsive disorders, head injuries, and conditions in which intracranial pressure is raised. They should not be given to comatose patients. They have an inhibitory effect on

gastrointestinal motility and should be avoided in patients at risk of paralytic ileus.

Opioid analgesics should be given with caution or in reduced doses to patients with hypothyroidism, adrenocortical insufficiency, asthma or decreased respiratory reserve, renal or hepatic impairment, prostatic hyperplasia, hypotension, shock, inflammatory or obstructive bowel disorders, or myasthenia gravis. Dosage should be reduced in elderly or debilitated patients.

Opioid analgesics should be given with great care to infants, especially neonates. Their use during labour may cause respiratory depression in the neonate. Babies born to opioid-dependent mothers may suffer withdrawal symptoms (see Neonatal Abstinence Syndrome, p. 110.1).

Therapy with opioid analgesics should be stopped gradually in patients who may have developed physical dependence, to avoid precipitating withdrawal symptoms (see Dependence, p. 109.1). Opioid analgesics with some antagonist activity, such as buprenorphine, butorphanol, nalbuphine, or pentazocine, may precipitate withdrawal symptoms in physically dependent patients who have recently used pure agonists such as morphine.

Drowsiness may affect the ability to perform skilled tasks; those so affected should not drive or operate machinery.

Asthma. Opioids appear to be safe and may be used with caution in controlled asthma; however, they should be avoided during acute exacerbations.[1]

1. Barnes PJ, Chung KF. Difficult asthma. *BMJ* 1989; 299: 1031–2.

Biliary-tract disorders. It is usually recommended that opioids such as morphine should either be avoided in patients with biliary disorders or that they should be given with an antispasmodic. Morphine can cause an increase in intrabiliary pressure as a result of effects on the sphincter of Oddi[1] and may therefore be expected to exacerbate rather than relieve pain in patients with biliary colic (p. 6.3) or other biliary-tract disorders. Biliary-type pain after cholecystectomy has also been associated with codeine[2] and morphine.[3]

Morphine caused a more marked delay in gallbladder emptying than pethidine, pentazocine, or butorphanol in a study[4] in healthy subjects; this was considered confirmation that morphine should be avoided in biliary disorders. In another study[5] fentanyl and sufentanil did not constrict the common bile duct like morphine; they may be suitable for perioperative pain control in patients in whom spasm of the common bile duct is undesirable. The suggestion that pethidine should be preferred to morphine in patients with acute pancreatitis (p. 10.2), because of its lesser effect on the bile duct, has been questioned.[6]

1. Helm JF, *et al.* Effects of morphine on the human sphincter of Oddi. *Gut* 1988; 29: 1402–7.
2. Druart-Blazy A, *et al.* The underestimated role of opiates in patients with suspected sphincter of Oddi dysfunction after cholecystectomy. *Gastroenterol Clin Biol* 2005; 29: 1220–3.
3. Roberts-Thomson IC, *et al.* Sympathetic activation: a mechanism for morphine induced pain and rises in liver enzymes after cholecystectomy? *Gut* 1990; 31: 217–21.
4. Hahn M, *et al.* The effect of four narcotics on cholecystokinin octapeptide stimulated gall bladder contraction. *Aliment Pharmacol Ther* 1988; 2: 129–34.
5. Vieira ZEG, *et al.* Evaluation of fentanyl and sufentanil on the diameter of the common bile duct by ultrasonography in man: a double blind, placebo controlled study. *Int J Clin Pharmacol Ther* 1994; 32: 274–7.
6. Thompson DR. Narcotic analgesic effects on the sphincter of Oddi: a review of the data and therapeutic implications in treating pancreatitis. *Am J Gastroenterol* 2001; 96: 1266–72.

Children. Children under 6 months of age may be more sensitive to opioids; neonates in particular may be more sensitive to respiratory depression with morphine than adults. Pharmacokinetic differences may contribute to this increased sensitivity. Nonetheless, neonates can be treated with opioids such as morphine (see p. 94.1) if receiving respiratory support.

Older infants and children can be treated effectively with morphine or other opioid analgesics and from the age of 5 or 6 months morphine metabolism follows the course seen in adults.

For a discussion of the choice of analgesic in children see p. 5.2. The use of opioids for sedation and analgesia in neonates in intensive care is mentioned on p. 1033.1.

References.

1. Choonara IA. Pain relief. *Arch Dis Child* 1989; 64: 1101–2.
2. Lloyd-Thomas AR. Pain management in paediatric patients. *Br J Anaesth* 1990; 64: 85–104.
3. Bhatt-Mehta V. Current guidelines for the treatment of acute pain in children. *Drugs* 1996; 51: 760–76.
4. Marsh DF, *et al.* Opioid systems and the newborn. *Br J Anaesth* 1997; 79: 787–95.

The elderly. Ageing can affect the pharmacokinetics and pharmacodynamics of opioids although the net effects of these changes on opioid analgesia in the elderly remain unclear.[1] Practical recommendations include careful review of indication for opioid use both initially and at regular intervals thereafter, starting opioids cautiously at lower doses and with longer dosing intervals, and regular consideration given to dose reduction and drug substitution or discontinuation. If possible, further drugs should not be prescribed to manage the adverse effects of opioids.

1. Wilder-Smith OHG. Opioid use in the elderly. *Eur J Pain* 2005; 9: 137–40.

Hepatic impairment. The pharmacokinetics of opioids may be altered in patients with hepatic dysfunction. A review[1] of opioid use in this patient group considered that opioids such as morphine and hydromorphone that are metabolised by glucuronidation were relatively safe when compared with those metabolised by cytochrome P450 isoenzymes; the half-lives of glucuronidated opioids were found to be maintained until late disease whereas the prolonged half-lives seen with opioids metabolised by P450 isoenzymes were not accurately predicted by disease severity. It was also recommended that oral immediate-release or parenteral, short-acting opioids were preferable to long-acting preparations such as transdermal or modified-release formulations.

1. Davis M. Cholestasis and endogenous opioids: liver disease and exogenous opioid pharmacokinetics. *Clin Pharmacokinet* 2007; 46: 825–50.

Phaeochromocytoma. Morphine and some other opioids can induce the release of endogenous histamine and thereby stimulate catecholamine release. Both diamorphine[1] and pethidine[2] have been reported to cause hypertension when given to patients with phaeochromocytoma and histamine-releasing opioids should be avoided in such patients. Alfentanil, like fentanyl, does not release histamine and may be the opioid of choice in the anaesthetic management of patients with phaeochromocytoma.[3]

1. Chaturvedi NC, *et al.* Diamorphine-induced attack of paroxysmal hypertension in phaeochromocytoma. *BMJ* 1974; 2: 538.
2. Lawrence CA. Pethidine-induced hypertension in phaeochromocytoma. *BMJ* 1978; 1: 149–50.
3. Hull CJ. Phaeochromocytoma: diagnosis, preoperative preparation and anaesthetic management. *Br J Anaesth* 1986; 58: 1453–68.

Renal impairment. A literature review[1] concluded that codeine and morphine are best avoided in patients with renal failure and/or on dialysis; hydromorphone may be used with caution and monitoring, and use of fentanyl and methadone appeared to be safe. Similar recommendations have been made for patients with end-stage renal disease who are not undergoing dialysis.[2] See also under the individual monographs.

1. Dean M. Opioids in renal failure and dialysis patients. *J Pain Symptom Manage* 2004; 28: 497–504.
2. Murtagh FE, *et al.* The use of opioid analgesia in end-stage renal disease patients managed without dialysis: recommendations for practice. *J Pain Palliat Care Pharmacother* 2007; 21: 5–16.

Interactions

As serious and sometimes fatal reactions have followed use of pethidine in patients receiving MAOIs (including moclobemide), pethidine and related drugs are contra-indicated in patients taking MAOIs or within 14 days of stopping such treatment; other opioid analgesics should be avoided or given with extreme caution (for further details, see p. 447.1). Life-threatening reactions have also been reported when selegiline, a selective inhibitor of monoamine oxidase type B, was given with pethidine. The depressant effects of opioid analgesics are enhanced by other CNS depressants such as alcohol, anaesthetics, anxiolytics, hypnotics, tricyclic antidepressants, and antipsychotics. Cyclizine may counteract the haemodynamic benefits of opioids. Cimetidine inhibits the metabolism of some opioids, especially pethidine.

The actions of opioids may in turn affect the activities of other drugs. For instance, their gastrointestinal effects may delay absorption as with mexiletine or may be counteractive as with cisapride, metoclopramide, or domperidone. Opioid premedicants such as papaveretum have been reported to reduce serum concentrations of ciprofloxacin.

Alcohol. Rapid release or dose-dumping of hydromorphone from a modified-release preparation (*Palladone; Purdue Frederick, USA*) has been associated with the ingestion of alcohol (for further details, see under Interactions of Hydromorphone, p. 68.2). Health Canada[1] has warned that this interaction may occur with all modified-release formulations of opioid analgesics. Licensed product information for some modified-release preparations of morphine sulfate also warns against such use (see Interactions of Morphine, p. 95.2).

1. Health Canada. Potentially fatal interaction between slow-release opioid painkillers and alcohol (issued 3rd August, 2005). Available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2005/2005_84-eng.php (accessed 26/06/08)

Antivirals. Interactions between opioid analgesics and *HIV-protease inhibitors* or *reverse transcriptase inhibitors* are complex, and the results of the limited number of studies and reports *in vivo* have not always borne out predictions about the nature of potential interactions.

- Substantial **decreases** in the area under the plasma concentration-time curve (AUC) and in the plasma concentration have been reported for pethidine when given with *ritonavir*; however, plasma concentrations of the toxic metabolite norpethidine are greatly **increased**, and licensed product information for ritonavir counsels against such combined use. Ritonavir is predicted to reduce plasma concentrations of morphine. Plasma concentrations of methadone may be reduced if given with HIV-protease inhibitors although the effect may not be clinically significant. The NNRTIs *nevirapine* and *efavirenz* have also been reported to reduce plasma-methadone levels and withdrawal symptoms have occurred when given to patients receiving methadone. (For further details on the interactions of methadone with antivirals, see p. 91.1.) In addition, efavirenz has been reported to decrease the AUC of buprenorphine (see p. 32.3).
- In contrast, an **increase** in AUC and in elimination half-life of fentanyl has been reported in subjects also receiving ritonavir (see p. 63.2). Licensed product information for ritonavir also considers that increased plasma concentrations of buprenorphine (p. 32.3), dextropropoxyphene, and tramadol, with an increased likelihood of opioid toxicity, may occur if these drugs are given during ritonavir treatment. Licensed information for meptazinol also states that increased plasma concentrations of meptazinol have been noted when given with ritonavir. The NNRTI *delavirdine* has been reported to increase the plasma concentrations of buprenorphine (see p. 32.3) and methadone (p. 91.1).

Histamine. For the effect of opioid analgesics on histamine given exogenously, see p. 2525.3.

Histamine H_2-antagonists. Histamine H_2-antagonists may enhance the effects of some opioid analgesics. *Cimetidine* was reported to alter the clearance and volume of distribution of pethidine[1] whereas *ranitidine* did not.[2] Morphine has been considered less likely to interact with cimetidine than pethidine because of differences in metabolism. In a study[3] cimetidine did not affect the disposition of morphine in healthy subjects. A later study[4] in patients undergoing major surgery suggested that pre- or postoperative intravenous cimetidine did not significantly affect outcomes such as morphine consumption and incidence of adverse effects when compared with placebo. Nevertheless, there have been isolated reports of possible interactions between morphine and H_2-antagonists; apnoea, confusion, and muscle twitching have been associated with cimetidine plus morphine,[5] and confusion associated with ranitidine plus morphine.[6] There has also been a report[7] of a patient receiving regular analgesia with oral methadone and subcutaneous morphine who became unresponsive 6 days after starting cimetidine for prophylaxis of peptic ulcer; treatment with naloxone was required.

1. Guay DRP, *et al.* Cimetidine alters pethidine disposition in man. *Br J Clin Pharmacol* 1984; 18: 907–14.
2. Guay DRP, *et al.* Ranitidine does not alter pethidine disposition in man. *Br J Clin Pharmacol* 1985; 20: 55–9.
3. Mojaverian P, *et al.* Cimetidine does not alter morphine disposition in man. *Br J Clin Pharmacol* 1982; 14: 809–13.
4. Chia Y-Y, *et al.* Randomized, double-blind study comparing postoperative effects of treatment timing with histamine H_2-receptor antagonist cimetidine. *Acta Anaesthesiol Scand* 2005; 49: 865–9.
5. Fine A, Churchill DN. Potentially lethal interaction of cimetidine and morphine. *Can Med Assoc J* 1981; 124: 1434, 1436.
6. Martínez-Abad M, *et al.* Ranitidine-induced confusion with concomitant morphine. *Drug Intell Clin Pharm* 1988; 22: 914–15.
7. Sorkin EM, Ogawa GS. Cimetidine potentiation of narcotic action. *Drug Intell Clin Pharm* 1983; 17: 60–1.

Opium

Gum Opium; Nyers ópium; Opijus, žaliavinis; Opio; Opium brut; Opium crudum; Opium surové; Raakaoopiumi; Råopium; Raw Opium; Опиум.

ATC — A07DA02; N02AA02.

ATC Vet — QA07DA02; QN02AA02.

ATC Herb — HN02AA5001 (Papaver somniferum: dry latex); HR05DA5001 (Papaver somniferum: dry latex); HN05CW5004 (Papaver somniferum: dry latex); HA03AD5001 (Papaver somniferum: dry latex); HA07DA5001 (Papaver somniferum: dry latex).

UNII — 37M3MZ001L.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of opium:

Ahpenyen; Ah-pen-yen; Aunti; Aunti Emma; Big O; Black; Black pill; Black shit; Black stuff; Black tar opium; Block; Boulette; Chandoo; Chandu; China; Chinese molasses; Chinese tobacco; Chocolate; Cruz; Dopium; Dover's deck; Dover's powder; Dream gum; Dream gun; Dream stick; Dreams; Dutch courage; Easing powder; Fidonie; Fi-do-nie; Fun-foon-fong; Gee; God's medicine; Goma; Gondola; Gong; Goric; Great tobacco; Gum; Guma;

Hard stuff; Hocus; Hop; Hops; Incense; Indonesian bud; Joy plant; Mash allah; Material negro; Midnight oil; Mira; Mud; O; Oj; Op; O.P.; Ope; O-Rock DC; Pen yan; Pen yen; Pin gon; Pin yen; Pox; Skee; Tar; Tin; Toxy; Toye; Toys; When-shee; Ze; Zero.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Chin., *Eur.*, and *US* include a monograph for prepared or powdered opium. *Eur.* also contains monographs for standardised opium dry extract or standardised opium tincture. *Jpn* includes prepared opium and a diluted opium powder containing 1% of anhydrous morphine.

Ph. Eur. 8: (Opium, Raw; Opium BP 2014). The air-dried latex obtained by incision from the unripe capsules of *Papaver somniferum* L. It has a characteristic odour and a blackish-brown colour. It should contain not less than 10% of anhydrous morphine, not less than 2% of anhydrous codeine, and not more than 3% of anhydrous thebaine. Protect from light.

Ph. Eur. 8: (Opium, Prepared; Opii Pulvis Normatus). Raw opium powdered and dried at a temperature not exceeding 70 degrees. It is a yellowish-brown or dark brown powder and contains 9.8 to 10.2% of morphine and not less than 1.0% of codeine, calculated with reference to the dried drug. The content may be adjusted by adding a suitable excipient or raw opium powder.

USP 36: (Opium). The air-dried milky exudate obtained by incising the unripe capsules of *Papaver somniferum* (Papaveraceae). Externally it is pale olive-brown or olive-grey; internally it is reddish-brown. It has a very characteristic odour and a very bitter taste. It yields not less than 9.5% of anhydrous morphine.

USP 36: (Powdered Opium). Opium dried at a temperature not exceeding 70 degrees, and reduced to a very fine light brown or moderately yellowish-brown powder that yields not less than 10% and not more than 10.5% of anhydrous morphine. It may contain any of the permitted diluents with the exception of starch.

Profile

Opium is the air-dried latex obtained by incision from the unripe capsules of *Papaver somniferum* (Papaveraceae). It contains morphine, codeine, and thebaine and a variable mixture of other alkaloids including noscapine and papaverine. The exuded latex is dried and manipulated to form cakes of uniform composition, variously shaped according to the country of origin, and known in commerce as Turkish, Indian, or European opium.

Opium has the properties of opioid analgesics (p. 108.1). Its analgesic and sedative actions are due mainly to its content of morphine (p. 93.2). It acts less rapidly than morphine since opium appears to be more slowly absorbed; the relaxing action of the papaverine and noscapine on intestinal muscle makes it more constipating than morphine.

Opium is intended only as the starting material for the manufacture of galenical preparations and is not dispensed as such. It is used as Prepared Opium (Ph. Eur. 8), as Powdered Opium (USP 36), as Opium Tincture (BP 2014 or USP 36), or as Camphorated Opium Tincture (BP 2014) or Paregoric (USP 36) in various oral preparations. These have included Opiate Squill Linctus (BP 2014) (Gee's linctus) for cough.

Paregoric (USP 36) has been advocated in the USA for the treatment of neonatal abstinence syndrome.

Abuse. Reports of squill-associated cardiotoxicity resulting from the abuse of opiate squill linctus (Gee's linctus).[1,2]

1. Thurston D, Taylor K. Gee's linctus. *Pharm J* 1984; 233: 63.
2. Smith W, *et al.* Wenckebach's phenomenon induced by cough linctus. *BMJ* 1986; 292: 868.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Elixir Paregorico; *Israel*: Opii Simplex.

Multi-ingredient Preparations. *Braz.*: Camomila; *Denm.*: Pectyl; *Fin.*: Tannopon†; *Fr.*: Colchimax; Lamaline; Paregorique†; *Hong Kong*: Brown Mixture†; *Israel*: Doveri†; *S.Afr.*: Paragorie-se-Eliksert†; Tandpyndruppels†; *Spain*: Tanagel; *Switz.*: Bromocod N†; Pectocalmine N; *USA*: B & O Supprettes No. 15A; B & O Supprettes No. 16A; *Venez.*: Atrobel.

Homoeopathic Preparations. *Fr.*: Abbe Chaupitre no 19†; *Switz.*: HerBalance.

Pharmacopoeial Preparations

BP 2014: Camphorated Opium Tincture; Concentrated Camphorated Opium Tincture; Opium Tincture;
Ph. Eur.: Opium Dry Extract, Standardised; Opium Tincture, Standardised;
USP 36: Opium Tincture; Paregoric.

Hydrochlorides of Mixed Opium Alkaloids

Alkaloidosum Opii Hydrochloridum; Extractum Concentratum Opii; Mezclas de hidrocloruros de alcaloides del opio; Omnoponum; Opialum; Opium Concentratum; Гидрохлориды Смешанных Алкалоидов Опия.

Pharmacopoeias. Preparations of the hydrochlorides of mixed opium alkaloids are included in *Jpn*.

Papaveretum *(BAN)*

Папаверетум.

A mixture of 253 parts of morphine hydrochloride, 23 parts of papaverine hydrochloride, and 20 parts of codeine hydrochloride.

CAS — 8002-76-4.
ATC — N02AA10.
ATC Vet — QN02AA10.

NOTE. Do not confuse papaveretum with papaverine (p. 2362.2).

Pharmacopoeias. In *Br.*

BP 2014: (Papaveretum). It contains 80.0 to 88.4% of anhydrous morphine hydrochloride, 8.3 to 9.2% of papaverine hydrochloride, and 6.6 to 7.4% of anhydrous codeine hydrochloride. A white or almost white crystalline powder. Soluble in water, sparingly soluble in alcohol. A 1.5% solution in water has a pH of 3.7 to 4.7. Protect from light.

Profile

The opium alkaloids are the prototypical opioid analgesics (p. 108.1). Mixtures of opium alkaloids such as papaveretum have the analgesic and sedative properties of morphine (p. 93.2) and are used in the treatment of moderate to severe pain including postoperative and severe chronic pain. They may also be used for pre-operative sedation and as an adjunct to anaesthesia. Papaveretum (BP 2014) 15.4 mg contains the equivalent of about 10 mg of the major component, anhydrous morphine.

- In the UK, papaveretum formerly contained the hydrochlorides of morphine, codeine, noscapine, and papaverine. However, because of concern over the potential genotoxicity of noscapine (see Pregnancy, p. 1671.1) UK preparations containing papaveretum were reformulated to exclude the noscapine component and the name papaveretum was redefined in the BP 1993 to reflect this change of formulation. It is possible that in other countries the term papaveretum is still being used to describe a mixture containing noscapine.

Doses. Papaveretum is generally given by subcutaneous or intramuscular injection in doses of 7.7 to 15.4 mg every 4 hours if necessary. The initial dose in the elderly or debilitated patients should not exceed 7.7 mg.

In the treatment of pain and as an adjunct in anaesthesia, papaveretum may also be given intravenously in doses of one-quarter to one-half the corresponding subcutaneous or intramuscular dose. For pre-operative medication papaveretum is given intramuscularly or subcutaneously sometimes with hyoscine hydrobromide.

For details of doses in children, see below.

Oral preparations containing papaveretum with aspirin have been given for the management of moderate to severe pain.

Papaveretum has been confused with papaverine (p. 2362.2) and in one such case[1] a patient became unconscious after self-injection of papaveretum in mistake for papaverine.

1. Robinson LQ, Stephenson TP. Self injection treatment for impotence. *BMJ* 1989; 299: 1568.

Administration in children. Papaveretum may be given to children in the treatment of moderate to severe pain including postoperative and severe chronic pain. It is also used for pre-operative sedation and as an adjunct to anaesthesia. Papaveretum is generally given by subcutaneous or intramuscular injection every 4 hours if necessary, according to age as follows:

- neonates: 115 micrograms/kg
- 1 to 12 months: 154 micrograms/kg
- 1 to 6 years: 1.93 to 3.85 mg
- 6 to 12 years: 3.85 to 7.7 mg

Older children may be given the usual adult dose (see above).

In the treatment of pain and as an adjunct to anaesthesia papaveretum may also be given intravenously in doses of one-quarter to one-half the corresponding subcutaneous or intramuscular dose.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Rus.*: Omnopon (Омнопон); *Afr.*: Omnopon.

Multi-ingredient Preparations. *UK*: Aspav†.

Pharmacopoeial Preparations

BP 2014: Papaveretum Injection.

Oxaprozin *(BAN, USAN, rINN)*

Oksaprotsiini; Oxaprozina; Oxaprozine; Oxaprozinum; Wy-21743; Оксапрозин.

3-(4,5-Diphenyloxazol-2-yl)propionic acid.

$C_{18}H_{15}NO_3$=293.3

CAS — 21256-18-8.
ATC — M01AE12.
ATC Vet — QM01AE12.
UNII — MHJ80W9LRB.

Pharmacopoeias. In *Chin.*, *Jpn.*, and *US*.

USP 36: (Oxaprozin). A white to yellowish-white crystalline powder. Store in airtight containers at a temperature of 20 degrees to 25 degrees. Protect from light.

Oxaprozin Potassium *(BANM, rINNM)*

Kalii Oxaprozinum; Oxaprozina potásico; Oxaprozine Potassique; Калия Оксапрозин.

$C_{18}H_{14}NO_3K$=331.4

CAS — 174064-08-5.
ATC — M01AE12.
ATC Vet — QM01AE12.
UNII — ML56O2Z92I.

Uses and Administration

Oxaprozin, a propionic acid derivative, is an NSAID (p. 102.3). Oxaprozin may be given orally as the base or potassium salt although doses are expressed in terms of the base; oxaprozin potassium 678 mg is equivalent to about 600 mg of oxaprozin. For the treatment of osteoarthritis and rheumatoid arthritis, a usual dose equivalent to 1.2 g of oxaprozin may be given once daily, although in osteoarthritis, patients with low body-weight or mild disease should be given an initial dose equivalent to 600 mg once daily. The recommended maximum daily dose is 1.8 g or 26 mg/kg, whichever is the lower.

For doses in patients with renal impairment and in children, see below.

References.

1. Miller LG. Oxaprozin: a once-daily nonsteroidal anti-inflammatory drug. *Clin Pharm* 1992; 11: 591–603.
2. Anonymous. Oxaprozin for arthritis. *Med Lett Drugs Ther* 1993; 35: 15–16.
3. Dallegri F, *et al.* A review of the emerging profile of the anti-inflammatory drug oxaprozin. *Expert Opin Pharmacother* 2005; 6: 777–85.

Administration in children. Oxaprozin is given orally in the treatment of juvenile idiopathic arthritis in children aged 6 years and over. Doses are expressed in terms of body-weight and may be given once daily as follows:

- 22 to 31 kg: 600 mg
- 32 to 54 kg: 900 mg
- 55 kg and over: 1200 mg

Administration in renal impairment. US licensed product information for oxaprozin recommends that the initial oral dose in patients with severe renal impairment or on dialysis is 600 mg once daily. The dose may be increased to 1.2 g once daily, if necessary.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3.

Diagnosis and testing. False-positive results for testing of benzodiazepines in urine have been reported in patients taking oxaprozin.[1] The manufacturer[2] has commented that the interaction occurs with some immunoassay tests and that thin-layer chromatography can successfully discriminate between benzodiazepines and oxaprozin. False-positive results for a fluorescence polarisation immunoassay for phenytoin have also been reported in patients receiving oxaprozin.[3]

1. Pulini M. False-positive benzodiazepine urine test due to oxaprozin. *JAMA* 1995; 273: 1905.
2. Raphan H, Adams MH. False-positive benzodiazepine urine test due to oxaprozin. *JAMA* 1995; 273: 1905–6.
3. Patel T, *et al.* Assay interaction between oxaprozin and phenytoin. *Ann Pharmacother* 1997; 31: 254.

Effects on the liver. Fatal fulminant hepatitis occurred[1] in a 56-year-old woman who had received 600 to 1200 mg of oxaprozin daily for about 6 weeks. In another patient

symptomatic hepatitis developing during oxaprozin use resolved on stopping the drug.[2]

1. Purdum PP, *et al.* Oxaprozin-induced fulminant hepatitis. *Ann Pharmacother* 1994; 28: 1159–61.
2. Kethu SR, *et al.* Oxaprozin-induced symptomatic hepatotoxicity. *Ann Pharmacother* 1999; 33: 942–4.

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Pharmacokinetics

Oxaprozin is slowly but extensively absorbed from the gastrointestinal tract; it is 99% bound to plasma proteins, mainly albumin. Peak plasma concentrations occur after about 2 to 3 hours. At steady state, the biological half-life is about 44 hours. Oxaprozin is metabolised mainly in the liver by microsomal oxidation and conjugation with glucuronic acid to form inactive metabolites which are excreted in the urine (65%) and faeces (35%).

References.

1. Karim A. Inverse nonlinear pharmacokinetics of total and protein unbound drug (oxaprozin): clinical and pharmacokinetic implications. *J Clin Pharmacol* 1996; 36: 985–97.
2. Karim A, *et al.* Oxaprozin and piroxicam, nonsteroidal antiinflammatory drugs with long half-lives: effect of protein-binding differences on steady-state pharmacokinetics. *J Clin Pharmacol* 1997; 37: 267–78.
3. Davies NM. Clinical pharmacokinetics of oxaprozin. *Clin Pharmacokinet* 1998; 35: 425–36.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Duraprox; *Canad.*: Daypro; *Chile*: Duraprox†; Walix; *China*: Ao Ke Qing (奥克清); Ao Pu Xin (澳谱欣); Lu Ming Ao Xin (鲁明奥欣); Nuo Bi Song (诺碧松); Nuo De Lun (诺德伦); Nuosong (诺松); *Cz.*: Dayrun†; *Gr.*: Duraprox; Misaf; Nisaid; Oxapron; Trimelot; *Ital.*: Walix; *Jpn*: Alvo; *S.Afr.*: Deflam†; *Turk.*: Duraprox; *USA*: Daypro.

Pharmacopoeial Preparations
USP 36: Oxaprozin Tablets.

Oxycodone *(BAN, USAN, rINN)* ⊗

Dihydrone; 14-Hydroxydihydrocodeinone; NSC-19043; Oksikodoni; Oxicodona; Oxikodon; Oxycodonum; Оксикодон.
6-Deoxy-7,8-dihydro-14-hydroxy-3-*O*-methyl-6-oxomorphine; (-)-(5*R*,6*S*,14*S*)-4,5-Epoxy-14-hydroxy-3-methoxy-9a-methylmorphinan-6-one.
$C_{18}H_{21}NO_4$=315.4
CAS — 76-42-6.
ATC — N02AA05.
ATC Vet — QN02AA05.
UNII — CD35PMG570.

NOTE. Compounded preparations of oxycodone may be represented by the following names:
- Co-oxycodAPAP (*PEN*)—oxycodone and paracetamol.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of oxycodone:

40; 40-bar; 80; Blue; Cotton; Hillbilly heroin; Kicker; OC; Os; Ox; Oxy; Oxy Cotton; Oxycotton; Percs; Perks; Pills; Pink spoons; Rushbo.

Oxycodone Hydrochloride

(BANM, USAN, rINNM) ⊗

7,8-Dihydro-14-hydroxycodeinone hydrochloride; Dihydrone Hydrochloride; Hidrocloruro de oxicodona; Oksikodonihydrokloridi; Oksikodono hidrochloridas; Oxicodona, hidrocloruro de; Oxikodonhydroklorid; Oxycodone, Chlorhydrate d'; Oxycodonhydrochlorid; Oxycodoni hydrochloridum; Oxycone Hydrochloride; Oxykodon-hydrochlorid; Thecodine; Оксикодона Гидрохлорид.
$C_{18}H_{21}NO_4HCl$=351.8
CAS — 124-90-3.
ATC — N02AA05.
ATC Vet — QN02AA05.
UNII — C1ENJ2TE6C.

Pharmacopoeias. In *Eur.* (see p. vii) and *US. Jpn* includes the trihydrate.

Ph. Eur. 8: (Oxycodone Hydrochloride). A white or almost white, hygroscopic, powder. Freely soluble in water; sparingly soluble in dehydrated alcohol; practically insoluble in toluene. Store in airtight containers. Protect from light.

USP 36: (Oxycodone Hydrochloride). A white to off-white, odourless, hygroscopic crystals or powder. Soluble in water; slightly soluble in alcohol. Store in airtight containers.

Oxycodone Terephthalate ⊗

Oxicodona, tereftalato de; Оксикодона Терефталат.
4,5α-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one 1,4-benzenedicarboxylate (2:1) salt.
$(C_{18}H_{21}NO_4)_2C_8H_6O_4$=796.9
CAS — 64336-55-6.
UNII — M04XWV43UF.

Pharmacopoeias. In *US.*

USP 36: (Oxycodone Terephthalate). Store in airtight containers.

Uses and Administration

Oxycodone, a phenanthrene derivative, is an opioid analgesic (p. 108.1). Oxycodone hydrochloride is given orally or by subcutaneous or intravenous injection for the relief of moderate to severe pain.

A usual oral starting dose for opioid-naive patients in severe pain is 5 mg every 4 to 6 hours increased thereafter as necessary according to response. For patients who have been receiving a strong opioid analgesic the initial dose of oxycodone should be based on the daily opioid requirement; UK licensed product information suggests that 10 mg of oral oxycodone is equivalent to about 20 mg of oral morphine. Most patients do not require more than 400 mg daily. Preparations containing oxycodone hydrochloride and aspirin, ibuprofen, or paracetamol are also used. Oxycodone hydrochloride may also be given orally as a modified-release preparation every 12 hours. To counteract opioid-induced constipation a combined modified-release oral preparation of oxycodone hydrochloride and naloxone hydrochloride is available in some countries.

For details of doses in children, see below.

For opioid-naive patients, intravenous doses of oxycodone hydrochloride range from 1 to 10 mg initially, given over 1 to 2 minutes, and repeated not more often than every 4 hours; a dose of 2 mg/hour is the recommended starting dose as an intravenous infusion. The intravenous route may also be used for patient-controlled analgesia. When given subcutaneously to opioid-naive patients, the starting dose is 5 mg every 4 hours; subcutaneous infusions should be started at 7.5 mg daily. When transferring between oral and parenteral oxycodone, UK licensed product information advises that, as a guide, 2 mg of oral oxycodone is equivalent to about 1 mg of parenteral oxycodone.

Oxycodone has been given rectally as suppositories containing 30 mg of oxycodone (as the pectinate) or 10 or 20 mg of oxycodone hydrochloride; the dose may be repeated every 6 to 8 hours.

For doses in patients with hepatic or renal impairment, see below.

Oxycodone terephthalate is also used orally.

Administration in children. Although oxycodone hydrochloride is not licensed in the UK for use in children under 18 years old, the *BNFC* suggests that it may be given for the treatment of moderate to severe pain in palliative care. Those aged from 1 month to 12 years may be given initial oral doses of 200 micrograms/kg (up to 5 mg) every 4 to 6 hours increased thereafter as necessary according to response; older children may be given the usual adult dose (see above). Oxycodone hydrochloride may also be given orally as a modified-release preparation every 12 hours to those aged 8 years and older.

Administration in hepatic or renal impairment. The plasma concentrations of oxycodone may be increased in patients with hepatic or renal impairment and consequently dosage adjustment may be necessary in such patients. In the UK, licensed product information recommends that the oral starting dose for adult patients with mild hepatic impairment or mild to moderate renal impairment should be 2.5 mg given every 6 hours; it contra-indicates the use of oxycodone in those with moderate to severe hepatic impairment or severe renal impairment. US product information permits the cautious use of oxycodone in adult patients with severe hepatic or severe renal impairment.

Pain. References.

1. Curtis GB, *et al.* Relative potency of controlled-release oxycodone and controlled-release morphine in a postoperative pain model. *Eur J Clin Pharmacol* 1999; 55: 425–9.
2. Gimbel JS, *et al.* Controlled-release oxycodone for pain in diabetic neuropathy: a randomized controlled trial. *Neurology* 2003; 60: 927–34.
3. Oldfield V, Perry CM. Oxycodone/ibuprofen combination tablet: a review of its use in the management of acute pain. *Drugs* 2005; 65: 2337–54.
4. Kalso E. Oxycodone. *J Pain Symptom Manage* 2005; 29 (suppl): S47–S56.
5. Bercovitch M, Adunsky A. High dose controlled-release oxycodone in hospice care. *J Pain Palliat Care Pharmacother* 2006; 20: 33–9.
6. Reid CM, *et al.* Oxycodone for cancer-related pain: meta-analysis of randomized controlled trials. *Arch Intern Med* 2006; 166: 837–43. Correction. *ibid.*; 2387.
7. Portenoy RK, *et al.* Long-term use of controlled-release oxycodone for noncancer pain: results of a 3-year registry study. *Clin J Pain* 2007; 23: 287–99.
8. Pan H, *et al.* Efficacy and tolerability of oxycodone hydrochloride controlled-release tablets in moderate to severe cancer pain. *Clin Drug Invest* 2007; 27: 259–67.
9. Gaskell H, *et al.* Single dose oral oxycodone and oxycodone plus paracetamol (acetaminophen) for acute postoperative pain in adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2009 (accessed 18/11/09).

Dependence and Withdrawal

As for Opioid Analgesics in general, p. 109.1.

Oxycodone has been subject to abuse (see under Adverse Effects, Treatment, and Precautions, below).

Takotsubo-like cardiomyopathy developed in a 61-year-old woman when her dose of oxycodone was inadvertently and greatly reduced 7 days after surgery for degenerative osteoarthritis.[1] The patient had a chronic history of opioid dependence and had been treated with oxycodone (80 mg daily) and hydromorphone (4 mg every 3 hours as needed) for several months before surgery; postoperatively, her dose of oxycodone had been increased to 120 mg daily with additional doses for breakthrough pain.

1. Rivera JM, *et al.* "Broken heart syndrome" after separation (from OxyContin). *Mayo Clin Proc* 2006; 81: 825–8.

Adverse Effects, Treatment, and Precautions

As for Opioid Analgesics in general, p. 110.1.

UK licensed product information contra-indicates the use of oxycodone in patients with moderate to severe hepatic impairment or severe renal impairment; however, product information in the USA permits its cautious use in patients with severe hepatic or severe renal impairment although doses may need to be reduced.

Abuse. Oxycodone hydrochloride modified-release tablets have been subject to abuse.[1-3] The crushed tablets have been inhaled or injected by addicts and in some cases this has resulted in fatalities.

1. Wolf BC, *et al.* One hundred seventy two deaths involving the use of oxycodone in Palm Beach County. *J Forensic Sci* 2005; 50: 192–5.
2. Cicero TJ, *et al.* Trends in abuse of OxyContin and other opioid analgesics in the United States: 2002-2004. *J Pain* 2005; 6: 662–72.
3. Adlaf EM, *et al.* Use of OxyContin by adolescent students. *Can Med Assoc J* 2006; 174: 1303.

Breast feeding. For a report on the effects of oxycodone in breast feeding, see Breast Feeding under Codeine, p. 41.2.

Effects on the respiratory system. References[1,2] to respiratory depression occurring in children given oxycodone.

1. Olkkola KT, *et al.* Pharmacokinetics and ventilatory effects of intravenous oxycodone in postoperative children. *Br J Clin Pharmacol* 1994; 38: 71–6.
2. Kalso E. Pharmacokinetics and ventilatory effects of intravenous oxycodone in postoperative children. *Br J Clin Pharmacol* 1995; 39: 214.

Hepatic impairment. The clearance and elimination of oxycodone were prolonged in 6 women with end-stage liver cirrhosis awaiting liver transplantations.[1] Significant ventilatory depression also occurred. Pharmacokinetic values after successful transplantation were similar to those previously reported for healthy adults. It was recommended that, when giving oxycodone to patients with end-stage liver disease, the dosing frequency should be reduced and the dose lowered.

1. Tallgren M, *et al.* Pharmacokinetics and ventilatory effects of oxycodone before and after liver transplantation. *Clin Pharmacol Ther* 1997; 61: 655–61.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies oxycodone as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/10/11)

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

Antibacterials. Negative urine oxycodone screening tests have been reported[1] in a patient taking oral oxycodone 60 mg daily with the potent enzyme inducer *rifampicin*, amongst other drugs. The presence of oxycodone metabolites in the urine led the authors to conclude that rifampicin increased the metabolism of oxycodone, necessitating an increase in the dose of the latter. A later pharmacokinetic study[2] found that rifampicin decreased the AUC of intravenous and oral oxycodone by 53% and 86%, respectively, and decreased the oral bioavailability of oxycodone from 69% to 21%.

Conversely, the enzyme inhibitor *telithromycin* was found[3] to increase the AUC of oral oxycodone by 80% and decrease its clearance by 43%; it was suggested that the dose

of oxycodone be reduced by 25 to 50% when used with telithromycin.

1. Lee H-K, *et al.* Negative urine opioid screening caused by rifampin-mediated induction of oxycodone hepatic metabolism. *Clin Chim Acta* 2006; 367: 196–200.
2. Nieminen TH, *et al.* Rifampin greatly reduces the plasma concentrations of intravenous and oral oxycodone. *Anesthesiology* 2009; 110: 1371–8.
3. Grönlund J, *et al.* Effect of telithromycin on the pharmacokinetics and pharmacodynamics of oral oxycodone. *J Clin Pharmacol* 2010; 50: 101–8.

Antidepressants. For reference to possible cases of serotonin syndrome associated with use of oxycodone and *SSRIs*, see Opioid Analgesics under Interactions of Fluoxetine, p. 427.1.

Antifungals. In a study,[1] the mean AUC, peak plasma concentration, and elimination half-life of oral oxycodone were increased 3.6-, 1.7-, and 2-fold, respectively, by the enzyme inhibitor *voriconazole*; lower doses of oxycodone may be needed when used together.

1. Hagelberg NM, *et al.* Voriconazole drastically increases exposure to oral oxycodone. *Eur J Clin Pharmacol* 2009; 65: 263–71.

Pharmacokinetics

Oxycodone is absorbed from the gastrointestinal tract; oral bioavailability is about 60 to 87% due to lower pre-systemic and/or first-pass metabolism compared with other opioids. About 45% is bound to plasma proteins. It is metabolised to noroxycodone, via cytochrome P450 isoenzymes of the CYP3A family, and, to a lesser extent, to oxymorphone (below) via CYP2D6. Both metabolites undergo glucuronidation and are excreted with unchanged drug in urine. The elimination half-life of oxycodone is reported to be 2 to 4 hours. Oxycodone crosses the placenta and is distributed into breast milk.

References.
1. Pöyhiä R, *et al.* The pharmacokinetics of oxycodone after intravenous injection in adults. *Br J Clin Pharmacol* 1991; 32: 516–18.
2. Leow KP, *et al.* Single-dose and steady-state pharmacokinetics and pharmacodynamics of oxycodone in patients with cancer. *Clin Pharmacol Ther* 1992; 52: 487–95.
3. Mandema JW, *et al.* Characterization and validation of a pharmacokinetic model for controlled-release oxycodone. *Br J Clin Pharmacol* 1996; 42: 747–56.
4. Katko RF, *et al.* Pharmacokinetic-pharmacodynamic relationships of controlled-release oxycodone. *Clin Pharmacol Ther* 1996; 59: 52–61.
5. Gammaitoni AR, Davis MW. Comparison of the pharmacokinetics of oxycodone administered in three Percocet® formulations. *J Clin Pharmacol* 2002; 42: 192–7.
6. Lalovic B, *et al.* Pharmacokinetics and pharmacodynamics of oral oxycodone in healthy human subjects: role of circulating active metabolites. *Clin Pharmacol Ther* 2006; 79: 461–79.
7. Liukas A, *et al.* Plasma concentrations of oral oxycodone are greatly increased in the elderly. *Clin Pharmacol Ther* 2008; 84: 462–7.

Children. The pharmacokinetics of oxycodone in children have been studied[1-4] and are generally considered similar to those in adults.[2,4] However, pharmacokinetics may be more variable in infants aged from 0 to 6 months, particularly those aged 2 months and under.[5]

1. Olkkola KT, *et al.* Pharmacokinetics and ventilatory effects of intravenous oxycodone in postoperative children. *Br J Clin Pharmacol* 1994; 38: 71–6.
2. Kokki H, *et al.* Pharmacokinetics of oxycodone after intravenous, buccal, intramuscular and gastric administration in children. *Clin Pharmacokinet* 2004; 43: 613–22.
3. El-Tahtawy A, *et al.* Population pharmacokinetics of oxycodone in children 6 months to 7 years old. *J Clin Pharmacol* 2006; 46: 433–42.
4. Kokki H, *et al.* Comparison of oxycodone pharmacokinetics after buccal and sublingual administration in children. *Clin Pharmacokinet* 2006; 45: 745–54.
5. Pokela ML, *et al.* Marked variation in oxycodone pharmacokinetics in infants. *Paediatr Anaesth* 2005; 15: 560–565.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Oxicalmans; Oxinovag; Oxycontin; *Austral.*: Endone; Oxycontin; Oxynorm; Proladone; Targin; *Austria*: Oxycontin; Oxynorm; Targin; *Belg.*: Oxycontin; Oxynorm; Targinact; *Braz.*: Oxycontin; *Canad.*: Oxy IR; Oxycontin†; Oxyneo; Supeudol; Targin; *Chile*: Oxycontin; *China*: Oxycontin (奥施康定); *Cz.*: Dolocodon; Oxycontin; Targin; *Denm.*: Oxycontin; Oxynorm; Targin; *Fin.*: Oxanest; Oxycontin; Oxynorm; Targiniq; *Fr.*: Oxycontin; Oxynorm; Oxynormoro; Targinact; *Ger.*: Oxygesic; Targin; *Hung.*: Oxycontin; *Irl.*: Dancex; Oxycontin; Oxydon; Oxynorm; Targin; *Israel*: Oxycod; Oxycontin; Targin; *Ital.*: Oxycontin; Targin; *Jpn*: Oxifast; Oxycontin; *Malaysia*: Oxycontin; *Neth.*: Oxycontin; Oxynorm; Targinact; *Norw.*: Oxycontin; Oxynorm; Targiniq; *NZ*: Oxycontin; Oxynorm; Targin; *Philipp.*: Oxycontin; Oxynorm; *Pol.*: Oxycontin; Oxynorm; *Port.*: Oxyconin†; Oxynormoro; *Singapore*: Oxycontin; Oxynorm; Targin; *Spain*: Oxycontin; Oxynorm; Targin; *Swed.*: Oxycontin; Oxynorm; Targiniq; *Switz.*: Oxycontin; Oxynorm; Targin; *UK*: Dolocodon; Longtec; Lynlor; Oxycontin; Oxynorm; Shortec; Targinact; *USA*: ETH-Oxydose†; Oxecta; Oxycontin; Oxyfast; OxyIR; Roxicodone; *Venez.*: Oxycontin.

Multi-ingredient Preparations. *Arg.*: Oxinovag Complex; *Canad.*: Endocet; Percocet; Percodan†; ratio-Oxycocet; ratio-Oxycodan; Rivacocet; *China*: Tailening (泰勒宁); *Israel*: Percocet; Percodan†; *Ital.*: Depalgos; *Mex.*: Plexicodim; *USA*: Combunox†; Endocet; Magnacet; Narvox; Percocet; Percodan; Perloxx; Pimalev; Primlev; Roxicet; Roxilox; Tylox; Xolox.

Pharmacopoeial Preparations
BP 2014: Oxycodone Capsules; Oxycodone Injection; Oxycodone Oral Solution; Prolonged-release Oxycodone Tablets;
USP 36: Oxycodone and Acetaminophen Capsules; Oxycodone and Acetaminophen Tablets; Oxycodone and Aspirin Tablets; Oxycodone Hydrochloride Extended-Release Tablets; Oxycodone Hydrochloride Oral Solution; Oxycodone Hydrochloride Tablets.

Oxymorphone Hydrochloride

(BANM, rINNM) ⊗

7,8-Dihydro-14-hydroxymorphinone hydrochloride; Hidrocloruro de oximorfona; Oximorfona, hidrocloruro de; Oximorphone Hydrochloride; Oxymorphone, Chlorhydrate d'; Oxymorphoni Hydrochloridum; Оксиморфона Гидрохлорид.

6-Deoxy-7,8-dihydro-14-hydroxy-6-oxomorphine hydrochloride; (-)-(5*R*,6*S*,14*S*)-4,5-Epoxy-3,14-dihydroxy-9a-methylmorphinan-6-one hydrochloride.

$C_{17}H_{19}NO_4.HCl$=337.8

CAS — 76-41-5 (oxymorphone); 357-07-3 (oxymorphone hydrochloride).

UNII — 5Y2EI94NBC.

Pharmacopoeias. In *US.*

USP 36: (Oxymorphone Hydrochloride). A white or slightly off-white odourless powder, darkening on exposure to light. Its aqueous solutions are slightly acidic. Soluble 1 in 4 of water, 1 in 100 of alcohol, and 1 in 25 of methyl alcohol; very slightly soluble in chloroform and in ether. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Oxymorphone hydrochloride, a phenanthrene derivative, is an opioid analgesic (p. 108.1) with actions and uses similar to those of morphine (p. 92.3), apart from a lack of cough suppressant activity. Oxymorphone is given orally, parenterally, or rectally for the relief of moderate to severe pain, including pain in obstetrics, and is reported to provide analgesia for 3 to 6 hours. It may also be used parenterally for premedication, as an adjunct to anaesthesia, and to relieve dyspnoea due to pulmonary oedema resulting from left ventricular failure.

A usual *oral* starting dose for opioid-naive patients is 10 to 20 mg of oxymorphone hydrochloride every 4 to 6 hours adjusted thereafter as necessary; some patients may be started on lower doses of 5 mg. For patients who have been receiving a strong opioid analgesic the initial dose of oxymorphone should be based on the daily opioid requirement; licensed product information suggests that 10 mg of oral oxymorphone is equivalent to about 30 mg of oral morphine and recommends giving half the calculated equivalent dose of oxymorphone initially. Oxymorphone hydrochloride may also be given orally as a modified-release preparation every 12 hours. Oral preparations of oxymorphone should be taken on an empty stomach.

Oxymorphone hydrochloride is given by *intramuscular* or *subcutaneous injection* in initial doses of 1 to 1.5 mg, repeated every 4 to 6 hours as necessary; 500 micrograms may be given by intravenous injection. The usual dose for analgesia during labour is 0.5 to 1 mg intramuscularly. When transferring between oral and parenteral oxymorphone, licensed product information advises that, as a guide, 10 mg of oral oxymorphone is equivalent to about 1 mg of parenteral oxymorphone.

Oxymorphone hydrochloride is also given *rectally* as a suppository in a dose of 5 mg every 4 to 6 hours.

References.
1. Prommer E. Oxymorphone: a review. *Support Care Cancer* 2006; 14: 109–15.
2. Chamberlin KW, *et al.* Oral oxymorphone for pain management. *Ann Pharmacother* 2007; 41: 1144–52.
3. Mayyas F, *et al.* A systematic review of oxymorphone in the management of chronic pain. *J Pain Symptom Manage* 2010; 39: 296–308.

Administration in hepatic impairment. Advice on the use of oxymorphone in patients with hepatic impairment is conflicting. Licensed product information for one range of preparations (*Opana* and *Opana ER tablets; Endo, USA*) recommends caution in patients with mild hepatic impairment; these patients should be started on the lowest oral dose and titrated slowly thereafter. In addition, it is stated that oxymorphone is contra-indicated in those with moderate or severe impairment. However, licensed information for another oxymorphone preparation (*Numorphan injection and suppositories; Endo, USA*) only recommends caution in hepatic disease although lower doses (unspecified) are advised in those patients with severe impairment.

Administration in renal impairment. In patients with moderate to severe renal impairment, the bioavailability of oxymorphone was found to increase by over 50%; consequently, it is recommended that oxymorphone is given with caution and in reduced doses (unspecified) to those with a creatinine clearance of less than 50 mL/minute.

Dependence and Withdrawal

As for Opioid Analgesics in general, p. 109.1.

Adverse Effects, Treatment, and Precautions

As for Opioid Analgesics in general, p. 110.1.

For details on the use of oxymorphone in patients with hepatic or renal impairment, see above.

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

Licensed product information for a modified-release preparation of oxymorphone hydrochloride (*Opana ER; Endo, USA*) states that patients must not ingest alcohol, including alcohol-containing medicines, at the same time due to the risk of increased plasma concentrations and potentially fatal overdose of oxymorphone.

Pharmacokinetics

Oxymorphone hydrochloride is absorbed from the gastrointestinal tract after oral doses, but bioavailability is only about 10% because of first-pass metabolism. Absorption is increased after a high-fat meal. About 10% is bound to plasma proteins. Oxymorphone is extensively metabolised in the liver by glucuronidation and less than 1% of a dose appears in the urine and faeces as unchanged drug. With regard to its major metabolites between 33 and 38% of a dose is excreted in the urine as oxymorphone-3-glucuronide and less than 1% as 6-OH-oxymorphone. Oxymorphone crosses the placenta.

References.
1. Adams MP, Ahdieh H. Pharmacokinetics and dose-proportionality of oxymorphone extended release and its metabolites: results of a randomized crossover study. *Pharmacotherapy* 2004; 24: 468–76.
2. Adams MP, Ahdieh H. Single- and multiple-dose pharmacokinetic and dose-proportionality study of oxymorphone immediate-release tablets. *Drugs R D* 2005; 6: 91–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Numorphan; Opana.

Pharmacopoeial Preparations
USP 36: Oxymorphone Hydrochloride Injection; Oxymorphone Hydrochloride Suppositories.

Oxyphenbutazone *(BAN, rINN)*

G-27202; Hydroxyphenylbutazone; Oksifenbutatsoni; Oxifenbutazon; Oxifenbutazona; Oxyphenbutazonum; Оксифенбутазон.

4-Butyl-1-(4-hydroxyphenyl)-2-phenylpyrazolidine-3,5-dione monohydrate.

$C_{19}H_{20}N_2O_3.H_2O$=342.4

CAS — 129-20-4 (anhydrous oxyphenbutazone); 7081-38-1 (oxyphenbutazone monohydrate).

ATC — M01AA03; M02AA04; S01BC02.

ATC Vet — QM01AA03; QM02AA04; QS01BC02.

UNII — H806S4B3NS (oxyphenbutazone); A7D84513GV (anhydrous oxyphenbutazone).

Profile

Oxyphenbutazone, a metabolite of phenylbutazone (p. 125.1), is an NSAID (p. 102.3). It has been applied topically to the eye as an anti-inflammatory ointment in conditions such as episcleritis. Oxyphenbutazone was used systemically in disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis but such use is no longer considered justified because of the risk of severe haematological adverse effects (see also Effects on the Blood, under Phenylbutazone, p. 125.2).

The piperazine salt has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Oxy-Triactin; Sioril.

Multi-ingredient Preparations. *Braz.*: Algiflamanil†; Febupen; Flamanan; *Mex.*: Dartrizon.

Paracetamol (BAN, rINN)

Acetaminofeno; Acetaminophen; *N*-Acetyl-*p*-aminophenol; Asetaminofen; Paracétamol; Paracetamolis; Paracetamolo; Paracetamolum; Parasetamol; Parasetamoli; Парацетамол.

4'-Hydroxyacetanilide; N-(4-Hydroxyphenyl)acetamide.

$C_8H_9NO_2$=151.2.

CAS — 103-90-2.

ATC — N02BE01.

ATC Vet — QN02BE01.

UNII — 362O9ITL9D.

NOTE. Compounded preparations of paracetamol may be represented by the following names:

- Co-bucafAPAP (*PEN*)—butalbital, paracetamol, and caffeine
- Co-codamol *x/y* (*BAN*)—where *x* and *y* are the strengths in milligrams of codeine phosphate and paracetamol respectively
- Co-codAPAP (*PEN*)—paracetamol and codeine phosphate
- Co-dydramol (*BAN*)—dihydrocodeine tartrate 1 part and paracetamol 50 parts (w/w)
- Co-hycodAPAP (*PEN*)—hydrocodone tartrate and paracetamol
- Co-methiamol *x/y* (*BAN*)—where *x* and *y* are the strengths in milligrams of DL-methionine and paracetamol respectively
- Co-oxycodAPAP (*PEN*)—oxycodone and paracetamol
- Co-proxamol (*BAN*)—dextropropoxyphene hydrochloride 1 part and paracetamol 10 parts (w/w)
- Co-proxAPAP (*PEN*)—dextropropoxyphene napsilate and paracetamol

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 8: (Paracetamol). A white or almost white, crystalline powder. Sparingly soluble in water; freely soluble in alcohol; very slightly soluble in dichloromethane. Protect from light.

USP 36: (Acetaminophen). A white odourless crystalline powder. Soluble 1 in 20 of boiling water, 1 in 10 of alcohol, and 1 in 15 of 1*N* sodium hydroxide. Store in airtight containers. Protect from light. Protect from moisture and heat.

Uses and Administration

Paracetamol, a para-aminophenol derivative, has analgesic and antipyretic properties and weak anti-inflammatory activity. Paracetamol is given orally or as a rectal suppository for mild to moderate pain (below) and for fever (p. 11.3). It may also be given by intravenous infusion for the short-term treatment of moderate pain, particularly after surgery, and of fever. Paracetamol is often the analgesic or antipyretic of choice, especially in the elderly and in patients in whom salicylates or other NSAIDs are contra-indicated. Such patients include asthmatics, those with a history of peptic ulcer, and children.

The usual **oral** dose is 0.5 to 1 g every 4 to 6 hours up to a maximum of 4 g daily. Paracetamol may also be given as suppositories in a **rectal** dose of 0.5 to 1 g every 4 to 6 hours, up to 4 times daily.

Paracetamol is given by **intravenous** infusion over 15 minutes; dosage may be calculated according to body-weight as follows:

- over 50 kg, single doses of 1 g every 4 or more hours, to a maximum of 4 g daily
- from 33 to 50 kg, single doses of 15 mg/kg every 4 or more hours, to a maximum of 60 mg/kg (up to 3 g) daily

A maximum intravenous dose of 3 g daily should also not be exceeded in patients with chronic alcoholism, chronic malnutrition, or dehydration, regardless of their body-weight.

For doses in children, or in hepatic or renal impairment, see below.

References.

1. Prescott LF. *Paracetamol (acetaminophen): a critical bibliographic review.* London: Taylor & Francis, 1996.
2. Bannwarth B, Péhourcq F. Bases pharmacologiques de l'emploi du paracétamol: aspects pharmacocinétiques et pharmacodynamiques. *Drugs* 2003; 63 (suppl 2): 5–13.
3. Prescott LF. Nouvelles perspectives avec le paracétamol. *Drugs* 2003; 63 (suppl 2): 51–6.
4. Duggan ST, Scott LJ. Intravenous paracetamol (acetaminophen). *Drugs* 2009; 69: 101–13.

Administration in children. In the UK, the licensed **oral** doses of paracetamol for pain and fever in children, given according to age, every 4 to 6 hours if necessary up to a maximum of 4 doses in 24 hours, are:

- 3 to 6 months: 60 mg
- 6 months to 2 years: 120 mg
- 2 to 4 years: 180 mg
- 4 to 6 years: 240 mg
- 6 to 8 years: 240 or 250 mg
- 8 to 10 years: 360 or 375 mg
- 10 to 12 years: 480 or 500 mg
- 12 to 16 years: 480 or 750 mg

In younger children the *BNFC* suggests the following doses:

- neonates 28 to 32 weeks postmenstrual age (gestational age at birth plus chronological age): 20 mg/kg as a single dose then 10 to 15 mg/kg every 8 to 12 hours if necessary up to a maximum of 30 mg/kg daily
- neonates over 32 weeks postmenstrual age: 20 mg/kg as a single dose then 10 to 15 mg/kg every 6 to 8 hours if necessary up to a maximum of 60 mg/kg daily
- 1 to 3 months of age: 30 to 60 mg every 8 hours if necessary

The *BNFC* also suggests higher oral doses for use in children with *severe* postoperative pain:

- 1 month to 12 years: 20 to 30 mg/kg as a single dose followed by 15 to 20 mg/kg every 4 to 6 hours if necessary up to a maximum of 90 mg/kg daily. Usual adult maximum single and daily doses (see above) should not be exceeded

UK licensed **rectal** doses, which may be given to children every 4 to 6 hours if necessary, up to 4 times daily are:

- 3 months to 1 year: 60 to 125 mg
- 1 to 5 years: 125 to 250 mg
- 5 to 12 years: 250 to 500 mg

The *BNFC* suggests the following rectal doses in younger children:

- neonates 28 to 32 weeks postmenstrual age: 20 mg/kg as a single dose then 15 mg/kg every 12 hours if necessary to a maximum of 30 mg/kg daily
- neonates over 32 weeks postmenstrual age: 30 mg/kg as a single dose then 20 mg/kg every 8 hours if necessary to a maximum of 60 mg/kg daily
- 1 to 3 months of age: 30 to 60 mg every 8 hours if necessary

The *BNFC* also suggests higher rectal doses for use in children with *severe* postoperative pain:

- 1 to 3 months: 30 mg/kg as a single dose followed by 15 to 20 mg/kg every 4 to 6 hours to a maximum of 90 mg/kg daily
- older children: 30 to 40 mg/kg as a single dose followed by 15 to 20 mg/kg every 4 to 6 hours to a maximum of 90 mg/kg daily. Usual adult maximum single and daily doses (see above) should not be exceeded

Doses by **intravenous** infusion in children, given, according to body-weight, over 15 minutes, are:

- full-term neonates and other children below 10 kg: single doses of 7.5 mg/kg every 4 or more hours, to a maximum of 30 mg/kg daily. The *BNFC* suggests a dose of 10 mg/kg every 4 to 6 hours to a maximum of 30 mg/kg daily; intravenous paracetamol has not been studied in premature neonates but the *BNFC* suggests for premature neonates over 32 weeks postmenstrual age, a dose of 7.5 mg/kg every 8 hours to a maximum of 25 mg/kg daily
- between 10 and 33 kg: single doses of 15 mg/kg every 4 or more hours, to a maximum of 60 mg/kg (up to 2 g) daily
- from 33 to 50 kg: single doses of 15 mg/kg every 4 or more hours, to a maximum of 60 mg/kg (up to 3 g) daily
- over 50 kg: usual adult doses (see above)

The intravenous solution may be diluted to a minimum strength of one-tenth of its original concentration in sodium chloride 0.9% or glucose 5%; the diluted solution should be used within 1 hour of preparation.

For ***post-immunisation pyrexia,*** an oral or rectal dose of 60 mg has been recommended for children 2 to 3 months of age. If necessary a second dose may be given after 4 to 6 hours; if the pyrexia persists after that dose, medical advice should be sought.

It has been suggested[1] that the recommended doses of paracetamol for children may result in subtherapeutic blood concentrations, and that an initial loading dose should be given, followed by regular doses up to the recommended maximum daily dose. However, the appropriate maximum daily dose remains controversial, and there is obvious concern given the risks of overdosage. Indeed, there have been concerns about the potential for hepatotoxicity with therapeutic doses of paracetamol in children (defined as an oral or intravenous dose of ≤75 mg/kg daily, maximum of 4 g daily, or a rectal dose of ≤100 mg/kg daily, maximum of 5 g daily). Nevertheless, a systematic review[2] of controlled studies and case reports suggested that the risk of developing symptomatic hepatotoxicity with such use is less than 0.01%.

1. Zacharias M, Watts D. Pain relief in children. *BMJ* 1998; 316: 1552.
2. Lavonas EJ, *et al.* Therapeutic acetaminophen is not associated with liver injury in children: a systematic review. *Pediatrics* 2010; 126: e1430–e1444.

Administration in hepatic impairment. There is evidence to suggest that paracetamol can be safely used in patients with hepatic impairment (see under Precautions, p. 118.2); however, reduced doses may be warranted to avoid accidental overdosages. The *BNF* recommends avoiding large doses in patients with hepatic impairment; others have suggested that doses of 2 to 3 g daily should not be exceeded in patients with cirrhosis requiring long-term use although a daily dose of 3 to 4 g may be safe for short-term or one-off use.[1] UK licensed product information recommends that the maximum dose of intravenous paracetamol should not exceed 3 g daily in patients with hepatic impairment or chronic alcoholism; it also states that those with severe impairment should not be given paracetamol by this route.

1. Chandok N, Watt KDS. Pain management in the cirrhotic patient: the clinical challenge. *Mayo Clin Proc* 2010; 85: 451–8.

Administration in renal impairment. In renally impaired patients with a creatinine clearance of 30 mL/minute or less it is recommended that the interval between each intravenous paracetamol dose is increased to 6 hours.

Headache. Non-opioid analgesics such as paracetamol, aspirin, and other NSAIDs are often tried first for the symptomatic treatment of various types of headache including migraine (see p. 670.3) and tension-type headache (see p. 671.3). These drugs given at the onset of symptoms can successfully treat an acute attack of migraine. However, absorption may be poor due to gastric stasis which is commonly present in migraine. For this reason dispersible and effervescent preparations and compound preparations containing drugs such as metoclopramide which relieve gastric stasis have been advocated.

References.

1. Derry S, *et al.* Paracetamol (acetaminophen) with or without an antiemetic for acute migraine headaches in adults. Available in The Cochrane Database of Systematic Reviews; Issue 11. Chichester: John Wiley; 2010 (accessed 03/12/10).

Pain. Paracetamol is used in the management of mild to moderate pain (see Choice of Analgesic, p. 4.2). It is of similar potency to aspirin, but with weak anti-inflammatory activity. Paracetamol may also be used as an adjunct to opioids in the management of severe pain such as cancer pain (p. 7.1). Paracetamol is the preferred choice for pain in children (p. 5.2) because of the association of aspirin with Reye's syndrome in this age group (see p. 25.3). In the treatment of rheumatic disorders, a weak anti-inflammatory effect limits the role of paracetamol. However, it may be of benefit for simple pain control in rheumatoid arthritis (p. 13.2) and ankylosing spondylitis (see under Spondyloarthropathies, p. 14.3), although these patients usually require the additional anti-inflammatory effects provided by NSAIDs. Synovial inflammation is usually only a minor component of osteoarthritis (p. 12.3), and paracetamol is generally recommended as first choice of treatment before NSAIDs are tried. Paracetamol is useful for the relief of acute low back pain (p. 9.2).

Dependence and tolerance are not a problem with non-opioid analgesics such as paracetamol, but there is a ceiling of efficacy, above which increasing the dose has no further therapeutic effect.

Adverse Effects and Treatment

Adverse effects of paracetamol are rare and usually mild, although haematological reactions including thrombocytopenia, leucopenia, pancytopenia, neutropenia, and agranulocytosis have been reported. Rashes and other hypersensitivity reactions occur occasionally.

Injection site reactions such as pain and a burning sensation are common after parenteral use; hypotension and tachycardia have been reported rarely. Application site reactions have also been noted after rectal use.

Overdosage with paracetamol can result in severe liver damage and sometimes acute renal tubular necrosis. Prompt treatment with acetylcysteine or methionine is essential and is discussed under Overdosage, p. 116.2.

References.

1. Graham GG, *et al.* Tolerability of paracetamol. *Drug Safety* 2005; 28: 227–40.

Carcinogenicity. A prospective cohort study[1] involving over 64 000 men and women between 50 and 76 years of age found that use of paracetamol for more than 4 days a week for longer than 4 years was associated with a two-fold increase in the risk of haematological malignancies. The authors considered that other prospective studies were required before any recommendations about paracetamol use could be made.

1. Walter RB, *et al.* Long-term use of acetaminophen, aspirin, and other nonsteroidal anti-inflammatory drugs and risk of hematologic malignancies: results from the prospective vitamins and lifestyle (VITAL) study. *J Clin Oncol* 2011; 29: 2424–31.

Effects on the cardiovascular system. Large cohort studies[1,2] have shown an association between the use of non-opioid analgesics, including paracetamol, and a significantly increased risk of hypertension in women; similar studies[3,4] in men have been equivocal but suggest a more moderate increase in risk. However, it has also been suggested[5] that the hypertension may have been caused by

pain itself or more likely to be detected in patients taking more paracetamol due to a higher frequency of visits to their doctor.

1. Dedier J, *et al.* Nonnarcotic analgesic use and the risk of hypertension in US women. *Hypertension* 2002; 40: 604–8.
2. Forman JP, *et al.* Non-narcotic analgesic dose and risk of incident hypertension in US women. *Hypertension* 2005; 46: 500–507.
3. Kurth T, *et al.* Analgesic use and risk of subsequent hypertension in apparently healthy men. *Arch Intern Med* 2005; 165: 1903–9.
4. Forman JP, *et al.* Frequency of analgesic use and risk of hypertension among men. *Arch Intern Med* 2007; 167: 394–9.
5. Montgomery B. Does paracetamol cause hypertension? *BMJ* 2008; 336: 1190–1.

Effects on the ears. A questionnaire study in nearly 27 000 male health professionals originally aged 40 years and over has examined the association between hearing loss and the regular use of aspirin, NSAIDs, and paracetamol.[1] During 369 079 person-years of follow-up, 3488 cases of hearing loss were reported; regular analgesic use (defined as 2 or more times a week) was found to be independently associated with an increased risk of hearing loss for all 3 types of analgesics. The hazard ratio of hearing loss for regular users of paracetamol was 1.22 when compared with those who used analgesics less frequently; the risk also increased with longer duration of use. Concomitant use of more than one type of analgesic also had an additive risk effect.

For reference to reports of hearing loss associated with the abuse or overuse of preparations containing paracetamol, see under Dextropropoxyphene, p. 44.2, and Hydrocodone, p. 67.2.

1. Curhan SG, *et al.* Analgesic use and the risk of hearing loss in men. *Am J Med* 2010; 123: 231–7.

Effects on the kidneys. For reference to evidence that abuse or prolonged excessive use of analgesics, including paracetamol, can produce nephropathy, see under NSAIDs, p. 106.2.

See also under Overdosage, below.

Effects on metabolism. Use of paracetamol, alone or with other drugs (see under Flucloxacillin, p. 302.1), has been associated with accumulation of pyroglutamic acid, resulting in pyroglutamic aciduria (5-oxoprolinuria) and high-anion gap metabolic acidosis.[1-4]

1. Humphreys BD, *et al.* Acetaminophen-induced anion gap metabolic acidosis and 5-oxoprolinuria (pyroglutamic aciduria) acquired in hospital. *Am J Kidney Dis* 2005; 46: 143–6.
2. Fenves AZ, *et al.* Increased anion gap metabolic acidosis as a result of 5-oxoproline (pyroglutamic acid): a role for acetaminophen. *Clin J Am Soc Nephrol* 2006; 1: 441–7.
3. Alados Arboledas FJ, *et al.* Acidosis piroglutámica asociada a paracetamol. *An Pediatr (Barc)* 2007; 67: 582–4.
4. Verma R, *et al.* 5-Oxoprolinuria as a cause of high anion gap metabolic acidosis. *Br J Clin Pharmacol* 2012; 73: 489–91.

Effects on the respiratory tract. The results of a case-control study[1] have suggested that the frequent (daily or weekly) use of paracetamol may be associated with asthma. However, the UK CSM has commented that the results of this study do not alter any advice regarding the use of paracetamol and that it remains a safe and effective pain killer for many patients including asthmatics.

Subsequently, others have found an increase in the prevalence of asthma[2,3] and COPD[2] with frequent (daily or weekly) use of paracetamol. A link between paracetamol use in pregnancy and asthma in children has also been suggested (see Pregnancy under Precautions, p. 118.2). However, one review[4] stated that there have been very few actual reports of paracetamol causing asthma; furthermore, bronchospasm is not a recognised feature of paracetamol overdosage. This review concluded that a strong link between paracetamol use and asthma was unlikely.

More recently, analysis of questionnaire data[5] for 205 487 children aged 6 to 7 years from 31 countries suggested that the use of paracetamol in the first year of life and later childhood was associated with an increased risk of asthma and also symptoms of rhinoconjunctivitis and eczema. In another questionnaire study[6] by the same group involving 322 959 adolescents aged 13 to 14 years from 50 countries, the recent use of paracetamol was also found to increase the risk of asthma, rhinoconjunctivitis, and eczema. However, after considering the first study, the UK CHM[7] expressed concerns over data interpretation and concluded that it did not provide strong evidence that paracetamol use in infancy can cause asthma; the CHM reiterated that paracetamol remains a safe and appropriate analgesic for children. Furthermore, a small cohort study[8] has also found that, although the use of paracetamol in the first 2 years of life increased the crude risk of asthma in children aged 6 to 7 years, this increase was not noted after adjustment for early respiratory-tract infections or when paracetamol use was limited to non-respiratory-tract infections.

1. Shaheen SO, *et al.* Frequent paracetamol use and asthma in adults. *Thorax* 2000; 55: 266–70.
2. McKeever TM, *et al.* The association of acetaminophen, aspirin, and ibuprofen with respiratory disease and lung function. *Am J Respir Crit Care Med* 2005; 171: 966–71.
3. Eneli I, *et al.* Acetaminophen and the risk of asthma: the epidemiologic and pathophysiologic evidence. *Chest* 2005; 127: 604–12.
4. Nuttall SL, *et al.* Does paracetamol cause asthma? *J Clin Pharm Ther* 2003; 28: 251–7.
5. Beasley R, *et al.* ISAAC Phase Three Study Group. Association between paracetamol use in infancy and childhood, and risk of asthma, rhinoconjunctivitis, and eczema in children aged 6-7 years: analysis from Phase Three of the ISAAC programme. *Lancet* 2008; 372: 1039–48.
6. Beasley RW, *et al.* ISAAC Phase Three Study Group. Acetaminophen use and risk of asthma, rhinoconjunctivitis, and eczema in adolescents: International Study of Asthma and Allergies in Childhood Phase Three. *Am J Respir Crit Care Med* 2011; 183: 171–8.
7. MHRA/CHM. Paracetamol use in infancy: no strong evidence for asthma link. *Drug Safety Update* 2008; 2(4): 9. Available at: http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON030923 (accessed 13/10/09)
8. Lowe AJ, *et al.* Paracetamol use in early life and asthma: prospective birth cohort study. Abridged version: *BMJ* 2010; 341: 713. Full version: http://www.bmj.com/content/341/bmj.c4616.full.pdf (accessed 06/05/11)

Hypersensitivity. Reactions characterised by urticaria, dyspnoea, and hypotension have occurred after use of paracetamol in adults[1-4] and children.[5,6] Angioedema has also been reported.[7] Fixed drug eruptions, confirmed by rechallenge, have been described,[8-11] and toxic epidermal necrolysis has occurred.[12]

1. Stricker BHC, *et al.* Acute hypersensitivity reactions to paracetamol. *BMJ* 1985; 291: 938–9.
2. Van Diem L, Grilliat JP. Anaphylactic shock induced by paracetamol. *Eur J Clin Pharmacol* 1990; 38: 389–90.
3. Kumar RK, Byard I. Paracetamol as a cause of anaphylaxis. *Hosp Med* 1999; 60: 66–7.
4. Bachmeyer C, *et al.* Acetaminophen (paracetamol)-induced anaphylactic shock. *South Med J* 2002; 95: 759–60.
5. Ellis M, *et al.* Immediate adverse reactions to acetaminophen in children: evaluation of histamine release and spirometry. *J Pediatr* 1989; 114: 654–6.
6. Bousetta K, *et al.* Hypersensitivity reactions to paracetamol in children: a study of 25 cases. *Allergy* 2005; 60: 1174–7.
7. Idoko JA, *et al.* Angioneurotic oedema following ingestion of paracetamol. *Trans R Soc Trop Med Hyg* 1986; 80: 175.
8. Thomas RHM, Munro DD. Fixed drug eruption due to paracetamol. *Br J Dermatol* 1986; 115: 357–9.
9. Coben HA, *et al.* Fixed drug eruption caused by acetaminophen. *Ann Pharmacother* 1992; 26: 1596–7.
10. Harris A, Burge SM. Vasculitis in a fixed drug eruption due to paracetamol. *Br J Dermatol* 1995; 133: 790–1.
11. Hern S, *et al.* Bullous fixed drug eruption due to paracetamol with an unusual immunofluorescence pattern. *Br J Dermatol* 1998; 139: 1129–31.
12. Halevi A, *et al.* Toxic epidermal necrolysis associated with acetaminophen ingestion. *Ann Pharmacother* 2000; 34: 32–4.

Overdosage. Acute *oral* overdosage with paracetamol, whether accidental or deliberate, is relatively common and can be extremely serious because of the narrow margin between therapeutic and **toxic doses**. Toxic doses of paracetamol may cause severe hepatocellular necrosis and, less often, renal tubular necrosis. Paracetamol-induced hepatotoxicity is a major cause of acute liver failure in western countries. Hepatotoxicity may occur after ingestion of more than 150 mg/kg, or rarely, as little as 75 mg/kg, of paracetamol within a 24-hour period. The risk of severe toxicity after acute paracetamol overdose appears to be less in children than in adults at comparable doses; however, chronic use of supratherapeutic doses in children has resulted in unintentional overdoses and severe hepatotoxicity.[1,2]

Patients receiving enzyme-inducing drugs or those with a history of alcohol abuse are at high risk of hepatic damage, as may be patients suffering from malnutrition such as those with anorexia, AIDS, or cystic fibrosis. Those who have not eaten for a few days or those with a low body-weight[3] are also predisposed to hepatotoxicity. These factors have previously been used for risk stratification in paracetamol overdosage; however, not all have been well characterised or applied consistently. Hence, the UK CHM has advised that individual risk factors should no longer be used for assessing the risk of toxicity.

Early signs of overdosage (very commonly nausea and vomiting although they may also include lethargy and sweating) usually settle within 24 hours. Abdominal pain may be the first indication of liver damage, which is not usually apparent for 24 to 48 hours and sometimes may be delayed for up to 4 to 6 days after ingestion. Liver damage is generally at a maximum 72 to 96 hours after ingestion. Hepatic failure, encephalopathy, coma, and death may result. Complications of hepatic failure include acidosis, cerebral oedema, haemorrhage, hypoglycaemia, hypotension, infection, and renal failure. Prothrombin time increases with deteriorating liver function and some recommend that it be measured regularly. However, as both paracetamol[4] and acetylcysteine[5] can independently affect prothrombin time in the absence of hepatic injury, the use of prothrombin time as a marker for hepatotoxicity has been questioned and it has been recommended that treatment decisions are based on the entire liver biochemistry.[6]

Acute renal failure with acute tubular necrosis may develop, even in the absence of severe liver damage. Other non-hepatic symptoms that have been reported following paracetamol overdosage include myocardial abnormalities and pancreatitis.

The **mechanism** of toxicity in overdosage with paracetamol is thought to be the production of a minor but highly reactive metabolite, *N*-acetyl-*p*-benzoquinone-imine (NABQI) by cytochrome P450 isoenzymes (mainly CYP2E1 and CYP3A4)[2] in the liver and kidney. The amount of NABQI produced after normal doses of paracetamol is usually completely detoxified by conjugation with glutathione and excreted as mercaptopurine and cysteine conjugates. In paracetamol overdosage, tissue stores of glutathione become depleted, allowing NABQI to accumulate and bind to sulfhydryl groups within hepatocytes causing cell damage. Substances capable of replenishing depleted stores of glutathione, such as acetylcysteine or methionine, are therefore used as antidotes in paracetamol overdosage. Acetylcysteine may also be involved in the repair of damaged tissue.

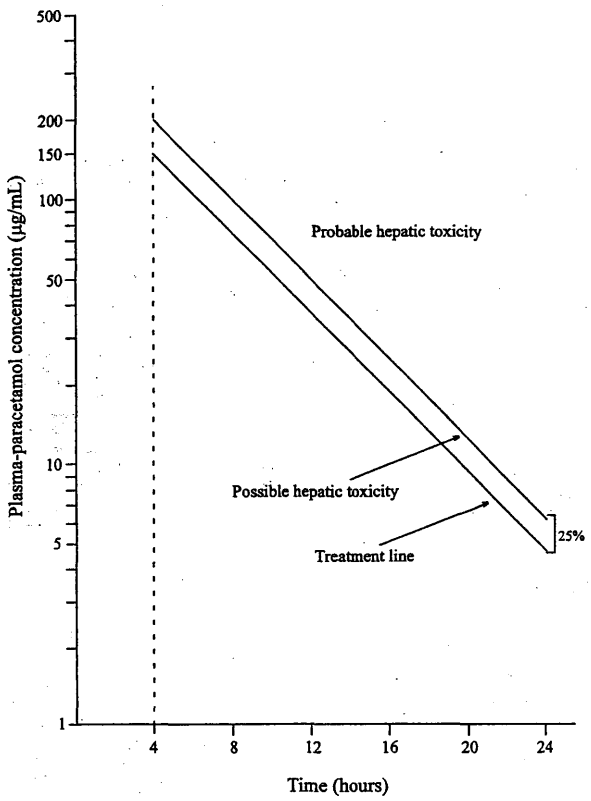
Treatment of oral paracetamol overdosage. The management of paracetamol overdosage as practised in the UK and USA has been the subject of many reviews.[6-15] Guidance is also available in the UK from the *National Poisons Information Service (NPIS)*. Separate consensus guidelines have been issued by clinical toxicologists in Australia and New Zealand.[16]

Prompt treatment is essential, even when there are no obvious symptoms, and patients should be admitted to hospital for full supportive measures to be instituted.

- Activated charcoal may be used to reduce gastrointestinal absorption, if it can be given within 1 hour of the overdose, and if more than 150 mg/kg of paracetamol has been ingested. However, if acetylcysteine or methionine is to be given orally the charcoal is best cleared from the stomach to prevent it reducing the absorption of the antidote.
- There is little evidence that gastric lavage is of benefit in those who have overdosed solely with paracetamol.
- The plasma-paracetamol concentration should be determined as soon as possible, but not within 4 hours of ingestion, to ensure that peak concentrations are recorded. The risk of liver damage is determined by comparison with a nomogram reference line on a plot of plasma-paracetamol concentration against hours after ingestion. A semi-logarithmic plot or a linear plot may be used, see Figure 1 (p. 117) and Figure 2 (p. 117). Generally, antidote treatment is required if the patient's plasma-paracetamol concentration is on or above the reference (treatment) line.
- Plasma-paracetamol concentrations measured more than 15 hours after ingestion are not reliable indicators of hepatotoxicity. Furthermore, the nomogram may not be suitable for use when patients have taken modified-release preparations of paracetamol.[17-19] Some suggestions for modified strategies for the use of the Rumack-Matthew nomogram in the face of overdosage with modified-release preparations have been made.[20-22]
- Plasma-paracetamol concentrations and the Rumack-Matthew nomogram are also of little value in patients who have taken repeated supratherapeutic doses or multiple overdoses of paracetamol over a short period of time: such patients should be considered at serious risk and given antidote treatment.
- If there is any doubt about timing or the need to treat, or where the overdose is staggered, then a patient should be treated with an antidote. In some centres, patients who have ingested 150 mg/kg or more of paracetamol are treated regardless of plasma-paracetamol concentrations.[23]
- Antidote treatment should be started as soon as possible after suspected paracetamol ingestion and should not be delayed while awaiting the results of plasma assays. Once the results become available, treatment may be stopped if the initial concentration was below the nomogram reference line. However, if the initial concentration is on or above the reference line, the full course of antidote must be given and should not be stopped when subsequent plasma concentrations fall below the reference line.

Choice of antidote. Acetylcysteine (p. 1652.2) is usually the antidote of choice but the route of administration varies, and the best protocol has yet to be determined.[6,24] Intravenous use has been associated with anaphylactic reactions but is the preferred route in some countries including Australia, New Zealand, and the UK because of fears that oral absorption might be reduced by vomiting or activated charcoal. However, in the USA the oral route is also licensed, and is clearly effective. The use of methionine (p. 1558.2) orally has the same risks of impaired absorption due to vomiting or activated charcoal. It is cheaper and easier to give than intravenous acetylcysteine and has been used in situations where a patient cannot be transferred to hospital, provided it is given within 10 to 12 hours of the overdose and the patient is not vomiting. However, it has been largely superseded by acetylcysteine.

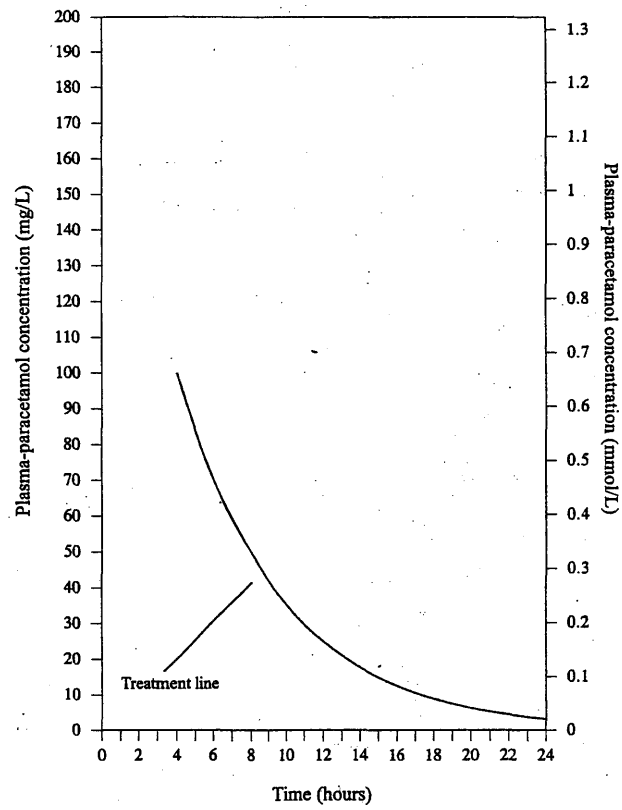
Figure 1. A semi-logarithmic plot of plasma-paracetamol concentration against hours after ingestion.



Adapted from Rumack BH, Matthew HJ. Acetaminophen poisoning and toxicity. *Pediatrics* 1975; 55: 871–6.

Notes for the use of this chart:
1. The time coordinates refer to time after ingestion.
2. Plasma-paracetamol concentrations drawn before 4 hours may not represent peak concentrations.
3. The graph should be used only in relation to a single acute ingestion.
4. The solid line 25% below the standard nomogram is included to allow for possible errors in plasma assays and estimated time from ingestion of an overdose. Patients whose plasma-paracetamol concentrations are on or above this line should be treated.
5. The value of such charts is uncertain if the patient is first seen 15 hours or more after ingestion, or has taken modified-release preparations of paracetamol.

Figure 2. A linear plot of plasma-paracetamol concentration against hours after ingestion.



Courtesy of MHRA.

Notes for the use of this chart:
1. The time coordinates refer to time after ingestion.
2. Plasma-paracetamol concentrations drawn before 4 hours may not represent peak concentrations.
3. The graph should be used only in relation to a single acute ingestion.
4. Patients whose plasma-paracetamol concentrations are on or above the treatment line should be treated.
5. The value of such charts is uncertain if the patient is first seen 15 hours or more after ingestion, or has taken modified-release preparations of paracetamol.

Acetylcysteine is most effective when given during the first 8 hours after taking the overdose and the effect diminishes progressively thereafter. It used to be believed that starting treatment more than 15 hours after overdosage was of no benefit and might aggravate the risk of hepatic encephalopathy. However, late treatment was subsequently shown to be safe,[25] and studies of patients treated up to 36 hours after ingestion suggest that benefit may be obtained up to and possibly beyond 24 hours.[26,27] Furthermore, giving intravenous acetylcysteine to patients who had already developed fulminant hepatic failure has been shown to reduce morbidity and mortality.[28]

- An initial dose of 150 mg/kg (maximum of 16.5 g) of acetylcysteine in 200 mL of glucose 5% is given intravenously over 60 minutes. This is followed by an intravenous infusion of 50 mg/kg (maximum of 5.5 g) in 500 mL of glucose 5% over the next 4 hours and then 100 mg/kg (maximum of 11 g) in one litre over the next 16 hours. Sodium chloride 0.9% may be used where glucose 5% is unsuitable. The volume of intravenous fluids should be modified for children or those with a body-weight of less than 40 kg. If an anaphylactoid reaction develops, the infusion should be stopped and an antihistamine given; it may be possible to continue the acetylcysteine infusion at a slower rate.
- In the USA, acetylcysteine is also licensed for oral use as an alternative to parenteral treatment. It is given as an initial dose of 140 mg/kg as a 5% solution followed by 70 mg/kg every 4 hours for an additional 17 doses. Similar doses have been recommended by the *NPIS* in the UK when venous access is not practicable. Some[29] have suggested increasing the loading dose of oral acetylcysteine when it is given after activated charcoal, whereas others[30] have found that the efficacy of acetylcysteine is not reduced by use of activated charcoal beforehand and consider a larger acetylcysteine dose unnecessary.
- *Pretreatment.* The *NPIS* recommends pretreating patients with antihistamines (histamine H_1- and H_2-antagonists) if they have previously had an anaphylactoid reaction to acetylcysteine: intravenous chlorphenamine 10 mg and intravenous ranitidine 50 mg diluted to 20 mL may be given over at least 2 minutes. Pretreatment with nebulised salbutamol can be used in those with a history of acetylcysteine-associated bronchospasm. A slower initial infusion rate may be warranted in patients who have previously had a severe reaction to acetylcysteine.

Methionine, like acetylcysteine, is most effective when given as early as possible after paracetamol overdosage. However, it is not as effective if treatment is delayed[31-33] and hepatic damage is more frequent and severe if treatment with methionine is started more than 10 hours after ingestion; it may also precipitate hepatic encephalopathy.

- The usual oral dose of methionine in adults and children aged 6 years or older is 2.5 g every 4 hours for 4 doses starting less than 10 to 12 hours after ingestion of the paracetamol and provided the patient is not vomiting. Children aged under 6 years should be given 1 g every 4 hours for 4 doses.

The literature relating to the use of methionine in paracetamol poisoning is, in general, imprecise as to the form of methionine used. Preparations containing both methionine and paracetamol (co-methiamol) have been formulated for use in situations where overdosage may occur.

Histamine H_2-antagonists. It has been suggested that since cimetidine blocks the hepatic cytochrome P450 mixed function oxidase system, it might be of use as an adjunct to acetylcysteine for patients whose production of the toxic metabolite of paracetamol is increased due to enzyme induction. Although there have been several anecdotal reports claiming benefit for cimetidine in patients with paracetamol poisoning, there is no current evidence to support these claims.[6,10,12,34]

Liver transplantation may be considered as a last recourse in some patients.

After maternal **overdosage during pregnancy** fetal metabolism of paracetamol that crosses the placenta can produce sufficient hepatotoxic metabolites to cause fetal hepatotoxicity. Limited data from case reports and a case series suggest that early treatment with oral or intravenous acetylcysteine can be safe and effective in such cases;[35] the *UK National Teratology Information Service* recommends the use of acetylcysteine if clinically indicated. Pre-pregnancy body-weight should be used to calculate the toxic paracetamol dose and actual pregnant body-weight to calculate the antidote dose.

Dosage errors with ***intravenous*** paracetamol have been reported, particularly in young children; rarely, such errors have resulted in substantial overdoses and liver damage.[36,37] The standard nomogram may not be appropriate in determining treatment from plasma-paracetamol concentrations after overdosage by intravenous infusion, as it is based on data from acute paracetamol ingestion rather than intravenous administration. Plasma-paracetamol concen-

trations more than 4 hours after intravenous injection are usually lower than those predicted for the same oral dose at the same time-point after ingestion. Furthermore, patients receiving intravenous paracetamol are likely to have an increased risk of hepatotoxicity due to poor nutrition from acute fasting. The *NPIS* recommends antidote treatment with intravenous acetylcysteine (see above for doses) when 60 mg/kg or more of paracetamol in total has been given intravenously to adults and children within 24 hours. If there is uncertainty about the actual dose of paracetamol given, the standard nomogram may be used to determine the risk of liver damage. Antidote treatment (see above) is required if plasma-paracetamol concentrations, measured at least 4 hours after administration, are up to 50% below the reference line (for example—treat if the concentration is above 50 mg/L at 4 hours) (see Figure 1 and Figure 2, p. 117).

1. Miles FK, *et al.* Accidental paracetamol overdosing and fulminant hepatic failure in children. *Med J Aust* 1999; 171: 472–5.
2. American Academy of Pediatrics Committee on Drugs. Acetaminophen toxicity in children. *Pediatrics* 2001; 108: 1020–4.
3. Claridge LC, *et al.* Acute liver failure after administration of paracetamol at the maximum recommended daily dose in adults. *BMJ* 2010; 341: 1269–70.
4. Whyte IM, *et al.* Acetaminophen causes an increased International Normalized Ratio by reducing functional factor VII. *Ther Drug Monit* 2000; 22: 742–8.
5. Schmidt LE, *et al.* Effect of acetylcysteine on prothrombin index in paracetamol poisoning without hepatocellular injury. *Lancet* 2002; 360: 1151–2.
6. Brok J *et al.* Interventions for paracetamol (acetaminophen) overdose. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 23/10/06).
7. Whitcomb DC, *et al.* Association of acetaminophen hepatotoxicity with fasting and ethanol use. *JAMA* 1994; 272: 1845–50.
8. Makin AJ, *et al.* Management of severe cases of paracetamol overdosage. *Br J Hosp Med* 1994; 52: 210–13.
9. Vale JA, Proudfoot AT. Paracetamol (acetaminophen) poisoning. *Lancet* 1995; 346: 547–52.
10. Prescott LF. Paracetamol overdose. In: *Paracetamol (acetaminophen): a critical bibliographic review.* London: Taylor & Francis, 1996: 401–73.
11. Routledge P, *et al.* Paracetamol (acetaminophen) poisoning. *BMJ* 1998; 317: 1609–10.
12. Zed PJ, Krenzelok EP. Treatment of acetaminophen overdose. *Am J Health-Syst Pharm* 1999; 56: 1081–91.
13. Kozer E, Koren G. Management of paracetamol overdose: current controversies. *Drug Safety* 2001; 24: 503–12.
14. Dart RC, *et al.* Acetaminophen poisoning: an evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol* 2006; 44: 1–18.
15. Ferner RE, *et al.* Management of paracetamol poisoning. *BMJ* 2011; 342: d2218.
16. Daly FFS, *et al.* Panel of Australian and New Zealand clinical toxicologists. Guidelines for the management of paracetamol poisoning in Australia and New Zealand—explanation and elaboration: a consensus statement from clinical toxicologists consulting to the Australasian poisons information centres. *Med J Aust* 2008; 188: 296–301. Also available at: http://www.mja.com.au/public/issues/188_05_030308/dal10916_fm.html (accessed 13/08/08)
17. Graudins A, *et al.* Overdose of extended-release acetaminophen. *N Engl J Med* 1995; 333: 196.
18. Vassallo S, *et al.* Use of the Rumack-Matthew nomogram in cases of extended-release acetaminophen toxicity. *Ann Intern Med* 1996; 125: 940.
19. Dart RC, *et al.* The safety profile of sustained release paracetamol during therapeutic use and following overdose. *Drug Safety* 2005; 28: 1045–56.
20. Temple AR, Mrazik TJ. More on extended-release acetaminophen. *N Engl J Med* 1995; 333: 1508.
21. Graudins A, *et al.* More on extended-release acetaminophen. *N Engl J Med* 1995; 333: 1508–9.
22. Cetaruk EW, *et al.* Extended-release acetaminophen overdose. *JAMA* 1996; 275: 686.
23. Aujla KS, *et al.* Nomogram does not show absolute concentration for treatment. *BMJ* 1998; 317: 1655.
24. Kanter MZ. Comparison of oral and i.v. acetylcysteine in the treatment of acetaminophen poisoning. *Am J Health-Syst Pharm* 2006; 63: 1821–7.
25. Parker D, *et al.* Safety of late acetylcysteine treatment in paracetamol poisoning. *Hum Exp Toxicol* 1990; 9: 25–7.
26. Smilkstein MJ, *et al.* Efficacy of oral N-acetylcysteine in the treatment of acetaminophen overdose: analysis of the National Multicenter Study (1976 to 1985). *N Engl J Med* 1988; 319: 1557–62.
27. Harrison PM, *et al.* Improved outcome of paracetamol-induced fulminant hepatic failure by late administration of acetylcysteine. *Lancet* 1990; 335: 1572–3.
28. Keays R, *et al.* Intravenous acetylcysteine in paracetamol induced fulminant hepatic failure: a prospective controlled trial. *BMJ* 1991; 303: 1026–9.
29. Chamberlain JM, *et al.* Use of activated charcoal in a simulated poisoning with acetaminophen: a new loading dose for N-acetylcysteine? *Ann Emerg Med* 1993; 22: 1398–1402.
30. Spiller HA, *et al.* A prospective evaluation of the effect of activated charcoal before oral N-acetylcysteine in acetaminophen overdose. *Ann Emerg Med* 1994; 23: 519–23.
31. Vale JA, *et al.* Intravenous N-acetylcysteine: the treatment of choice in paracetamol poisoning? *BMJ* 1979; 2: 1435–6.
32. Vale JA, *et al.* Treatment of acetaminophen poisoning: the use of oral methionine. *Arch Intern Med* 1981; 141: 394–6.
33. Tee LGB, *et al.* N-Acetylcysteine for paracetamol overdose. *Lancet* 1986; i: 331–2.
34. Kaufenberg AJ, Shepherd MF. Role of cimetidine in the treatment of acetaminophen poisoning. *Am J Health-Syst Pharm* 1998; 55: 1516–19.
35. Wilkes JM, *et al.* Acetaminophen overdose in pregnancy. *South Med J* 2005; 98: 1118–22.
36. Beringer RM, *et al.* Intravenous paracetamol overdose: two case reports and a change to national treatment guidelines. *Arch Dis Child* 2011; 96: 307–8.
37. Dart RC, Rumack BH. Intravenous acetaminophen in the United States: iatrogenic dosing errors. *Pediatrics* 2012; 129: 349–53.

Pancreatitis. Drug-induced pancreatitis associated with paracetamol was reported[1] to be a rare reaction only occurring in patients taking more than recommended doses. In a retrospective study of data from 814 patients who had taken paracetamol overdoses, hyperamylasaemia was detected in 246, and was more common and more severe in patients transferred to a specialist unit because of more severe poisoning.[2] However, acute pancreatitis was diagnosed only in 33 cases.

1. Underwood TW, Prye CB. Drug-induced pancreatitis. *Clin Pharm* 1993; 12: 440–8.
2. Schmidt LE, Dalhoff K. Hyperamylasaemia and acute pancreatitis in paracetamol poisoning. *Aliment Pharmacol Ther* 2004; 20: 173–9.

Precautions

Paracetamol should be given with care to patients with impaired kidney or liver function; the *BNF* recommends that large doses should be avoided in patients with hepatic impairment. It should also be given with care to patients with alcohol dependence, chronic malnutrition, or dehydration.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving paracetamol, and the last available guidance from the American Academy of Pediatrics considered[1] that it is therefore usually compatible with breast feeding. The *BNF* also considers that the amount of paracetamol distributed into breast milk is too small to be harmful to a breast-fed infant.

Pharmacokinetic studies in 12 nursing mothers given a single dose of paracetamol showed that peak paracetamol concentrations in breast milk of 10 to 15 micrograms/mL were achieved in 1 to 2 hours. Plasma concentrations were determined in 2 mothers; a breast milk to plasma ratio of about 1 was reported.[2] Similar findings have been reported from other studies.[3,4]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *Ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 19/10/06)
2. Berlin CM, *et al.* Disposition of acetaminophen in milk, saliva, and plasma of lactating women. *Pediatr Pharmacol* 1980; 1: 135–41.
3. Hurden EL, *et al.* Excretion of paracetamol in human breast milk. *Arch Dis Child* 1980; 55: 969–72.
4. Bitzén P-O, *et al.* Excretion of paracetamol in human breast milk. *Eur J Clin Pharmacol* 1981; 20: 123–5.

Hepatic impairment. Reviews[1,2] have concluded that there is evidence that paracetamol could be and had been used safely in patients with liver disease. Studies had also shown that although the half-life of paracetamol was prolonged in such patients, glutathione concentrations in those taking recommended doses were not depleted to the critical levels that would enable accumulation of paracetamol's hepatotoxic metabolite.

1. Benson GD, *et al.* The therapeutic use of acetaminophen in patients with liver disease. *Am J Ther* 2005; 12: 133–41.
2. Chandok N, Watt KDS. Pain management in the cirrhotic patient: the clinical challenge. *Mayo Clin Proc* 2010; 85: 451–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies paracetamol as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Pregnancy. The *UK National Teratology Information Service* recommends that paracetamol may be used in pregnancy if appropriate. As a whole, *animal* and epidemiological studies show that the therapeutic use of paracetamol during pregnancy does not increase the risk of an adverse outcome.[1]

A large prospective study has reported that the frequent use of paracetamol (defined as most days or daily use) in late pregnancy (20 to 32 weeks of gestation) may be associated with an increased risk of persistent wheezing in the infant[2] which may persist into childhood;[3] use during early pregnancy was not associated with an increased risk. Several reviews and meta-analyses have considered the link between childhood asthma and wheezing and prenatal paracetamol exposure;[4-6] however, while some consider that there may be a link, others consider that the data were conflicting and evidence for a causal association is inconclusive (see also Effects on the Respiratory Tract, p. 116.1). Furthermore, the authors of the original study[2] emphasised that the number of pregnant women taking frequent doses was very small and they recommended that *infrequent* paracetamol should remain the analgesic of choice in pregnancy.

For reference to a possible association between simple analgesics including paracetamol and congenital cryptorchidism, see under NSAIDs, p. 107.2.

1. Scialli AR, *et al.* A review of the literature on the effects of acetaminophen on pregnancy outcome. *Reprod Toxicol* 2010; 30: 495–507.
2. Shaheen SO, *et al.* Paracetamol use in pregnancy and wheezing in early childhood. *Thorax* 2002; 57: 958–63.
3. Shaheen SO, *et al.* Prenatal paracetamol exposure and risk of asthma and elevated immunoglobulin E in childhood. *Clin Exp Allergy* 2005; 35: 18–25.
4. Scialli AR, *et al.* Childhood asthma and use during pregnancy of acetaminophen: a critical review. *Reprod Toxicol* 2010; 30: 508–19.
5. Etminan M, *et al.* Acetaminophen use and the risk of asthma in children and adults: a systematic review and metaanalysis. *Chest* 2009; 136: 1316–23.
6. Byers S, *et al.* Paracetamol in pregnancy and the risk of wheezing in offspring: a systematic review and meta-analysis. *Clin Exp Allergy* 2011; 41: 482–9.

Renal impairment. Caution is recommended when giving paracetamol to patients with renal impairment. Plasma concentrations of paracetamol and its glucuronide and sulfate conjugates are increased in patients with moderate renal failure and in patients on dialysis.[1-3] It has been suggested that paracetamol itself may be regenerated from these metabolites.[1,2] There are conflicting data on whether the conjugates of paracetamol accumulate in patients with renal impairment receiving multiple doses.[2,3]

1. Prescott LF, *et al.* Paracetamol disposition and metabolite kinetics in patients with chronic renal failure. *Eur J Clin Pharmacol* 1989; 36: 291–7.
2. Martin U, *et al.* The disposition of paracetamol and the accumulation of its glucuronide and sulphate conjugates during multiple dosing in patients with chronic renal failure. *Eur J Clin Pharmacol* 1991; 41: 43–6.
3. Martin U, *et al.* The disposition of paracetamol and its conjugates during multiple dosing in patients with end-stage renal failure maintained on haemodialysis. *Eur J Clin Pharmacol* 1993; 45: 141–5.

Interactions

The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic drugs or drugs that induce liver microsomal enzymes. The absorption of paracetamol may be accelerated by drugs such as metoclopramide. Excretion may be affected and plasma concentrations altered when given with probenecid. Colestyramine reduces the absorption of paracetamol if given within 1 hour of paracetamol.

Reviews.

1. Toes MJ, *et al.* Drug interactions with paracetamol. *Am J Ther* 2005; 12: 56–66.

Antibacterials. The plasma-paracetamol concentrations considered an indication for antidote treatment (see Overdosage, p. 116.2) should be halved in patients receiving enzyme-inducing drugs such as *rifampicin*. Severe hepatotoxicity at therapeutic doses or moderate overdoses of paracetamol has been reported in patients receiving *isoniazid*, alone[1-3] or with other drugs for tuberculosis.[4]

For the effects of paracetamol on *chloramphenicol*, see p. 260.3.

For reports of metabolic effects when paracetamol is given with *flucloxacillin*, see under Adverse Effects and Precautions of Flucloxacillin, p. 302.1.

1. Murphy R, *et al.* Severe acetaminophen toxicity in a patient receiving isoniazid. *Ann Intern Med* 1990; 113: 799–800.
2. Moulding TS, *et al.* Acetaminophen, isoniazid, and hepatic toxicity. *Ann Intern Med* 1991; 114: 431.
3. Crippin JS. Acetaminophen hepatotoxicity: potentiation by isoniazid. *Am J Gastroenterol* 1993; 88: 590–2.
4. Nolan CM, *et al.* Hepatotoxicity associated with acetaminophen usage in patients receiving multiple drug therapy for tuberculosis. *Chest* 1994; 105: 408–11.

Anticoagulants. For the effects of paracetamol on oral anticoagulants, see under Warfarin, p. 1530.2.

Antiepileptics. The plasma-paracetamol concentrations considered an indication for antidote treatment (see Overdosage, p. 116.2) should be halved in patients receiving enzyme-inducing drugs such as *carbamazepine, phenobarbital, phenytoin,* or *primidone*.

For the effects of paracetamol on *lamotrigine*, see p. 530.1.

Antivirals. For reports of adverse effects on the liver associated with use of paracetamol with antiviral drugs, see under Interferon Alfa, p. 997.2 and Zidovudine, p. 1026.2.

Probenecid. Pretreatment with probenecid can decrease paracetamol clearance and increase its plasma half-life.[1] Although urinary excretion of the sulfate and glucuronide conjugates of paracetamol are reduced, that of paracetamol is unchanged.

1. Kamali F. The effect of probenecid on paracetamol metabolism and pharmacokinetics. *Eur J Clin Pharmacol* 1993; 45: 551–3.

Pharmacokinetics

Paracetamol is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur about 10 to 60 minutes after oral doses. Paracetamol is distributed into most body tissues. It crosses the placenta and is present in breast milk. Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations. The elimination half-life of paracetamol varies from about 1 to 3 hours.

Paracetamol is metabolised mainly in the liver and excreted in the urine mainly as the glucuronide and sulfate conjugates. Less than 5% is excreted as unchanged

paracetamol. A minor hydroxylated metabolite (*N*-acetyl-*p*-benzoquinoneimine), is usually produced in very small amounts by cytochrome P450 isoenzymes (mainly CYP2E1 and CYP3A4) in the liver and kidney. It is usually detoxified by conjugation with glutathione but may accumulate after paracetamol overdosage and cause tissue damage.

References.
1. van der Marel CD, *et al.* Paracetamol and metabolite pharmacokinetics in infants. *Eur J Clin Pharmacol* 2003; **59**: 243–51.
2. Gregoire N, *et al.* Safety and pharmacokinetics of paracetamol following intravenous administration of 5 g during the first 24 h with a 2-g starting dose. *Clin Pharmacol Ther* 2007; **81**: 401–5.
3. Kumpulainen E, *et al.* Paracetamol (acetaminophen) penetrates readily into the cerebrospinal fluid of children after intravenous administration. *Pediatrics* 2007; **119**: 766–71.
4. Palmer GM, *et al.* I.V. acetaminophen pharmacokinetics in neonates after multiple doses. *Br J Anaesth* 2008; **101**: 523–30.
5. Liukas A, *et al.* Pharmacokinetics of intravenous paracetamol in elderly patients. *Clin Pharmacokinet* 2011; **50**: 121–9.
6. Allegaert K, *et al.* The pharmacokinetics of intravenous paracetamol in neonates: size matters most. *Arch Dis Child* 2011; **96**: 575–80.
7. Zuppa AF, *et al.* Safety and population pharmacokinetic analysis of intravenous acetaminophen in neonates, infants, children, and adolescents with pain or fever. *J Pediatr Pharmacol Ther* 2011; **16**: 246–61.
8. Kulo A, *et al.* Pharmacokinetics of paracetamol and its metabolites in women at delivery and postpartum. *Br J Clin Pharmacol* 2012. Available at: doi:10.1111/j.1365-2125.2012.04402.x

Absorption. The absorption of paracetamol was slow and incomplete in vegetarian subjects compared with non-vegetarian subjects.[1]

1. Prescott LF, *et al.* Impaired absorption of paracetamol in vegetarians. *Br J Clin Pharmacol* 1993; **36**: 237–40.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Acetolit; Alikal Dolor; Apracur Antifebril†; Apracur Te Antifebril; Bio Grip-T; Causalon; Dirox; Doxidol†; Fiebrolex†; Fiebrolito†; Flash; Inmunogrip T Caliente; Itedal; Mejoral; Nodipir; Novo Asat; Para Z Mol; Parageniol; Paratral; Parclen; Piovacal; Qura Plus; Tafirol T; Tafirol; Termofren; Tetradox; Vick Vitapyrena; Viclor; *Austral.*: Chemists Own Pain & Fever; Childrens Panadol; Dymadon; Febridol; Lemsip; Panadol; Panamax; Parahexal†; Paralgin; Perfalgan; *Austria*: Ben-u-ron; Duaneo; Grippostad; Mexalen; Momentum; Parakapton†; Paraspeed†; Perfalgan; Trimedil; *Belg.*: Algostase Mono; Croix Blanche Mono†; Curpol†; Dafalgan; Docpara†; Dolol-Instant; Dolprone; Lemsip; Panadol; Pe-Tam; Perdolan; Perfusalgan; Sanicopyrine; *Braz.*: Acetamil; Acetofen; Anador PRT; Analgisen; Anatyl; Cefabrina; Cimegripe Bebe; Cimegripe-77c; Cyfenol; Din; Dorfen; Dorfenol; Dorico; Dorsanol; Emsgrip; Fervex; Gripotermon†; Paracen; Paracetrex; Paraflan; Paralgen; Paramol; Piramin†; Pratium; Pyrimel†; Sonridor; Termol; Tilekin†; Trifen; Trimedal D&F; Tyflen; Tylalgin; Tylecetamol; Tylenol; Tylephen; Tylidol; Tyneo; Unigrip; Zuplyn; *Canad.*: Abenol; Acet; Apap; Arthritis Pain; Artritol; Atasol; Benylin DM-D-E-A Cold and Sinus; Childrens Feverhalt; Cold and Flu-in-One; Double Strength Children's Tempra; Fortolin; Infant Tempra; Infants Tylenol; Novo-Gesic; Painaid Free; Panadol; Pediaphen; Pediatrix; Procet; Rapid Action; Relief; Taminol; Tantaphen†; Tempra; Tylenol Arthritis Pain; Tylenol Muscle Aches & Body Pain; Tylenol; Vicks Custom Care Body Aches; *Chile*: Acamol; Algiafin; Cotibin Analgesico Antipiretico; Cotibin Compuesto; Dolo-Esan; Geniol; Gesidol; Kitadol; Panadol; Panagesic; Parox Meltab; Rapidol; Sinflu; Supracalm; Tapsin Infantil; Tapsin Puro sin Cafeina†; Tapsin Puro; Tapsin SC; Winasorb; Xumadol; Zolben; *China*: Ai Er Xing (爱尔星); Ai Sen (爱森); AnYi (安怡); Bei Le Xin (倍乐信); Ben-u-ron (悦诺清); Bufferin (百服宁); Childrens Bufferin (儿童百服咛); Childrens Tylenol (泰诺林); Er He Yi (尔合依); Er Re An (而热安); Fan Nuo (凡诺); Fortolin (保达琳); Infant's Tylenol (泰诺林口服); Kang Yu Deng Tong (康裕登通); Pa La Xin (帕拉辛); Panadol (必理通); Pu Le Er (普乐尔); Shi Ning (施宁); Snaplets-FR (斯耐普); Su Ting (素廷); Tylenol (泰诺林); Xing Le Ning (兴乐宁); Yi Di Qing (一滴清); Yi Li Miao (宜利妙); Yi Shang (易尚); Cz.: Ben-u-ron; Calpol†; Daleron; Effect Comfort†; Efferalgan; Medipyrin; Mexalen; Panadol; Paralen; Paramax Rapid; Paramegal; Perfalgan; *Denm.*: Arax; Pamol; Panam†; Panodil; Paratabs†; Perfalgan; Pinex; *Fin.*: Pamol P; Pamol; Panadol; Para-Hot; Para-Suppo; Para-Tabs; Paraceon; Paramax; Perfalgan; *Fr.*: Algodol; Claradol; Dafalgan; Dafalganhop; Doliprane; Dolipranelib; Doliproneoro; Dolko; Dolotec†; Efferalgan; Efferalganodis; Expandox†; Geluprane; Panadol; Paralyoc; Perfalgan; Sedarene†; *Ger.*: Ben-u-ron; Captin; Contac Erkaltungs-Trunk†; Enelfa†; Grippex; Grippostad Heisstrank; Paedialgon†; Parapaed†; Perfalgan; Sinpro N†; Vivimed N; *Gr.*: Algocit; Anadin; Apotel; Biocetamol; Calmodor; Cetinject; Dalminette; Depon Maximum; Depon Odis; Depon; Dolal; Efferalgan; Genspir; Lonarid Aplo; Neo-Kalmol; Panadol; Par; Paramin; Perfalgan; protAlgon; Tempra; Tunelzin; Tylenol; Zenol; *Hong Kong*: Acetamol†; Ben-u-ron; BF-Paradact†; Biogesic; Childrens Fortolin†; Christamol; Cortal for Children; Dhamol; Europain; Panadol; Paracet†; Paracetal†; Paragram†; Parcemol†; Parmol; Pharmadol†; Progesic; Serimol; Setamol; Tiffy†; Uni-Febrin; Uni-Pamol†; *Hung.*: Ben-u-ron; Efferalgan; Febrilin; Grippostad; Mexalen; Panadol; Paramax Rapid; Perfalgan; Rubophen; *India*: A-125; Acticlofiex; Alcocin; Algina; Alice; Anamol; Anthol; Asimol; Babygesic; Bactpar; Bambiti Kid; Bepamol; Calpol; Cemol; Cetanil; Cetofeb; Cofamol; Copanat; Crocin; Cropara; Disprin Paracetamol†; Doliprane; Dolko; Dolo; Dolodart; Dolopar; Essmol; Eupyric; Ezeepara; F-Nil; Fastpara; Febrex; Febridol; Febrinil; Penace; Fenil; Fep; Fepamol; Fepanil; Fevastin; Flupara; Genmole; Hidol; Histacold; Hitem-MD; Hitz; Ibumax; Ifimol; Infadil; Jagcin†; Junimol; Kelvin; Lanol; Lit-King; Lotemp; Low-Deg; Lupipara; Malidens; Medomol; Metacin; Metalgin; Mino; Mol; Mortrin; Narmo; NBace-P; Neomol; Nofiva; Orimol; Oyup; P-125; P-37; Pacimol; Pamol; Panact; Parabig; Paracetanal; Paracin; Paradip; Parafizz; Parafort; Parage; Paraglow; Paral; Paralife; Parameter; Parasym; Paratel; Parazine; PF Drops; Pyrexon; Pyrigesic; Ultragin; *Indon.*: Afebrin†; Alphamol; Biogesic; Bodrex Forte†; Bodrexin Demam; Calapol†; Contratemp; Cupanol; Dapyrin†; Dumin; Erphamol; Farmadol; Fevrin; Grafadon†; Gunaceta†; Ikacetamol; Itamol; Kamolas; Lanamol; Maganol; Moretic; Naprex; Nasamol; Nufadol; Ottopan; Pamol; Panadol Extra; Panadol; Paracetol†; Praxion; Progesic; Propyretic; Pyrex; Pyrexin; Pyridol; Sanmol; Sumagesic†; Tempra; Termorex†; Turpan; Xepamol; *Irl.*: Anadin Paracetamol†; Calpol; Disprol†; Dolflash; Hedex; Lemsip Children's Cold Relief†; Medinol; Panadol; Panagram Max; Paralief; Paralink; Parapaed; Paratabs; Perfalgan; Rimadol†; Tipol; *Israel*: Abrol; Abrolet; Acamol; Acamoli; Aldolor†; Avcamol; Avcamoli; Dexamol Kid; Dexamol; Maccabimol; Novimol; Panadol; Paracet; Paramol; Perfalgan; Rokamol; Sensamol; Supramol; Vimoli†; *Ital.*: Acetamol; Adolef; Babyrinolo Feb Dol; Efferalgan; Liatamolo; Minofen; Normaflu; Panadol; Perfalgan; Piros; Sanipirina; Tachipirina; Termol; *Malaysia*: Arfen; Avadol; Biogesic†; Dhamol; Hoemal; Panadol; Parafizz; Partamol; Poro; Rapidol; Remedol; Tempol; Uphamol; *Mex.*: Abatem; Ac-Fast†; Acetafen; Acetif; Alpirex; Amolgen; Analphen; Andox†; Antidol; Biofer; Calinofen†; Coriver; Datril; Dismifen; Dolgan Flash†; Doluvital; Dolviran; Facetol; Farpik; Ferridal†; Filanc; Frilen; Icetazol; Infalgina†; Magnidol-Plus; Mejoral Acti-Rapido; Mejoral; Mejoralito; Minofen; Neodol; Nordinet Infantil; Notem; Panofen; Pharmacen; Piralgina 650†; Piralgina; Piralyn; Piremol; Precifen; Prosedal; Quitadol; Resfin†; Sedalito; Sinedol†; Soltadol; Sons Piral; Tafirol; Temperal; Tempire†; Tempofin†; Tempra; Temprin; Temzzard; Tylenol; Tylex; Ulpafie; Winasorb†; *Neth.*: Daro; Democyl; Hedex; Momentum†; Panadol; Perfalgan†; Sinaspril-Paracetamol; Tylenol; Vicks Paracetamol; *Norw.*: Pamol; Panodil; Paracet; Perfalgan; Pinex; *NZ*: Lemsip Cold & Flu Original, Cold & Flu Max; Pacimol†; Pamol; Panadol; Paracare; Parapaed; Perfalgan; *Philipp.*: Acet; Acetadol; Aeknil; Alvedon; Anaseran; Baropyrine; Biogesic; Biopain; Bioretic; Calpol; Clocephen; Cloxina; Corgic; Crocin†; Detramol; Dolexpel; Dolonil; Febrinil; Gendol†; Geran; Gifaril P; Kiddilets; Lexalgin; Medgenol; Myremol; Napalgin; Napran; Naprex; Nektol†; Neo-Kiddielets†; Nordex; Opigesic; Para-4-Kids; Para-IV; Paracef; Parvid; Poro; PRC; Rapidol; Rexidol; Riber; Rongesic; Saridon; Selegesic; Sinomol; Tempain; Tempcaire; Tempra; Teramol; Tylenol; Ultragesic; Zestagesic; Zydinol†; *Pol.*: Acenol; Apap; Calpol; Codipar; Efferalgan; Gemipar; Grippostad; Novo-Gesic†; Panadol; Perfalgan; Tazamol†; *Port.*: Anti-Gripe Asclepius; Atralidon; Beluron†; Ben-u-ron; Bisolgrip†; Cetol; Cofedron; Dafalgan; Efferalgan; Febridol; Gelocatil; Hubert†; Katagrip†; Kelin†; Lisopan; Molpireos; Neogrip; Olpira†; Panadol; Panasorbe; Pantadolor; Paracetol; Paramolan; Parsel; Perfalgan; Singrips; Supofen; Takipirina; Tylenol; Xumadol; *Rus.*: Apap (Апап); Calpol (Калпол); Cefecon D (Цефекон Д); Daleron (Далерон); Dolomol (Доломол)†; Efferalgan (Эффералган); Flutabs (Флютабс); Panadol (Панадол); Perfalgan (Перфалган); Strimol (Стримол); *S.Afr.*: Actamol; Anadin-3†; Antalgic; Brunamol; Calpol; Dolorol; Dynadol; Empaped; Entalgic; Fevamol; Feverpain; Gencetamol; Go-Pain P; Medpramol†; Micro-Gesic; Napamol; Pacimol†; Painamol; Painblok; Painogesic; Panado; Paracet; Paradco†; Paramed; Parapane; Perfalgan; Prollef; Pyradol†; Pyralen; Tylenol; Varipan; Winpain; *Singapore*: Acet; Alcetamol; Biogesic; Calpol; Cetamol; Childrens Panadol; Dhamol; Dolo; Double Parrot Brand; Familin; Fepril; Hoemal; Kame; Lemsip Cold & Flu Head Cold; Mei-Mei Children's Fever; Napa; Pacemol; Panadol; Panamol; Paramol-F; Paratab; Parcemol; Parmol; Paximol; Poro; Progesic; Rapidol; Remedol; Senkon Junior Fever; Setamol; Sunny Fever; Tylenol; Uphamol; *Spain*: Acecat; Acertol†; Alador; Antidol; Apiredol; Apiretal; Cupanol; Dafalgan†; Dolgesic†; Dolocatil; Dolostop; Duorol†; Efetamol; Efferalgan; Febrectal; Frenagial†; Gelocatil; Nupeldol; Octomol†; Panadol; Parafludeten; Perfalgan; Resolvebohm; Sinmol†; Takipirina; Talgo; Termalgin; Termocatil†; Tylenol†; Unebril; Xumadol; *Swed.*: Alvedon; Pamol; Panodil; Paracut; Perfalgan; Pinex; Reliv; *Switz.*: Acetalgin; Arthrolur; Becetamol; Ben-u-ron; Contre-Douleurs P; Dafalgan; Dololur; Dolprone†; Influbene N; Kafa†; Panadol Extend; Panadol; Para-schmerz†; Perfalgan; Treupel Dolo Paracetamol; Treuphadol†; Tylenol; Zolben; *Thai.*: A-Mol; Aceta-P; Aceta; Acetasil; Algogen; Ampol; Angela; Antispa Plus; Aoricet; Aspamol; Asumol; Bakamol; Biogesic†; Calpol; Cemol; Cetamol; Cetapol; Cetta; Codamol; Cotemp; Daga†; Denamol; Depyret; Diamol; Faron; Fenn†; Foramol; Icolid Plus; KB Gin; Kit; Lotemp; M-Aceta; Mymol; Mypara; Nasa; New-um; Newtol; Pamol; Panadol; Para-G†; Para; Paracap; Paracet; Paragin; Paraman; Paramed; Paramol TP; Paramol; Paranal-L†; Paranal†; Parano; Paranol; Parapro; Parat; Paratol†; Parcet†; Pardon; Partamol; Pat; Patum; Pemol; Poro; Pyracon; Pyrimed; Ramol; Saebegin; Salenol†; Sara; Sinogesic; Somagin†; St Luke's Fever; Temnol; Tempra; Thoho; TM Gin†; Totamol; Tumdi†; Tylenol Arthritis Pain; Tylenol; Tymol; Typanol; Umeda Para-J; Unicap†; Unimol; Uracet†; Vemol; Vetamol; Vikool; Xebramol; *Turk.*: A-Per; Asomal; Babinoks; Berko-Setamol; Calpol; Derman; Durapan; Efferalgan; Efpa; Ekosetol; Geralgine-P; Gripin; Kataprin; Medaset; Minafen; Minoset; Noral†; Panadol; Para-Nox; Paracet; Paradine; Parasedol; Parcetol; Parol; Paroma; Pedipar; Perfalgan; Pharmadol; Pirofen; Polmofen; Sedalon; Seskamol; Setamol; Sifenol; Tamol; Tempo; Termacet; Termalgine; Tylol; Vermidon; Volpan; Zaldaks; *UAE*: Adol; *UK*: Abdine Cold Relief; Alvedon; Anadin Paracetamol; Boots Pain Relief Suspension 6 Years Plus; Calpol; Disprol; Fennings Childrens Cooling Powders; Galpamol; Hedex; Infadrops; Mandanol; Medinol; Miradol†; Obimol; Paldesic; Panadol; Panaleve; Paracets; Paraclear; Parapaed; Perfalgan; Salzone; *Ukr.*: Cefecon D (Цефекон Д); Daleron Cold 3 (Далерон Колд 3); Efferalgan (Эффералган); Glycodin (Гликодин)†; Infulgan (Инфулган); Militsan For Children (Милитсан Детский); Panadol (Панадол); Rapidol (Рапидол); *USA*: Acephen; Aceta; Apacet; Apap; Aphen; Apra†; Arthritis Pain Formula Aspirin Free; Aspirin Free Anacin; Aspirin Free Pain Relief; BetaTemp; Bromo Seltzer†; Childrens Mapap; Comtrex Maximum Strength Sore Throat; Dolono; Feverall; Genapap; Genebs†; Halenol; Infantaire; Liquiprin; Mapap; Maranox; Nortemp; Ofirmev; Oraphen-PD; Panadol; Panitone; Pharbetol; Redutemp; Ridenol; Silapap; Tempra; Triaminic Infant's Fever Reducer/ Pain Reliever; Tylenol Sore Throat Daytime; Tylenol; UN-Aspirin; Uni-Ace; *Venez.*: Acetafen; Acetalis; Aceval; Agurin; Alivax; Amifen; Ananty; Apiret; Apyrene; Atamel; Brexin; Paracor; Tachipirin; Tempra; Tylenol; Tylex; Vestax.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

BP 2014: Co-codamol Capsules; Co-codamol Tablets; Co-dydramol Tablets; Co-proxamol Tablets; Dispersible Paracetamol Tablets; Effervescent Co-codamol Tablets; Effervescent Paracetamol Tablets; Paediatric Paracetamol Oral Solution; Paediatric Paracetamol Oral Suspension; Paracetamol and Caffeine Tablets; Paracetamol Capsules; Paracetamol Oral Suspension; Paracetamol Suppositories; Paracetamol Tablets; Paracetamol, Codeine Phosphate and Caffeine Capsules; Paracetamol, Codeine Phosphate and Caffeine Tablets; Soluble Paracetamol and Caffeine Tablets; Soluble Paracetamol Tablets;

USP 36: Acetaminophen and Aspirin Tablets; Acetaminophen and Caffeine Tablets; Acetaminophen and Codeine Phosphate Capsules; Acetaminophen and Codeine Phosphate Oral Solution; Acetaminophen and Codeine Phosphate Oral Suspension; Acetaminophen and Codeine Phosphate Tablets; Acetaminophen and Diphenhydramine Citrate Tablets; Acetaminophen and Pseudoephedrine Hydrochloride Tablets; Acetaminophen and Tramadol Hydrochloride Tablets; Acetaminophen Capsules; Acetaminophen Extended-Release Tablets; Acetaminophen for Effervescent Oral Solution; Acetaminophen Oral Solution; Acetaminophen Oral Suspension; Acetaminophen Suppositories; Acetaminophen Tablets; Acetaminophen, Aspirin, and Caffeine Tablets; Acetaminophen, Chlorpheniramine Maleate, and Dextromethorphan Hydrobromide Tablets; Acetaminophen, Dextromethorphan Hydrobromide, Doxylamine Succinate, and Pseudoephedrine Hydrochloride Oral Solution; Acetaminophen, Diphenhydramine Hydrochloride, and Pseudoephedrine Hydrochloride Tablets; Butalbital, Acetaminophen, and Caffeine Capsules; Butalbital, Acetaminophen, and Caffeine Tablets; Hydrocodone Bitartrate and Acetaminophen Tablets; Isometheptene Mucate, Dichloralphenazone, and Acetaminophen Capsules; Oxycodone and Acetaminophen Capsules; Oxycodone and Acetaminophen Tablets; Propoxyphene Hydrochloride and Acetaminophen Tablets; Propoxyphene Napsylate and Acetaminophen Tablets; Tramadol Hydrochloride and Acetaminophen Oral Suspension.

Parecoxib Sodium *(BANM, USAN, rINNM)*

Natrii Parecoxibum; Parecoxib sódico; Parécoxib Sodique; SC-69124A; Натрий Парекоксиб.

N-[[*p*-(5-Methyl-3-phenyl-4-isoxazolyl)phenyl]sulfonyl]propionamide sodium.

$C_{19}H_{17}N_2NaO_4S$=392.4

CAS — 198470-84-7 (parecoxib); 197502-82-2 (parecoxib sodium).

ATC — M01AH04.

ATC Vet — QM01AH04.

UNII — EB87433V6F.

Incompatibility. Parecoxib sodium should not be mixed with products other than those recommended in licensed product information (see Uses and Administration, below). In particular, the use of glucose 5% in lactated Ringer's solution will cause parecoxib to precipitate. Parecoxib should also not be given in the same syringe as opioids. The use of sterile water for injection is not recommended as the resulting solution is not isotonic.

Uses and Administration

Parecoxib is an NSAID (p. 102.3) reported to be a selective inhibitor of cyclo-oxygenase-2 (COX-2). It is a prodrug of valdecoxib (p. 141.3) and is used for the short-term treatment of postoperative pain in patients aged 18 years and over. Parecoxib is given as the sodium salt although doses are expressed as the base; 42.4 mg of parecoxib sodium is equivalent to about 40 mg of parecoxib. The recommended dose is 40 mg given by intravenous or slow intramuscular injection; this may be followed by 20 or 40 mg every 6 to 12 hours as required. The maximum daily dose is 80 mg. Elderly patients weighing less than 50 kg should begin treatment with half the usual dose, repeated to

a maximum of 40 mg daily. Doses may need to be reduced in hepatic impairment, see below.

Parecoxib should be reconstituted with either sodium chloride 0.9%, glucose 5%, or sodium chloride 0.45% with glucose 5%; no other solvents are recommended in licensed product information. In addition the reconstituted solution may only be injected into intravenous lines delivering sodium chloride 0.9%, glucose 5%, sodium chloride 0.45% with glucose 5%, or lactated Ringer's solution. (See p. 119.3 for details on incompatibilities.)

References.

1. Cheer SM, Goa KL. Parecoxib (parecoxib sodium). *Drugs* 2001; 61: 1133–41.
2. Amabile CM, Spencer AP. Parecoxib for parenteral analgesia in postsurgical patients. *Ann Pharmacother* 2004; 38: 882–6.
3. Mehlisch DR, *et al.* The analgesic efficacy of intramuscular parecoxib sodium in postoperative dental pain. *J Am Dent Assoc* 2004; 135: 1578–90.
4. Malan TP, *et al.* The cyclooxygenase-2-specific inhibitor parecoxib sodium is as effective as 12 mg of morphine administered intramuscularly for treating pain after gynecologic laparotomy surgery. *Anesth Analg* 2005; 100: 454–60.
5. Beaussier M, *et al.* A randomized, double-blind comparison between parecoxib sodium and propacetamol for parenteral postoperative analgesia after inguinal hernia repair in adult patients. *Anesth Analg* 2005; 100: 1309–15.
6. Sindhvananda W, *et al.* Parecoxib versus tramadol for post-appendectomy pain. *J Med Assoc Thai* 2005; 88: 1557–62.
7. Gajraj NM. COX-2 inhibitors celecoxib and parecoxib: valuable options for postoperative pain management. *Curr Top Med Chem* 2007; 7: 235–49.
8. Lloyd R, *et al.* Intravenous or intramuscular parecoxib for acute postoperative pain in adults. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 21/09/09).

Administration in hepatic impairment. Licensed product information in the UK states that no dosage adjustment is generally necessary for parecoxib in patients with *mild* hepatic impairment (Child-Pugh score 5 or 6) and for those with *moderate* impairment (Child-Pugh score 7 to 9) parecoxib should be given at half the usual dose (see p. 119.3), repeated to a maximum dose of 40 mg daily. Use in patients with *severe* impairment (Child-Pugh score 10 and over) is not recommended as there is no clinical experience in such patients.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3.

Hypersensitivity reactions, including anaphylaxis and angioedema and serious skin reactions, have been reported with valdecoxib and may therefore occur with parecoxib, a prodrug of valdecoxib (see also Effects on the Skin, p. 141.3). Parecoxib should be stopped at the first signs of hypersensitivity. Some of these reactions occurred in patients with a history of allergic reactions to sulfonamides and the use of parecoxib is contra-indicated in such patients. (For discussion of cross-reactivity in sulfonamides and sulfa drugs see Hypersensitivity under Sulfamethoxazole, p. 367.3.)

Parecoxib should be avoided in patients with severe hepatic impairment (Child-Pugh score of 10 or more), inflammatory bowel disease, and moderate to severe heart failure (NYHA class II to IV). It should not be used in patients with ischaemic heart disease, peripheral arterial disease, or cerebrovascular disease. It should also not be used after coronary artery bypass graft surgery as there may be an increased risk of adverse effects such as myocardial infarction, deep-vein thrombosis, pulmonary embolism, stroke, renal impairment, deep surgical infections, and sternal wound complications. This may apply especially to obese patients or those with a history of cerebrovascular disease. Parecoxib should be used with caution in patients with significant risk factors for cardiovascular disease such as hypertension, hyperlipidaemia, and diabetes mellitus. Caution is also recommended when using parecoxib in dehydrated patients; rehydration may be advisable before giving parecoxib. Patients with severe renal impairment (creatinine clearance less than 30 mL/min) or those who may be predisposed to fluid retention should be started at the lowest recommended dose and renal function closely monitored.

Effects on the cardiovascular system. There have been concerns about the adverse cardiovascular effects of selective cyclo-oxygenase-2 (COX-2) inhibitors after the general worldwide withdrawal of rofecoxib (see p. 128.3). The short-term use of parecoxib after coronary artery bypass graft surgery has been associated with an increased risk of adverse effects such as myocardial infarction, deep-vein thrombosis, pulmonary embolism, and stroke.[1] When compared with patients in the placebo group, the risk of such effects was almost 4 times greater in those given intravenous parecoxib for 3 days followed by oral valdecoxib for the next 7 days.

For discussion and advice on the use of selective COX-2 inhibitors in patients with cardiovascular or cerebrovascular disease, see under Celecoxib, p. 37.3.

1. Nussmeier NA, *et al.* Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. *N Engl J Med* 2005; 352: 1081–91.

Effects on the gastrointestinal tract. It is generally accepted that the inhibition of cyclo-oxygenase-1 (COX-1) plays a role in the adverse gastrointestinal effects of the NSAIDs, and that the selective inhibition of the other isoform, COX-2, by NSAIDs such as parecoxib may cause less gastrotoxicity than that seen with the non-selective inhibition of the traditional NSAIDs. However, licensed product information reports that upper gastrointestinal perforation, ulceration, and bleeds have occurred with parecoxib treatment and therefore it should be used with caution in patients with a history of such events.

Effects on the kidneys. Increasing evidence of the renal toxicity of the selective cyclo-oxygenase-2 (COX-2) inhibitors such as parecoxib suggests that such NSAIDs appear to have effects on renal function similar to those of the non-selective NSAIDs (see p. 106.2).

Up to June 2004, the Australian Adverse Drug Reactions Advisory Committee had received 20 reports of adverse reactions associated with parecoxib.[1] Of these, 13 mentioned renal impairment with raised creatinine levels and/or oliguria; acute renal failure was reported in 4 of the 13 cases and multiple doses of parecoxib had been given in 6 cases. (In Australia, parecoxib was approved for single-dose use only because of safety concerns about multiple doses.)

1. Adverse Drug Reactions Advisory Committee (ADRAC). Parecoxib—one shot only. *Aust Adverse Drug React Bull* 2004; 23: 10–11. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0406.pdf (accessed 08/11/07)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies parecoxib as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 23/10/11)

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Parecoxib is rapidly hydrolysed to its active metabolite, valdecoxib; the metabolism of valdecoxib is mainly mediated by the cytochrome P450 isoenzymes CYP3A4 and CYP2C9. Consequently, caution is recommended when using parecoxib with inhibitors of such isoenzymes. Licensed product information advises that the dose of parecoxib should be reduced if given with fluconazole, a CYP2C9 inhibitor; however, dose adjustment of parecoxib is not generally necessary when giving with ketoconazole, a CYP3A4 inhibitor, despite increased plasma concentrations of valdecoxib. The effects of enzyme inducers such as carbamazepine, dexamethasone, phenytoin, and rifampicin have not been studied; theoretically, the metabolism of valdecoxib may be increased by these drugs.

Valdecoxib has been noted to increase the plasma levels of dextromethorphan, a CYP2D6 substrate, and therefore caution is recommended when giving parecoxib with drugs that are metabolised via CYP2D6 and that have a narrow therapeutic index. Such drugs include flecainide, metoprolol, and propafenone. Valdecoxib may also affect the plasma levels of drugs that are metabolised via CYP2C19: an increase in the plasma levels of omeprazole was seen in patients using valdecoxib.

Pharmacokinetics

On intravenous or intramuscular injection, parecoxib is rapidly hydrolysed in the liver to its active metabolite, valdecoxib, and propionic acid; the plasma half-life of parecoxib is about 22 minutes. Plasma protein binding is about 98%. Valdecoxib is also extensively metabolised in the liver; pathways involved include those via the cytochrome P450 isoenzymes CYP3A4 and CYP2C9, and glucuronidation. Another active metabolite has been identified but it is not considered to contribute a significant clinical effect. Excretion is mainly via the urine with about 70% of a dose appearing as inactive metabolites. Less than 5% of a dose appears as unchanged valdecoxib in the urine. No unchanged parecoxib is found in the urine with only trace amounts in the faeces. The elimination half-life of valdecoxib is about 8 hours.

References.

1. Karim A, *et al.* A pharmacokinetic study of intramuscular (IM) parecoxib sodium in normal subjects. *J Clin Pharmacol* 2001; 41: 1111–19.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Dynastat; *Austria*: Dynastat; *Belg.*: Dynastat; *Braz.*: Bextra IM/IV; *Chile*: Pro-Bextra; *China*: Dynastat (特耐); *Cz.*: Dynastat; *Denm.*: Dynastat; *Fin.*: Dynastat; *Fr.*: Dynastat; *Ger.*: Dynastat; *Gr.*: Dynastat; *Hong Kong*: Dynastat; *Hung.*: Dynastat; *India*: Bioval-P; Coxegesic; Valcox; Valdixx; Valdone-P; Valus-P; Vorth-P; *Indon.*: Dynastat; *Irl.*: Dynastat; *Ital.*: Dynastat; *Malaysia*: Dynastat; *Mex.*: Dynastat; *Neth.*: Dynastat; *Norw.*: Dynastat; *NZ*: Dynastat; *Philipp.*: Dynastat; *Pol.*: Dynastat; *Port.*: Dynastat; *Rus.*: Dynastat (Династат); *S.Afr.*: Rayzon; *Spain*: Dynastat; *Swed.*: Dynastat; *Thal.*: Dynastat; *UK*: Dynastat; *Ukr.*: Dynastat (Династат).

Pentazocine *(BAN, USAN, rINN)* ⊗

NIH-7958; NSC-107430; Pentatsosiini; Pentazocin; Pentazocina; Pentazocinas; Pentazocinum; Win-20228; Пентазоцин.

(2*R**,6*R**,11*R**)-1,2,3,4,5,6-Hexahydro-6,11-dimethyl-3-(3-methylbut-2-enyl)-2,6-methano-3-benzazocin-8-ol.

$C_{19}H_{27}NO$=285.4

CAS — 359-83-1.

ATC — N02AD01.

ATC Vet — QN02AD01.

UNII — RP4A60D26L.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Pentazocine). A white or almost white powder. It shows polymorphism. Practically insoluble in water; soluble in alcohol; freely soluble in dichloromethane. Protect from light.

USP 36: (Pentazocine). A white or very pale, tan-coloured powder. Practically insoluble in water; soluble 1 in 11 of alcohol, 1 in 2 of chloroform, and 1 in 42 of ether; soluble in acetone; sparingly soluble in ethyl acetate and in benzene. Store in airtight containers. Protect from light.

Pentazocine Hydrochloride

(BANM, USAN, rINNM) ⊗

Hidrocloruro de pentazocina; Pentatsosiinihydrokloridi; Pentazocina, hidrocloruro de; Pentazocine, Chlorhydrate de; Pentazocin-hidroklorid; Pentazocinhydrochlorid; Pentazocin-hydrochlorid; Pentazocinhydrokloríd; Pentazocini hydrochloridum; Pentazocino hidrochloridas; Пентазоцина Гидрохлорид.

$C_{19}H_{27}NO,HCl$=321.9

CAS — 2276-52-0; 64024-15-3.

UNII — A36BXO4PPX.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Pentazocine Hydrochloride). A white or almost white powder. It shows polymorphism. Sparingly soluble in water and in dichloromethane; soluble in alcohol. A 1% solution in water has a pH of 4.0 to 6.0. Protect from light.

USP 36: (Pentazocine Hydrochloride). A white crystalline powder. It exhibits polymorphism, one form melting at about 254 degrees and the other at about 218 degrees. Soluble 1 in 30 of water, 1 in 20 of alcohol, and 1 in 4 of chloroform; very slightly soluble in acetone and in ether; practically insoluble in benzene. Store in airtight containers. Protect from light.

Pentazocine Lactate *(BANM, USAN, rINNM)* ⊗

Lactato de pentazocina; Pentatsosiinilaktaatti; Pentazocina, lactato de; Pentazocine, Lactate de; Pentazocini lactas; Pentazocinlactat; Pentazocinlaktat; Pentazocin-laktát; Pentazocino laktatas; Пентазоцина Лактат.

$C_{19}H_{27}NO,C_3H_6O_3$=375.5

CAS — 17146-95-1.

UNII — 1P2XIB5100.

Pharmacopoeias. In *Eur.* (see p. vii). *US* includes only Pentazocine Lactate Injection.

Ph. Eur. 8: (Pentazocine Lactate). A white or almost white powder. Sparingly soluble in water; slightly soluble in dichloromethane; freely soluble in methyl alcohol. A 1% solution in water has a pH of 5.5 to 6.5. Protect from light.

BP 2014: (Pentazocine Lactate). A white to pale cream powder. Sparingly soluble in water, in alcohol, and in chloroform; freely soluble in methyl alcohol. A 1% solution in water has a pH of 5.5 to 6.5.

Incompatibility. Commercial injections of pentazocine lactate are reported to be incompatible with soluble barbiturates and other alkaline substances including sodium bicarbonate. Diazepam and chlordiazepoxide have also been reported to be incompatible, as have glycopyrronium bromide[1] and nafcillin sodium.[2]

1. Ingallinera TS, *et al.* Compatibility of glycopyrrolate injection with commonly used infusion solutions and additives. *Am J Hosp Pharm* 1979; 36: 508–10.
2. Jeglum EL, *et al.* Nafcillin sodium incompatibility with acidic solutions. *Am J Hosp Pharm* 1981; 38: 462, 464.

Uses and Administration

Pentazocine, a benzomorphan derivative, is an opioid analgesic (p. 108.1) that has mixed opioid agonist and antagonist actions. Agonist activity is thought to be mainly at κ opioid receptors (with possibly some σ receptor activity); it acts as a weak antagonist or partial agonist at μ

receptors. Pentazocine is used for the relief of moderate to severe pain including the pain of labour. Combined preparations with paracetamol or aspirin may also be used in the treatment of moderate pain. It may also be used for pre-operative sedation and as an adjunct to anaesthesia. Its analgesic effect declines more rapidly than that of morphine.

Pentazocine is given orally as the hydrochloride; doses may be expressed as either the base or the salt. Pentazocine is also given parenterally as the lactate; doses are expressed in terms of the base. Pentazocine 100 mg is equivalent to about 112.8 mg of pentazocine hydrochloride or 131.6 mg of pentazocine lactate.

A usual oral dose is the equivalent of 50 to 100 mg of pentazocine or pentazocine hydrochloride every 3 to 4 hours after food, to a maximum of 600 mg daily.

The usual initial dose by subcutaneous, intramuscular, or intravenous injection is the equivalent of pentazocine 30 mg as a single dose. Thereafter, the dose may be adjusted according to response; licensed product information recommends that single doses should not usually exceed 30 mg (500 micrograms/kg) intravenously, or 60 mg (1 mg/kg) intramuscularly or subcutaneously. Doses may be repeated every 3 to 4 hours; it should not be necessary to exceed 360 mg daily. Also if frequent injections are needed, the intramuscular route should be used rather than the subcutaneous route, and the injection sites should be varied. In obstetric analgesia 30 mg may be given as a single dose by intramuscular injection during labour; alternatively, 20 mg may be given by intravenous injection as soon as contractions occur at regular intervals and repeated 2 or 3 times at intervals of 2 to 3 hours if necessary.

For details of doses in children, see below.

Pentazocine lactate has also been given rectally as suppositories.

As a deterrent to abuse a combined oral preparation of pentazocine hydrochloride and naloxone hydrochloride is available in some countries.

Administration in children. In the UK, pentazocine is licensed for the relief of moderate to severe pain in children and doses may be repeated every 3 to 4 hours if necessary. Those aged 6 to 12 years may be given a usual oral dose of 25 mg. Children aged 1 to 12 years may be given doses of up to 1 mg/kg by intravenous injection.

Dependence and Withdrawal

As for Opioid Analgesics, p. 109.1.

Pentazocine is subject to abuse.

Pentazocine does produce physical dependence, but withdrawal symptoms are substantially less severe than with morphine. It does not typically produce drug-seeking behaviour of the same degree or intensity as morphine or other prototypic μ agonists, nor does it substitute for morphine in dependent subjects.[1] Pentazocine injection has been abused,[2] but street abuse, especially in the USA, has more often involved the intravenous use of crushed tablets of pentazocine and tripelennamine ('T's and Blues').[3-5] A decreased incidence of pentazocine abuse in the USA appeared to coincide with the introduction of oral tablets incorporating naloxone,[1] the rationale being that naloxone antagonises the effect of pentazocine if illicitly injected, but has no effect when taken orally. Some continued to abuse the new pentazocine/naloxone formulation;[6] intravenous abuse in one woman, who was unaware of the reformulation, resulted in opioid withdrawal symptoms and severe hypertension.[7] A 1989 report from the WHO committee[1] rated the likelihood of abuse of pentazocine as moderate, based on its pharmacological profile, dependence potential, and actual abuse. The committee considered that it should continue to be scheduled as a psychotropic substance rather than a narcotic drug.

1. WHO. WHO expert committee on drug dependence: twenty-fifth report. *WHO Tech Rep Ser* 775 1989. Also available at: http://libdoc.who.int/trs/WHO_TRS_775.pdf (accessed 27/06/08)
2. Hunter R, Ingram IM. Intravenous pentazocine abuse by a nurse. *Lancet* 1983; ii: 227.
3. Poklis A, Whyatt PL. Current trends in the abuse of pentazocine and tripelennamine: the metropolitan St. Louis experience. *J Forensic Sci* 1980; 25: 72–8.
4. Senay EC. Clinical experience with T's and B's. *Drug Alcohol Depend* 1985; 14: 305–11.
5. Jackson C, *et al.* Fatal intracranial hemorrhage associated with phenylpropanolamine, pentazocine, and tripelennamine overdose. *J Emerg Med* 1985; 3: 127–32.
6. Reed DA, Schnoll SH. Abuse of pentazocine-naloxone combination. *JAMA* 1986; 256: 2562–4.
7. Reinhart S, Barrett SM. An acute hypertensive response after intravenous use of a new pentazocine formulation. *Ann Emerg Med* 1985; 14: 591–3.

Adverse Effects

As for Opioid Analgesics in general, p. 110.1.

Pentazocine may cause hallucinations and other psychotomimetic effects such as nightmares and thought disturbances. High doses may result in hypertension and tachycardia; increased aortic and pulmonary artery pressure with an increase in cardiac work has followed intravenous use in patients with myocardial infarction. Like morphine it causes respiratory depression, but pentazocine is said to have a 'ceiling' effect and the depth of respiratory depression does not increase proportionately with higher doses.

Rare adverse effects with pentazocine have included agranulocytosis and serious skin reactions such as erythema multiforme and toxic epidermal necrolysis.

Pentazocine injections may be painful. Local tissue damage may occur at injection sites particularly after subcutaneous injection or multiple doses; there have been reports of muscle fibrosis associated with intramuscular injections.

Effects on the blood. There have been reports of agranulocytosis associated with pentazocine.[1-3]

1. Marks A, Abramson N. Pentazocine and agranulocytosis. *Ann Intern Med* 1980; 92: 433.
2. Haibach H, *et al.* Pentazocine-induced agranulocytosis. *Can Med Assoc J* 1984; 130: 1165–6.
3. Sheehan M, *et al.* Pentazocine-induced agranulocytosis. *Can Med Assoc J* 1985; 132: 1401.

Effects on the CNS. Oculogyric crisis has been associated with the use of pentazocine.[1]

1. Burstein AH, Fullerton T. Oculogyric crisis possibly related to pentazocine. *Ann Pharmacother* 1993; 27: 874–6.

Effects on the skin. Toxic epidermal necrolysis in a 62-year-old man was attributed to pentazocine;[1] he had taken 50 to 75 mg every 4 hours for 8 days. His severe uraemia was attributed to fluid loss through the skin.

1. Hunter JAA, Davison AM. Toxic epidermal necrolysis associated with pentazocine therapy and severe reversible renal failure. *Br J Dermatol* 1973; 88: 187–90.

Treatment of Adverse Effects

As for Opioid Analgesics in general, p. 110.3.

As pentazocine has both opioid agonist and antagonist activity its effects may not be completely reversed by naloxone, but use of the latter is still recommended in pentazocine overdosage.

Precautions

As for Opioid Analgesics in general, p. 110.3.

Pentazocine has weak opioid antagonist actions and may precipitate withdrawal symptoms if given to patients who are physically dependent on opioids. It should generally be avoided after myocardial infarction and in patients with heart failure or arterial or pulmonary hypertension.

When frequent injections are needed, pentazocine should be given intramuscularly rather than subcutaneously and the injection sites should be varied.

Abuse. See under Dependence and Withdrawal, above.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, has not classified pentazocine for porphyrinogenicity;[1] however licensed product information advises caution in the use of pentazocine in patients with porphyria.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 10/11/11)

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

Tobacco smoking. Smokers metabolised about 40% more pentazocine than non-smokers, although there was large inter-subject variation;[1] tobacco smoking might induce liver enzymes responsible for drug oxidation.

1. Vaughan DP, *et al.* The influence of smoking on the inter-subject variation in pentazocine elimination. *Br J Clin Pharmacol* 1976; 3: 279–83.

Pharmacokinetics

Pentazocine is well absorbed from the gastrointestinal tract and peak plasma concentrations occur in 1 to 3 hours after an oral dose; the half-life is reported to be about 2 to 3 hours. After intramuscular injection, peak plasma concentrations occur in 15 minutes to 1 hour and the half-life is about 2 to 5 hours. About 50 to 75% has been reported to be bound to plasma proteins. Pentazocine undergoes extensive first-pass metabolism in the liver; oral bioavailability is low with only about half of a dose reaching the systemic circulation. Metabolites and a small amount of unchanged drug are excreted in the urine. It crosses the placenta and is distributed into breast milk.

Hepatic impairment. Clearance of pentazocine was significantly reduced and terminal half-life and oral bioavailability increased in cirrhotic patients when compared with healthy subjects.[1]

1. Neal EA, *et al.* Enhanced bioavailability and decreased clearance of analgesics in patients with cirrhosis. *Gastroenterology* 1979; 77: 96–102.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Fortal; *Canad.*: Talwin; *Cz.*: Fortral; *Gr.*: Fortal; *India*: Fortstar; Fortwin; Pentawin; *Ital.*: Talwin; *Jpn*: Peltazon; Pentagin; Sosegon; *Neth.*: Fortral; *S.Afr.*: Ospronim†; Sosenol; *Singapore*: Talwin†; *Spain*: Sosegon; *Thai.*: Pangon; Sosegon; Tazcine; *UK*: Fortral; *USA*: Talwin NX†; Talwin.

Multi-ingredient Preparations. *India*: Expergesic; Foracet; Fortagesic; *USA*: Emergent-Ez; Talacen†.

Pharmacopoeial Preparations

BP 2014: Pentazocine Capsules; Pentazocine Injection; Pentazocine Suppositories; Pentazocine Tablets;

USP 36: Pentazocine and Aspirin Tablets; Pentazocine and Naloxone Tablets; Pentazocine Injection.

Pethidine Hydrochloride

(BANM, rINNM) ⊗

Hidrocloruro de petidina; Meperidine Hydrochloride; Péthidine, Chlorhydrate de; Pethidinhydrochlorid; Pethidinhydrochlorid; Pethidini Hydrochloridum; Petidiinihydroklo-idi; Petidin Hidroklorür; Petidina, hidrocloruro de; Petidin-hidroklorid; Petidinhydroklorid; Petidino hidrochloridas; Petydyny chlorowodorek; Петидина Гидрохлорид.

Ethyl 1-methyl-4-phenylpiperidine-4-carboxylate hydrochloride.

$C_{15}H_{21}NO_2HCl$=283.8

CAS — 57-42-1 (pethidine); 50-13-5 (pethidine hydrochloride).

ATC — N02AB02.

ATC Vet — QN02AB02.

UNII — N8E7F7Q170.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of pethidine:

Bam; Peth.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Pethidine Hydrochloride). A white or almost white, crystalline powder. Very soluble in water; freely soluble in alcohol. Store in airtight containers. Protect from light.

USP 36: (Meperidine Hydrochloride). A fine white odourless crystalline powder. Very soluble in water; soluble in alcohol; sparingly soluble in ether. pH of a 5% solution in water is about 5. Protect from light.

Incompatibility. Solutions of pethidine hydrochloride are acidic. They are incompatible with barbiturate salts and loss of clarity was also seen in an early additive study[1] with other drugs including aminophylline, heparin sodium, meticillin sodium, morphine sulfate, nitrofurantoin sodium, phenytoin sodium, sodium iodide, sulfadiazine sodium, and sulfafurazole diolamine. Colour change from pale yellow to light green occurred when solutions of minocycline hydrochloride or tetracycline hydrochloride were mixed with pethidine hydrochloride in 5% glucose injection.[2] In the same study an immediate precipitate occurred on admixture with cefoperazone sodium or mezlocillin sodium; with nafcillin sodium an immediate cloudy appearance cleared on agitation. Incompatibility has also been seen between pethidine hydrochloride and aciclovir sodium, imipenem, furosemide,[3] liposomal doxorubicin hydrochloride,[4] and idarubicin.[5] Solutions of cefazolin sodium[6] and pethidine hydrochloride mixed in 5% glucose injection turned light yellow after storage for 5 days at 25 degrees; the admixture was stable for at least 20 days at 4 degrees.

1. Patel JA, Phillips GL. A guide to physical compatibility of intravenous drug admixtures. *Am J Hosp Pharm* 1966; 23: 409–11.
2. Nieves-Cordero AL, *et al.* Compatibility of narcotic analgesic solutions with various antibiotics during simulated Y-site injection. *Am J Hosp Pharm* 1985; 42: 1108–9.
3. Pugh CB, *et al.* Visual compatibility of morphine sulfate and meperidine hydrochloride with other injectable drugs during simulated Y-site injection. *Am J Hosp Pharm* 1991; 48: 123–5.
4. Trissel LA, *et al.* Compatibility of doxorubicin hydrochloride liposome injection with selected other drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; 54: 2708–13.
5. Turowski RC, Durthaler JM. Visual compatibility of idarubicin hydrochloride with selected drugs during simulated Y-site injection. *Am J Hosp Pharm* 1991; 48: 2181–4.
6. Lee DKT, *et al.* Stability of cefazolin sodium and meperidine hydrochloride. *Am J Health-Syst Pharm* 1996; 53: 1608–10.

Stability. Pethidine hydrochloride injection 100 mg/mL was stable[1] for at least 24 hours at room temperature when diluted to a concentration of 300 mg/litre in glucose

5% and 4% and in sodium chloride injection (0.9%) and sodium chloride injection (0.9%) diluted 1 in 5.

Accelerated stability studies using elevated temperatures and humidities to simulate tropical conditions classified pethidine hydrochloride as a 'less stable drug substance'.[2] It was suggested that during quality assurance of preparations containing pethidine hydrochloride particular attention should be paid to their stability.

1. Rudd L, Simpson P. Pethidine stability in intravenous solutions. *Med J Aust* 1978; 2: 34.
2. WHO. WHO expert committee on specifications for pharmaceutical preparations: thirty-first report. *WHO Tech Rep Ser* 790 1990. Also available at: http://libdoc.who.int/trs/WHO_TRS_790.pdf (accessed 26/06/08)

Uses and Administration

Pethidine, a phenylpiperidine derivative, is a synthetic opioid analgesic (p. 108.1) that acts mainly as a μ-opioid agonist. Pethidine is used for the relief of most types of moderate to severe acute pain including the pain of labour. It is more lipid soluble than morphine and has a less potent and shorter lasting analgesic effect; analgesia usually lasts for 2 to 4 hours. Its short duration of action and accumulation of its potentially neurotoxic metabolite norpethidine on repeated dosage make it unsuitable for the management of chronic pain. Pethidine has a weaker action on smooth muscle than morphine and its lower potential to increase biliary pressure may make it a more suitable opioid analgesic for pain associated with biliary colic and pancreatitis (but see Biliary-tract Disorders, p. 111.1). It is also used for premedication and as an adjunct to anaesthesia. It has been given with phenothiazines such as promethazine to achieve basal narcosis. Pethidine has little effect on cough or on diarrhoea.

For the relief of **pain**, pethidine hydrochloride is given in oral doses of 50 to 150 mg every 4 hours if necessary. It may also be given by intramuscular or subcutaneous injection in doses of 25 to 100 mg and by slow intravenous injection in doses of 25 to 50 mg repeated after 4 hours. For *postoperative* pain, the *BNF* suggests that the subcutaneous or intramuscular doses may be given every 2 to 3 hours if necessary.

In *obstetric analgesia* 50 to 100 mg may be given by intramuscular or subcutaneous injection as soon as contractions occur at regular intervals. This dose may be repeated after 1 to 3 hours if necessary up to a maximum of 400 mg in 24 hours.

For **premedication** 25 to 100 mg may be given intramuscularly about 1 hour before surgery. It may also be given subcutaneously in similar doses. As an **adjunct to anaesthesia** 10 to 25 mg may be given by slow intravenous injection.

For details of doses in children, see below.

Administration. In addition to the conventional routes pethidine has been given epidurally,[1-4] intraperitoneally,[5,6] and intrathecally.[7-9] It has also been given by various routes as a patient-controlled system.[10-13] However, some consider that the use of pethidine should be avoided for patient-controlled analgesia because of the increased risk of norpethidine-induced seizures[14] (see also Incidence of Adverse Effects and Effects on the Nervous System, below).

1. Perriss BW. Epidural pethidine in labour: a study of dose requirements. *Anaesthesia* 1980; 35: 380–2.
2. Husemeyer RP, *et al.* A study of pethidine kinetics and analgesia in women in labour following intravenous, intramuscular and epidural administration. *Br J Clin Pharmacol* 1982; 13: 171–6.
3. Perriss BW, *et al.* Analgesia following extradural and im pethidine in post-caesarean section patients. *Br J Anaesth* 1990; 64: 355–7.
4. Blythe JG, *et al.* Continuous postoperative epidural analgesia for gynecologic oncology patients. *Gynecol Oncol* 1990; 37: 307–10.
5. Colbert ST, *et al.* An assessment of the value of intraperitoneal meperidine for analgesia postlaparoscopic tubal ligation. *Anesth Analg* 2000; 91: 667–70.
6. O'Hanlon DM, *et al.* Intraperitoneal pethidine versus intramuscular pethidine for the relief of pain after laparoscopic cholecystectomy: randomized trial. *World J Surg* 2002; 26: 1432–6.
7. Acalovschi I, *et al.* Saddle block with pethidine for perineal operations. *Br J Anaesth* 1986; 58: 1012–16.
8. Yu SC, *et al.* Addition of meperidine to bupivacaine for spinal anaesthesia for caesarean section. *Br J Anaesth* 2002; 88: 379–83.
9. Vranken JH, *et al.* Plasma concentrations of meperidine and normeperidine following continuous intrathecal meperidine in patients with neuropathic cancer pain. *Acta Anaesthesiol Scand* 2005; 49: 665–70.
10. Striebel HW, *et al.* Patient-controlled intranasal analgesia (PCINA) for the management of postoperative pain: a pilot study. *J Clin Anesth* 1996; 8: 4–8.
11. Kee N, *et al.* Comparison of patient-controlled epidural analgesia with patient-controlled intravenous analgesia using pethidine or fentanyl. *Anaesth Intensive Care* 1997; 25: 126–32.
12. Sharma SK, *et al.* Cesarean delivery: a randomized trial of epidural versus patient-controlled meperidine analgesia during labor. *Anesthesiology* 1997; 87: 487–94.
13. Chen PP, *et al.* Patient-controlled pethidine after major upper abdominal surgery: comparison of the epidural and intravenous routes. *Anaesthesia* 2001; 56: 1106–12.
14. Hagmeyer KO, *et al.* Meperidine-related seizures associated with patient-controlled analgesia pumps. *Ann Pharmacother* 1993; 27: 29–32.

Administration in children. Pethidine is licensed for the relief of moderate to severe acute pain and for premedication in children. However, the *BNFC* does not recommend its use in this patient set.

For the relief of **pain**, pethidine hydrochloride may be given orally or by intramuscular injection in doses of 0.5 to 2 mg/kg, repeated after 4 hours if necessary. For *postoperative* pain, the *BNF* suggests that this dose may be given intramuscularly every 2 to 3 hours if necessary.

For **premedication**, the *BNF* suggests giving 0.5 to 2 mg/kg intramuscularly about 1 hour before surgery.

See also Lytic Cocktails, below.

Eclampsia and pre-eclampsia. See Lytic Cocktails under Sedation, below.

Pain. Pethidine produces prompt but short-lasting analgesia, and may be preferred to morphine when rapid control of acute pain is required. It has been widely used in obstetrics to control the pain of labour (although the *BNF* notes that morphine or other opioids are often preferred for obstetric pain), and for postoperative pain relief after caesarean section or other surgical procedures.

In a study of patients with intractable pain the minimum effective analgesic blood concentration ranged from 100 to 820 nanograms/mL (median 250 nanograms/mL) in 15 of 16; the remaining patient failed to obtain analgesia with pethidine. Additional measures were considered necessary[1] if the minimum effective concentration exceeded 400 nanograms/mL.

Pethidine has traditionally been given by intermittent intramuscular injection in the treatment of acute pain, but inconsistent pain relief can be expected because of fluctuating blood-pethidine concentrations;[2] continuous intravenous infusion might be more effective for acute pain. For reference to use by other routes see Administration, above.

1. Mather LE, Glynn CJ. The minimum effective analgesic blood concentration of pethidine in patients with intractable pain. *Br J Clin Pharmacol* 1982; 14: 385–90.
2. Edwards DJ, *et al.* Clinical pharmacokinetics of pethidine: 1982. *Clin Pharmacokinet* 1982; 7: 421–33.

SICKLE-CELL CRISIS. Concern has been expressed over the continued use of pethidine for analgesia in painful crises in sickle-cell disease. Control of pain may be inadequate and doses commonly used to manage crises may lead to accumulation of norpethidine, the neuroexcitatory metabolite of pethidine, and precipitate seizures.[1,2] See also Effects on the Nervous System, below.

1. Pryle BJ, *et al.* Toxicity of norpethidine in sickle cell crisis. *BMJ* 1992; 304: 1478–9.
2. Harrison JFM, *et al.* Pethidine in sickle cell crisis. *BMJ* 1992; 305: 182.

Sedation. Some references[1-3] to the use of pethidine for endoscopy.

1. Bahal-O'Mara N, *et al.* Sedation with meperidine and midazolam in pediatric patients undergoing endoscopy. *Eur J Clin Pharmacol* 1994; 47: 319–23.
2. Diab FH, *et al.* Efficacy and safety of combined meperidine and midazolam for EGD sedation compared with midazolam alone. *Am J Gastroenterol* 1996; 91: 1120–5.
3. Laluna L, *et al.* The comparison of midazolam and topical lidocaine spray versus the combination of midazolam, meperidine, and topical lidocaine spray to sedate patients for upper endoscopy. *Gastrointest Endosc* 2001; 53: 289–93.

LYTIC COCKTAILS. Lytic cocktails consisting of chlorpromazine, pethidine, and/or promethazine have been given intravenously in some countries for the management of pre-eclampsia and imminent eclampsia. However, the use of phenothiazines is generally not recommended late in pregnancy, and other treatments are preferred for hypertension (see Hypertension in Pregnancy, under Hypertension, p. 1251.1); the management of eclampsia, which is the convulsive phase, is discussed on p. 511.1.

Lytic cocktails have also been used for sedation and analgesia in children, by intramuscular or occasionally intravenous injection. However, there is a high rate of therapeutic failure as well as serious adverse effects with such combinations, and the American Academy of Pediatrics[1] had recommended that alternative sedatives and analgesics should be considered. Lytic cocktails are not the most appropriate means of sedation for short procedures since patients must be monitored for about 1 hour before the procedure while the drugs take effect, and for even longer during the recovery period.[2]

1. American Academy of Pediatrics Committee on Drugs. Reappraisal of Lytic cocktail/Demerol, Phenergan, and Thorazine (DPT) for the sedation of children. *Pediatrics* 1995; 95: 598–602.
2. Barst SM, *et al.* A comparison of propofol and Demerol-Phenergan-Thorazine for brief, minor, painful procedures in a pediatric hematology-oncology clinic. *Int J Pediatr Hematol/Oncol* 1995; 1: 587–91.

Shivering. For reference to the use of pethidine in the management of shivering associated with anaesthesia, see under Adverse Effects of General Anaesthetics, p. 1900.2. Pethidine has also been used to treat amphotericin B-induced shaking chills.[1]

1. Burks LC, *et al.* Meperidine for the treatment of shaking chills and fever. *Arch Intern Med* 1980; 140: 483–4.

Dependence and Withdrawal

As for Opioid Analgesics, p. 109.1.

Doses of pethidine as large as 3 or 4 g daily have been taken by addicts. As tolerance to the CNS stimulant and antimuscarinic effects is not complete with these very large doses, muscle twitching, tremor, mental confusion, dilated pupils, and sometimes convulsions may be present.

Withdrawal symptoms appear more rapidly than with morphine and are of shorter duration.

For the abuse of pethidine analogues, see under Precautions, p. 123.1.

Adverse Effects and Treatment

As for Opioid Analgesics in general, p. 110.1.

The effects on smooth muscle may be relatively less intense than with morphine and constipation occurs less frequently. Local reactions often follow injection of pethidine; general hypersensitivity reactions including anaphylaxis have been reported rarely. Pethidine given intravenously may increase the heart rate. After overdosage, symptoms are generally similar to those of morphine poisoning. However, stimulation of the CNS and convulsions may also occur, especially in tolerant individuals or after toxic oral doses; these have been attributed mainly to the metabolite norpethidine.

Incidence of adverse effects. The incidence of adverse effects in hospitalised patients receiving pethidine was monitored by the Boston Collaborative Drug Surveillance Program.[1] Adverse reactions to oral pethidine were reported in 16 of 366 patients and mainly involved the gastrointestinal tract. After pethidine by injection 102 of 3268 patients had adverse effects, the CNS being involved in 38.

More recently, 20 adverse reactions were identified in a chart review of 141 patients given pethidine and considered to be at high risk of developing toxicity;[2] high-risk patients were defined as those with renal impairment (creatinine clearance 50 mL/minute or less), those receiving patient-controlled analgesia (PCA) with pethidine, and those given intravenous pethidine in doses of over 200 mg daily for several days. The most common adverse reactions were confusion and anxiety; other reported adverse effects included nervousness, seizures, and hallucinations. Patients who developed adverse reactions were significantly older, more likely to be taking a benzodiazepine, and had longer hospital stays than those without adverse effects. Out of the 20 reports, 16 adverse effects were noted in the 123 patients who received pethidine via a PCA pump; cumulative doses for patients using PCA were found to be a significant risk factor in the development of adverse effects.

1. Miller RR, Jick H. Clinical effects of meperidine in hospitalized medical patients. *J Clin Pharmacol* 1978; 18: 130–9.
2. Seifert CF, Kennedy S. Meperidine is alive and well in the new millennium: evaluation of meperidine usage patterns and frequency of adverse drug reactions. *Pharmacotherapy* 2004; 24: 776–83.

Effects on the cardiovascular system. Histamine release was more frequent after pethidine than after morphine, fentanyl, or sufentanil given intravenously for the induction of anaesthesia.[1] Increased plasma-histamine concentrations occurred in 5 of 16 patients given pethidine in a mean dose of 4.3 mg/kg and were generally accompanied by hypotension, tachycardia, erythema, and increased plasma-adrenaline concentrations. Only 1 of 10 given morphine and none of those receiving fentanyl or sufentanil showed evidence of histamine release. All of the histamine releasers were young women.

1. Flacke JW, *et al.* Histamine release by four narcotics: a double-blind study in humans. *Anesth Analg* 1987; 66: 723–30.

Effects on the nervous system. CNS excitatory effects of pethidine such as tremors, muscle twitches, and convulsions have been associated with toxic doses and have been attributed to the metabolite norpethidine. Accumulation of norpethidine may occur if large doses of pethidine are repeated at short intervals (including for patient-controlled analgesia) and is especially likely when renal function is impaired.[1-13]

1. Kaiko RF, *et al.* Central nervous system excitatory effects of meperidine in cancer patients. *Ann Neurol* 1983; 13: 180–5.
2. Lieberman AN, Goldstein M. Reversible parkinsonism related to meperidine. *N Engl J Med* 1985; 312: 509.
3. Mauro VF, *et al.* Meperidine-induced seizure in a patient without renal dysfunction or sickle cell anemia. *Clin Pharm* 1986; 5: 837–9.
4. Morisy L, Platt D. Hazards of high-dose meperidine. *JAMA* 1986; 255: 467–8.
5. Armstrong PJ, Bersten A. Normeperidine toxicity. *Anesth Analg* 1986; 65: 536–8.
6. Elsendrath SJ, *et al.* Meperidine-induced delirium. *Am J Psychiatry* 1987; 144: 1062–5.
7. Kyff JV, Rice TL. Meperidine-associated seizures in a child. *Clin Pharm* 1990; 9: 337–8.
8. Pryle BJ, *et al.* Toxicity of norpethidine in sickle cell crisis. *BMJ* 1992; 304: 1478–9.
9. Hagmeyer KO, *et al.* Meperidine-related seizures associated with patient-controlled analgesia pumps. *Ann Pharmacother* 1993; 27: 29–32.

10. Stone PA, *et al.* Norpethidine toxicity and patient controlled analgesia. *Br J Anaesth* 1993; 71: 738–40.
11. Marinella MA. Meperidine-induced generalized seizures with normal renal function. *South Med J* 1997; 90: 556–8.
12. McHugh GJ. Norpethidine accumulation and generalized seizure during pethidine patient-controlled analgesia. *Anaesth Intensive Care* 1999; 27: 289–91.
13. Hubbard GP, Wolfe KR. Meperidine misuse in a patient with sphincter of Oddi dysfunction. *Ann Pharmacother* 2003; 37: 534–7.

Precautions

As for Opioid Analgesics in general, p. 110.3.

Pethidine should also be given cautiously to patients with a history of convulsive disorders or supraventricular tachycardias.

Abuse. A synthetic analogue of pethidine, MPPP (1-methyl-4-phenyl-4-propionoxypiperidine), manufactured illicitly for recreational use, achieved notoriety when it was accidentally contaminated with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) leading to an epidemic of parkinsonism among intravenous drug abusers.[1] WHO has also identified another analogue, PEPAP (1-phenylethyl-4-phenyl-4-acetoxypiperidine) as being liable to abuse.[2]

1. Buchanan JF, Brown CR. Designer drugs': a problem in clinical toxicology. *Med Toxicol* 1988; 3: 1–17.
2. WHO. WHO expert committee on drug dependence: twenty-fourth report. *WHO Tech Rep Ser 761* 1988. Also available at: http://libdoc.who.int/trs/WHO_TRS_761.pdf (accessed 26/06/08)

Breast feeding. No adverse effects have been seen in breast-feeding infants whose mothers were given pethidine, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/06/08)

The elderly. Pethidine had a slower elimination rate in elderly compared with young patients and a reduction in total daily dose might be necessary in elderly patients receiving repeated doses of pethidine.[1] Another study concluded that age-related changes in disposition were not sufficient to warrant modification of pethidine dosage regimens.[2]

1. Holmberg L, *et al.* Comparative disposition of pethidine and norpethidine in old and young patients. *Eur J Clin Pharmacol* 1982; 22: 175–9.
2. Herman RJ, *et al.* Effects of age on meperidine disposition. *Clin Pharmacol Ther* 1985; 37: 19–24.

Phaeochromocytoma. Pethidine provoked episodes of hypertension in a patient with phaeochromocytoma; the effect was suppressed by labetalol.[1] Like other histamine-releasing opioids, pethidine should be used with caution in such patients.

1. Lawrence CA. Pethidine-induced hypertension in phaeochromocytoma. *BMJ* 1978; 1: 149–50.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pethidine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/10/11)

Pregnancy and the neonate. Pethidine has been widely used for analgesia during labour. It rapidly crosses the placenta and like other opioid analgesics may cause respiratory depression in the neonate, although perhaps less so than morphine. Respiratory depression varies according to the timing and size of the maternal dose.

Fetal depression was not apparent when delivery occurred within 1 hour of giving pethidine, but was present in 6 of 24 infants delivered 1 to 3 hours after injection and in all of 5 infants delivered 3 to 6 hours after injection.[1] However, higher blood concentrations of pethidine were seen in infants delivered within 1 hour of an intramuscular dose of pethidine compared with those delivered 1 to 4 hours after injection. The role of pethidine metabolites was uncertain. It has also been reported[2] that depressed neonatal responses persisted for the first 2 days of life; depression was dose-related being greatest with the highest dose of pethidine (75 to 150 mg within 4 hours of delivery). Neonates appear able to metabolise pethidine, although probably more slowly than adults.[3] The amounts of pethidine and norpethidine excreted by the neonate increased significantly with the maternal dose-delivery interval for intervals of up to 5 hours and most of the placentally transferred pethidine should be excreted by the third day. Elimination of pethidine took up to 6 days in the neonates in another study.[4]

Further references on the transplacental transfer of pethidine can be found in Pregnancy under Pharmacokinetics, below.

Neither psychological nor physical effects were found in 5-year-olds born to mothers who had received pethidine during labour.[5] Neonatal behaviour does not appear to have been affected significantly by pethidine, although it has been acknowledged that the relationship between maternal analgesia in labour and subsequent infant behaviour is by no means simple.[6] The results of early studies that suggested an excess of cases of cancer in children whose mothers received pethidine during labour have been refuted by a later and larger study.[7]

1. Morrison JC, *et al.* Metabolites of meperidine related to fetal depression. *Am J Obstet Gynecol* 1973; 115: 1132–7.
2. Hodgkinson R, *et al.* Double-blind comparison of the neurobehaviour of neonates following the administration of different doses of meperidine to the mother. *Can Anaesth Soc J* 1978; 25: 405–11.
3. Hogg MIJ, *et al.* Urinary excretion and metabolism of pethidine and norpethidine in the newborn. *Br J Anaesth* 1977; 49: 891–9.
4. Cooper LV, *et al.* Elimination of pethidine and bupivacaine in the newborn. *Arch Dis Child* 1977; 52: 638–41.
5. Buck C. Drugs in pregnancy. *Can Med Assoc J* 1975; 112: 1285.
6. Anonymous. To measure life. *Lancet* 1981; ii: 291–2.
7. Golding J, *et al.* Childhood cancer, intramuscular vitamin K and pethidine given during labour. *BMJ* 1992; 305: 341–6.

Renal impairment. Caution is necessary when pethidine is given to patients with renal impairment; UK licensed product information recommends that it should be avoided in those with severe impairment, whereas US product information suggests to use reduced doses. Evidence of CNS excitation, including seizures and twitches, in 2 patients with renal insufficiency given multiple doses of pethidine was attributed to accumulation of the metabolite norpethidine; both patients had high norpethidine to pethidine plasma concentration ratios.[1]

See also under Pharmacokinetics, p. 124.1.

1. Szeto HH, *et al.* Accumulation of normeperidine, an active metabolite of meperidine, in patients with renal failure or cancer. *Ann Intern Med* 1977; 86: 738–41.

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

Very severe reactions, including coma, severe respiratory depression, cyanosis, and hypotension have occurred in patients receiving MAOIs (including moclobemide and selegiline) and given pethidine. There are also reports of hyperexcitability, convulsions, tachycardia, hyperpyrexia, and hypertension. Pethidine should not be given to patients receiving MAOIs or within 14 days of their discontinuation. Use of pethidine with phenothiazines has produced severe hypotensive episodes and may prolong the respiratory depression due to pethidine.

Plasma concentrations of norpethidine are increased by ritonavir, with a resultant risk of toxicity; use together should be avoided (see also p. 111.2).

Antibacterials. See MAOIs below for interactions between pethidine and *isoniazid* and *linezolid*.

Antidepressants. For reference to possible cases of serotonin syndrome associated with use of pethidine and *SSRIs*, see Opioid Analgesics under Interactions of Fluoxetine, p. 427.1. See also MAOIs, below.

Antiepileptics. Opioid analgesics and barbiturates can be expected to have additive CNS depressant effects. Prolonged sedation with pethidine in the presence of *phenobarbital* has also been attributed to induction of *N*-demethylation of pethidine, resulting in the enhanced formation of the potentially neurotoxic metabolite norpethidine.[1,2] The hepatic metabolism of pethidine appears to be enhanced by *phenytoin*; use together resulted in reduced half-life and bioavailability in healthy subjects; blood concentrations of norpethidine were increased.[3]

1. Stambaugh JE, *et al.* A potentially toxic drug interaction between pethidine (meperidine) and phenobarbitone. *Lancet* 1977; i: 398–9.
2. Stambaugh JE, *et al.* The effect of phenobarbital on the metabolism of meperidine in normal volunteers. *J Clin Pharmacol* 1978; 18: 482–90.
3. Pond SM, Kretschzmar KM. Effect of phenytoin on meperidine clearance and normeperidine formation. *Clin Pharmacol Ther* 1981; 30: 680–6.

Histamine H_2-antagonists. See under Opioid Analgesics, p. 111.3.

MAOIs. Some of the most serious interactions involving pethidine have been with non-selective MAOIs and have been manifest as enhanced depressant effects or hyperexcitability (see Interactions, above). However, a life-threatening interaction has also been reported between pethidine and *selegiline*, a selective monoamine oxidase type B inhibitor.[1] Also, symptoms suggestive of a mild serotonin syndrome developed in a 73-year-old woman taking *moclobemide* (a reversible inhibitor of monoamine oxidase type A), nortriptyline, and lithium after she was given pethidine intravenously.[2]

Use of the antibacterial *isoniazid* with pethidine led to a drop in blood pressure and lethargy in a 54-year-old man.[3] Serotonin syndrome developed in a 27-year-old man after the use of pethidine with *linezolid*;[4] symptoms resolved when pethidine was stopped. The authors of both studies attributed the interaction to the inhibitory action of isoniazid and linezolid on monoamine oxidase.

1. Zornberg GL, *et al.* Severe adverse interaction between pethidine and selegiline. *Lancet* 1991; 337: 246. Correction. *ibid.*; 440.
2. Gillman PK. Possible serotonin syndrome with moclobemide and pethidine. *Med J Aust* 1995; 162: 554.
3. Gannon R, *et al.* Isoniazid, meperidine, and hypotension. *Arch Intern Med* 1983; 99: 415. Correction. *ibid.*; 740.
4. Das PK, *et al.* Serotonin syndrome after concomitant treatment with linezolid and meperidine. *Clin Infect Dis* 2008; 46: 264–5.

Phenothiazines. *Prochlorperazine* prolonged the respiratory depressant effect of pethidine in healthy subjects.[1] Enhanced CNS depression and hypotension were reported when healthy subjects were given *chlorpromazine* in addition to pethidine; there was evidence of increased *N*-demethylation of pethidine.[2]

1. Steen SN, Yates M. Effects of benzquinamide and prochlorperazine, separately and combined with meperidine, on the human respiratory center. *Clin Pharmacol Ther* 1972; 13: 153.
2. Stambaugh JE, Wainer IW. Drug interaction: meperidine and chlorpromazine, a toxic combination. *J Clin Pharmacol* 1981; 21: 140–6.

Pharmacokinetics

Pethidine hydrochloride is absorbed from the gastrointestinal tract, but only about 50% of the drug reaches the systemic circulation because of first-pass metabolism. Absorption after intramuscular injection is variable. Peak plasma concentrations have been reported 1 to 2 hours after oral doses. It is about 60 to 80% bound to plasma proteins.

Pethidine is metabolised in the liver by hydrolysis to pethidinic acid (meperidinic acid) or demethylation to norpethidine (normeperidine) and hydrolysis to norpethidinic acid (normeperidinic acid), followed by partial conjugation with glucuronic acid. Norpethidine is pharmacologically active and its accumulation may result in toxicity. Pethidine is reported to have a plasma elimination half-life of about 3 to 6 hours in healthy subjects; the metabolite norpethidine is eliminated more slowly, with a half-life reported to be up to about 20 hours. Both pethidine and norpethidine appear in the CSF. At the usual values of urinary pH or if the urine is alkaline, only a small amount of pethidine is excreted unchanged; urinary excretion of pethidine and norpethidine is enhanced by acidification of the urine. Pethidine crosses the placenta and is distributed into breast milk.

Reviews.

1. Edwards DJ, *et al.* Clinical pharmacokinetics of pethidine: 1982. *Clin Pharmacokinet* 1982; 7: 421–33.
2. Moore RA, *et al.* Opiate metabolism and excretion. *Baillieres Clin Anaesthesiol* 1987; 1: 829–58.

Administration. The elimination half-life of pethidine was prolonged and plasma clearance decreased when given perioperatively compared with postoperatively.[1]

During labour the pharmacokinetics of pethidine may depend on how it is given. In a comparison of intramuscular injection at different sites, absorption of pethidine from the gluteus muscle was impaired and the deltoid muscle was preferred.[2]

No statistically significant differences were found in pharmacokinetic parameters for deltoid and gluteal intramuscular injections in elderly postoperative patients.[3] However, substantial interpatient variability was noted for both sites, and the authors suggested that more rapid and predictable routes such as intravenous injection may be more appropriate for postoperative use in the elderly.

1. Tamsen A, *et al.* Patient-controlled analgesic therapy, part 1: pharmacokinetics of pethidine in the per- and postoperative periods. *Clin Pharmacokinet* 1982; 7: 149–63.
2. Lazebnik N, *et al.* Intravenous, deltoid, or gluteus administration of meperidine during labor? *Am J Obstet Gynecol* 1989; 160: 1184–9.
3. Erstad BL, *et al.* Site-specific pharmacokinetics and pharmacodynamics of intramuscular meperidine in elderly postoperative patients. *Ann Pharmacother* 1997; 31: 23–8.

Hepatic impairment. The terminal half-life of pethidine was prolonged to about 7 hours in cirrhotic patients compared with 3 hours in healthy subjects, which was attributed to impairment of the drug-metabolising activity of the liver.[1] Another study concluded that although impaired hepatic metabolism might confer relative protection from norpethidine toxicity in patients with cirrhosis, there might be an increased risk of cumulative toxicity because of slow elimination of the metabolite.[2]

1. Klotz U, *et al.* The effect of cirrhosis on the disposition and elimination of meperidine in man. *Clin Pharmacol Ther* 1974; 16: 667–75.
2. Pond SM, *et al.* Presystemic metabolism of meperidine to normeperidine in normal and cirrhotic subjects. *Clin Pharmacol Ther* 1981; 30: 183–8.

Pregnancy. Some references[1-3] to the pharmacokinetics of pethidine during labour.

1. Tomson G, *et al.* Maternal kinetics and transplacental passage of pethidine during labour. *Br J Clin Pharmacol* 1982; 13: 653–9.
2. Kuhnert BR, *et al.* Disposition of meperidine and normeperidine following multiple doses during labor: I mother. *Am J Obstet Gynecol* 1985; 151: 406–9.

3. Kuhnert BR, *et al.* Disposition of meperidine and normeperidine following multiple doses during labor: II fetus and neonate. *Am J Obstet Gynecol* 1985; 151: 410–15.

Renal impairment. Plasma protein binding of pethidine was reported to be decreased in renal disease and ranged from 58.2% in healthy subjects to 31.8% in anuric patients.[1] The same workers also reported prolonged elimination of pethidine in patients with renal dysfunction.[2]

See also under Precautions, p. 123.2.

1. Chan K, *et al.* Plasma protein binding of pethidine in patients with renal disease. *J Pharm Pharmacol* 1983; 35: 94P.
2. Chan K, *et al.* Pharmacokinetics of low-dose intravenous pethidine in patients with renal dysfunction. *J Clin Pharmacol* 1987; 27: 516–22.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Cluyer; Meperol; ***Austria***: Alodan; ***Belg.***: Dolantine; ***Braz.***: Dolantina; Dolosal; Dornot; Petinan; ***Canad.***: Demerol; ***Cz.***: Dolsin; ***Ger.***: Dolantin†; Dolcontral; ***Hung.***: Dolargan; ***Israel***: Dolestine; ***Philipp.***: Deme; Demerol; ***Pol.***: Dolargan; Dolcontral; ***Spain***: Dolantina; ***Turk.***: Aldolan; ***USA***: Demerol.

Multi-ingredient Preparations. *UK*: Pamergan P100; ***USA***: Meprozine†.

Pharmacopoeial Preparations
BP 2014: Pethidine Injection; Pethidine Tablets;
USP 36: Meperidine Hydrochloride Injection; Meperidine Hydrochloride Syrup; Meperidine Hydrochloride Tablets.

Phenacetin *(rINN)*

Aceto-*p*-phenetidide; Acetophenetidin; Acetylphenetidin; Fenacetin; Fenacetina; Fenacetine; Fenacetyna; Fenasetiini; Fenasetin; Paracetophenetidin; Phénacétine; Phenacetinum; Фенацетин.

p-Acetophenetidide; 4′-Ethoxyacetanilide; *N*-(4-Ethoxyphenyl)acetamide.

$C_{10}H_{13}NO_2$=179.2.
CAS — 62-44-2.
ATC — N02BE03.
ATC Vet — QN02BE03.
UNII — ER0CTH01H9.

Uses and Administration

Phenacetin, a para-aminophenol derivative, has analgesic and antipyretic properties. It was usually given with aspirin, caffeine, or codeine but is now little used because of adverse haematological effects and nephrotoxicity.

Adverse Effects and Precautions

Phenacetin may cause methaemoglobinaemia, sulfhaemoglobinaemia, and haemolytic anaemia.

Prolonged use of large doses of analgesic mixtures containing phenacetin has been associated with the development of renal papillary necrosis (see Effects on the Kidneys, p. 106.2) and transitional-cell carcinoma of the renal pelvis.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Hung.*: Antineuralgica; Dolor†.

Phenazone *(BAN, rINN)*

Analgésine; Antipyrin; Antipyrine; Azophenum; Fenatsoni; Fenazon; Fenazona; Fenazonas; Phenazon; Phénazone; Phenazonum; Phenyldimethylpyrazolone; Феназон.

1,5-Dimethyl-2-phenyl-4-pyrazolin-3-one.

$C_{11}H_{12}N_2O$=188.2.
CAS — 60-80-0.
ATC — N02BB01; S02DA03.
ATC Vet — QN02BB01; QS02DA03.
UNII — T3CHA1B51H.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Phenazone). White or almost white crystalline powder or colourless crystals. Very soluble in water, in alcohol, and in dichloromethane. Protect from light.

USP 36: (Antipyrine). Colourless crystals or white crystalline powder. Is odourless. Very soluble in water; freely soluble in alcohol and in chloroform; sparingly soluble in ether. Solutions are neutral to litmus. Store in airtight containers.

Phenazone and Caffeine Citrate

Antipyrino-Coffeinum Citricum; Fenazona y citrato de cafeína; Migrenin; Феназон и Кофеина Цитрат.

UNII — 3Z4LOI7NPG.

Description. Phenazone and caffeine citrate is a powder usually containing phenazone 90%, caffeine 9%, and citric acid monohydrate 1%.

Pharmacopoeias. In *Jpn*.

Phenazone Salicylate

Antipyrin Salicylate; Fenatsonisalisylaatti; Fenazona salicilato; Fenazonsalicylat; Phenazoni Salicylas; Salipyrin; Феназона Салицилат.

$C_{11}H_{12}N_2O.C_7H_6O_3$=326.4
CAS — 520-07-0.
ATC — N02BB01; S02DA03.
ATC Vet — QS02DA03.
UNII — F558OJK9JG.

Pharmacopoeias. In *Fr*.

Uses and Administration

Phenazone is an NSAID (p. 102.3) and has been given orally; phenazone and caffeine citrate and phenazone salicylate have similarly been given orally as analgesics.

Solutions containing about 5% of phenazone have been used topically as ear drops in disorders such as acute otitis media (but see below).

Phenazone is used as a test for the activity of drug-metabolising enzymes in the liver.

Diagnosis and testing. A review[1] of normal plasma-phenazone pharmacokinetics, urinary metabolite disposition, and total body clearances of phenazone in the presence of cirrhosis, fatty liver, hepatitis, and cholestatis.

1. St Peter JV, Awni WM. Quantifying hepatic function in the presence of liver disease with phenazone (antipyrine) and its metabolites. *Clin Pharmacokinet* 1991; 20: 50–65.

Otitis media. There appears to be no justification[1] for the inclusion of phenazone in topical preparations used in treating acute otitis media (p. 197.2). It is presumably included in such preparations because it is believed to have a local anti-inflammatory and, therefore, analgesic action. It would, however, seem unlikely that phenazone would have any action on the skin of the intact tympanic membrane and, therefore, on the pain which is due mainly to the stretching and distention of the membrane.

1. Carlin WV. Is there any justification for using phenazone in a local application prescribed for the treatment of acute otitis media? *BMJ* 1987; 294: 1333.

Adverse Effects, Treatment, and Precautions

Phenazone is liable to give rise to skin eruptions and in susceptible individuals even small doses may have this effect. Hypersensitivity reactions and nephrotoxicity have been reported. Large oral doses may cause nausea, drowsiness, methaemoglobinaemia, coma, and convulsions. Although the benefit of gastric decontamination is uncertain, activated charcoal may be given to adults or children who have ingested more than 20 mg/kg within 1 hour of presentation. Thereafter, symptomatic and supportive therapy should be given as appropriate.

Effects on the blood. Phenazone can cause haemolytic anaemia in certain individuals with a deficiency of G6PD.[1] Episodes of agranulocytosis were reported[2] in 6 women using a cream containing phenazone; all recovered on withdrawal.

1. Prankerd TAJ. Hemolytic effects of drugs and chemical agents. *Clin Pharmacol Ther* 1963; 4: 334–50.
2. Delannoy A, Schmit J-C. Agranulocytosis after cutaneous contact with phenazone. *Eur J Haematol* 1993; 50: 124.

Effects on the kidneys. Phenazone is considered nephrotoxic but only limited clinical information on phenazone is available because it has been mainly used with phenacetin.[1]

1. Prescott LF. Analgesic nephropathy: a reassessment of the role of phenacetin and other analgesics. *Drugs* 1982; 23: 75–149.

Effects on the skin. In a summary[1] of 77 cases of fixed drug eruption phenazone derivatives were considered to be the causative agent in 9 of the 14 cases that were severe generalised reactions.

1. Stubb S, *et al.* Fixed drug eruptions: 77 cases from 1981 to 1985. *Br J Dermatol* 1989; 120: 583.

Hypersensitivity. Immediate allergic reactions to phenazone have been reported.[1,2] In one patient leucopenia was detected 8 weeks later.[1]

1. Kadar D, Kalow W. Acute and latent leukopenic reaction to antipyrine. *Clin Pharmacol Ther* 1980; 28: 820–22.
2. McCrea JB, *et al.* Allergic reaction to antipyrine, a marker of hepatic enzyme activity. *DICP Ann Pharmacother* 1989; 23: 38–40.

Interactions

Phenazone affects the metabolism of some other drugs and its own metabolism is affected by other drugs that increase or reduce the activity of liver enzymes.

Pharmacokinetics

Phenazone is absorbed from the gastrointestinal tract and peak plasma concentrations occur within 1 to 2 hours of ingestion. It is distributed throughout the body fluids and concentrations in the saliva and breast milk reach about the same levels as those in plasma. Less than 10% is bound to plasma proteins and it has an elimination half-life of about 12 hours. Phenazone is metabolised in the liver to 3 major metabolites 3-hydroxymethylphenazone, 4-hydroxyphenazone, and norphenazone. Phenazone, 3-hydroxymethylphenazone, and glucuronidated metabolites are all excreted in the urine. A small portion may be eliminated via the bile.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Erasol†; ***Ger.***: Eu-Med; Migrane-Kranit; Migranin Phenazon†; ***Hong Kong***: Tropex; ***Irl.***: Tropex; ***Pol.***: Antotalgin; ***S.Afr.***: Adco-Otophen; Aurone; ***Venez.***: Otamina.

Multi-ingredient Preparations. ***Arg.***: Aqua Lent Colirio; Bideon Free; Bideon; Cerosporin; Clarisoft; Coliria; Cristalomicina; Irix Clasico; Kalopsis; Otalex G; Otocalmia Biotic; Otocerol; Otocuril; Otonorthia; Prednifarma; Sincerum; Usualix; Vislus; ***Austral.***: Auralgan; Ear Clear For Ear Ache Relief; ***Austria***: Coffo Selt; Otalgan; ***Belg.***: Hemorhinol†; ***Canad.***: Auralgan; Formule L2; ***Cz.***: Otipax; ***Denm.***: Koffisal; ***Fr.***: Brulex; HEC; Otipax; ***Ger.***: Otalgan; ***Gr.***: Otil; ***Hong Kong***: Neo-Active Antirheumatic†; ***Hung.***: Otipax; ***India***: Tytin; ***Israel***: Anaesthetic Ear Drops; Otidin; ***Ital.***: Otalgan; Otomidone; Otopax; ***Norw.***: Antineuralgica†; Fanalgin; ***NZ***: Auralgan; ***Philipp.***: Auralgan; ***Rus.***: Policap (Фолликап); Otipax (Отипакс); Otirelax (Отирелакс); ***S.Afr.***: Adco-Otised; Auralyt†; Aurasept; Aurone Forte†; Covancaine; Ilvico†; Oto-Phen Forte†; Universal Earache Drops†; ***Singapore***: Tropex; ***Spain***: Epistaxol; Otosedol†; Quimpedor; Tabletas Quimpe†; ***Swed.***: Koffazon; ***Switz.***: Otalgan; Otipax; Otosan; Otothricinol; ***Thai.***: Auralgan; ***Ukr.***: Otipax (Отипакс); Otisol (Отисол); ***USA***: AABP; Allergen; Auralgan; Aurax; Auroguard Otic; Cy-Gesic; Ear-Gesic; Neotic†; Otic Edge†; Otozin; Treagan; ***Venez.***: Otan; Otirilin.

Pharmacopoeial Preparations
USP 36: Antipyrine and Benzocaine Otic Solution; Antipyrine, Benzocaine, and Phenylephrine Hydrochloride Otic Solution.

Phenazopyridine Hydrochloride

(BANM, USAN, rINNM)

Fenazopiridin Hidroklorür; Cloridrato de Fenazopiridina; Fenazopiridina, hidrocloruro de; Fenazopirydyny chlorowodorek; Hidrocloruro de fenazopiridina; NC-150; NSC-1879; Phénazopyridine, Chlorhydrate de; Phenazopyridini Hydrochloridum; W-1655; Феназопиридина Гидрохлорид.

3-Phenylazopyridine-2,6-diyldiamine hydrochloride.

$C_{11}H_{11}N_5HCl$=249.7
CAS — 94-78-0 (phenazopyridine); 136-40-3 (phenazopyridine hydrochloride).
ATC — G04BX06.
ATC Vet — QG04BX06.
UNII — 0EWG668W17.

Pharmacopoeias. In *Pol.* and *US*.

USP 36: (Phenazopyridine Hydrochloride). A light or dark red to dark violet crystalline powder. Is odourless or with a slight odour. Soluble 1 in 300 of cold water, 1 in 20 of boiling water, 1 in 59 of alcohol, 1 in 331 of chloroform, and 1 in 100 of glycerol; very slightly soluble in ether. Store in airtight containers.

Removal of stains. Phenazopyridine stains may be removed from fabric by soaking in a 0.25% solution of sodium dithionite.

Uses and Administration

Phenazopyridine is an azo dye that exerts an analgesic effect on the mucosa of the urinary tract and is used to provide symptomatic relief of pain and irritability in conditions such as cystitis (p. 2347.3), prostatitis (p. 2350.2), and urethritis (p. 214.3). Phenazopyridine hydrochloride has been given in usual oral doses of about 200 mg three times daily after food. If given with an antibacterial for the treatment of urinary-tract infections (see below), treatment should usually not exceed 2 days, although lower doses have been given as part of a combined preparation for at least a week.

Urinary-tract infections. There is no well-substantiated role for phenazopyridine in the treatment of urinary-tract

infections (p. 215.1) and its adverse effects are potentially serious.[1]

1. Zelenitsky SA, Zhanel GG. Phenazopyridine in urinary tract infections. *Ann Pharmacother* 1996; 30: 866–8.

Adverse Effects

Phenazopyridine hydrochloride has caused gastrointestinal adverse effects, headache, and rashes. Hepatotoxicity, haemolytic anaemia, methaemoglobinaemia, and acute renal failure have also been reported, generally associated with overdosage or with therapeutic doses in patients with renal impairment. Crystal deposits of phenazopyridine have formed in the urinary tract.

Abnormal coloration of body tissues or fluids may occur. Urine is tinged either orange or red and underclothes are apt to be stained.

Effects on the CNS. Aseptic meningitis, with distinct episodes of fever and confusion, was associated with the use of phenazopyridine.[1]

1. Herlihy TE. Phenazopyridine and aseptic meningitis. *Ann Intern Med* 1987; 106: 172–3.

Overdosage. A 2-year-old child developed cyanosis and methaemoglobinaemia after ingesting at most three 200-mg tablets of phenazopyridine hydrochloride;[1] she recovered after treatment with methylthioninium chloride. Acute renal failure has been reported in a 17-year-old HIV-positive girl, with no history of kidney disease, who took 1.2 g of phenazopyridine in a suicide attempt.[2]

1. Gold NA, Bithoney WG. Methemoglobinemia due to ingestion of at most three pills of pyridium in a 2-year-old: case report and review. *J Emerg Med* 2003; 25: 143–8.
2. Onder AM, *et al.* Acute renal failure due to phenazopyridine (Pyridium) overdose: case report and review of the literature. *Pediatr Nephrol* 2006; 21: 1760–4.

Precautions

Phenazopyridine hydrochloride is contra-indicated in patients with renal impairment or severe hepatitis and should be used with caution in those with G6PD deficiency. Treatment should be stopped if the skin or sclerae become discoloured; this may indicate accumulation as a result of impaired renal excretion. Phenazopyridine may interfere with urinalysis based on colour reactions or spectrometry.

Staining of contact lenses may occur.

Pharmacokinetics

Phenazopyridine hydrochloride is absorbed from the gastrointestinal tract. It is excreted mainly in the urine; up to 65% may be excreted as unchanged phenazopyridine and 18% as paracetamol.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cistalgina; ***Belg.***: Uropyrine; ***Braz.***: Pyridium; Pyrisept; Urologin; Urovit; ***Canad.***: Phenazo; Pyridium; ***Chile***: Nazamit†; Nordox; ***China***: Karidine (科力定); Yi Du (怡度); ***Hong Kong***: CP-Pyridine; Phenadine; Phenazo; Pyridin†; Pyridium; ***India***: Pyridium; ***Indon.***: Pyridium†; Urogetix; ***Israel***: Sedural; ***Mex.***: Alvena; Azofur†; Bioferina; Pirimir; Urezol; ***Philipp.***: Azomir†; ***Pol.***: Nefrecit†; ***S.Afr.***: Pyridium†; ***Singapore***: Urogesic; ***Thai.***: Ammilazo†; Anazo; Phendiridine; Sumedium; Uzone-T; ***USA***: Azo-Standard; Baridium; Prodium; Pyridium; Re-Azo; Urogesic.

Multi-ingredient Preparations. ***Arg.***: Bacti-Uril; Medaflox Dol; Nor 2; Priper Plus; Urotem Dol; ***Braz.***: Minazol; Uroctrim; Uropac; Uropielon; ***Chile***: Uro-Micinovo; ***Hong Kong***: Urobilin†; ***India***: Nephrogesic; ***Mex.***: Azo-Uronalin; Azo-Wintomylon; Azogen; Azuron; Mictasol; Nalixone; Naxilan-Plus; Norflen; Pirifur; Urovec†; Vodelan; ***Spain***: Micturol Sedante; ***Thai.***: Pyrizole; ***Turk.***: Azo Gantrisin; Azosilin; Uriseptin; ***USA***: Phenazo-Forte Plus; Phenazopyridine Plus; Pyrelle HB†; Pyridium Plus; Trellitum Plus†; Urelief Plus; Urobiotic-250; ***Venez.***: Azo-Mandelamine; Bacteval.

Pharmacopoeial Preparations

USP 36: Phenazopyridine Hydrochloride Tablets.

Phenylbutazone *(BAN, rINN)*

Butadione; Fenilbutazon; Fenilbutazona; Fenilbutazonas; Fenylbutazon; Fenylobutazon; Fenyylibutatsoni; Phenylbutazon; Phénylbutazone; Phenylbutazonum; Фенилбутазон.

4-Butyl-1,2-diphenylpyrazolidine-3,5-dione.

$C_{19}H_{20}N_2O_2$=308.4

CAS — 50-33-9 (phenylbutazone); 129-18-0 (phenylbutazone sodium); 4985-25-5 (phenylbutazone piperazine).

ATC — M01AA01; M02AA01.

ATC Vet — QM01AA01; QM02AA01.

UNII — GN5P7K3T8S.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Phenylbutazone). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; it dissolves in alkaline solutions. Protect from light.

USP 36: (Phenylbutazone). A white to off-white, odourless, crystalline powder. Very slightly soluble in water; soluble in alcohol; freely soluble in acetone and in ether. Store in airtight containers.

Profile

Phenylbutazone, a pyrazolone derivative, is an NSAID (p. 102.3). However, because of its toxicity and in particular its adverse haematological reactions (see *Effects* on the Blood, below), it is not used as a general analgesic or antipyretic. Although phenylbutazone is effective in almost all musculoskeletal and joint disorders including ankylosing spondylitis, acute gout, osteoarthritis, and rheumatoid arthritis, it should only be used in acute conditions where less toxic drugs have failed. In the UK its use has been restricted to the hospital treatment of ankylosing spondylitis unresponsive to other drugs. Initial oral doses of up to 600 mg daily in divided doses have been used in the treatment of rheumatic disorders. After 1 to 3 days, the dose should be reduced to the minimum effective amount, usually 100 to 300 mg daily; treatment should be given for the shortest period possible, up to a usual maximum of 1 week. If treatment is expected to continue for more than 1 week, blood cell counts should be performed before and regularly during therapy; monitoring of hepatic and renal function is also recommended. Reduced doses are recommended in elderly patients.

In some countries phenylbutazone has also been given as a rectal suppository and applied topically for musculoskeletal pain and in soft-tissue injury. It has also been given intramuscularly as the sodium salt. Other salts of phenylbutazone that have been used in musculoskeletal, joint, and soft-tissue disorders include the calcium, megallate, and piperazine salts.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were given phenylbutazone, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding. However, UK licensed product information states that phenylbutazone should be avoided during breast feeding as small amounts are distributed into breast milk.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/11/07)

Effects on the blood. Both phenylbutazone[1-3] and oxyphenbutazone[2,3] are well known for their adverse effects on the blood and especially for fatal agranulocytosis and aplastic anaemia. Leucopenia, pancytopenia, haemolytic anaemia, and thrombocytopenia may also occur. The UK CSM[4] noted that between July 1963 and January 1993 it had received 74 reports of agranulocytosis (39 fatal) associated with phenylbutazone and 40 reports of neutropenia (4 fatal). Up-to-date figures were not provided on oxyphenbutazone, but it is considered to be more toxic to the bone marrow than phenylbutazone.[2]

1. Böttiger LE, Westerholm B. Drug-induced blood dyscrasias in Sweden. *BMJ* 1973; 3: 339–43.
2. Anonymous. Phenylbutazone and oxyphenbutazone: time to call a halt. *Drug Ther Bull* 1984; 22: 5–6.
3. The International Agranulocytosis and Aplastic Anemia Study. Risks of agranulocytosis and aplastic anemia: a first report of their relation to drug use with special reference to analgesics. *JAMA* 1986; 256: 1749–57.
4. CSM/MCA. Drug-induced neutropenia and agranulocytosis. *Current Problems* 1993; 19: 10–11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024456&RevisionSelectionMethod=LatestReleased (accessed 27/04/07)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Butazolidina; Butazona; Neo Butazol; ***Fr.***: Butazolidine†; ***Ger.***: Ambene; exrheudon OPT; ***Indon.***: Akrofen; Berlison; Irgapan; ***Ital.***: Kadol; ***Mex.***: Astrofen†; Bloken; Bresal; Butalen; Butazolidina; Meprosona-P; ***Neth.***: Butazolidin; ***Pol.***: Butapirazol; ***Rus.***: Butadion (Бутадион); ***S.Afr.***: Inflazone; ***Spain***: Butazolidina; ***Switz.***: Butadion†; ***Thai.***: Butarzol; Butazone; KB Tazone; Leophen; Neo-Pyrazol†; Pantazone; Phenazone; Pyrazolone; Rhumacap; Rhumatab; Sugrarine; ***Ukr.***: Butadion (Бутадион); ***Venez.***: Ticinil Calcio.

Multi-ingredient Preparations. ***Braz.***: Mioflex; ***Chile***: Balsamo Analgesico con Fenilbutazona; Esanfrix; ***Fr.***: Dextrarine Phenylbutazone; ***Hung.***: Rheosolon; ***India***: Aristopyrin; ***Indon.***: Butamidon; Cetapyrin†; Enkapyrin; New Skelan; ***Mex.***: Butayonacol; Butisel; Dexaduil; Dibutasona; ***Rus.***: Ambene (Амбене); ***Spain***: Artrodesmol Extra; Doctofril Antiinflamat†; ***Switz.***: Butaparin†; ***Thai.***: Alaxan†; Asialax†; Butarion†; Myophen†.

Picolamine Salicylate *(rINNM)*

Picolamine Salicylate de; Picolamini Salicylas; 3-Pyridylmethylamine Salicylate; Salicilato de picolamina; Пиколамина Салицилат.

3-(Aminomethyl)pyridine Salicylate.

CAS — 3731-52-0 (picolamine).

Profile

Picolamine salicylate is a salicylic acid derivative that has been used topically in rubefacient preparations in the treatment of musculoskeletal, peri-articular, and soft-tissue disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Algiospray.

Piketoprofen *(rINN)*

Piképtofène; Piketoprofeno; Piketoprofenum; Пикетопрофен.

m-Benzoyl-*N*-(4-methyl-2-pyridyl)hydratropamide.

$C_{22}H_{20}N_2O_2$=344.4

CAS — 60576-13-8.

UNII — 362QBC4NL0.

Profile

Piketoprofen is an NSAID (p. 102.3) that has been used topically as the hydrochloride in concentrations of about 2% in musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Port.***: Picalm; Zemalex; ***Spain***: Calmatel; Triparsean†.

Piritramide *(BAN, rINN)*

Pirinitramide; Piritramid; Piritramida; Piritramidi; Piritramidum; R-3365; Пиритрамид.

1-(3-Cyano-3,3-diphenylpropyl)-4-piperidinopiperidine-4-carboxamide.

$C_{27}H_{34}N_4O$=430.6

CAS — 302-41-0.

ATC — N02AC03.

ATC Vet — QN02AC03.

UNII — 4RP92LYZ2F.

Profile

Piritramide is an opioid analgesic (p. 108.1).

It is used for the management of severe pain including postoperative pain, for premedication, and to provide analgesia during anaesthesia. It is given by intramuscular, subcutaneous, or slow intravenous injection as the tartrate in doses equivalent of up to about 30 mg of the base.

Reviews.

1. Kumar N, Rowbotham DJ. Piritramide. *Br J Anaesth* 1999; 82: 3–5.
2. Bouillon T, *et al.* The pharmacokinetics of piritramide after prolonged administration to intensive care patients. *Eur J Anaesthesiol* 2004; 21: 673–8.
3. Müller C, *et al.* Pharmacokinetics of piritramide in newborns, infants and young children in intensive care units. *Eur J Pediatr* 2006; 165: 229–39.
4. Huenseler C, *et al.* Prospective evaluation of the pharmacodynamics of piritramide in neonates and infants. *Eur J Pediatr* 2008; 167: 867–72.
5. Remane D, *et al.* Stability of piritramide in patient-controlled analgesia (PCA) solutions. *Pharmazie* 2009; 64: 380–1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Dipidolor; ***Belg.***: Dipidolor; ***Cz.***: Dipidolor; ***Ger.***: Dipidolor; ***Neth.***: Dipidolor.

Piroxicam *(BAN, USAN, rINN)*

CP-16171; Piroksikaami; Piroksikam; Piroksikamas; Piroxicamum; Piroxikam; Piroxikám; Пироксикам.

4-Hydroxy-2-methyl-*N*-(2-pyridyl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide.

$C_{15}H_{13}N_3O_4S$=331.3

CAS — 36322-90-4.

ATC — M01AC01; M02AA07; S01BC06.

ATC Vet — QM01AC01; QM02AA07; QS01BC06.

UNII — 13T4O6VMAM.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Piroxicam). A white or slightly yellow, crystalline powder. It shows polymorphism. Practically insoluble in water; slightly soluble in dehydrated alcohol; soluble in dichloromethane. Protect from light.

USP 36: (Piroxicam). An off-white to light tan or light yellow, odourless powder. It forms a monohydrate that is yellow. Very slightly soluble in water, in dilute acids, and in most organic solvents; slightly soluble in alcohol and in aqueous alkaline solutions. Store in airtight containers. Protect from light.

Piroxicam Betadex *(USAN, rINNM)*

CHF-1194; Piroxicam Beta Cyclodextrin; Piroxicam Beta Cyclodextrin Complex; Piroxicam Bétadex; Piroxicamum Betadexum; Пироксикам Бетадекс.

$(C_{15}H_{13}N_3O_4S)_2(C_{42}H_{70}O_{35})_5$=6337.6

CAS — 96684-40-1.

Uses and Administration

Piroxicam, an oxicam derivative, and piroxicam betadex are NSAIDs (p. 102.3). Piroxicam betadex may have a more rapid onset of therapeutic effect due to its enhanced solubility (see Pharmacokinetics below). Both have been used in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, rheumatoid arthritis including juvenile idiopathic arthritis, in soft-tissue disorders, in acute gout, and in postoperative pain but systemic usage in the EU is now restricted (see below) to chronic painful and inflammatory conditions.

In rheumatic disorders the usual maximum recommended oral dose of *piroxicam* is 20 mg daily as a single dose; divided doses may be used if necessary. Piroxicam has been given in similar doses as a rectal suppository or on a short-term basis by intramuscular injection.

For dosage in children, see below.

Piroxicam is also used in the local treatment of a variety of painful or inflammatory conditions as a topical gel in a concentration of 0.5% applied three or four times daily; treatment should be reviewed after 4 weeks. A 1% gel is also available. Piroxicam has been used in some countries as a 0.5 or 1% cream and as eye drops in a concentration of 0.5%.

Doses of piroxicam betadex are expressed in terms of the equivalent amount of piroxicam. Piroxicam betadex 191.3 mg is equivalent to about 20 mg of piroxicam. In rheumatic disorders *piroxicam betadex* is given in an oral dose equivalent to 20 mg of piroxicam daily as a single dose. This dose may be reduced to 10 mg daily in elderly patients.

Other salts or compounds that have also been used include piroxicam cinnamate (cinnoxicam), piroxicam choline, and piroxicam pivalate.

After a review[1] of the benefit-risk balance for piroxicam the EMEA placed restrictions on its systemic use and stated that:

- *its use in acute painful and inflammatory conditions should be abandoned*
- *its use should be limited only to the symptomatic relief of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis*
- *it should not be used as a first-line treatment*
- *the dose should be limited to 20 mg daily*
- *treatment should be reviewed within 14 days of starting*
- *it should only be started by doctors experienced in treating chronic painful and inflammatory conditions*
- *use with a gastroprotective drug should be considered*
- *it should not be given to patients at risk of gastrointestinal disorders associated with bleeding or to those who have had skin reactions to other drugs*
- *it should not be used with another NSAID or an anticoagulant*

1. EMEA. Questions and answers on the review of piroxicam (issued 21st June, 2007). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/piroxicam_26457807en.pdf (accessed 08/11/07)

Administration in children. Piroxicam has been used in children with juvenile idiopathic arthritis. The following doses, given according to body-weight, are recommended in the *BNFC* for children aged 6 years and over:

- less than 15 kg: 5 mg once daily
- 16 to 25 kg: 10 mg once daily
- 26 to 45 kg: 15 mg once daily
- 46 kg or over: 20 mg once daily

Adverse Effects and Treatment

As for NSAIDs in general, p. 104.3.

Local irritation and occasionally bleeding may occur with piroxicam suppositories and there may be pain and occasionally tissue damage at the injection site on intramuscular use. Application site reactions have also occurred with topical preparations of piroxicam.

Piroxicam is considered to be associated with an intermediate risk of gastrointestinal effects although there is some suggestion that the risk may be higher than for other intermediate-risk NSAIDs (p. 105.3).

A report[1] of the adverse reactions associated with piroxicam in South Africa during 1981 to 1986 included two reactions, paraesthesia and hair loss, not previously recorded in the literature.

1. Gerber D. Adverse reactions of piroxicam. *Drug Intell Clin Pharm* 1987; 21: 707–10.

Effects on the blood. Decreases in haemoglobin and haematocrit not associated with obvious gastrointestinal bleeding, have occurred in patients taking piroxicam. Thrombocytopenia, thrombocytopenic purpura,[1] and aplastic anaemia[2] have been described in patients on piroxicam.

1. Bjørnstad H, Vik Ø. Thrombocytopenic purpura associated with piroxicam. *Br J Clin Pract* 1986; 40: 42.
2. Lee SH, *et al.* Aplastic anaemia associated with piroxicam. *Lancet* 1982; i: 1186.

Effects on electrolytes. Reversible hyperkalaemic hyperchloraemic acidosis has been reported[1,2] in patients receiving piroxicam. Severe hyponatraemia and symptoms resembling the syndrome of inappropriate antidiuretic hormone secretion have also been associated with piroxicam.[3]

See also Effects on the Kidneys, below.

1. Grossman LA, Moss S. Piroxicam and hyperkalemic acidosis. *Ann Intern Med* 1983; 99: 282.
2. Miller KP, *et al.* Severe hyperkalemia during piroxicam therapy. *Arch Intern Med* 1984; 144: 2414–15.
3. Petersson I, *et al.* Water intoxication associated with non-steroidal anti-inflammatory drug therapy. *Acta Med Scand* 1987; 221: 221–3.

Effects on the kidneys. Acute nephropathy with characteristic features of Henoch-Schönlein purpura,[1] acute renal failure,[2] uraemia with hyperkalaemia, and acute interstitial nephritis[3] have been associated with systemic use of piroxicam. Nephrotic syndrome and interstitial nephritis have followed topical use of piroxicam gel.[4]

1. Goebel KM, Mueller-Brodmann W. Reversible overt nephropathy with Henoch-Schönlein purpura due to piroxicam. *BMJ* 1982; 284: 311–12.
2. Prais MA, *et al.* Piroxicam-induced renal failure and hyperkalemia. *Ann Intern Med* 1983; 99: 129–30.
3. Mitnick PD, Klein WJ. Piroxicam-induced renal disease. *Arch Intern Med* 1984; 144: 63–4.
4. O'Callaghan CA, *et al.* Renal disease and use of topical non-steroidal anti-inflammatory drugs. *BMJ* 1994; 308: 110–11.

Effects on the liver. Necrosis of the liver, sometimes fatal, has been associated with piroxicam.[1,2]

1. Lee SM, *et al.* Subacute hepatic necrosis induced by piroxicam. *BMJ* 1986; 293: 540–1.
2. Paterson D, *et al.* Piroxicam induced submassive necrosis of the liver. *Gut* 1992; 33: 1436–8.

Effects on the skin. As with other NSAIDs, rash has occurred in patients taking piroxicam. Phototoxic reactions have been described.[1] Serious skin reactions attributed to piroxicam therapy include toxic epidermal necrolysis,[2] pemphigus vulgaris,[3] erythema multiforme,[4] and Stevens-Johnson syndrome.[5] Fixed drug eruptions have also been reported.[6]

Concern by the EMEA over the serious nature of skin reactions associated with piroxicam has led to restrictions on the systemic use of piroxicam in the EU (see Uses and Administration, above).

1. Stern RS. Phototoxic reactions to piroxicam and other nonsteroidal antiinflammatory agents. *N Engl J Med* 1983; 309: 186–7.
2. Chosidow O, *et al.* Intestinal involvement in drug-induced toxic epidermal necrolysis. *Lancet* 1991; 337: 928.
3. Martin RL, *et al.* Fatal pemphigus vulgaris in a patient taking piroxicam. *N Engl J Med* 1983; 309: 795–6.
4. Prieto A, *et al.* Piroxicam-induced erythema multiforme. *Contact Dermatitis* 2004; 50: 263.
5. Katoh N, *et al.* Piroxicam induced Stevens-Johnson syndrome. *J Dermatol* 1995; 22: 677–80.
6. Cuerda Galindo E, *et al.* Fixed drug eruption from piroxicam. *J Eur Acad Dermatol Venereol* 2004; 18: 586–7.

Overdosage. Details of 16 patients who were considered to have taken an overdosage of piroxicam alone were reported[1] to the National Poisons Information Service of the UK. Thirteen patients (including 5 children) had no symptoms after doses estimated to be up to 300 to 400 mg; 2 patients complained of dizziness and blurred vision after 200 to 300 mg; the last patient, who claimed to have taken 600 mg presented in coma, regained consciousness within one hour, and had recovered fully within 24 hours. Severe multisystem toxicity has been reported in a 2-year-old child after ingestion of 100 mg of piroxicam.[2]

1. Court H, Volans GN. Poisoning after overdose with non-steroidal anti-inflammatory drugs. *Adverse Drug React Acute Poisoning Rev* 1984; 3: 1–21.
2. MacDougall LG, *et al.* Piroxicam poisoning in a 2-year-old child: a case report. *S Afr Med J* 1984; 66: 31–3.

Pancreatitis. Pancreatitis has been associated with piroxicam use.[1,2]

1. Raye OL. Piroxicam and pancreatitis. *Ann Intern Med* 1986; 104: 895.
2. Heluwaert F, *et al.* Pancréatite aiguë au piroxicam. *Gastroenterol Clin Biol* 2006; 30: 635–6.

Precautions

As for NSAIDs in general, p. 107.1.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were given piroxicam, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding. The *BNF* also considers the amount excreted into breast milk to be too small to be harmful to a breast-fed infant.

Piroxicam appears in breast milk in concentrations of about 1% of those in the maternal plasma.[2] Similar data are also included in the licensed product information although it does not recommend piroxicam use during breast feeding as clinical safety has not been established.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/11/07)
2. Østensen M. Piroxicam in human breast milk. *Eur J Clin Pharmacol* 1983; 25: 829–30.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies piroxicam as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 23/10/11)

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Use of aspirin with piroxicam results in decreased plasma concentrations of piroxicam to about 80% of normal. The UK licensed product information for ritonavir suggests that use of piroxicam with ritonavir may result in increased plasma concentrations of piroxicam and an increased risk of toxicity; it recommends that use together should be avoided.

Pharmacokinetics

Piroxicam is well absorbed from the gastrointestinal tract and peak plasma concentrations occur 3 to 5 hours after an oral dose. It is more rapidly absorbed after intramuscular use and is also absorbed to some degree after topical application. Piroxicam is 99% bound to plasma proteins. It has been detected in breast milk. Piroxicam has a long plasma elimination half-life of about 50 hours and steady-state concentrations are not reached for 7 to 12 days. It is metabolised in the liver by hydroxylation and conjugation with glucuronic acid and excreted mainly in the urine with smaller amounts in the faeces. Enterohepatic recycling occurs. Less than 5% of the dose is excreted unchanged in the urine and faeces.

Piroxicam betadex dissociates in the gastrointestinal tract to its components piroxicam and betadex (p. 2180.3). Piroxicam absorption from piroxicam betadex is more rapid than that of unmodified piroxicam; peak plasma concentrations of piroxicam occur 30 to 60 minutes after an oral dose. Betadex is not absorbed but is metabolised in the colon to various sugars.

References.

1. Richardson CJ, *et al.* Piroxicam and 5'-hydroxypiroxicam kinetics following multiple dose administration of piroxicam. *Eur J Clin Pharmacol* 1987; 32: 89–91.
2. Mäkelä A-L, *et al.* Steady state pharmacokinetics of piroxicam in children with rheumatic diseases. *Eur J Clin Pharmacol* 1991; 41: 79–81 (higher clearance and shorter half-life in children).
3. Rudy AC, *et al.* The pharmacokinetics of piroxicam in elderly persons with and without renal impairment. *Br J Clin Pharmacol* 1994; 37: 1–5.
4. Deroubaix X, *et al.* Oral bioavailability of CHF1194, an inclusion complex of piroxicam and β-cyclodextrin, in healthy subjects under single dose and steady-state conditions. *Eur J Clin Pharmacol* 1995; 47: 531–6.
5. Karim A, *et al.* Oxaprozin and piroxicam, nonsteroidal antiinflammatory drugs with long half-lives: effect of protein-binding differences on steady-state pharmacokinetics. *J Clin Pharmacol* 1997; 37: 267–78.
6. Wang D, *et al.* Comparative population pharmacokinetic-pharmacodynamic analysis for piroxicam-β-cyclodextrin and piroxicam. *J Clin Pharmacol* 2000; 40: 1257–66.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Benisan; Brionot; Fabopxicam†; Flogosine; Homocalmefyba; Maxtol; Micar; Nac; Nalgesic; Osteocalmine; Piroalgin; Samaruc; Solocalm; Tirovel; Trixicam; ***Austral.***: Feldene; Mobilis; Pirohexal-D†; ***Austria***: Brexin; Felden; Pirocam; Pirorheum†; Piroxistad; ***Belg.***: Brexine; Docpiroxi†; Feldene; Piromed; Piroxitop†; Polydene; Solicam; ***Braz.***: Anartrit; Anflene; Brexin; Cicladol; Feldanax; Feldene; Flamostat; Flogene; Floxicam; Inflamene; Inflanan; Inflax; Piroflan; Pirogreen; Piroxene; Piroxifar†; Piroxil; Piroxin; Piroxinid; Prodoxidil†; ***Canad.***: Novo-Pirocam; Nu-Pirox; ***Chile***: Fabudol; Feldene; Foldox†; Pemar; Pricam; ***China***: An Er Ke (安尔克); Cycladol (喜来通); Ji Ke (基克); JiWei (吉维); Liang Ke (亮克); Luo Lin (络林); Reliagic (洛尔定); Trast; ***Cz.***: Flamexin; Hotemin; ***Denm.***: Felden; Feldene†; Pirom; ***Fin.***: Brexidol†; Felden;

Piroxin; *Fr.*: Brexin; Cycladol; Feldene; Geldene; Inflaced†; Proxalyoc; Zofora; *Ger.*: Brexidol†; Flexase†; Pirobeta; Piroflam; Pirox; *Gr.*: Bleduran; Brexin; Calmopyrol; Conzila; Feldene; Fidinor; Flodeneu; Grecotens; Inflamase-N; Neo Axedil; Nilvo; Oximezin; Painrelipt-D; Pedifan; Proponol; Pyrcost; Reumaplus; Ruvamed; Sinartrol; Valopon; Zerospasm; Zitumex; *Hong Kong*: CP-Pirox; Feldene; Mobills†; Piram-D†; Piroxica†; Sefdene; Synoxicam†; Vidapirocam†; *Hung.*: Brexin; Feldene; Flamexin; Hotemin; Pirorheum†; *India*: Amida; Brexic; Camrox; Camsun; Cycladol; Dolocare; Dolocip; Dolodil; Dolokam; Doloiup; Dolonex; Dolopir; Doloswift; Dupox; Estcom; Felcam; Feldex; Flexar; Kemonex; Lincitrax; Medicam; Meloxi; Micropec; Mobicam; Mobidin; Movon; Noxicam-MD; Pam; Panorox; Pirox; Suganril; *Indon.*: Faxiden†; Felcam; Feldene; Infeld; Kifadene; Lanareuma; Licofel; Maxicam†; Pirocam; Pirodene†; Pirofel; Rexicam; Rexil; Rosic†; Roxidene; Scandene; Sofden†; Tropidene; Xicalom; *Irl.*: Feldene; Pericam†; *Israel*: Brexin; Exipan; Feldene; *Ital.*: Antiflog; Artroxicam; Brexidol; Brexin; Brexivel; Bruxicam†; Cicladol; Clevian; Dexicam†; Euroxi; Feldene; Flodol; Ipsoflog; Kinski; Lampoflex; Lenotac; Pirobec; Piroftal; Reumagil; Roxene†; Roxenil†; Roxiden; Sinartrol; Zelis†; *Jpn*: Baxo; *Malaysia*: Brexin; Feldene; Rhumagel; Uphaxicam; *Mex.*: Androxicam†; Arlexicam; Artyflam; Asabon†; Axtrim; Bapixied; Bioximil; Brexicam; Brexodin; Brucam; Campirex; Citoken T; Dixonal; Dolzycam; Edecam†; Facicam; Feldene; Glandicin; Laspiro; Osteral; Oxi-Reul; Oxicanol†; Pirodax†; Pirox; Piroxan†; R-Tyflam†; Reucam; Reutricam; Ripox; Serpicam; Tripirol; Vatrem; *Neth.*: Brexine†; *Norw.*: Brexidol; *NZ*: Candyl; Piram-D†; Pirohexal-D†; *Philipp.*: Feldene; Flamastat; Flaxine; Macroxam; Neperlan†; Palpasin; Parixam†; Pirostad†; Pixacor; Proximax; Raxicam; *Pol.*: Feldene; Flamexin; Hotemin†; *Port.*: Brexin; Feldene; Flexar; Flogocan†; Remisil; Reumoxican; Roxazin; *Rus.*: Erazon (Эразон); Finalgel (Финалгель); *S.Afr.*: Brexecam; Pixicam; Pyrocaps; Rheugesic; Roxifen; Xycam; *Singapore*: Feldene; Rhumagel; Rosiden; Roxifen; Sefdene; Vitaxicam†; *Spain*: Brexinil†; Cycladol†; Feldegel; Feldene; Improntal; Salvacam; Sasulen; Vitaxicam†; *Swed.*: Brexidol; *Switz.*: Felden; Pirocam†; Pirosol; *Thai.*: Ammidene; Brexin; Butacinon; Cyclodex; Dexalin; Fasden; Felcam; Feldene; Felgesic; Felicam; Felnox; Felpac; Felrox; Felxicam; Flamic; Heropedd; Ifemed; Kobixam; Manoxicam; Maswin; Moxicam†; Neogel†; Neotica; Nutarzol; PC-20†; Pherazone; Pi-rock; Pidoxam; Piram; Pirax; Piraxil; Pircam; Pirox-Man; Pirox; Piroxal; Piroxam; Piroxcin; Piroxen†; Piroxidon; Piroxone; Piroxsil; Polyxicam; Posedene†; Rocki; Roxicam; Roxifen; Roxium; Roxycam; Roxycan; Rumadene; Rumaxicam; Setarox; Sotilen; Spamic; Verox; Xicam; *Turk.*: Cycladol; Felden; Inflamex†; Oksikam; *UK*: Brexidol; Feldene; *Ukr.*: Finalgel (Финалгель); *USA*: Feldene; *Venez.*: Feldene; Feldenedi; Flamalit; Maxipiro; Pixorid.

Multi-ingredient Preparations. *Arg.*: Buta Rut B12; Flexicamin A; Flexicamin B12; Flexicamin B12; Flexicamin; Flogiatrin B12; Flogiatrin B12; Flogiatrin; Peganix; Rumisedan Fuerte; Rumisedan; Solocalm Plus; Solocalm Plus; Solocalm-B; Solocalm-Flex; *Braz.*: Rheumafim; *India*: Capsidol; *Indon.*: Counterpain-PXM; *Thai.*: Counterpain Plus.

Pharmacopoeial Preparations
BP 2014: Piroxicam Capsules; Piroxicam Gel;
USP 36: Piroxicam Capsules; Piroxicam Cream.

Pranoprofen *(rINN)*

Pranoprofène; Pranoprofeno; Pranoprofenum; Пранопрофен.

α-Methyl-5*H*-[1]-benzopyrano[2,3-*b*]pyridine-7-acetic acid.

$C_{15}H_{13}NO_3$=255.3

CAS — 52549-17-4.

ATC — S01BC09.

ATC Vet — QS01BC09.

UNII — 2R7O1ET613.

Pharmacopoeias. In *Jpn*.

Profile

Pranoprofen, a propionic acid derivative, is an NSAID (p. 102.3). It is used as eye drops in a concentration of 0.1% for ocular inflammation. Pranoprofen has also been given orally for the treatment of pain, inflammation, and fever.

References.
1. Notivol R, *et al.* Treatment of chronic nonbacterial conjunctivitis with a cyclo-oxygenase inhibitor or a corticosteroid. *Am J Ophthalmol* 1994; **117**: 651–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Pranox; *Braz.*: Difen; *China*: Pranopulin (普南扑灵); *Gr.*: Pranofen; *Ital.*: Oftalar; Pranoflog; *Jpn*: Niflan; *Mex.*: Niflan; *Port.*: Oftalar†; *Spain*: Oftalar†; *Turk.*: Oftalar.

Proglumetacin Maleate *(BANM, rINNM)*

CR-604; Maleato de proglumetacina; Proglumetacina, maleato de; Proglumétacine, Maléate de; Proglumetacinum Maleas; Protacine Maleate; Пролуметацина Малеат.

3-[4-[2-(1-*p*-Chlorobenzoyl-5-methoxy-2-methylindol-3-ylacetoxy)ethyl]piperazin-1-yl]propyl 4-benzamido-*N,N*-dipropylglutaramate dimaleate.

$C_{46}H_{58}ClN_5O_8.2C_4H_4O_4$=1076.6

CAS — 57132-53-3 (proglumetacin); 59209-40-4 (proglumetacin maleate).

ATC — M01AB14.

ATC Vet — QM01AB14.

UNII — F2PUN24B8C.

Profile

Proglumetacin maleate, an indoleacetic acid derivative related to indometacin (p. 71.2), is an NSAID (p. 102.3). It has been used in musculoskeletal and joint disorders in oral doses of up to 600 mg daily, in divided doses. Proglumetacin maleate has also been given as rectal suppositories and topically as a 5% cream.

References.
1. Appelboom T, Franchimont P. Proglumetacin versus indometacin in rheumatoid arthritis: a double-blind multicenter study. *Adv Therapy* 1994; **11**: 228–34.
2. Martens M. Double-blind randomized comparison of proglumetacin and naproxen sodium in the treatment of patients with ankle sprains. *Curr Ther Res* 1995; **56**: 639–48.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Bruxel; *Belg.*: Tolindol; *Ger.*: Protaxon; *Hong Kong*: Afloxan; *Ital.*: Proxil; *Jpn*: Miridacin; *Philipp.*: Afloxan; *Port.*: Protaxil; *Thai.*: Afloxan.

Propacetamol Hydrochloride *(BANM, rINNM)*

Hidrocloruro de propacetamol; Propacétamol, Chlorhydrate de; Propacetamol, hidrocloruro de; Propacetamol-hidroklorid; Propacetamolhydrochlorid; Propacetamol-hydrochlorid; Propacetamolhydroklorid; Propacetamoli Hydrochloridum; Propacetamolio hidrochloridas; Propasetamolihydrokloridi; Пропацетамола Гидрохлорид.

The hydrochloride of *N,N*-diethylglycine ester with paracetamol; 4-Acetamidophenyl diethylaminoacetate hydrochloride.

$C_{14}H_{20}N_2O_3.HCl$=300.8

CAS — 66532-85-2 (propacetamol).

ATC — N02BE05.

ATC Vet — QN02BE05.

UNII — SH41QYH8E5.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Propacetamol Hydrochloride). A white or almost white crystalline powder. Freely soluble in water; slightly soluble in dehydrated alcohol; practically insoluble in acetone. Protect from moisture.

Profile

Propacetamol hydrochloride, a para-aminophenol derivative, is hydrolysed to paracetamol (p. 115.1) in the plasma; 1 g of propacetamol hydrochloride is hydrolysed to release about 500 mg of paracetamol. It has been given intramuscularly or intravenously for the treatment of pain and fever.

References.
1. Allegaert K, *et al.* Pharmacokinetics of single dose intravenous propacetamol in neonates: effect of gestational age. *Arch Dis Child Fetal Neonatal Ed* 2004; **89**: F25–F28.
2. Walson PD, *et al.* Antipyretic efficacy and tolerability of a single intravenous dose of the acetaminophen prodrug propacetamol in children: a randomized, double-blind, placebo-controlled trial. *Clin Ther* 2006; **28**: 762–9.
3. Prins SA, *et al.* Pharmacokinetics and analgesic effects of intravenous propacetamol vs rectal paracetamol in children after major craniofacial surgery. *Paediatr Anaesth* 2008; **18**: 582–92.
4. McNicol ED, *et al.* Single-dose intravenous paracetamol or propacetamol for prevention or treatment of postoperative pain: a systematic review and meta-analysis. *Br J Anaesth* 2011; **106**: 764–75.

Adverse effects. Occupational contact dermatitis has been reported in healthcare professionals after preparing injections of propacetamol.[1-3]

Propacetamol is the hydrochloride of *N,N*-diethylglycine ester with paracetamol and the results of a study[4] have suggested that allergic reactions to propacetamol are related to sensitisation to the activated ester rather than to paracetamol itself.

A significant decrease in blood pressure was noted in 14 critically-ill patients following an intravenous infusion of propacetamol for the treatment of fever.[5] Interventions to control blood pressure were necessary.

1. Barbaud A, *et al.* Occupational allergy to propacetamol. *Lancet* 1995; **346**: 902.
2. Szczurko C, *et al.* Occupational contact dermatitis from propacetamol. *Contact Dermatitis* 1996; **35**: 299–301.
3. Gielen K, *et al.* Occupational allergic contact dermatitis from drugs in healthcare workers. *Contact Dermatitis* 2001; **45**: 273–9.
4. Berl V, *et al.* Mechanism of allergic contact dermatitis from propacetamol: sensitization to activated *N,N*-diethylglycine. *Contact Dermatitis* 1998; **38**: 185–8.
5. Hersch M, *et al.* Effect of intravenous propacetamol on blood pressure in febrile critically ill patients. *Pharmacotherapy* 2008; **28**: 1205–10.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies propacetamol as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Pro-Dafalgan†; *Mex.*: Tempra.

Propyl Nicotinate

Nicotinato de propilo; Пропилникотинат.

$C_9H_{11}NO_2$=165.2

CAS — 7681-15-4.

UNII — 80CZF4GX8N.

Profile

Propyl nicotinate is used in topical preparations as a rubefacient.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Elacur.

Propyphenazone *(BAN, rINN)*

Isopropylantipyrine; Isopropylantipyrinum; Isopropylphenazone; Propifenazon; Propifenazona; Propifenazonas; Propyfenatsoni; Propyfenazon; Propyphénazone; Propyphenazonum; Пропифеназон.

4-Isopropyl-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one.

$C_{14}H_{18}N_2O$=230.3

CAS — 479-92-5.

ATC — N02BB04.

ATC Vet — QN02BB04.

UNII — OED8FV75PY.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*.

Ph. Eur. 8: (Propyphenazone). A white or slightly yellowish crystalline powder. Slightly soluble in water; freely soluble in alcohol and in dichloromethane. Protect from light.

Profile

Propyphenazone, a pyrazolone derivative related to phenazone (p. 124.1), has analgesic and antipyretic properties. It has been given orally and as a rectal suppository in the treatment of pain and fever. The usual oral dose is 0.5 to 1 g up to four times daily. There have been some reports of severe hypersensitivity reactions in patients receiving propyphenazone.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Demex.

Multi-ingredient Preparations. *Arg.*: Algio-Bladuril; Espasmo Cibalena; Saridon; *Austria*: Adolorin; Avamigran; Gewadal; Melabon; Migradon; Montamed; Nervan; Rapidol; Saridon; Spasmoplus; Tonopan; Vivimed; *Braz.*: Saridon; Tonopan; *Chile*: Abalgin; Droxel†; Espasmo Cibalgina Compuesta†; Espasmo Cibalgina; Gripasan Compuesto DN; Gripasan Compuesto; SAE; *China*: Saridon (散利痛); *Cz.*: Saridon; Valetol; *Denm.*: Kodamid; *Ger.*: Optalidon N†; Saridon†; *Hong Kong*: Saridon†; *Hung.*: Saridon; Trinell Pro; *India*: Aristopyrin; Ciplador; Dart; Jiffy; *Indon.*: Bodrex Migra; Butamidon; Cetapyrin†; Enkapyrin; Migran†; Oskadon Migra; Paramex†; Saridon; *Ital.*: Cistalgan; Influvit; Neo-Optalidon; Odontalgico Dr. Knapp; Optalidon; Saridon; Sedol†; Spasmoplus; Uniplus; Veramon; *Mex.*: Espasmo Cibalgina; Tonopan; *Neth.*: Daro Hoofdpijnpoeders; Kruidvat PPC; Kruidvat; Para-don; Propyfenazon comp; Sanalgin; Saridon; *Pol.*: Analget†; Cefalgin; Gardan-P†; Krople Zoladkowe†; Krople Zoladkowe; Pabialgin P†; Saridon; *Port.*: Optalidon; Saridon N; *Rus.*: Algofetin (Альгофетин); Caffetin (Каффетин); Coffedon (Коффедон)†; Flucomp (Флюкомп); Gewadal (Гевадал)†; Kofan (Кофан); Pentalgin Plus (Пенталгин Плюс); Saridon (Саридон); *S.Afr.*: Ilvico†; *Spain*: Abdominol†; Calmoplex†; Dolodens†; Melabon†; Meloka†; Optalidon; Quimpedor; Saridon; Sulmetin Papaver†; Tabletas Quimpet†; Tonopan; *Turk.*: Aljil; Bioptan†; Minoset Plus; Optalidon; Panalgine; *Ukr.*: Caffetin (Каффетин); Kofan (Кофан); Nomigren (Номигрен); Novalgin (Новалгин); Pentased (Пентасед); Trinell (Тринелл)†.

The symbol † denotes a preparation no longer actively marketed

Proquazone *(BAN, USAN, rINN)*

43-715; Procuazona; Prokuazon; Prokvatsoni; Prokvazon; Proquazonum; RU-43-715-n; Проквазон.
1-Isopropyl-7-methyl-4-phenylquinazolin-2(1*H*)-one.
$C_{18}H_{18}N_2O$=278.4
CAS — 22760-18-5.
ATC — M01AX13.
ATC Vet — QM01AX13.
UNII — 42VPJ2980S.

Profile

Proquazone is an NSAID (p. 102.3) that has been used orally and rectally in musculoskeletal and joint disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Turk.*: Biarison.

Remifentanil Hydrochloride

(BANM, USAN, rINNM) ⊗

GI-87084B; Hidrocloruro de remifentanilo; Rémifentanil, Chlorhydrate de; Remifentanili Hydrochloridum; Remifentanilo, hidrocloruro de; Ремифентанила Гидрохлорид.
4-Carboxyl-4-(*N*-phenylpropionamido)-1-piperidine propionic acid dimethyl ester monohydrate.
$C_{20}H_{28}N_2O_5$,HCl=412.9
CAS — 132539-07-2.
ATC — N01AH06.
ATC Vet — QN01AH06.
UNII — 5V444H5WIC.

Incompatibility. Remifentanil hydrochloride should not be mixed in the same intravenous solution as blood products. UK licensed product information states that it should not be mixed with lactated Ringer's injection with or without 5% glucose; however, in the USA the product literature states that remifentanil hydrochloride is stable for 4 hours at room temperature after reconstitution and dilution to 20 to 250 micrograms/mL with lactated Ringer's injection and for 24 hours if lactated Ringer's with 5% glucose is used. Incompatibilities have been reported between chlorpromazine hydrochloride 2 mg/mL and remifentanil 25 micrograms/mL (as the hydrochloride) in 5% glucose and cefoperazone sodium 40 mg/mL or amphotericin B 600 micrograms/mL and remifentanil 250 micrograms/mL (as the hydrochloride) in 5% glucose.[1]

1. Trissel LA, *et al.* Compatibility of remifentanil hydrochloride with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; 54: 2192–6.

Uses and Administration

Remifentanil, an anilidopiperidine derivative, is an opioid analgesic (p. 108.1) related to fentanyl (p. 60.2). It is a short-acting μ-receptor opioid agonist used for analgesia during induction and/or maintenance of general anaesthesia. It is also used to provide analgesia into the immediate postoperative period, and may be used as the analgesic component of local or regional anaesthesia with or without benzodiazepine sedation. Remifentanil is also used to provide analgesia and sedation in mechanically ventilated patients under intensive care. It has also been tried in labour pain.

Remifentanil is given intravenously as the hydrochloride, usually by infusion. Its onset of action is within 1 minute and the duration of action is 5 to 10 minutes. Doses are expressed in terms of the base; remifentanil hydrochloride 1.1 mg is equivalent to about 1 mg of remifentanil. Initial doses for anaesthesia in elderly patients should be half the recommended adult doses and then titrated to individual requirements. Obese patients may require doses based on their ideal (lean) body-weight. For details of doses in children, see below.

When used to provide **analgesia** during *induction* of anaesthesia an intravenous infusion is given in doses of 0.5 to 1 micrograms/kg per minute. An additional initial intravenous bolus of 1 microgram/kg may be given over 30 to 60 seconds particularly if the patient is to be intubated less than 8 minutes after the start of the infusion.

For provision of analgesia during *maintenance* of anaesthesia in ventilated patients, usual infusion doses range from 50 nanograms/kg to 2 micrograms/kg per minute depending on the anaesthetic drug employed and adjusted according to response. Supplemental intravenous boluses of 500 nanograms/kg to 1 microgram/kg may be given every 2 to 5 minutes in response to light anaesthesia or intense surgical stress. The infusion dosage in spontaneous respiration is initially 40 nanograms/kg per minute adjusted according to response within a usual range of 25 to 100 nanograms/kg per minute. Bolus doses are not recommended during spontaneous ventilation.

For continuation of analgesia into the immediate *postoperative* period typical doses by intravenous infusion have ranged from 100 to 200 nanograms/kg per minute; supplemental intravenous bolus doses are not recommended during the postoperative period.

To provide **analgesia and sedation** in ventilated patients under intensive care, remifentanil is given as an intravenous infusion at an initial rate of 100 to 150 nanograms/kg per minute. Doses should then be titrated to provide adequate analgesia and sedation; a period of 5 minutes should be allowed between dose adjustments. Additional sedative drugs should be given to those patients inadequately sedated with remifentanil infusions of 200 nanograms/kg per minute. An increase in the rate of remifentanil infusion may be necessary if additional analgesia is required to cover stimulating or painful procedures such as wound dressing. Doses of up to 750 nanograms/kg per minute have been given to some patients. Bolus doses of remifentanil are not recommended in intensive care.

Remifentanil is also used as an analgesic in patients receiving monitored anaesthesia care. In the USA, it may be given intravenously in a single dose of 1 microgram/kg 90 seconds before the local anaesthetic; alternatively, a dose of 100 nanograms/kg per minute may be given as an intravenous infusion, starting 5 minutes before the local anaesthetic, which should be reduced to 50 nanograms/kg per minute after the local anaesthetic. Subsequent adjustments of 25 nanograms/kg per minute at 5-minute intervals may be made to maintain a balanced analgesia.

Remifentanil has a very rapid offset of action and no residual opioid action remains 5 to 10 minutes after stopping an infusion. When appropriate, alternative analgesics should be given before stopping remifentanil, in sufficient time to provide continuous and more prolonged pain relief.

References and reviews.

1. Davis PJ, Cladis FP. The use of ultra-short-acting opioids in paediatric anaesthesia: the role of remifentanil. *Clin Pharmacokinet* 2005; 44: 787–96.
2. Scott LJ, Perry CM. Remifentanil: a review of its use during the induction and maintenance of general anaesthesia. *Drugs* 2005; 65: 1793–1823. Correction. *ibid.*; 2286.
3. Battershill AJ, Keating GM. Remifentanil: a review of its analgesic and sedative use in the intensive care unit. *Drugs* 2006; 66: 365–85.
4. Welzing L, Roth B. Experience with remifentanil in neonates and infants. *Drugs* 2006; 66: 1339–50.
5. Komatsu R, *et al.* Remifentanil for general anaesthesia: a systematic review. *Anaesthesia* 2007; 62: 1266–80.
6. Hill D. Remifentanil in obstetrics. *Curr Opin Anaesthesiol* 2008; 21: 270–4.
7. Wilhelm W, Kreuer S. The place for short-acting opioids: special emphasis on remifentanil. *Crit Care* 2008; 12 (suppl 3): S5. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2391266/pdf/cc6152.pdf (accessed 25/01/10)
8. Marsh DF, Hodkinson B. Remifentanil in paediatric anaesthetic practice. *Anaesthesia* 2009; 64: 301–8.
9. Hinova A, Fernando R. Systemic remifentanil for labor analgesia. *Anesth Analg* 2009; 109: 1925–9.

Administration in children. Remifentanil hydrochloride, given by continuous intravenous infusion, is used for analgesia during maintenance of general anaesthesia in children. Usual infusion doses (expressed as the base) for those aged from 1 to 12 years range from 50 nanograms/kg to 1.3 micrograms/kg per minute depending on the anaesthetic drug employed and adjusted according to response; supplemental intravenous boluses of 1 microgram/kg may be given over at least 30 seconds. US licensed product information also states that neonates and children aged up to 2 months may be given infusion doses of 400 nanograms/kg to 1 microgram/kg per minute with supplemental boluses of 1 microgram/kg. Similar doses are suggested in the *BNFC* for use in neonates although in the UK remifentanil is not licensed for use in children under 1 year of age.

Dependence and Withdrawal

As for Opioid Analgesics, p. 109.1.

Adverse Effects and Treatment

As for Opioid Analgesics in general, p. 110.1 and for Fentanyl, p. 62.1.

Precautions

As for Opioid Analgesics in general, p. 110.3.

Administration. Remifentanil hydrochloride injections containing glycine should not be given by the epidural or intrathecal routes.

Hepatic impairment. Although the pharmacokinetics of remifentanil are not changed in patients with severe hepatic impairment, such patients may be more sensitive to the respiratory depressant effects and should be monitored with doses titrated to individual requirements.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies remifentanil as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/10/11)

Renal impairment. The pharmacokinetics of remifentanil are not changed in patients with severe renal impairment (a creatinine clearance of less than 10 mL/minute) and licensed product information states that the carboxylic acid metabolite is unlikely to accumulate to clinically active concentrations in such patients after remifentanil infusions given for up to 3 days. Dosage adjustment is considered to be unnecessary. This is supported by pharmacokinetic studies[1,2] in intensive care patients with renal impairment given remifentanil infusions at a rate of 100 to 150 nanograms/kg per minute for up to 3 days.

1. Breen D, *et al.* Offset of pharmacodynamic effects and safety of remifentanil in intensive care unit patients with various degrees of renal impairment. *Crit Care* 2004; 8: R21–R30.
2. Pitsiu M, *et al.* Pharmacokinetics of remifentanil and its major metabolite, remifentanil acid, in ICU patients with renal impairment. *Br J Anaesth* 2004; 92: 493–503.

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

Pharmacokinetics

After parenteral doses remifentanil hydrochloride has a rapid onset and short duration of action. Its effective biological half-life is about 3 to 10 minutes and is independent of dose. Remifentanil is about 70% bound to plasma proteins, mainly to α_1-acid glycoprotein. It is hydrolysed by non-specific esterases in blood and tissues to an essentially inactive carboxylic acid metabolite. About 95% of a dose of remifentanil is excreted in the urine as the metabolite. Studies in *animals* suggest that remifentanil may cross the placenta and is distributed into breast milk.

Licensed product information for remifentanil gives values for a three-compartment pharmacokinetic model with a rapid distribution half-life of 1 minute, a slower distribution half-life of 6 minutes, and a terminal elimination half-life of 10 to 20 minutes.

References.

1. Egan TD. Remifentanil pharmacokinetics and pharmacodynamics: a preliminary appraisal. *Clin Pharmacokinet* 1995; 29: 80–94.
2. Egan TD. Pharmacokinetics and pharmacodynamics of remifentanil: an update in the year 2000. *Curr Opin Anaesthesiol* 2000; 13: 449–55.
3. Ross AK, *et al.* Pharmacokinetics of remifentanil in anesthetized pediatric patients undergoing elective surgery or diagnostic procedures. *Anesth Analg* 2001; 93: 1393–1401.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Remicit; Remiflo; Ultiva; *Austral.*: Ultiva; *Austria*: Ultiva; *Belg.*: Ultiva; *Braz.*: Ultiva; *Canad.*: Ultiva; *Chile*: Ultiva; *China*: Rui Jie (瑞捷); *Cz.*: Ultiva; *Denm.*: Ultiva; *Fin.*: Ultiva; *Fr.*: Ultiva; *Ger.*: Ultiva; *Gr.*: Ultiva; *Hong Kong*: Ultiva; *Irl.*: Ultiva; *Israel*: Ultiva; *Ital.*: Ultiva; *Mex.*: Ultiva; *Neth.*: Ultiva; *Norw.*: Ultiva; *NZ*: Ultiva; *Pol.*: Ultiva; *Port.*: Ultiva; *Rus.*: Ultiva (Ультива); *S.Afr.*: Ultiva; *Singapore*: Ultiva; *Spain*: Ultiva; *Swed.*: Ultiva; *Switz.*: Ultiva; *Turk.*: Ultiva; *UK*: Ultiva; *USA*: Ultiva; *Venez.*: Ultiva.

Rofecoxib *(BAN, USAN, rINN)*

MK-0966; MK-966; Rofécoxib; Rofecoxibum; Rofekoksibi; Rofekoxib; Рофекоксиб.
4-[*p*-(Methylsulfonyl)phenyl]-3-phenyl-2(5*H*)-furanone.
$C_{17}H_{14}O_4S$=314.4
CAS — 162011-90-7.
ATC — M01AH02.
ATC Vet — QM01AH02.
UNII — 0QTW8Z7MCR.

Profile

Rofecoxib is an NSAID (p. 102.3) reported to be a selective inhibitor of cyclo-oxygenase-2 (COX-2). It was given orally for symptomatic relief in the treatment of osteoarthritis and rheumatoid arthritis, and in the management of acute pain, dysmenorrhoea, and migraine but was generally withdrawn worldwide after reports of cardiovascular adverse effects (see below).

Rofecoxib has been applied topically in some countries.

Effects on the cardiovascular system. As of February 2001, the UK CSM had received a small number of reports of *myocardial infarction* or *ischaemia* associated with the selective cyclo-oxygenase-2 (COX-2) inhibitors.[1] At that time it noted that COX-2 inhibitors such as rofecoxib did

not possess the intrinsic antiplatelet activity associated with aspirin, and consequently did not provide protection against ischaemic cardiac events. Data from a large, randomised study also showed the incidence of myocardial infarction to be greater in patients taking rofecoxib than in those taking naproxen.[2] Postmarketing surveillance of rofecoxib continued to provide further case reports of adverse cardiovascular effects. In addition, results of the then unpublished APPROVe study of rofecoxib for prevention of adenomatous polyposis indicated that the risk of myocardial infarction and stroke was markedly increased in patients receiving the drug compared with those on placebo; however, this difference was only apparent after 18 months of treatment. As a result, the study was stopped early and, in September 2004, the manufacturer generally withdrew rofecoxib worldwide. The cardiovascular findings from the APPROVe study were published in 2005;[3] the results showed a twofold increase in the risk of adverse cardiovascular events in patients receiving rofecoxib 25 mg daily when compared with those on placebo. More recently, data for patients in the APPROVe study have been re-analysed to include extended follow-up findings.[4] Overall, this analysis confirmed the increased risk of cardiovascular events such as myocardial infarction and stroke in patients taking rofecoxib when compared with those given placebo; there was also a non-significant increase in the risk of such events in the year after rofecoxib was stopped. Small patient numbers made it difficult to given any more precise details about when the increased risk began or ended; however, the data suggested an early increase in risk that persists for about 1 year after 3 years of treatment. Similar data, suggesting a 1.5-fold increase in risk of thrombotic events with rofecoxib, were reported from a study of adjuvant use for colorectal cancer.[5] A cumulative meta-analysis also indicated an increased risk of myocardial infarction in patients receiving rofecoxib.[6]

Subsequent investigation by US and European regulatory authorities has confirmed that other COX-2 inhibitors are also associated with some increased cardiovascular risk (see under Celecoxib, p. 37.3), as are some non-selective NSAIDs (see Thrombotic Events, p. 105.1).

A review[7] of prospective studies evaluating the effect of selective COX-2 inhibitors on blood pressure was unable to determine if there was any association between the use of these drugs and blood pressure elevations. Of the studies considered, a randomised study in elderly, hypertensive patients with osteoarthritis has suggested that the risk of developing *increased systolic blood pressure* is greater in those patients receiving rofecoxib than in those receiving celecoxib.[8] However, the manufacturers of rofecoxib have pointed out that the study used doses of rofecoxib greater than those recommended for elderly or hypertensive patients.

1. CSM/MCA. COX-2 selective NSAIDs lack antiplatelet activity. *Current Problems* 2001; 27: 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON0074586RevisionSelectionMethod=LatestReleased (accessed 08/11/07)
2. Bombardier C, *et al.* Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000; 343: 1520–8.
3. Bresalier RS, *et al.* Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005; 352: 1092–1102. Correction. *ibid.* 2006; 355: 221.
4. Baron JA, *et al.* Cardiovascular events associated with rofecoxib: final analysis of the APPROVe trial. *Lancet* 2008; 372: 1756–64. Correction. *ibid.*; 1732.
5. Kerr DJ, *et al.* Rofecoxib and cardiovascular adverse events in adjuvant treatment of colorectal cancer. *N Engl J Med* 2007; 357: 360–9.
6. Jüni P, *et al.* Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. *Lancet* 2004; 364: 2021–9.
7. Johnson DL, *et al.* Effect of cyclooxygenase-2 inhibitors on blood pressure. *Ann Pharmacother* 2003; 37: 442–6.
8. Whelton A, *et al.* Cyclooxygenase-2-specific inhibitors and cardiorenal function: a randomized, controlled trial of celecoxib and rofecoxib in older hypertensive osteoarthritis patients. *Am J Ther* 2001; 8: 85–95.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies rofecoxib as possibly porphyrinogenic: it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 23/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Peroxx; *India*: Doliib; Rofib†; Rofizt†; *Turk.*: Ecrox; Raxtane; Reox; Rofemax; Romaryd; Vioref; *Ukr.*: Denebol (Денебол); Rofica (Рофіка)†.

Multi-ingredient Preparations. *Ukr.*: Denebol Gel (Денебол Гель).

Salamidacetic Acid

Carbamoylphenoxyacetic acid; Salamidacético, ácido; Salicylamide *O*-acetic acid; Натрия Салициламидацетат (sodium salamidacetate).

(2-Carbamoylphenoxy)acetic acid.

$C_9H_9NO_4$=195.2

CAS — 25395-22-6 (salamidacetic acid); 3785-32-8 (sodium salamidacetate).

Profile

Salamidacetic acid is a salicylic acid derivative (see Aspirin, p. 22.2) that has also been used as the sodium and diethylamine salts for the treatment of musculoskeletal and joint disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Akistin.

Multi-ingredient Preparations. *Austria*: Rheumesser; *Rus.*: Ambene (Амбене).

Salicylamide *(BAN, rINN)*

Salicilamida; Salicylamid; Salicylamidum; Salisyyliamidi; Салициламид.

2-Hydroxybenzamide.

$C_7H_7NO_2$=137.1

CAS — 65-45-2.

ATC — N02BA05.

ATC Vet — QN02BA05.

UNII — EM8BM710ZC.

Pharmacopoeias. In *Pol.* and *US.*

USP 36: (Salicylamide). A white practically odourless crystalline powder. Slightly soluble in water and in chloroform; soluble in alcohol and in propylene glycol; freely soluble in ether and in solutions of alkalis.

Profile

Salicylamide is a salicylic acid derivative (see Aspirin, p. 22.2) but is not hydrolysed to salicylate; it is almost completely metabolised to inactive metabolites during absorption and on first pass through the liver. It is given in usual oral doses of 325 to 650 mg, or more, three or four times daily for pain and fever; lower doses are used in combination preparations with other analgesics. Salicylamide has also been applied topically in various preparations in concentrations of up to 8.5% for the relief of muscular and rheumatic pain.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Waldheim Rheuma-Creme†; *Ukr.*: Cefecon N (Цефекон Н).

Multi-ingredient Preparations. *Arg.*: Funciogrip†; Venter; *Austria*: Rubriment; *Belg.*: Percutalgine; *Braz.*: Coristina R; Gripinew; Respraxt; Vita Grip†; *China*: Feidile (菲迪乐); Neosed (尔可适); *Denm.*: Kodamid; Koffisal; *Fr.*: Percutalgine; *Gr.*: Myalgesic; *Hong Kong*: Antamin†; Anticol†; Co-Fluenza†; DF Multi-Symptom†; Flu-Zep†; Flucap†; Neozep; Qualizep; *Indon.*: Cold Cap; Corexin†; Neozep; *Mex.*: Artrilan†; Butayonacol; *NZ*: Calm-U; *Pol.*: Reumosol; Scorbolamid; *Rus.*: Cefecon N (Цефекон Н); *S.Afr.*: Colcaps†; Flutex Cold and Flu†; Histamed Compound; Ilvico†; Specific Nerve Pain Remedy†; *Singapore*: Con-Z-Lin; Consu; Fongtit; Semor Pain & Fever Relief; *Spain*: Pridio†; Rinomicine Activada†; Rinomicine; Rinomicine; Yendol; *Switz.*: Osa Gel de dentition; *Thai.*: Apracur; Fecol; Painol; *UAE*: Flukit; *Ukr.*: Percutalgine (Перкутальжин)†; *USA*: Anabar†; Be-Flex Plus†; By-Ache†; Combiflex†; Duraxin†; Levacet; Lobac†; Medi-First Extra Strength Pain Relief; Painaid; Saleto; *Venez.*: Praxona.

Salix

Corteza de sauce; Écorce de Saule; Fűzfakéreg; Gluosnių žievė; Kora wierzby; Pajunkuori; Salgbark; Salicis Cortex; Saule, Écorce de; Vrbová kůra; Weidenbaumrinde; Weidenrinde; White Willow Bark; Willow Bark; Ива.

UNII — S883J9JDYX.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Willow Bark). The whole or fragmented dried bark of young branches or whole dried pieces of current year twigs of various species of the genus *Salix*, including *Salix purpurea, S. daphnoides*, and *S. fragilis*. It contains not less than 1.5% of total salicylic derivatives, expressed as salicin ($C_{13}H_{18}O_7$ = 286.3), calculated with reference to the dried drug. Protect from light.

Profile

Salix contains variable amounts of tannin and also of salicin, which has antipyretic and analgesic actions similar to those of aspirin (p. 22.2). Salix has been used in a variety of herbal remedies for painful and inflammatory conditions and for fever. It was once used as a bitter.

Adverse effects. An *anaphylactic reaction* developed in a 25-year-old woman with asthma and a known allergy to aspirin, within 75 minutes of ingesting a dietary supplement containing willow bark extract.[1] The link between salicylate and willow bark allergy was also reported in a carpenter who developed a widespread *rash*, similar to that he had with aspirin, when working with willow wood.[2]

1. Boullata JI, *et al.* Anaphylactic reaction to a dietary supplement containing willow bark. *Ann Pharmacother* 2003; 37: 832–5.
2. Jennings A. Link between salicylate and willow bark. *Pharm J* 2006; 276: 417.

Pain. Preparations containing willow bark extract have been tried with some success in the treatment of musculoskeletal disorders such as low back pain[1-3] and osteoarthritis.[4] A report[5] by the Arthritis Research Campaign in the UK concluded that, based on limited evidence, willow bark may have a moderate effect in treating pain due to osteoarthritis and rheumatoid arthritis; however, it was not as effective as NSAIDs for pain relief in osteoarthritis. It appeared to be relatively safe when taken in the recommended doses.

1. Chrubasik S, *et al.* Treatment of low back pain exacerbations with willow bark extract: a randomized double-blind study. *Am J Med* 2000; 109: 9–14.
2. Chrubasik S, *et al.* Treatment of low back pain with a herbal or synthetic anti-rheumatic: a randomized controlled study. Willow bark extract for low back pain. *Rheumatology (Oxford)* 2001; 40: 1388–93.
3. Gagnier JJ, *et al.* Herbal medicine for low back pain. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 05/10/06).
4. Biegert C, *et al.* Efficacy and safety of willow bark extract in the treatment of osteoarthritis and rheumatoid arthritis: results of 2 randomized double-blind controlled trials. *J Rheumatol* 2004; 31: 2121–30.
5. Arthritis Research Campaign. Complementary and alternative medicines for the treatment of rheumatoid arthritis, osteoarthritis and fibromyalgia (issued February 2009). Available at: http://www.arthritisresearchuk.org/pdf/Complementary%20and%20alternative%20medicines_110120101543331.pdf (accessed 28/07/10).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Zortrix; *Ger.*: Assalix; Optovit actiflex; Proaktiv; *Pol.*: Salicortex; *Switz.*: Assalix; *Ukr.*: Assalix (Ассалікс).

Multi-ingredient Preparations. *Austral.*: Accelerex; Arthri Plus†; Cold & Flu Day/Night; Extralife Migrai-Care†; Extralife PMS-Care†; Full Motion; Nyal Cold + Flu Fighter Day + Night; Nyal Cold + Flu Fighter; Nyal Cough, Cold & Flu Day + Night; Nyal Head Cold Fighter Day + Night; Nyal Sinus Relief Day + Night; Nyal Sinus Relief; *Austria*: Digestodoron; *Braz.*: Calman; Calmiplan; Floriny; Pasalix; Pasic; *Canad.*: Rheuma Heilkrauter Tee†; *Cz.*: Antirevmaticky Caj†; Calmonal†; Valofyt Neo†; *Fr.*: Arkophytum†; Arthritisane†; Arthroflorine†; Dolores; Fibromyalgine Fort; Gripponyl†; Phytheol Force†; Santane A$_4$†; Silibiol; *Ger.*: Digestodoron; Dr Wiemanns Rheumatonikum†; *Gr.*: Passiflorine; *Hung.*: Uroherb; *Indon.*: Ositin; *Ital.*: Biothymus DS; Biothymus DS; Body Guard; Donalg; Influ-Zinc; Influpiol C; Linfolipase; Nevril; Reumafort; *Mex.*: Ifupasil; *Pol.*: Enterosol; Infektoten†; Pyrosal; Reumacor; Reumosol; Rutinosal C; Termasil; *S.Afr.*: Digestodoron†; *Singapore*: Mincifit Body Shaper; *Spain*: Passiflorine; *Switz.*: Tisane antirhumatismale; *UK*: Bio-Strath Willow Formula; Gerard House Reumalex; Herbal Pain Relief; St Johnswort Compound; *Ukr.*: Insti (Інсті); Osteoartisi Active (Остеоартизи Актив); Osteoartisi Active Plus (Остеоартизи Актив Плюс); Osteoartisi Max (Остеоартизи Макс); *Venez.*: Passiflorum.

Homoeopathic Preparations. *Canad.*: Homeodel 15†; *Ger.*: Chelidonium comp; *UK*: Digestodoron.

Salol

Benzofenolsalicylaat; Benzophénol Salicylate; Fenylsalicylat; Fenylu salicylan; Fenyylisalisylaatti; Phenyli Salicylas; Phenylis Salicylas; Salicilato de fenilo; Canon.

Phenyl salicylate.

$C_{13}H_{10}O_3$=214.2

CAS — 118-55-8.

ATC — G04BX12.

ATC Vet — QG04BX12.

UNII — 28A37T47QQ.

Pharmacopoeias. In *Pol.*

Profile

Salol is a salicylic acid derivative (see Aspirin, p. 22.2). It was formerly used as an intestinal antiseptic, but effective doses were toxic owing to the liberation of phenol. It is used in

oral preparations containing methenamine for the treatment of lower urinary-tract infections.

Salol has been used topically as a sunscreen.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Aussie Tan Sunstick†; *Turk.*: Sanodolin.

Multi-ingredient Preparations. *Austria*: Carl Baders Divinal; *Belg.*: Borostyrol; *Canad.*: Watkins Settelz†; *Fr.*: Borostyrol; Dermophil Indien; Nisacalm†; *Pol.*: Salotannal†; Urosal; *Rus.*: Besalol (Бесалол); Parodontocide (Пародонтоцид); *Switz.*: Dermophil Indien; Penta†; *Thai.*: Mist Salol Menthol; *Turk.*: Sandolin†; *USA*: Atrosept; Darpaz†; Hyophen; MHP-A; MSP-Blu; Phosphasal; Prosed/DS; UAA; Urelle; Uretron; Urimar-T; Urimax; Uriseptic; Uritact; Uro Blue; Ustell; Uticap; Utira; Utrona-C.

Salsalate *(BAN, USAN, rINN)*

NSC-49171; Salicyl Salicylate; Salicylosalicylic Acid; Salicylsalicylic Acid; Salsalato; Salsalatum; Salysal; Sasapyrine; Сальсалат.

O-(2-Hydroxybenzoyl)salicylic acid.

$C_{14}H_{10}O_5$=258.2

CAS — 552-94-3.

ATC — N02BA06.

ATC Vet — QN02BA06.

UNII — V9MO595C9I.

Pharmacopoeias. In *Chin.* and *US.*

USP 36: (Salsalate). Store in airtight containers.

Uses and Administration

Salsalate is a salicylic acid derivative that has analgesic, anti-inflammatory, and antipyretic actions similar to those of aspirin (see p. 22.3). It is used for pain and fever and also in inflammatory disorders such as osteoarthritis and rheumatoid arthritis. The usual initial oral dose for inflammatory disorders is 3 g daily, given in 2 or 3 divided doses with food; the usual maintenance dose is 2 to 4 g daily, adjusted according to response.

Adverse Effects, Treatment, and Precautions

As for Aspirin, p. 24.2.

The use of aspirin and other acetylated salicylates is generally not recommended for children because of the risk of Reye's syndrome, unless specifically indicated. Some licensed product information extends this precaution to salsalate.

Effects on the gastrointestinal tract. Salsalate is associated with less faecal blood loss than aspirin and has been reported to cause fewer gastric lesions than piroxicam.[1] However, small-bowel ulcerations were reported in a patient when salsalate was added to a regimen of ranitidine and metoclopramide which had been prescribed for duodenal ulcer.[2]

1. Porro GB, *et al.* Salsalate in the treatment of rheumatoid arthritis: a double-blind clinical and gastroscopic trial versus piroxicam: II—endoscopic evaluation. *J Int Med Res* 1989; 17: 320–3.
2. Souza Lima MA. Ulcers of the small bowel associated with stomach-bypassing salicylates. *Arch Intern Med* 1985; 145: 1139.

Effects on the kidneys. A case of minimal-change nephrotic syndrome associated with salsalate use.[1]

1. Vallès M, Tovar JL. Salsalate and minimal-change nephrotic syndrome. *Ann Intern Med* 1987; 107: 116.

Effects on the mouth. Ulcerated lesions on the tongue of a 77-year-old man were caused by taking salsalate tablets incorrectly.[1] The patient had placed the tablets under his tongue rather than swallowing them whole, resulting in prolonged, direct contact with the tongue.

1. Ruscin JM, Astroth JD. Lingual lesions secondary to prolonged contact with salsalate tablets. *Ann Pharmacother* 1998; 32: 1248.

Interactions

For interactions associated with salicylates, see Aspirin, p. 26.3.

Pharmacokinetics

Salsalate is insoluble in acidic gastric fluids but is soluble in the small intestine. One molecule of salsalate is hydrolysed to 2 molecules of salicylic acid; hydrolysis occurs both in the small intestine and after absorption of the parent compound. Additional details on the pharmacokinetics of salicylic acid are provided in aspirin (see p. 27.1). Not all of the absorbed salsalate is hydrolysed and about 13% of salsalate is excreted as glucuronide conjugates in the urine; thus, the amount of salicylic acid available from salsalate is less than that from aspirin when the two drugs are given in equimolar equivalents of salicylic acid.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Amigesic; Argesic-SA; Artha-G; Disalcid; Marthritic; Salflex; Salsitab.

Pharmacopoeial Preparations

USP 36: Salsalate Capsules; Salsalate Tablets.

Sarracenia Purpurea

Pitcher Plant; Саррацения Пурпурная.

UNII — FOP08H143P.

Profile

The roots and leaves of *Sarracenia purpurea* (Sarraceniaceae) have been used in the form of an aqueous distillate, given by local injection, for neuromuscular or neuralgic pain.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Sarapin; *USA*: Sarapin.

Sodium Aurothiomalate *(rINN)*

Aurothiomalate de Sodium; Aurotiomalato de sodio; Gold Sodium Thiomalate; Natrii aurothiomalas; Natriumaurothiomalat; Natrium-aurothiomalát; Natriumaurotiomalaatti; Natriumaurotiomalat; Sodium, aurothiomalate de; Sodium Aurothiosuccinate; Sodu aurotiojabłczan; Sodyum Orotiyomalat; Натрия ауротиомалат.

CAS — 12244-57-4 (anhydrous xNa); 39377-38-3 (disodium monohydrate).

ATC — M01CB01.

ATC Vet — QM01CB01.

UNII — E4768ZY6GM.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Sodium Aurothiomalate). A mixture of monosodium and disodium salts of (2*RS*)-2-(aurosulphanyl)butanedioic acid. It contains 44.5 to 46.0% of gold and 10.8 to 11.8% of sodium, calculated with reference to the dried substance. A fine, pale yellow, hygroscopic powder. Very soluble in water; practically insoluble in alcohol and in dichloromethane. A 10% solution in water has a pH of 6.0 to 7.0. Store in airtight containers.

USP 36: (Gold Sodium Thiomalate). A mixture of the monosodium and disodium salts of gold thiomalic acid [(aurothio)succinic acid] ($C_4H_4AuNaO_4S$ = 368.1 and $C_4H_3AuNa_2O_4S$ = 390.1) that has a gold content of 44.8 to 49.6%, and 49.0 to 52.5% calculated on the dried alcohol-free and glycerol-free material. pH of a 10% solution in water is between 5.8 and 6.5. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Sodium aurothiomalate and other gold compounds are used mainly for their anti-inflammatory effect in active progressive rheumatoid arthritis and progressive juvenile idiopathic arthritis; they may also be beneficial in psoriatic arthritis. (See Rheumatic Disorders, below). They are generally used as disease-modifying antirheumatic drugs (DMARDs) in patients whose symptoms are unresponsive to or inadequately controlled by NSAIDs alone.

Sodium aurothiomalate therapy should only be undertaken where facilities are available to carry out the tests specified under Precautions, p. 131.3.

Sodium aurothiomalate is given by deep intramuscular injection; the area should be gently massaged and, due to the possibility of vasomotor reactions, the patient should remain recumbent for 10 minutes and kept under close observation for 30 minutes after each injection.

The following dosage regimen is recommended in UK licensed product information; US licensed information also suggests a similar regimen. A dose of 10 mg is given in the first week to test the patient's tolerance. If satisfactory, this may be followed by doses of 50 mg at weekly intervals until signs of remission occur; the dosage interval is then increased to 2 weeks until full remission occurs and then increased gradually to every 4 to 6 weeks. Treatment may be continued for up to 5 years after remission.

Improvement may not be seen until a total dose of 300 to 500 mg has been given. If no major improvement has occurred after a total of 1 g has been given (excluding the test dose), therapy should be stopped; alternatively in the absence of toxicity, 100 mg may be given weekly for a further 6 weeks; should there be no response at this dose other forms of therapy should be tried. In patients who relapse while receiving maintenance therapy, the interval between doses should be reduced to one week and should not be increased again until control has been obtained; however, if no response is obtained within 2 months, alternative treatment should be used. It is important to avoid complete relapse since a second course of gold therapy is not usually effective.

For doses in juvenile idiopathic arthritis, see Administration in Children, below.

NSAIDs may be continued when sodium aurothiomalate therapy is begun.

Other gold compounds that have been used include auranofin (p. 27.3), aurothioglucose (p. 28.2), aurotioprol (p. 28.2), gold keratinate (p. 66.3), and sodium aurotiosulfate (p. 132.1).

Reviews.

1. Kean WF, Kean IRL. Clinical pharmacology of gold. *Inflammopharmacology* 2008; 16: 112–25.

Administration in children. For children with progressive juvenile idiopathic arthritis, the suggested initial weekly dose of sodium aurothiomalate is 1 mg/kg by deep intramuscular injection to a maximum of 50 mg weekly (one-tenth to one-fifth of the calculated initial weekly dose may be given for 2 to 3 weeks to test the patient's tolerance). Weekly doses should continue until signs of remission occur, at which point the dosage interval may be increased to fortnightly. With full remission, the dosage interval may again be increased gradually to every 4 weeks. If no improvement has occurred after 20 weeks, the dose could be raised slightly or another antirheumatic drug tried.

In the UK, gold compounds are no longer used to treat juvenile idiopathic arthritis, see Rheumatic Disorders, below.

Asthma. For comment on the use of parenteral gold compounds in the treatment of asthma, see under Auranofin, p. 27.3.

Pemphigus and pemphigoid. Corticosteroids are the main treatment for blistering in pemphigus and pemphigoid (p. 1687.1). Intramuscular gold therapy has been used concomitantly to permit a reduction in corticosteroid dosage; evidence for the corticosteroid-sparing effect is limited[1-3] and such use has waned with the advent of other adjunctive therapy, although it may still be of value in patients unresponsive to other treatment[3] or for those who cannot tolerate corticosteroids or in whom they are contra-indicated.[1] However, it should be noted that there have been isolated reports of pemphigus associated with the use of gold therapy itself.[4]

1. Bystryn J-C, Steinman NM. The adjuvant therapy of pemphigus: an update. *Arch Dermatol* 1996; 132: 203–12.
2. Pandya AG, Dyke C. Treatment of pemphigus with gold. *Arch Dermatol* 1998; 134: 1104–7.
3. Iranzo P, *et al.* Gold: an old drug still working in refractory pemphigus. *J Eur Acad Dermatol Venereol* 2007; 21: 902–7.
4. Lo Schiavo A, *et al.* Pemphigus and chrysotherapy: all that glitters is not gold! *Int J Dermatol* 2008; 47: 645–7.

Rheumatic disorders. Gold compounds are among the disease-modifying antirheumatic drugs (DMARDs) that may be used in the treatment of rheumatoid arthritis (p. 13.2). Although toxicity has now reduced its popularity, intramuscular gold has long been used for the treatment of rheumatoid arthritis[1-4] and was often the standard against which the efficacy of other treatments was measured. Oral gold is less toxic but is also much less effective. It is unclear if there are differences between available intramuscular forms, but a study[5] in 120 patients converted from aurothioglucose to aurothiomalate found that 29 withdrew from the latter drug within 12 months, mostly because of lack of efficacy or the development of adverse effects not seen with the previous drug.

Gold compounds have also been used in the treatment of juvenile idiopathic arthritis (p. 12.1); however, the *BNFC* states that gold is no longer used for this indication. (For suggested doses in juvenile idiopathic arthritis, see Administration in Children, above.)

Gold compounds may also be of benefit in psoriatic arthritis (see under Spondyloarthropathies, p. 14.3).

1. Epstein WV, *et al.* Effect of parenterally administered gold therapy on the course of adult rheumatoid arthritis. *Ann Intern Med* 1991; 114: 437–44.
2. Anonymous. Gold therapy in rheumatoid arthritis. *Lancet* 1991; 338: 19–20.
3. Klinkhoff AV, Teufel A. How low can you go? Use of very low dosage of gold in patients with mucocutaneous reactions. *J Rheumatol* 1995; 22: 1657–9.
4. Clark P, *et al.* Injectable gold for rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews: Issue 4. Chichester: John Wiley; 1997 (accessed 13/11/06).
5. van Roon, EN, *et al.* Parenteral gold preparations: efficacy and safety of therapy after switching from aurothioglucose to aurothiomalate. *J Rheumatol* 2005; 32: 1026–30.

Adverse Effects

Reports show a wide range for the incidence of adverse effects of sodium aurothiomalate. With careful treatment about one-third of patients will have adverse effects; in about 5% of patients these will be severe and sometimes fatal.

The most common effects involve the skin and mucous membranes with pruritus (an early sign of intolerance) and stomatitis (often with a metallic taste) being the most prominent. Rashes with pruritus often occur after 2 to 6 months of intramuscular treatment and may require stopping therapy. Other reactions affecting the skin and mucous membranes include erythema, maculopapular eruptions, erythema multiforme, urticaria, eczema, seborrhoeic dermatitis, lichenoid eruptions, alopecia, exfoliative dermatitis, glossitis, pharyngitis, vaginitis, photosensitivity reactions, and irreversible pigmentation (chrysiasis).

Toxic effects on the blood include eosinophilia, thrombocytopenia, leucopenia, agranulocytosis, and aplastic anaemia.

Effects on the kidneys include mild transient proteinuria which may lead to heavy proteinuria, haematuria, and nephrosis.

Other effects reported include pulmonary fibrosis, dyspnoea, toxic hepatitis, cholestatic jaundice, peripheral neuritis, encephalitis, psychoses, fever, and gastrointestinal disorders including enterocolitis. Gold deposits may occur in the eyes. Vasomotor or nitritoid reactions, with weakness, flushing, palpitations, and syncope, may occur after injection of sodium aurothiomalate. Local irritation may also follow injection.

Sometimes there is an initial exacerbation of the arthritic condition.

Some adverse effects of gold have an immunogenic component.

Reviews.

1. Tozman EC5, Gottlieb NL. Adverse reactions with oral and parenteral gold preparations. *Med Toxicol* 1987; 2: 177–89.
2. van Roon EN, *et al.* Parenteral gold preparations. Efficacy and safety of therapy after switching from aurothioglucose to aurothiomalate. *J Rheumatol* 2005; 32: 1026–30.

Effects on the blood. Blood disorders such as eosinophilia, leucopenia, granulocytopenia, and thrombocytopenia have occurred in patients receiving gold therapy. Eosinophilia has been reported to be the most frequent haematological abnormality.[1] It has been estimated that thrombocytopenia develops in 1 to 3% of patients receiving gold salts.[2]

Fatal consumption coagulopathy occurred in 4 children after the second injection of sodium aurothioglucose or sodium aurothiomalate.[3]

1. Foster RT. Eosinophilia—a marker of gold toxicity. *Can J Hosp Pharm* 1985; 85: 150–1.
2. Coblyn JS, *et al.* Gold-induced thrombocytopenia: a clinical and immunogenetic study of twenty-three patients. *Ann Intern Med* 1981; 95: 178–81.
3. Jacobs JC, *et al.* Consumption coagulopathy after gold therapy for JRA. *J Pediatr* 1984; 105: 674–5.

Effects on the cardiovascular system. Vasomotor or nitritoid reactions associated with gold compounds are usually transient and self-limiting and although they may be mild there have been isolated reports of associated complications such as myocardial infarction, stroke, transient ischaemic attack, and transient monocular visual loss.[1] Most reactions have been associated with sodium aurothiomalate (a reported incidence of 4.7%) but they have also occurred with auranofin and sodium aurothioglucose. Tachyphylaxis usually occurs to the reactions and most patients are able to continue treatment but paradoxically in some the severity increases with repeated doses; 2.8% of patients receiving sodium aurothiomalate may require a change of treatment due to recurrent reactions. It is important to distinguish such reactions from true anaphylactic reactions to gold.[1] Patients taking ACE inhibitors may be at increased risk of nitritoid reactions.[2,3] Transfer of the patient to sodium aurothioglucose or reduction of the dose by 50%, injection in the recumbent position, and observation for 20 minutes have been recommended for the next few injections after a reaction.[2]

1. Ho M, Pullar T. Vasomotor reactions with gold. *Br J Rheumatol* 1997; 36: 154–6.
2. Arthur AB, *et al.* Nitritoid reactions: case reports, review, and recommendations for management. *J Rheumatol* 2001; 28: 2209–12.
3. Nixon J, Pande I. Gold, nitritoid reactions and angiotensin-converting enzyme inhibitors. *Rheumatology (Oxford)* 2006; 45: 118–19.

Effects on the gastrointestinal tract. Enterocolitis due to sodium aurothiomalate has been reported[1] and 27 other cases associated with gold therapy reviewed. For colitis associated with oral gold, see also under Auranofin, p. 28.1.

1. Jackson CW, *et al.* Gold induced enterocolitis. *Gut* 1986; 27: 452–56.

Effects on the immune system. Details of a patient who developed an immune deficiency syndrome that was attributed to gold therapy with sodium aurothiomalate.[1]

1. Haskard DO, Macfarlane D. Adult acquired combined immune deficiency in a patient with rheumatoid arthritis on gold. *J R Soc Med* 1988; 81: 548–9.

Effects on the kidneys. Proteinuria developed in 21 patients while receiving a standard regimen of sodium aurothiomalate.[1] The severity of the proteinuria varied greatly and in 11 it increased for 4 months after treatment was stopped. Eight patients were considered to have developed the nephrotic syndrome. The median duration of proteinuria was 11 months, resolving in all 21 patients when treatment was stopped; at 24 months 3 patients still had proteinuria and it was not until 39 months that all were free of the condition. Renal biopsy indicated several types of kidney damage.

See under Auranofin (p. 28.1) for a comparative incidence of proteinuria in patients receiving sodium aurothiomalate or auranofin.

1. Hall CL, *et al.* The natural course of gold nephropathy: long term study of 21 patients. *BMJ* 1987; 295: 745–8.

Effects on the lungs. 'Gold lung' is the term used to describe symptoms of dyspnoea on exertion, weakness, dry cough, and malaise that are seen rarely in patients on gold treatment.[1] Such symptoms usually develop some weeks or months after starting gold treatment and are associated with cumulative doses of several hundred milligrams although, very rarely, they have been seen with cumulative doses of less than 100 mg.[2] Pulmonary insufficiency may eventually develop and there have been occasional fatalities.[3] The pulmonary lesions usually subside on stopping of gold therapy, although persistent symptoms have been reported.

Nonbacterial thrombotic endocarditis associated with gold-induced pulmonary disease has also been reported.[4] This was considered to be a manifestation of gold-induced immune complex deposition.

1. Sinha A, *et al.* Gold-induced pneumonitis: computed tomography findings in a patient with rheumatoid arthritis. *Rheumatology (Oxford)* 2001; 40: 712–14.
2. Hafejee A, Burke MJ. Acute pneumonitis starting 2 hours after intramuscular gold administration in a patient with rheumatoid arthritis. *Ann Rheum Dis* 2004; 63: 1525–6.
3. Soler MJ, *et al.* Fatal gold-induced pneumonitis. *Rheumatol Int* 2003; 23: 207–10.
4. Kollef MH, *et al.* Nonbacterial thrombotic endocarditis associated with gold induced pulmonary disease. *Ann Intern Med* 1988; 108: 903–4.

Effects on the nails. A 34-year-old woman with severe rheumatoid arthritis receiving intramuscular gold developed yellow thickened toenails and fingernails after 2 years of treatment.[1] Although there was some improvement in nail growth on stopping treatment, some light yellow discoloration in all 20 nails persisted.

1. Roest MAB, Ratnavel R. Yellow nails associated with gold therapy for rheumatoid arthritis. *Br J Dermatol* 2001; 145: 855–6.

Effects on the nervous system. Neurological complications with gold salts are infrequent but may include peripheral neuropathy, Guillain-Barré syndrome, myokymia (repeated involuntary contractions of muscle fibre), and encephalopathy. Some reports[1-6] are given below.

1. Dick DJ, Raman D. The Guillain-Barre syndrome following gold therapy. *Scand J Rheumatol* 1982; 11: 119–20.
2. Schlumpf U, *et al.* Neurologic complications induced by gold treatment. *Arthritis Rheum* 1983; 26: 825–31.
3. Cerinic MM, *et al.* Gold polyneuropathy in juvenile rheumatoid arthritis. *BMJ* 1985; 290: 1042.
4. Cohen M, *et al.* Acute disseminated encephalomyelitis as a complication of treatment with gold. *BMJ* 1985; 290: 1179–80.
5. Dubowitz MN, *et al.* Gold-induced neuroencephalopathy responding to dimercaprol. *Lancet* 1991; 337: 850–1.
6. Garrido JA, *et al.* Mioquimias inducidas por sales de oro. *Neurologia* 1995; 10: 235–7.

Effects on the skin. Chrysiasis is a distinctive pigmentation that develops in light-exposed skin of patients receiving parenteral gold salts. In a study[1] of 31 patients with chrysiasis who were receiving intramuscular sodium aurothiomalate for rheumatoid arthritis, it was noted that visible changes developed above a threshold equivalent to 20 mg/kg gold content. The severity of the pigmentation depended upon cumulative dose. Focal aggregates of gold are deposited in the reticular and papillary dermis with no obvious increase in melanin. The pigmentation is permanent but benign, although the cosmetic effects may cause some patients distress. Prevention of chrysiasis is difficult but avoidance of exposure to sunlight may be helpful.

For reference to pemphigus associated with gold therapy, see Pemphigus under Uses, p. 130.3.

1. Smith RW, *et al.* Chrysiasis revisited: a clinical and pathological study. *Br J Dermatol* 1995; 133: 671–8.

Hypersensitivity. Many adverse effects associated with gold treatment have an immunological basis. Patients with contact allergy to gold may show a flare-up, associated with cytokine release, when given sodium aurothiomalate intramuscularly.[1] Small amounts of nickel have been detected in sodium aurothiomalate injection[2] and in sodium aurothioglucose injection[3] and it has been suggested that gold therapy may also exacerbate or induce hypersensitivity to nickel.[2-4] In some patients contact allergy to gold has been correlated to the presence of dental gold alloys.[5]

Anaphylaxis may occur occasionally[6] but vasomotor or nitritoid reactions (see Effects on the Cardiovascular System, above) may produce similar symptoms.

1. Möller H, *et al.* The flare-up reactions after systemic provocation in contact allergy to nickel and gold. *Contact Dermatitis* 1999; 40: 200–4.
2. Choy EHS, *et al.* Nickel contamination of gold salts: link with gold-induced skin rash. *Br J Rheumatol* 1997; 36: 1054–8.
3. Wijnands MJH, *et al.* Chrysotherapy provoking exacerbation of contact hypersensitivity to nickel. *Lancet* 1990; 335: 867–8.
4. Fulton RA, *et al.* Another hazard of gold therapy? *Ann Rheum Dis* 1982; 41: 100–1.
5. Ahlgren C, *et al.* Contact allergy to gold is correlated to dental gold. *Acta Derm Venereol* 2002; 82: 41–4.
6. Neustadt DH. Another anaphylactic reaction after gold (aurothiomalate) injection. *J Rheumatol* 1995; 22: 190.

Overdosage. A patient who received a total dose of 600 mg of aurotioprol intramuscularly, of which 400 mg was given in less than a week, developed cholestatic hepatotoxicity with cholangitis.[1] This evolved into ductopenia resulting in cholestasis still present 15 months later.

1. Basset C, *et al.* Prolonged cholestasis and ductopenia following gold salt therapy. *Liver Int* 2003; 23: 89–93.

Pancreatitis. It was suggested that pancreatitis reported in a woman receiving gold injections and in a woman on oral gold therapy may have been due to a hypersensitivity reaction.[1]

1. Eisemann AD, *et al.* Pancreatitis and gold treatment of rheumatoid arthritis. *Ann Intern Med* 1989; 111: 860–1.

Treatment of Adverse Effects

The treatment of the adverse effects of gold is usually symptomatic and most effects resolve when gold therapy is stopped. In severe cases a chelator such as dimercaprol (p. 1549.3) may be used.

Precautions

Gold therapy is contra-indicated in exfoliative dermatitis, SLE, necrotising enterocolitis, and pulmonary fibrosis. It should be used with caution in the elderly and in renal or hepatic impairment; use is contra-indicated if renal or hepatic disorders are severe. Patients with a history of haematological disorders or who have previously shown toxicity to heavy metals should not be given gold salts, nor should any severely debilitated patient.

It is recommended that diabetes mellitus and heart failure should be adequately controlled in any patient before gold is given. Patients with a history of urticaria, eczema, or colitis should be treated with caution. Patients with a poor sulfoxidation status may be more susceptible to adverse effects of sodium aurothiomalate.

Use of gold compounds with other therapy capable of inducing blood disorders should be undertaken with caution, if at all.

Because of the risk of vasomotor reactions, patients should remain recumbent for about 10 minutes after each injection.

Urine should be tested for albumin before each injection and a full blood count carried out. Patients receiving gold compounds either orally or parenterally should be warned to report the appearance of sore throat or tongue, metallic taste, pruritus, rash, buccal ulceration, easy bruising, purpura, epistaxis, bleeding gums, unexplained bleeding, menorrhagia, pyrexia, indigestion, diarrhoea, or unexplained malaise. The development of breathlessness or cough should also be reported. Effects such as eosinophilia, proteinuria, pruritus, and rash arising during gold treatment should be allowed to resolve before therapy is continued.

Licensed product information recommends that annual chest X-rays should be carried out.

Breast feeding. The last available guidance from the American Academy of Pediatrics considered that gold compounds are usually compatible with breast feeding.[1]

Gold has been detected in breast milk[2-4] and found bound to the red blood cells of breast-fed babies.[2,3] In a report[4] of a breast-fed infant it was calculated that the weight-adjusted dose of gold received by the infant exceeded that received by the mother although the infant showed no ill-effects during 100 days of breast feeding and developed normally thereafter. Nonetheless, because of the relatively high exposure it was recommended that breast-fed infants should be closely monitored.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 13/11/06)

2. Blau SP. Metabolism of gold during lactation. *Arthritis Rheum* 1973; 16: 777–8.
3. Needs CJ, Brooks PM. Antirheumatic medication during lactation. *Br J Rheumatol* 1985; 24: 291–7.
4. Bennett PN, *et al.* Use of sodium aurothiomalate during lactation. *Br J Clin Pharmacol* 1990; 29: 777–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sodium aurothiomalate as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 20/07/11)

Pregnancy. Based on evidence from *animal* studies and a report[1] of malformation in a child born to a woman treated with sodium aurothiomalate it has been suggested that gold might possibly have teratogenic effects. Indeed, licensed product information advises that sodium aurothiomalate should be avoided during pregnancy. However, others[2] consider that gold may be a suitable treatment option in women planning a pregnancy. Over a 14-year period, 20 pregnancies in 14 women taking gold were followed in an arthritis centre; 5 miscarriages and 16 healthy babies including one set of twins were noted. The majority of women stopped their gold treatment on discovering they were pregnant although 4 continued their treatment throughout. The authors of this report also pointed out that published literature supported the use of gold in pregnant women.

1. Rogers JG, *et al.* Possible teratogenic effects of gold. *Aust Paediatr J* 1980; 16: 194–5.
2. Almarzouqi M, *et al.* Gold therapy in women planning pregnancy: outcomes in one center. *J Rheumatol* 2007; 34: 1827–31.

Interactions

There is an increased risk of toxicity when gold compounds are given with other nephrotoxic, hepatotoxic, or myelosuppressive drugs. Use of gold compounds with penicillamine may increase the risk of haematologic or renal adverse reactions.

ACE inhibitors. For a possible increased risk of nitritoid reactions when gold compounds are given to patients taking ACE inhibitors, see Effects on the Cardiovascular System, p. 131.1.

Penicillamine. For a discussion on the effects of previous therapy with gold salts affecting penicillamine toxicity, see p. 1570.2.

Pharmacokinetics

Sodium aurothiomalate is absorbed readily after intramuscular injection and 85 to 95% becomes bound to plasma proteins. With doses of 50 mg weekly a steady-state serum concentration of gold of about 3 to 5 micrograms/mL occurs in 5 to 8 weeks. It is widely distributed to body tissues and fluids, including synovial fluid, and accumulates in the body.

The serum half-life of gold is about 5 to 6 days but this increases after successive doses and after a course of treatment, gold may be found in the urine for up to 1 year or more owing to its presence in deep body compartments. Sodium aurothiomalate is mainly excreted in the urine, with smaller amounts in the faeces.

Gold has been detected in the fetus when sodium aurothiomalate was given to the mother. Gold is distributed into breast milk.

Reviews.

1. Blocka KLN, *et al.* Clinical pharmacokinetics of oral and injectable gold compounds. *Clin Pharmacokinet* 1986; 11: 133–43.
2. Tett SE. Clinical pharmacokinetics of slow-acting antirheumatic drugs. *Clin Pharmacokinet* 1993; 25: 392–407.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Myocrisin; *Canad.*: Myochrysine; *Cz.*: Tauredon; *Denm.*: Myocrisin†; *Fin.*: Myocrisin; *Ger.*: Tauredon; *Gr.*: Miocrin; Tauredon; *India*: Aurocris; *Irl.*: Myocrisin†; *Neth.*: Tauredon; *NZ*: Myocrisin; *Port.*: Tauredon; *Singapore*: Miocrin; *Spain*: Miocrin†; *Swed.*: Myocrisin; *Switz.*: Tauredon; *Thal.*: Myocrisin; *UK*: Myocrisin; *Ukr.*: Tauredon (Тауредон)†; *USA*: Aurolate†; Myochrysine†.

Pharmacopoeial Preparations
BP 2014: Sodium Aurothiomalate Injection;
USP 36: Gold Sodium Thiomalate Injection.

Sodium Aurotiosulfate *(rINN)*

Aurotiosulfate de Sodium; Aurotiosulfato de sodio; Gold Sodium Thiosulphate; Natrii Aurotiosulfas; Natrii Aurotiosulphas; Natriumaurotiosulfaatti; Natriumaurotiosulfat; Sodium Aurothiosulphate; Sodium Dithiosulfatoaurate; Натрия Ауротиосульфат.

$Na_3Au(S_2O_3)_2.2H_2O$=526.2

CAS — 10233-88-2 (anhydrous sodium aurotiosulfate); 10210-36-3 (sodium aurotiosulfate dihydrate).

ATC — M01CB02.

ATC Vet — QM01CB02.

UNII — CKS1YQ9W1J (sodium aurotiosulfate dihydrate); 6GKU52ZCI0 (anhydrous sodium aurotiosulfate).

Profile

Sodium aurotiosulfate has a gold content of about 37%. It has similar actions and uses to those of sodium aurothiomalate (p. 130.2). It is given by intramuscular injection for the treatment of rheumatoid arthritis (p. 13.2) in a usual dose of 56.1 mg every 5 to 7 days.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Crytion; *Chile*: Crytioro†; *Ital.*: Fosfocrisolo.

Sodium Gentisate *(rINN)*

Gentisate de Sodium; Gentisato de sodio; Gentisato Sodico; Natrii Gentisas; Натрия Гентизат.

Sodium 2,5-dihydroxybenzoate dihydrate.

$C_7H_5NaO_4.2H_2O$=212.1

CAS — 490-79-9 (gentisic acid); 4955-90-2 (anhydrous sodium gentisate).

UNII — DX2PUD5H82 (anhydrous sodium gentisate); Y75S75SFI3 (sodium gentisate hydrate).

Pharmacopoeias. In *Fr.*

Profile

Sodium gentisate has been used as an analgesic in the treatment of musculoskeletal and joint disorders. It is also used as a preservative.

Sodium Salicylate

Natrii salicylas; Natrio salicilatas; Natriumsalicylat; Natriumsalisylaatti; Nátrium-szalicilát; Salicilato sódico; Salicylan sodný; Sodium salicylate de; Sodu salicylan; Sodyum Salisilat; Салицилат Натрия.

Sodium 2-hydroxybenzoate.

$C_7H_5NaO_3$=160.1

CAS — 54-21-7.

ATC — N02BA04.

ATC Vet — QN02BA04.

UNII — WIQ1H85SYP.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Sodium Salicylate). Colourless small crystals or shiny flakes, or white or almost white, crystalline powder. Freely soluble in water; sparingly soluble in alcohol. Store in airtight containers. Protect from light.

USP 36: (Sodium Salicylate). Amorphous or microcrystalline powder or scales. It is colourless or has not more than a faint pink tinge. It is odourless or has a faint characteristic odour. A freshly made 10% solution in water is neutral or acid to litmus. Freely (and slowly) soluble in water and in glycerol; very soluble in boiling water and in boiling alcohol; slowly soluble in alcohol. Protect from light.

Uses and Administration

Sodium salicylate is a salicylic acid derivative that has analgesic, anti-inflammatory, and antipyretic actions similar to those of aspirin (p. 22.3). Sodium salicylate 1 g is equivalent to about 1.1 g of aspirin. It is used in the treatment of pain, fever, and in rheumatic disorders such as osteoarthritis and rheumatoid arthritis. The usual oral dose of sodium salicylate for pain or fever is 325 to 650 mg every four hours as required. The oral dose for rheumatic disorders is 3.6 to 5.4 g daily in divided doses. Sodium salicylate has also been used in the symptomatic treatment of rheumatic fever but its high sodium content may cause problems in patients with cardiac complications.

Sodium salicylate has also been given by intravenous infusion and topically.

Adverse Effects, Treatment, and Precautions

As for Aspirin, p. 24.2.

Although sodium salicylate has been used in the treatment of rheumatic fever, its high sodium content may cause problems in patients with cardiac complications.

The use of aspirin and other acetylated salicylates is generally not recommended for children because of the risk of Reye's syndrome, unless specifically indicated. Some licensed product information extends this precaution to sodium salicylate.

Effects on the eyes. Retinal haemorrhages were reported in a 60-year-old woman taking oral sodium salicylate 6 g daily for 2 months and in a 10-year-old girl taking oral sodium salicylate 4 g daily for 40 days.[1] In both cases the haemorrhages gradually resolved after the treatment was stopped.

1. Mortada A, Abboud L. Retinal haemorrhages after prolonged use of salicylates. *Br J Ophthalmol* 1973; 57: 199–200.

Interactions

For interactions associated with salicylates, see Aspirin, p. 26.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Dodds†; Saliject; *Turk.*: Enter-Sal; *UK*: Jackson's Pain & Fever; *USA*: Avosil.

Multi-ingredient Preparations. *Braz.*: A Saude da Mulher; A Saude da Mulher; *Canad.*: Formule L2; Plax†; *Chile*: Eucerin Shampoo Anticaspa†; Eucerin Shampoo para el Tratamiento de la Caspa; Pectokast; *Fr.*: Brulex; *Hong Kong*: Gly Thymol; Glycerine Thymol Co†; *Irl.*: TCP; *Mon.*: Glyco-Thymoline; *S.Afr.*: Colphen†; Doans Backache Pills†; Ilvico†; TCP†; *UK*: Antiseptic Mouthwash; Doans Backache Pills; TCP; TCP; *USA*: Cystex; Scot-Tussin Original 5-Action; Tussirex.

Homoeopathic Preparations. *Canad.*: Urarthone†; *Fr.*: Euphorbium Complexe No 88; Urarthone.

Pharmacopoeial Preparations
USP 36: Sodium Salicylate Tablets.

Sufentanil *(BAN, rINN)* ⊗

R-30730; Sufentanilili; Sufentanilis; Sufentanilo; Sufentanilum; Szufentanil; Суфентанил.

N-[4-(Methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidyl]propionanilide.

$C_{22}H_{30}N_2O_2S$=386.6

CAS — 56030-54-7.

ATC — N01AH03.

ATC Vet — QN01AH03.

UNII — AFE2YW0IIZ.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Sufentanil). A white or almost white powder. Practically insoluble in water; freely soluble in alcohol and in methyl alcohol. Protect from light.

Sufentanil Citrate *(BANM, USAN, rINNM)* ⊗

Citrato de sufentanilo; R-33800; Sufentaniilisitraatti; Sufentanil citrát; Sufentanil, Citrate de; Sufentanil Sitrat; Sufentanilcitrat; Sufentanili citras; Sufentanilio citratas; Sufentanilo, citrato de; Szufentanil-citrát; Суфентанила Цитрат.

N-[4-(Methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidyl]propionanilide citrate.

$C_{22}H_{30}N_2O_2S.C_6H_8O_7$=578.7

CAS — 60561-17-3.

ATC — N01AH03.

ATC Vet — QN01AH03.

UNII — S9ZFX8403R.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Sufentanil Citrate). A white or almost white powder. Soluble in water and in alcohol; freely soluble in methyl alcohol. Protect from light.

USP 36: (Sufentanil Citrate). A white powder. Soluble in water; sparingly soluble in alcohol, in acetone, and in chloroform; freely soluble in methyl alcohol. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Stability. Sufentanil (as the citrate) diluted to 50 micrograms/mL with sodium chloride 0.9% remained stable for at least 14 days when stored at room temperature in PVC reservoirs for portable patient-controlled systems.[1]

1. Chapalain-Pargarde S, *et al.* Microbiological and physicochemical stability of fentanyl and sufentanil solutions for patient-controlled delivery systems. *J Pain Symptom Manage* 2006; 32: 90–7.

Uses and Administration

Sufentanil, a phenylpiperidine derivative, is an opioid analgesic (p. 108.1) related to fentanyl (p. 60.2). It is highly lipid-soluble and more potent than fentanyl. Sufentanil is used as an analgesic adjunct in anaesthesia and as a primary anaesthetic in procedures requiring assisted ventilation. It has a rapid onset and recovery is considered to be more

rapid than with fentanyl. It is also used as an analgesic in the management of postoperative pain and labour pain.

Sufentanil is given as the citrate either intravenously by slow injection or as an infusion, or epidurally. Doses are expressed as the base; sufentanil citrate 15 micrograms is equivalent to about 10 micrograms of sufentanil. Lower initial doses are advised in the elderly and debilitated patients. For obese patients more than 20% above ideal body-weight the dosage of sufentanil should be determined on the basis of their lean body-weight. For details of doses in children, see below.

In all patients supplementary maintenance doses should be based on individual response and length of procedure. Doses of up to the equivalent of 8 micrograms/kg of sufentanil produce profound analgesia. Higher doses produce a deep level of anaesthesia but are associated with prolonged respiratory depression and assisted ventilation may be required in the postoperative period.

When used as an analgesic **adjunct to anaesthesia** with nitrous oxide and oxygen for surgical procedures lasting up to 8 hours, the total *intravenous* dosage should not exceed 1 microgram/kg per hour. It is usual to give about 75% of the dose before intubation followed as necessary during surgery by additional injections of 10 to 50 micrograms or by a suitable continuous or intermittent infusion given so that the total hourly dose is not exceeded. Thus, for an operation lasting 1 to 2 hours the total dose would be 1 to 2 micrograms/kg with 0.75 to 1.5 micrograms/kg being given before intubation.

When used as a **primary anaesthetic** in major surgery *intravenous* doses of 8 to 30 micrograms/kg are given with 100% oxygen; doses of 25 to 30 micrograms/kg block sympathetic response including catecholamine release and are indicated in procedures such as cardiovascular surgery or neurosurgery. Anaesthesia may be maintained by additional injections of 0.5 to 10 micrograms/kg or by a suitable continuous or intermittent infusion given so that the total dosage for the procedure does not exceed 30 micrograms/kg.

In postoperative **pain**, sufentanil is given *epidurally* in an initial dose of 30 to 60 micrograms, which should provide analgesia for 4 to 6 hours. Additional boluses of up to 25 micrograms may be given at intervals of not less than 1 hour if necessary.

Sufentanil is also given *epidurally* for the relief of pain during labour and delivery. Recommended doses are 10 to 15 micrograms given with 10 mL of bupivacaine 0.125% (or its equivalent) with or without adrenaline; the dose may be repeated twice at not less than one-hour intervals until delivery. The total dose of sufentanil should not exceed 30 micrograms.

Reviews.

1. Monk JP, *et al.* Sufentanil: a review of its pharmacological properties and therapeutic use. *Drugs* 1988; 36: 286–313.
2. Clotz MA, Nahata MC. Clinical uses of fentanyl, sufentanil, and alfentanil. *Clin Pharm* 1991; 10: 581–93.
3. Savoia G, *et al.* Sufentanil: an overview of its use for acute pain management. *Minerva Anestesiol* 2001; 67 (suppl 1): 206–16.

Administration. Sufentanil is usually given intravenously, but the epidural route is also used (see below). Intranasal (see Anaesthesia, Pain, and Sedation, all below), intrathecal (see below), and sublingual use (see Pain, below) have also been tried.

EPIDURAL In a laboratory assessment of epidural sufentanil in healthy subjects,[1] a dose of 50 micrograms produced analgesia for 2 to 3 hours; analgesia was intensified and prolonged, and respiratory and other adverse effects, especially drowsiness, were reduced by the addition of adrenaline. Epidural sufentanil or fentanyl provided effective postoperative analgesia following caesarean section with comparable adverse effect profiles.[2] Sufentanil doses of 20 and 30 micrograms showed equivalent efficacy and provided greater analgesia for a longer duration than a dose of 10 micrograms. Addition of sufentanil to local anaesthetics such as bupivacaine during labour has considerably reduced the local anaesthetic requirements[3] and improved the quality of epidural analgesia.[4] Combination of sufentanil with a local anaesthetic (ropivacaine or bupivacaine) has been used for patient-controlled epidural analgesia (PCEA),[5-9] although an early study suggested that PCEA with sufentanil alone had little advantage over patient-controlled analgesia with intravenous morphine.[10]

Effective analgesia has been achieved in children with epidural sufentanil.[11]

1. Klepper ID, *et al.* Analgesic and respiratory effects of extradural sufentanil in volunteers and the influence of adrenaline as an adjuvant. *Br J Anaesth* 1987; 59: 1147–56.
2. Grass JA, *et al.* A randomized, double-blind, dose-response comparison of epidural fentanyl versus sufentanil analgesia after cesarean section. *Anesth Analg* 1997; 85: 365–71.
3. Buyse I, *et al.* Effect of sufentanil on minimum local analgesic concentrations of epidural bupivacaine, ropivacaine and levobupivacaine in nullipara in early labour. *Int J Obstet Anesth* 2007; 16: 22–8.
4. Reynolds F. Extradural opioids in labour. *Br J Anaesth* 1989; 63: 251–3.
5. Gogarten W, *et al.* A multicentre trial comparing different concentrations of ropivacaine plus sufentanil with bupivacaine plus sufentanil for patient-controlled epidural analgesia in labour. *Eur J Anaesthesiol* 2004; 21: 38–45.
6. Boselli E, *et al.* Background infusion is not beneficial during labor patient-controlled analgesia with 0.1% ropivacaine plus 0.5 microg/ml sufentanil. *Anesthesiology* 2004; 100: 968–72.
7. Bremerich DH, *et al.* Comparison of continuous background infusion plus demand dose and demand-only parturient-controlled epidural analgesia (PCEA) using ropivacaine combined with sufentanil for labor and delivery. *Int J Obstet Anesth* 2005; 14: 114–20.
8. Missant C, *et al.* Patient-controlled epidural analgesia following combined spinal-epidural analgesia in labour: the effects of adding a continuous epidural infusion. *Anaesth Intensive Care* 2005; 33: 452–6.
9. Schenk MR, *et al.* Postoperative analgesia after major spine surgery: patient-controlled epidural analgesia versus patient-controlled intravenous analgesia. *Anesth Analg* 2006; 103: 1311–17.
10. Grass JA, *et al.* Patient-controlled analgesia after cesarean delivery: epidural sufentanil versus intravenous morphine. *Reg Anesth* 1994; 19: 90–7.
11. Benlabed M, *et al.* Analgesia and ventilatory response to CO_2 following epidural sufentanil in children. *Anesthesiology* 1987; 67: 948–51.

INTRATHECAL Sufentanil, alone or in combination, has been given intrathecally for labour pain: a combination of sufentanil, bupivacaine, and adrenaline given intrathecally provided excellent analgesia during labour and had a more rapid onset, a longer duration of action, and reduced local anaesthetic requirements compared with epidural administration.[1] Intrathecal sufentanil and bupivacaine provided shorter duration of analgesia when given during the advanced stages of labour compared with early labour.[2] There has been some concern about the effect of intrathecal use on fetal heart rate. An early study[3] found no significant difference in the heart rate when intrathecal sufentanil was compared with epidural bupivacaine; however, a more recent study[4] reported that high-dose intrathecal sufentanil (7.5 micrograms) when given on its own increased the risk of fetal heart rate abnormalities when compared with low-dose intrathecal sufentanil (1.5 micrograms) given with bupivacaine and adrenaline. Nonetheless, there was no evidence of a difference in adverse neonatal outcomes between the groups.

A small study in patients undergoing hip replacement found that intrathecal sufentanil 7.5 micrograms produced better and longer lasting analgesia than the same dose given intravenously.[5]

Intrathecal sufentanil has also been tried in the treatment of chronic pain.[6]

1. Kartawiadi SL, *et al.* Spinal analgesia during labor with low-dose bupivacaine, sufentanil, and epinephrine: a comparison with epidural analgesia. *Reg Anesth* 1996; 21: 191–6.
2. Visconi CM, *et al.* Duration of intrathecal labor analgesia: early versus advanced labor. *Anesth Analg* 1997; 84: 1108–12.
3. Nielsen PE, *et al.* Fetal heart rate changes after intrathecal sufentanil or epidural bupivacaine for labor analgesia: incidence and clinical significance. *Anesth Analg* 1996; 83: 742–6.
4. Van de Velde M, *et al.* Intrathecal sufentanil and fetal heart rate abnormalities: a double-blind, double placebo-controlled trial comparing two forms of combined spinal epidural analgesia with epidural analgesia in labor. *Anesth Analg* 2004; 98: 1153–9.
5. Fournier R, *et al.* Intrathecal sufentanil is more potent than intravenous for postoperative analgesia after total-hip replacement. *Reg Anesth Pain Med* 2005; 30: 249–54.
6. Waara-Wolleat KL, *et al.* A review of intrathecal fentanyl and sufentanil for the treatment of chronic pain. *Pain Med* 2006; 7: 251–9.

Administration in children. Although experience of paediatric use is limited, sufentanil citrate is licensed for the induction and maintenance of anaesthesia in children under 12 years of age undergoing cardiovascular surgery. Intravenous doses of 10 to 25 micrograms/kg are given with 100% oxygen with maintenance doses of up to 25 to 50 micrograms.

Anaesthesia. Sufentanil, like fentanyl (p. 61.2), appears to produce fewer circulatory changes than morphine, which may offer some advantages in cardiovascular surgery.

Premedication with sufentanil given intranasally has been tried in children[1-3] and in adults.[4]

Sufentanil is one of the opioids that have been used with a neuroleptic to produce *neuroleptanalgesia*.

1. Henderson JM, *et al.* Pre-induction of sufentanil. *Anesthesiology* 1988; 68: 671–5.
2. Zedie N, *et al.* Comparison of intranasal midazolam and sufentanil premedication in pediatric outpatients. *Clin Pharmacol Ther* 1996; 59: 341–8.
3. Bayrak F, *et al.* A comparison of oral midazolam, oral tramadol, and intranasal sufentanil premedication in pediatric patients. *J Opioid Manag* 2007; 3: 74–8.
4. Helmers JHJH, *et al.* Comparison of intravenous and intranasal sufentanil absorption and sedation. *Can J Anaesth* 1989; 36: 494–7.

Pain. For the epidural or intrathecal use of sufentanil in the management of pain, see above. Intranasal sufentanil has been tried for breakthrough cancer pain[1] and postoperative analgesia.[2] It has also been tried sublingually in the management of breakthrough cancer pain.[3]

1. Jackson K, *et al.* Pilot dose finding study of intranasal sufentanil for breakthrough and incident cancer-associated pain. *J Pain Symptom Manage* 2002; 23: 450–2.
2. Mathieu N, *et al.* Intranasal sufentanil is effective for postoperative analgesia in adults. *Can J Anesth* 2006; 53: 60–6.
3. Gardner-Nix J. Oral transmucosal fentanyl and sufentanil for incident pain. *J Pain Symptom Manage* 2001; 22: 627–30.

Sedation. Some references[1-3] to the use of sufentanil for sedation. See also Anaesthesia, above.

1. Bates BA, *et al.* A comparison of intranasal sufentanil and midazolam to intramuscular meperidine, promethazine, and chlorpromazine for conscious sedation in children. *Ann Emerg Med* 1994; 24: 646–51.
2. Lefrant JY, *et al.* Sufentanil short duration infusion for postoperative sedation in critically ill patients. *Br J Anaesth* 1995; 74 (suppl 1): 114.
3. Kinirons BP, *et al.* Sedation with sufentanil and midazolam decreases pain in patients undergoing upper limb surgery under multiple nerve block. *Anesth Analg* 2000; 90: 1118–21.

Dependence and Withdrawal

As for Opioid Analgesics, p. 109.1.

Adverse Effects, Treatment, and Precautions

As for Opioid Analgesics in general, p. 110.1 and Fentanyl, p. 62.1.

Breast feeding. Concentrations of sufentanil were similar in colostrum and serum in 7 women given sufentanil by continuous epidural infusion during the first postoperative day after caesarean section. In the light of its poor oral availability such an amount was not considered to be a hazard to the breast-fed infant, and a maternal dose of 5 micrograms/hour epidurally was considered to be safe for such infants.[1]

1. Ausseur A, *et al.* Continuous epidural infusion of sufentanil after caesarean section: concentration in breast milk. *Br J Anaesth* 1994; 72 (suppl 1): 106.

Effects on the cardiovascular system. For a reference to the effects of sufentanil on histamine release compared with some other opioids, see under Pethidine, p. 122.3.

Effects on the nervous system. Tonic-clonic movements or seizures have been seen in a few patients receiving sufentanil.[1] There was no evidence of cortical seizure activity in a patient whose EEG was recorded,[2] suggesting that the myoclonus was not a convulsion or seizure.

1. Zaccara G, *et al.* Clinical features, pathogenesis and management of drug-induced seizures. *Drug Safety* 1990; 5: 109–51.
2. Bowdle TA. Myoclonus following sufentanil without EEG seizure activity. *Anesthesiology* 1987; 67: 593–5.

Effects on the respiratory system. Sufentanil, like other opioid agonists, causes dose-related respiratory depression. There have been reports of significant respiratory depression associated with chest wall rigidity in the early postoperative period after anaesthesia with intravenous sufentanil.[1,2] Respiratory depression has also been reported after intrathecal sufentanil for postoperative analgesia[3] and labour pain.[4] A retrospective chart review[3] of a 6-year period, during which 4870 patients received intrathecal sufentanil for the management of labour pain, found that the case above was the only one of respiratory arrest reported in the group.

1. Goldberg M, *et al.* Postoperative rigidity following sufentanil administration. *Anesthesiology* 1985; 63: 199–201.
2. Chang J, Fish KJ. Acute respiratory arrest and rigidity after anesthesia with sufentanil: a case report. *Anesthesiology* 1985; 63: 710–11.
3. Fournier R, *et al.* Respiratory depression after 5 microgramsrams of intrathecal sufentanil. *Anesth Analg* 1998; 87: 1377–8.
4. Ferouz F, *et al.* Risk of respiratory arrest after intrathecal sufentanil. *Anesth Analg* 1997; 85: 1088–90.

The elderly. The pharmacokinetics of sufentanil in elderly patients have been variable in different studies, but a review[1] considered that there had been no evidence overall for differences between the elderly and younger adults. Nevertheless, as with fentanyl, reduced initial doses have been advised in the elderly.

1. Monk JP, *et al.* Sufentanil: a review of its pharmacological properties and therapeutic use. *Drugs* 1988; 36: 286–313.

Handling. Avoid contact with skin and the inhalation of particles of sufentanil citrate.

Obesity. The elimination half-life and volume of distribution of sufentanil were increased in obese subjects.[1,2] Licensed product information recommends that for obese patients more than 20% above ideal body-weight the dosage of sufentanil should be determined on the basis of their lean body-weight.

1. Schwartz AE, *et al.* Pharmacokinetics of sufentanil in the obese. *Anesthesiology* 1986; 65 (suppl 3A): A562.
2. Schwartz AE, *et al.* Pharmacokinetics of sufentanil in obese patients. *Anesth Analg* 1991; 73: 790–3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sufentanil as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/10/11)

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

Benzodiazepines. For the effects of using opioids such as sufentanil with benzodiazepines, see Analgesics under Interactions of Diazepam, p. 1068.1.

Pharmacokinetics

After parenteral doses sufentanil citrate has a rapid onset and short duration of action. The terminal elimination half-life of sufentanil is about 2.5 hours. It is extensively bound to plasma proteins (about 90%). It is metabolised in the liver and small intestine by *N*-dealkylation and *O*-demethylation and the inactive metabolites are excreted in the urine and faeces. About 80% of a dose is excreted within 24 hours and 2% is eliminated as unchanged drug. Sufentanil crosses the placenta and is distributed into breast milk.

The pharmacokinetics of sufentanil have been reviewed.[1,2] Sufentanil is very lipid-soluble. Like alfentanil it is highly bound to plasma proteins, mainly to α_1-acid glycoprotein. The elimination half-life lies between that of alfentanil and fentanyl. The manufacturers of sufentanil have given values for a three-compartment pharmacokinetic model with a distribution half-life of 1.4 minutes, a redistribution half-life of 17.1 minutes, and an elimination half-life of 164 minutes. Accumulation may be relatively limited when compared with fentanyl. In practice the pharmacokinetics of sufentanil may vary according to the age and condition of the patient and the procedures undertaken. For example, the elimination half-life of sufentanil has been reported to be longer in patients undergoing cardiac surgery (595 minutes),[3] in hyperventilated patients (232 minutes),[4] in those undergoing abdominal aortic surgery (more than 12 hours),[5] and in ventilated intensive care patients under sedation (25.5 hours).[6]

1. Monk JP, *et al.* Sufentanil: a review of its pharmacological properties and therapeutic use. *Drugs* 1988; 36: 286–313.
2. Scholz J, *et al.* Clinical pharmacokinetics of alfentanil, fentanyl and sufentanil: an update. *Clin Pharmacokinet* 1996; 31: 275–92.
3. Howie MB, *et al.* Serum concentrations of sufentanil and fentanyl in the post-operative course in cardiac surgery patients. *Anesthesiology* 1984; 61: A131.
4. Schwartz AE, *et al.* Pharmacokinetics of sufentanil in neurosurgical patients undergoing hyperventilation. *Br J Anaesth* 1989; 63: 385–8.
5. Hudson RJ, *et al.* Pharmacokinetics of sufentanil in patients undergoing abdominal aortic surgery. *Anesthesiology* 1989; 70: 426–31.
6. Ethuin P, *et al.* Pharmacokinetics of long-term sufentanil infusion for sedation in ICU patients. *Intensive Care Med* 2003; 29: 1916–20.

Administration. References to the pharmacokinetics of sufentanil given epidurally,[1,2] intrathecally,[1] or transdermally.[3]

1. Ionescu TI, *et al.* Pharmacokinetic study of extradural and intrathecal sufentanil anaesthesia for major surgery. *Br J Anaesth* 1991; 66: 458–64.
2. Hansdottir V, *et al.* The cerebrospinal fluid and plasma pharmacokinetics of sufentanil after thoracic or lumbar epidural administration. *Anesth Analg* 1995; 80: 724–9.
3. Sebel PS, *et al.* Transdermal absorption of fentanyl and sufentanil in man. *Eur J Clin Pharmacol* 1987; 32: 529–31.

Children. Neonates (up to 1 month old) had a significantly lower plasma clearance rate and greater elimination half-life than infants (1 month to 2 years), children, and adolescents.[1] Others[2] have found that infants and small children (1 month to 3 years) with cardiac disease had higher clearance rates and shorter elimination half-lives than reported for adults. Older children (aged 2 to 8 years) with no history of cardiac, renal, or hepatic disease have also been noted to have shorter elimination half-lives and higher clearance rates than adults.[3]

1. Greeley WJ, *et al.* Sufentanil pharmacokinetics in pediatric cardiovascular patients. *Anesth Analg* 1987; 66: 1067–72.
2. Davis PJ, *et al.* Pharmacodynamics and pharmacokinetics of high-dose sufentanil in infants and children undergoing cardiac surgery. *Anesth Analg* 1987; 66: 203–8.
3. Guay J, *et al.* Pharmacokinetics of sufentanil in normal children. *Can J Anaesth* 1992; 39: 14–20.

Hepatic impairment. Because of the efficient hepatic extraction and clearance of sufentanil[1] liver dysfunction might be expected to affect its pharmacokinetics. However, elimination kinetics and plasma protein binding were found to be similar in cirrhotic and non-cirrhotic patients after a single dose of sufentanil.[2]

1. Schedewie H, *et al.* Sufentanil and fentanyl hepatic extraction rate and clearance in obese patients undergoing gastroplasty. *Clin Pharmacol Ther* 1988; 43: 132.
2. Chauvin M, *et al.* Sufentanil pharmacokinetics in patients with cirrhosis. *Anesth Analg* 1989; 68: 1–4.

Renal impairment. The pharmacokinetics of sufentanil were reported[1] to be unaffected in patients with chronic renal failure, although elevated plasma concentrations of sufentanil have been noted[2] in one such patient.

1. Sear JW. Sufentanil disposition in patients undergoing renal transplantation: influence of choice of kinetic model. *Br J Anaesth* 1989; 63: 60–7.
2. Wiggum DC, *et al.* Postoperative respiratory depression and elevated sufentanil levels in a patient with chronic renal failure. *Anesthesiology* 1985; 63: 708–10.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Sufenta; *Austria*: Sufenta; *Belg.*: Sufenta; *Braz.*: Biosufenil; Fastfen; Sufenta; *Chile*: Sufenta; *China*: Su Fen Ni (舒芬尼); *Cz.*: Sufenta; *Denm.*: Sufenta; *Fin.*: Sufenta; *Fr.*: Sufenta; *Ger.*: Sufenta; *Gr.*: Fentamorf; *Indon.*: Sufenta; *Ital.*: Disufen; Fentatienil; *Neth.*: Sufenta; *Norw.*: Sufenta; *Port.*: Sufenta; *S.Afr.*: Sufenta; *Swed.*: Sufenta; *Switz.*: Sufenta; *Turk.*: Sufenta; *USA*: Sufenta.

Pharmacopoeial Preparations
USP 36: Sufentanil Citrate Injection.

Sulindac *(BAN, USAN, rINN)*

MK-231; Sulindaakki; Sulindaco; Sulindacum; Sulindak; Szulindak; Сулиндак.

(*Z*)-[5-Fluoro-2-methyl-1-(4-methylsulphinylbenzylidene) inden-3-yl]acetic acid.

$C_{20}H_{17}FO_3S$=356.4

CAS — 38194-50-2.

ATC — M01AB02.

ATC Vet — QM01AB02.

UNII — 184SN58VUH.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Sulindac). A yellow, polymorphic, crystalline powder. Very slightly soluble in water and in ether; sparingly soluble in alcohol; soluble in dichloromethane; dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 36: (Sulindac). A yellow, odourless or practically odourless, crystalline powder. Practically insoluble in water and in hexane; slightly soluble in alcohol, in acetone, in chloroform, and in methyl alcohol; very slightly soluble in ethyl acetate and in isopropyl alcohol.

Uses and Administration

Sulindac is an NSAID (p. 102.3) structurally related to indometacin (p. 71.3); its activity appears to be due to its sulfide metabolite. Sulindac is used in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis, and also in the short-term management of acute gout and peri-articular conditions such as bursitis and tendinitis. It has also been used to reduce fever.

A usual initial oral dose of sulindac is 150 or 200 mg twice daily, reduced according to response; the maximum recommended daily dose is 400 mg. Licensed product information recommends that the treatment of peri-articular disorders should be limited to 7 to 14 days; for acute gout, 7 days of therapy is usually adequate.

Sulindac sodium has been given by rectal suppository.

Administration in hepatic or renal impairment. The dose of sulindac may need to be reduced in patients with hepatic or renal impairment but see Adverse Effects and Precautions, below.

Gastrointestinal disorders. In placebo-controlled studies[1,2] sulindac 150 to 200 mg twice daily for 6 to 9 months has reduced the number and size of polyps in patients with familial adenomatous polyposis but the effect may be incomplete and in a study[2] only polyps less than 2 mm in size regressed. In addition, the size and number of polyps have been reported[1] to increase on stopping treatment. The benefit of long-term therapy has therefore been studied. Reduced efficacy has been seen[3] with long-term use but others[4] have reported management of recurrences by adjustment of maintenance dosage; there seemed to be individual variations in sensitivity to sulindac with respect to prevention of polyp recurrence although an average maintenance dose of 200 mg daily appeared to be needed.[4]

There is evidence[5] that sulindac alters the ratio of apoptosis of surface cells relative to those lying deeper in the crypt of rectal mucosa, thus altering epithelial homoeostasis. Whether sulindac prevents malignant degeneration is unknown but there have been reports[6-8] of patients who developed rectal cancer during or after long-term therapy for adenomatous polyposis. A more recent, placebo-controlled study[9] has also reported that sulindac did not reduce the development of adenomas in patients with familial adenomatous polyposis. Some[1,9] consider that sulindac is unlikely to replace surgery as primary therapy for familial adenomatous polyposis.

A sulfone metabolite of sulindac, exisulind (p. 793.1) has also been investigated for the treatment of familial adenomatous polyposis.

Sulindac has also been reported to have produced beneficial effects in a patient with duodenal polyps associated with Gardner's syndrome[10] but a placebo-controlled study has suggested that it may not be effective against sporadic type colonic polyps.[11]

For a discussion of evidence suggesting that regular use of NSAIDs may protect against various types of malignant neoplasms of the gastrointestinal tract, see Malignant Neoplasms in NSAIDs, p. 104.1.

1. Giardiello FM, *et al.* Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. *N Engl J Med* 1993; 328: 1313–16.
2. Debinski HS, *et al.* Effect of sulindac on small polyps in familial adenomatous polyposis. *Lancet* 1995; 345: 655–6.
3. Tonelli F, Valanzano R. Sulindac in familial adenomatous polyposis. *Lancet* 1993; 342: 1120.
4. Labayle D, *et al.* Sulindac in familial adenomatous polyposis. *Lancet* 1994; 343: 417–18.
5. Keller JJ, *et al.* Rectal epithelial apoptosis in familial adenomatous polyposis patients treated with sulindac. *Gut* 1999; 45: 822–8.
6. Thorson AG, *et al.* Rectal cancer in FAP patient after sulindac. *Lancet* 1994; 343: 180.
7. Matsuhashi N, *et al.* Rectal cancer after sulindac therapy for a sporadic adenomatous colonic polyp. *Am J Gastroenterol* 1998; 93: 2261–6.
8. Cruz-Correa M, *et al.* Long-term treatment with sulindac in familial adenomatous polyposis: a prospective cohort study. *Gastroenterology* 2002; 122: 641–5.
9. Giardiello FM, *et al.* Primary chemoprevention of familial adenomatous polyposis with sulindac. *N Engl J Med* 2002; 346: 1054–9.
10. Parker AL, *et al.* Disappearance of duodenal polyps in Gardner's syndrome with sulindac therapy. *Am J Gastroenterol* 1993; 88: 93–4.
11. Ladenheim J, *et al.* Effect of sulindac on sporadic colonic polyps. *Gastroenterology* 1995; 108: 1083–7.

Premature labour. The most common approach to postponing premature labour (p. 2131.1) with drugs has historically been with a selective beta$_2$ agonist. However, as prostaglandins have a role in uterine contraction and cervical ripening and dilatation, prostaglandin synthetase inhibitors such as indometacin have also been used. Sulindac has also been tried[1,2] as an alternative to indometacin as it appears to have little placental transfer and may therefore have fewer fetal adverse effects.[1] However, the authors of a subsequent study suggested that sulindac had many of the same adverse fetal effects as indometacin and its use could only be described as investigational.[3] A study[4] using relatively low doses of sulindac (100 mg twice daily) did not note any significant fetal or maternal adverse effects but also found the drug to be ineffective in extending gestation or improving outcome.

1. Carlan SJ, *et al.* Randomized comparative trial of indomethacin and sulindac for the treatment of refractory preterm labor. *Obstet Gynecol* 1992; 79: 223–8.
2. Carlan SJ, *et al.* Outpatient oral sulindac to prevent recurrence of preterm labor. *Obstet Gynecol* 1995; 85: 769–74.
3. Kramer WB, *et al.* A randomized double-blind study comparing the fetal effects of sulindac to terbutaline during the management of preterm labor. *Am J Obstet Gynecol* 1999; 180: 396–401.
4. Humphrey RG, *et al.* Sulindac to prevent recurrent preterm labor: a randomized controlled trial. *Obstet Gynecol* 2001; 98: 555–62.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3. Urine discoloration has occasionally been reported with sulindac.

Sulindac metabolites have been reported as major or minor components in renal stones. It should therefore be used with caution in patients with a history of renal stones and such patients should be kept well hydrated while receiving sulindac.

UK licensed product information recommends that patients with hepatic impairment should not be given sulindac; in the USA, however, licensed information states that patients with poor hepatic function may be given a reduced dose of sulindac with close monitoring. The dose of sulindac may also need to be reduced in those with renal impairment. Licensed information recommends that sulindac is not used in patients with advanced renal disease, but this appears to be based on a lack of data in such patients.

Effects on the blood. Agranulocytosis,[1] thrombocytopenia,[2] haemolytic anaemia,[3] and aplastic anaemia[4] have been reported in patients taking sulindac.

1. Romeril KR, *et al.* Sulindac induced agranulocytosis and bone marrow culture. *Lancet* 1981; II: 523.
2. Karachalios GN, Parigorakis JG. Thrombocytopenia and sulindac. *Ann Intern Med* 1986; 104: 128.
3. Johnson FP, *et al.* Immune hemolytic anemia associated with sulindac. *Arch Intern Med* 1985; 145: 1515–16.
4. Andrews R, Russell N. Aplastic anaemia associated with a non-steroidal anti-inflammatory drug: relapse after exposure to another such drug. *BMJ* 1990; 301: 38.

Effects on the CNS. Acute deterioration of parkinsonism occurred in a patient after starting sulindac.[1]

See also Hypersensitivity, p. 135.1.

1. Sandyk R, Gillman MA. Acute exacerbation of Parkinson's disease with sulindac. *Ann Neurol* 1985; 17: 104–5.

Effects on the endocrine system. A case of reversible gynaecomastia associated with sulindac therapy has been reported.[1] There has also been a report[2] of reversible hypothyroidism in an elderly patient taking sulindac.

1. Kapoor A. Reversible gynecomastia associated with sulindac therapy. *JAMA* 1983; 250: 2284–5.

2. Iyer RP, Duckett GK. Reversible secondary hypothyroidism induced by sulindac. *BMJ* 1985; **290:** 1788.

Effects on the gallbladder. A "sludge" composed of crystalline metabolites of sulindac has been found in the common bile duct during surgery for biliary obstruction in patients who had been taking sulindac.[1]

1. Anonymous. Rare complication with sulindac. *FDA Drug Bull* 1989; **19:** 4.

Effects on the kidneys. Sulindac-induced renal impairment, interstitial nephritis, and nephrotic syndrome have been reported.[1] It has been suggested that sulindac, as a prodrug, may not inhibit renal prostaglandin synthesis in therapeutic doses. However, this potentially important therapeutic advantage has not been uniformly seen in short-term studies in patients with renal dysfunction.[2-4]

There have been reports of renal stones consisting of between 10 and 90% of sulindac metabolites developing in patients given sulindac.[5]

1. Whelton A, *et al.* Sulindac and renal impairment. *JAMA* 1983; **249:** 2892.
2. Klassen DK, *et al.* Sulindac kinetics and effects on renal function and prostaglandin excretion in renal insufficiency. *J Clin Pharmacol* 1989; **29:** 1037–42.
3. Eriksson L-O, *et al.* Effects of sulindac and naproxen on prostaglandin excretion in patients with impaired renal function and rheumatoid arthritis. *Am J Med* 1990; **89:** 313–21.
4. Whelton A, *et al.* Renal effects of ibuprofen, piroxicam, and sulindac in patients with asymptomatic renal failure. *Ann Intern Med* 1990; **112:** 568–76.
5. Anonymous. Rare complication with sulindac. *FDA Drug Bull* 1989; **19:** 4.

Effects on the liver. Hepatotoxicity reported in patients receiving sulindac includes hepatocellular injury and cholestatic jaundice.[1,2] Symptoms of hypersensitivity including rash, fever, or eosinophilia have been reported in 35 to 55% of patients with sulindac-induced liver damage;[2] in these patients the liver damage occurred usually within 4 to 8 weeks of beginning sulindac therapy. For reference to a report citing the strongest evidence for an association of sulindac with liver disease compared with other NSAIDs, see under NSAIDs, p. 106.3.

See also Effects on the Skin, below.

1. Gallanosa AG, Spyker DA. Sulindac hepatotoxicity: a case report and review. *Clin Toxicol* 1985; **23:** 205–38.
2. Tarazi EM, *et al.* Sulindac-associated hepatic injury: analysis of 91 cases reported to the Food and Drug Administration. *Gastroenterology* 1993; **104:** 569–74.

Effects on the lungs. For reference to pneumonitis associated with sulindac therapy, see Hypersensitivity, below.

Effects on the skin. Toxic epidermal necrolysis has occurred in patients taking sulindac.[1] In a patient toxic hepatitis and the Stevens-Johnson/toxic epidermal necrolysis syndrome resulted in death.[2]

An unusual pernio-like reaction affecting the toes, which was also confirmed by rechallenge, has been reported.[3]

Sulindac has also been reported to cause photosensitivity reactions.[4]

1. Small RE, Garnett WR. Sulindac-induced toxic epidermal necrolysis. *Clin Pharm* 1988; **7:** 766–71.
2. Klein SM, Khan MA. Hepatitis, toxic epidermal necrolysis and pancreatitis in association with sulindac therapy. *J Rheumatol* 1983; **10:** 512–13.
3. Reinertsen JL. Unusual pernio-like reaction to sulindac. *Arthritis Rheum* 1981; **24:** 1215.
4. Anonymous. Drugs that cause photosensitivity. *Med Lett Drugs Ther* 1986; **28:** 51–2.

Hypersensitivity. Hypersensitivity reactions to sulindac include pneumonitis,[1,2] generalised lymphadenopathy,[3] aseptic meningitis,[4] and anaphylactoid reaction.[5]

See also Effects on the Liver and Effects on the Skin, above.

1. Smith FE, Lindberg PJ. Life-threatening hypersensitivity to sulindac. *JAMA* 1980; **244:** 269–70.
2. Fein M. Sulindac and pneumonitis. *Ann Intern Med* 1981; **95:** 245.
3. Sprung DJ. Sulindac causing a hypersensitivity reaction with peripheral and mediastinal lymphadenopathy. *Ann Intern Med* 1982; **97:** 564.
4. Fordham von Reyn C. Recurrent aseptic meningitis due to sulindac. *Ann Intern Med* 1983; **99:** 343–4.
5. Hyson CP, Kazakoff MA. A severe multisystem reaction to sulindac. *Arch Intern Med* 1991; **151:** 387–8.

Pancreatitis. Reports[1-4] of pancreatitis associated with sulindac therapy.

1. Goldstein J, *et al.* Sulindac associated with pancreatitis. *Ann Intern Med* 1980; **93:** 151.
2. Siefkin AD. Sulindac and pancreatitis. *Ann Intern Med* 1980; **93:** 932–3.
3. Lilly EL. Pancreatitis after administration of sulindac. *JAMA* 1981; **246:** 2680.
4. Memon AN. Pancreatitis and sulindac. *Ann Intern Med* 1982; **97:** 139.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sulindac as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 23/10/11)

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Dimethyl sulfoxide reduces plasma concentrations of the active metabolite of sulindac and use of the two drugs together has also resulted in peripheral neuropathy. Diflunisal and aspirin are reported to reduce the plasma concentration of the active metabolite of sulindac. Unlike other NSAIDs, sulindac is reported not to reduce the antihypertensive effects of drugs such as thiazide diuretics, but nevertheless licensed product information recommends that blood pressure be closely monitored in patients taking antihypertensives with sulindac.

Pharmacokinetics

Sulindac is absorbed from the gastrointestinal tract. It is metabolised by reversible reduction to the sulfide metabolite, which appears to be the active form, and by irreversible oxidation to the sulfone metabolite. Peak plasma concentrations of the sulfide metabolite occur in about 2 hours. The mean elimination half-life of sulindac is about 7.8 hours and of the sulfide metabolite about 16.4 hours. Sulindac and its metabolites are over 90% bound to plasma proteins. About 50% is excreted in the urine mainly as the sulfone metabolite and its glucuronide conjugate, with smaller amounts of sulindac and its glucuronide conjugate; about 25% appears in the faeces, primarily as sulfone and sulfide metabolites. Sulindac and its metabolites are also excreted in bile and undergo extensive enterohepatic circulation.

References.

1. Davies NM, Watson MS. Clinical pharmacokinetics of sulindac: a dynamic old drug. *Clin Pharmacokinet* 1997; **32:** 437–59.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Adin; ***Belg.***: Clinoril†; ***Canad.***: Apo-Sulin; Novo-Sundac†; ***China***: Clinoril (奇诺力); Zulida (祖力达); ***Fr.***: Arthrocine; ***Gr.***: Norilafin; Sulen; Udolac; Zirofalen; ***Hong Kong***: Adin; Clinoril†; ***Irl.***: Clinoril†; ***Ital.***: Clinoril; ***Mex.***: Atriser; Bio-Dac; Clinoril; Clison; Copal†; Kenalin; Renidac; Sulifur†; Vindacin; Zulsol†; ***NZ***: Clinoril; Daclin; ***Singapore***: Apo-Sulin; ***Spain***: Sulindal†; ***Swed.***: Clinoril†; ***Thai.***: Cenlidac; Clinoril; ***UK***: Clinoril†; ***USA***: Clinoril.

Pharmacopoeial Preparations
BP 2014: Sulindac Tablets;
USP 36: Sulindac Tablets.

Superoxide Dismutase

NK-341 (recombinant human superoxide dismutase); SOD; Superóxido dismutasa; Супероксиддисмутаза.

Description. Superoxide dismutase represents a group of water-soluble protein congeners widely distributed in nature which catalyse the conversion of superoxide radicals to peroxide. Several different forms exist, which vary in their metal content; forms containing copper or copper and zinc are common.

Orgotein *(BAN, USAN, rINN)*

Bovine Superoxide Dismutase; Orgoteiini; Orgoteína; Orgotéine; Orgoteinum; Ormetein; Оротеин.

CAS — 9016-01-7.
ATC — M01AX14.
ATC Vet — QM01AX14.
UNII — PKE82W49V1.

Description. Orgotein is a superoxide dismutase produced from beef liver as Cu-Zn mixed chelate. Mol. wt about 33 000 with a compact conformation maintained by about 4 gram-atoms of chelated divalent metal.

Pegorgotein *(USAN, rINN)*

Pegorgoteína; Pégorgotéine; Pegorgoteinum; PEG-SOD; Win-22118; Пегоротеин.

CAS — 155773-57-2.

Description. Pegorgotein is a superoxide dismutase conjugated with polyethylene glycol to prolong its duration of action.

Sudismase *(rINN)*

Sudismasa; Sudismasum; Судизмаза.

CAS — 110294-55-8.

Description. Sudismase is a human *N*-acetylsuperoxide dismutase produced by recombinant DNA technology and containing a copper and zinc prosthetic group.

Uses and Administration

Superoxide dismutases have anti-inflammatory properties. Orgotein, a bovine derived superoxide dismutase, has been given by local injection, into the joints for degenerative joint disorders, but hypersensitivity reactions have limited its use. It has also been tried for the amelioration of adverse effects from radiotherapy. Forms of human superoxide dismutase derived by recombinant DNA technology have been developed.

Superoxide dismutases have also been investigated for their free-radical scavenging properties in a variety of conditions; however, their value has been limited.

Bronchopulmonary dysplasia. Use of sudismase in premature infants treated for respiratory distress syndrome did not prevent development of bronchopulmonary dysplasia (p. 1602.1) in the first month.[1] However, treated infants subsequently showed a lower incidence of severe respiratory disease and hospitalisations in the first year, suggesting a reduction in chronic lung injury. The antioxidant was given intratracheally in a dose of 5 mg/kg every 48 hours as long as intubation and ventilation were necessary. A systematic review[2] was unable to reach a firm conclusion about the efficacy of superoxide dismutases in preventing chronic lung disease.

1. Davis JM, *et al.* Pulmonary outcome at 1 year corrected age in premature infants treated at birth with recombinant human CuZn superoxide dismutase. *Pediatrics* 2003; **111:** 469–76.
2. Suresh GK, *et al.* Superoxide dismutase for preventing chronic lung disease in mechanically ventilated preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2001 (accessed 09/05/05).

Adverse Effects

Anaphylaxis and other hypersensitivity reactions, sometimes fatal, have been reported with orgotein. Local reactions and pain may occur at the site of injection of orgotein.

Pharmacokinetics

References.

1. Rosenfeld WN, *et al.* Safety and pharmacokinetics of recombinant human superoxide dismutase administered intrathecally to premature neonates with respiratory distress syndrome. *Pediatrics* 1996; **97:** 811–17.
2. Davis JM, *et al.* Safety and pharmacokinetics of multiple doses of recombinant human CuZn superoxide dismutase administered intrathecally to premature neonates with respiratory distress syndrome. *Pediatrics* 1997; **100:** 24–30.
3. Schwedhelm E, *et al.* Clinical pharmacokinetics of antioxidants and their impact on systemic oxidative stress. *Clin Pharmacokinet* 2003; **42:** 437–59.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Sodermix; ***Rus.***: Rexod (Рексод).

Multi-ingredient Preparations. ***Fr.***: GliSODine Antioxidant; GliSODine Defenses; GliSODine Solaire; Proselem; Ultraselem; ***Indon.***: Glisodin; nutrivision; ***Ital.***: Legalon Plus; ***Mex.***: Avitil; Sodimel; ***Singapore***: Nutrivision†.

Suprofen *(BAN, USAN, rINN)*

R-25061; Suprofeeni; Suprofène; Suprofeno; Suprofenum; Sutoprofen; Супрофен.

2-[4-(2-Thenoyl)phenyl]propionic acid.

$C_{14}H_{12}O_3S$=260.3.

CAS — 40828-46-4.
ATC — M01AE07.
ATC Vet — QM01AE07.
UNII — 988GU2F9PE.

Pharmacopoeias. In *US*.

USP 36: (Suprofen). A white to off-white powder, odourless or having a slight odour. Sparingly soluble in water.

Profile

Suprofen is an NSAID (p. 102.3). Suprofen has been used as 1% eye drops to inhibit the miosis that may occur during ocular surgery.

It was formerly given orally in mild to moderate pain and in osteoarthritis and rheumatoid arthritis but, after reports of adverse renal reactions, marketing of the oral dose form was suspended worldwide.

Preparations

Pharmacopoeial Preparations
USP 36: Suprofen Ophthalmic Solution.

Suxibuzone *(BAN, rINN)*

Suksibutsoni; Suksibuzonas; Suxibuzon; Suxibuzona; Suxibuzonum; Szuxibuzon; Сукси бузон.

4-Butyl-4-hydroxymethyl-1,2-diphenylpyrazolidine-3,5-dione hydrogen succinate (ester).

$C_{24}H_{26}N_2O_6$=438.5.

CAS — 27470-51-5.
ATC — M02AA22.
ATC Vet — QM01AA90; QM02AA22.
UNII — 86TDZ5WP28.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Suxibuzone). A white or almost white, crystalline powder. Practically insoluble in water; soluble in alcohol; freely soluble in acetone; practically insoluble in cyclohexane.

Profile

Suxibuzone, a derivative of phenylbutazone (p. 125.1), is an NSAID (p. 102.3) that has been applied topically at a concentration of about 7% in musculoskeletal and joint disorders. Concern over safety and toxicity after oral use has led to its withdrawal from the market in many countries.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Spain*: Danilon†.

Tapentadol *(USAN, rINN)*

BN-200; CG-5503; Tapentadolum; Тапентадол.
3-[(1*R*,2*R*)-3-(Dimethylamino)-1-ethyl-2-methylpropyl] phenol.
$C_{14}H_{23}NO$=221.3
CAS — 175591-23-8.
ATC — N02AX06.
ATC Vet — QN02AX06.
UNII — H8A007M585.

Tapentadol Hydrochloride *(rINNM)*

Hidrocloruro de tapentadol; Tapentadol, Chlorhydrate de; Tapentadolii Hydrochloridum; Тапентадола гидрохлорид.
$C_{14}H_{23}NO,HCl$=257.8
CAS — 175591-09-0.
ATC — N02AX06.
ATC Vet — QN02AX06.
UNII — 71204KI153.

Uses and Administration

Tapentadol is an opioid analgesic (p. 108.1) that is primarily a μ-opioid agonist and also a noradrenaline reuptake inhibitor. It is used in the treatment of moderate to severe acute pain and is given orally as the hydrochloride but doses are expressed in terms of the base; 58.2 mg of tapentadol hydrochloride is equivalent to about 50 mg of tapentadol. Doses of 50, 75, or 100 mg are given every 4 to 6 hours depending on the intensity of pain. On the first day, a second dose may be given 1 hour after the initial dose if pain relief is inadequate; subsequent doses should be given every 4 to 6 hours, adjusted according to response, to a maximum total dose of 700 mg on the first day and of 600 mg daily on subsequent days.

For doses in patients with hepatic impairment, see below.

References.

1. Hale M, *et al.* Tolerability of tapentadol immediate release in patients with lower back pain or osteoarthritis of the hip or knee over 90 days: a randomized, double-blind study. *Curr Med Res Opin* 2009; **25**: 1095–1104.
2. Hartrick C, *et al.* Efficacy and tolerability of tapentadol immediate release and oxycodone HCl immediate release in patients awaiting primary joint replacement surgery for end-stage joint disease: a 10-day, phase III, randomized, double-blind, active- and placebo-controlled study. *Clin Ther* 2009; **31**: 260–71.
3. Daniels S, *et al.* A randomized, double-blind, placebo-controlled phase 3 study of the relative efficacy and tolerability of tapentadol IR and oxycodone IR for acute pain. *Curr Med Res Opin* 2009; **25**: 1551–61.
4. Wade WE, Spruill WJ. Tapentadol hydrochloride: a centrally acting oral analgesic. *Clin Ther* 2009; **31**: 2804–18.

Administration in hepatic impairment. Tapentadol hydrochloride should be given with caution to patients with moderate hepatic impairment; treatment should be started with oral doses equivalent to 50 mg of tapentadol given at intervals of no less than every 8 hours (maximum of 3 doses in 24 hours). Thereafter, maintenance of analgesia may be achieved by adjusting the dosing interval according to tolerability.

Use in patients with severe impairment has not been studied.

Dependence and Withdrawal

As for Opioid Analgesics in general, p. 109.1.

Adverse Effects, Treatment, and Precautions

As for Opioid Analgesics in general, p. 110.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tapentadol as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/10/11)

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

Pharmacokinetics

Tapentadol is subject to extensive first-pass metabolism with a mean absolute bioavailability of about 32%. It is widely distributed throughout the body and plasma protein binding is about 20%. Tapentadol is extensively metabolised, mainly by glucuronidation. It is also metabolised, to a lesser extent, via the cytochrome P450 isoenzymes CYP2C9, CYP2C19, and CYP2D6, before further conjugation. None of the metabolites have analgesic activity. After oral dosing, about 70% of the dose is excreted in the urine in the conjugated form and 3% as unchanged drug. The terminal half-life is about 4 hours after oral dosing.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Nucynta; *Cz.*: Palexia; Yantil; *Denm.*: Palexia; *Ger.*: Palexia; *Irl.*: Palexia; Yantil; *Neth.*: Palexia; Yantil; *Norw.*: Palexia; *Spain*: Palexia; *Swed.*: Palexia; *Switz.*: Palexia; *UK*: Palexia; *USA*: Nucynta.

Tenoxicam *(BAN, USAN, rINN)*

Ro-12-0068; Ro-12-0068/000; Tenoksikaami; Tenoksikam; Tenoksikamas; Ténoxicam; Tenoxicamum; Tenoxikam; Tenoxikám; Теноксикам.
4-Hydroxy-2-methyl-*N*-(2-pyridyl)-2*H*-thieno[2,3-*e*][1,2]thiazine-3-carboxamide 1,1-dioxide.
$C_{13}H_{11}N_3O_4S_2$=337.4
CAS — 59804-37-4.
ATC — M01AC02.
ATC Vet — QM01AC02.
UNII — Z1R9N0A399.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Tenoxicam). A yellow, polymorphic, crystalline powder. Practically insoluble in water; very slightly soluble in dehydrated alcohol; sparingly soluble in dichloromethane; it dissolves in solutions of acids and alkalis. Protect from light.

Stability. An admixture of tenoxicam 0.02% and ceftazidime 0.5% (as the sodium salt) in glucose injection 5% appeared stable when stored for up to 120 hours at 25 degrees in glass bottles;[1] when stored in PVC bags, the admixture was stable for up to 72 hours at 25 degrees and for up to 144 hours at 4 degrees.

1. Wang D-P, *et al.* Compatibility and stability of ceftazidime sodium and tenoxicam in 5% dextrose injection. *Am J Health-Syst Pharm* 2004; **61**: 1924–7.

Uses and Administration

Tenoxicam, a piroxicam (p. 125.3) analogue, is an NSAID (p. 102.3). It is used in the symptomatic management of musculoskeletal and joint disorders such as osteoarthritis and rheumatoid arthritis, and also in the short-term management of soft-tissue injury. Tenoxicam is given as a single oral daily dose usually of 20 mg. In acute musculoskeletal disorders treatment for up to 7 days is usually sufficient but in severe cases it may be given for up to a maximum of 14 days. Doses similar to those given orally have been given by intramuscular or intravenous injection for initial treatment for 1 or 2 days. Tenoxicam has also been given by rectal suppository.

References.
1. Todd PA, Clissold SP. Tenoxicam: an update of its pharmacology and therapeutic efficacy in rheumatic diseases. *Drugs* 1991; **41**: 625–46.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3.

Incidence of adverse effects. Adverse effects associated with tenoxicam have been reviewed.[1] The majority of adverse effects relate to the gastrointestinal tract (11.4%), nervous system (2.8%), or skin (2.5%).

Gastrointestinal disturbances including nausea and vomiting (14.7%) and dyspepsia (2.3%), surgical site bleeding (4.3%), wound infection (2.7%), dizziness (5.7%), and headache (10.7%) were the most common adverse effects reported in a placebo-controlled study involving 1001 patients after the perioperative use of oral and intravenous tenoxicam.[2] It was noted, however, that the incidence of dizziness, nausea and vomiting, and headache was greater in the placebo group and that the difference in the incidence of dyspepsia between the 2 groups was not significant.

1. Todd PA, Clissold SP. Tenoxicam: an update of its pharmacology and therapeutic efficacy in rheumatic diseases. *Drugs* 1991; **41**: 625–46.
2. Merry AF, *et al.* Clinical tolerability of perioperative tenoxicam in 1001 patients—a prospective, controlled, double-blind, multi-centre study. *Pain* 2004; **111**: 313–22.

Effects on the kidneys. A review[1] of the effects of tenoxicam on renal function concluded that tenoxicam could be given at normal recommended doses to elderly patients or those with mild to moderate renal impairment who were not at high risk of renal failure or receiving potentially nephrotoxic therapy. Data from the manufacturer's database[1] on 67 063 patients, including 17 005 over 65 years of age, who had received tenoxicam indicated that there had been 45 adverse events relating to urinary system function, described as severe in 7. The prevalence of adverse events was similar in elderly and non-elderly patients, the most common effects being dysuria and renal pain.

1. Heintz RCA. Tenoxicam and renal function. *Drug Safety* 1995; **12**: 110–19.

Effects on the liver. A report[1] of acute hepatitis associated with the use of tenoxicam.

1. Sungur C, *et al.* Acute hepatitis caused by tenoxicam. *Ann Pharmacother* 1994; **28**: 1309.

Effects on the skin. A report of 3 cases of toxic epidermal necrolysis (Lyell's syndrome) associated with tenoxicam.[1]

For the general incidence of dermatological effects see above.

1. Chosidow O, *et al.* Toxidermies sévères au ténoxicam (Tilcotil). *Ann Dermatol Venereol* 1991; **118**: 903–4.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tenoxicam as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 23/10/11)

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Pharmacokinetics

Tenoxicam is well absorbed after oral doses; peak plasma concentrations occur within about 2 hours in fasting subjects; this may be delayed to about 6 hours when tenoxicam is given with food but the extent of absorption is unaffected. It is also rapidly absorbed after intramuscular injection. Tenoxicam is about 99% protein bound and penetrates synovial fluid. The plasma elimination half-life ranges from 42 to 81 hours; with daily dosage, steady-state concentrations occur within 10 to 15 days. Tenoxicam is completely metabolised to inactive metabolites, which are excreted mainly in the urine; there is some biliary excretion of glucuronide conjugates of the metabolites.

References.

1. Nilsen OG. Clinical pharmacokinetics of tenoxicam. *Clin Pharmacokinet* 1994; **26**: 16–43.
2. Guentert TW, *et al.* Relative bioavailability of oral dosage forms of tenoxicam. *Arzneimittelforschung* 1994; **44**: 1051–4.
3. Nilsen OG, *et al.* Single- and multiple-dose pharmacokinetics, kidney tolerability and plasma protein binding of tenoxicam in renally impaired patients and healthy volunteers. *Pharmacol Toxicol* 2001; **89**: 265–72.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Tilcotil; *Braz.*: Inflagel; Prodoxican†; Teflan; Tenotec; Tilatil; Tilonax; Tiloxican; Titenil; *Chile*: Bioflam; Mitrotil; Recaflex†; Tilcotil; *Denm.*: Tilcitin; Tilcotil; *Fin.*: Tilcotil†; *Fr.*: Tilcotil; *Gr.*: Admiral; Algin-Vek; Amcinafal; Ampirovix; Artroxicam; Aspagin; Biodruff; Docticam; Dranat; Hobaticam; Indo-bros; Istotosal; Liaderyl; Neo-adlibamin; Neo-antiperstam; Neo-endusix; Octiveran; Oxytel; Palitenox; Ponsolit; Portonal; Redac; Soral; Tenox; Tentepanil; Tilcitin; Toscacalm; Velasor; Voir; Zibelant; *Hong Kong*: Tenox†; Tilcotil†; *Hung.*: Tilcotil; *India*: Novotil; Tobitil; *Indon.*: Artricom; Meditil†; Notritis; Oxaflam; Pilopil; Thenil; Tilarco; Tilcotil; Tilflam; Xotilon; *Ital.*: Bart; Dolmen; Rexalgan†; Tilcotil; *Jpn*: Tilcotil†; *Malaysia*: Analcam; Seftil; Tilcotil; *Mex.*: Tilcotil†; *NZ*: Tilcotil; *Philipp.*: Rheuflex; Tilcotil†; *Port.*: Doxican; Tenalgin; Tilcotil; *Rus.*: Teksamen (Тексамен); *S.Afr.*: Tilcotil†; *Singapore*: Analcam; Nadamen†; *Spain*: Reutenox; *Swed.*: Alganex; *Switz.*: Tilcotil; *Thai.*: Memzotil; Sefril; Sinoral†; Teconam; Tenax; Tenocam; Tenogesic; Tenox; Tenoxil; Tenoxman; Tenxil†; Tilcotil†; Tilnoxcam; Tonox; *Turk.*: Artroksin; Ilkoten; Nobateks; Oksamen; Tenoksan; Tenoktil; Tenox; Tilcotil; Tilko; VienOks; Zikaral; *UAE*: Tenoflam; *UK*: Mobiflex; *Ukr.*: Texamen (Тексамен); *Venez.*: Rodix; Tenoxin.

Pharmacopoeial Preparations
BP 2014: Tenoxicam Injection; Tenoxicam Tablets.

Tepoxalin *(USAN, rINN)*

ORF-20485; RWJ-20485; Tepoksaliini; Tepoxalina; Tépoxaline; Tepoxalinum; Тепоксалин.
5-(*p*-Chlorophenyl)-1-(*p*-methoxyphenyl)-*N*-methylpyrazole-3-propionohydroxamic acid.
$C_{20}H_{20}ClN_3O_3$=385.8
CAS — 103475-41-8.
ATC Vet — QM01AE92.
UNII — TZ4OX61974.

Profile

Tepoxalin, a propionic acid derivative, is an NSAID (p. 102.3) used in veterinary medicine for the treatment of inflammation and pain in dogs.

Tetridamine *(rINN)*

POLI-67; Tetridamina; Tétridamine; Tetridaminum; Tetrydamine (USAN); Tetrydamine; Тетридамин.
4,5,6,7-Tetrahydro-2-methyl-3-(methylamino)-2*H*-indazole.
$C_9H_{15}N_3$=165.2
CAS — 17289-49-5.
UNII — NQ7W02PF6S.

Profile

Tetridamine is an NSAID (p. 102.3) that has been used as the maleate as a douche in the treatment of vaginitis.

Between January 1991 and December 2003 the Spanish Poison Control Center had received 77 reports where vaginal preparations containing tetridamine had been ingested alone, mainly due to erroneous misuse.[1] Of these, 60 patients were asymptomatic and in the remainder the most frequent symptoms were vomiting (5), epigastric pain (4), heartburn or oesophageal irritation (4), dizziness (4), and nausea (3). The clinical severity was mainly benign but 1 patient became comatose after taking 4 g in a suicide attempt. No deaths occurred.

1. Ballesteros S, *et al.* Oral tetridamine exposures. *Clin Toxicol* 2009; **47**: 150–2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Deb†; *Spain*: Fomene†.

Thurfyl Salicylate

Salicilato de furfilo.
Tetrahydrofurfuryl salicylate.
$C_{12}H_{14}O_4$=222.2
CAS — 2217-35-8.

Profile

Thurfyl salicylate is a salicylic acid derivative that has been used similarly to methyl salicylate (p. 92.1) in topical rubefacient preparations at concentrations of up to 14% for musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Biosal Arthritis†; *Belg.*: Transvane; *Irl.*: Transvasin†; *UK*: Boots Pain Relief Heat Rub; Transvasin Heat Rub.

Tiaprofenic Acid *(BAN, rINN)*

Acide Tiaprofénique; Ácido tiaprofénico; Acidum Tiaprofenicum; FC-3001; Kyselina tiaprofenová; RU-15060; Tiaprofeenihappo; Tiaprofénico, ácido; Tiaprofenik Asit; Tiaprofeno rūgštis; Tiaprofensäure; Tiaprofensyra; Тиапрофеновая Кислота.
2-(5-Benzoyl-2-thienyl)propionic acid.
$C_{14}H_{12}O_3S$=260.3
CAS — 33005-95-7.
ATC — M01AE11.
ATC Vet — QM01AE11.
UNII — 1LS1T6R34C.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Tiaprofenic Acid). A white or almost white, crystalline powder. Practically insoluble in water; freely soluble in alcohol, in acetone, and in dichloromethane. Protect from light.

Uses and Administration

Tiaprofenic acid, a propionic acid derivative, is an NSAID (p. 102.3). It is used for the relief of pain and inflammation in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis, in peri-articular disorders such as fibrositis and capsulitis, and in soft-tissue disorders such as sprains and strains. The usual oral dose is 600 mg daily given in 2 or 3 divided doses; in patients with cardiac, hepatic, or renal impairment, licensed product information suggests that the dose is reduced to 200 mg twice daily. A modified-release preparation may be available for once-daily use. Tiaprofenic acid has also been given rectally. It has been given intramuscularly as the trometamol salt in acute conditions.

References.
1. Plosker GL, Wagstaff AJ. Tiaprofenic acid: a reappraisal of its pharmacological properties and use in the management of rheumatic diseases. *Drugs* 1995; **50**: 1050–75.

Administration in hepatic or renal impairment. Tiaprofenic acid is contra-indicated in patients with severe hepatic or renal impairment; for dosage details in those with more moderate impairment, see Uses and Administration, above.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3.

Tiaprofenic acid may cause cystitis, bladder irritation, and other urinary-tract symptoms (see below). It should not be given to patients with active urinary-tract disorders or prostatic disease or a history of recurrent urinary-tract disorders. It should be stopped immediately if urinary-tract symptoms occur and urinalysis and urine culture performed.

Tiaprofenic acid is contra-indicated in patients with severe hepatic or renal impairment.

Breast feeding. Although tiaprofenic acid is distributed into breast milk, the amount is considered by the *BNF* to be too small to be harmful to a breast-fed infant. Licensed product information also states that exposure to tiaprofenic acid via breast milk is unlikely to be of pharmacological significance; however, it is recommended that either treatment or breast feeding is stopped as necessary.

Effects on the urinary tract. Cystitis and bladder irritation have been associated with the use of tiaprofenic acid.[1-6] In August 1994 the UK CSM stated[4] that since the introduction of tiaprofenic acid in the UK in 1982 they had received 69 reports of cystitis and 32 other reports of urinary-tract symptoms associated with tiaprofenic acid including frequency, dysuria, and haematuria whereas only 8 cases of cystitis had been reported for all other NSAIDs combined. Analysis of spontaneous reports received by WHO[7] confirmed that cystitis was more commonly associated with tiaprofenic acid than with other NSAIDs. The Australian Adverse Drug Reactions Advisory Committee had received similar reports.[3] Since the 1994 warning, the CSM[8] had received reports of a further 74 cases of cystitis, but the majority of these had occurred before the warning was issued. The duration of treatment in patients affected had varied considerably. Most patients recovered when tiaprofenic acid was withdrawn.

The CSM recommended that tiaprofenic acid should not be given to patients with urinary-tract disorders and that it should be stopped in patients who develop urinary-tract symptoms. Patients should be advised that if they develop symptoms such as urinary frequency, nocturia, urgency, or pain on urination, or have blood in their urine they should stop taking tiaprofenic acid and consult their doctor. Older patients may be at increased risk.[9]

1. Ahmed M, Davison OW. Severe cystitis associated with tiaprofenic acid. *BMJ* 1991; **303**: 1376.
2. O'Neill GFA. Tiaprofenic acid as a cause of non-bacterial cystitis. *Med J Aust* 1994; **160**: 123–5.
3. Australian Adverse Drug Reactions Advisory Committee (ADRAC). Update on tiaprofenic acid and urinary symptoms. *Aust Adverse Drug React Bull* 1994; **13**: 6.
4. CSM/MCA. Severe cystitis with tiaprofenic acid (Surgam). *Current Problems* 1994; **20**: 11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015615&RevisionSelectionMethod=LatestReleased (accessed 08/11/07)
5. Harrison WJ, *et al.* Adverse reactions to tiaprofenic acid inimicking interstitial cystitis. *BMJ* 1994; **309**: 574.
6. Mayall FG, *et al.* Cystitis and ureteric obstruction in patients taking tiaprofenic acid. *BMJ* 1994; **309**: 599.
7. The ADR Signals Analysis Project (ASAP) Team. How does cystitis affect a comparative risk profile of tiaprofenic acid with other non-steroidal antiinflammatory drugs? An international study based on spontaneous reports and drug usage data. *Pharmacol Toxicol* 1997; **80**: 211–17.
8. Crawford MLA, *et al.* Severe cystitis associated with tiaprofenic acid. *Br J Urol* 1997; **79**: 578–84.
9. Buchbinder R, *et al.* Clinical features of tiaprofenic acid (surgam) associated cystitis and a study of risk factors for its development. *J Clin Epidemiol* 2000; **53**: 1013–19.

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Pharmacokinetics

Tiaprofenic acid is absorbed from the gastrointestinal tract and peak plasma concentrations occur within about 1.5 hours after oral doses. It has a short elimination half-life of about 2 hours and is highly bound to plasma proteins (about 98%). Excretion of tiaprofenic acid and its metabolites is mainly in the urine in the form of acyl glucuronides; some is excreted in the bile. Tiaprofenic acid crosses the placenta and is distributed into breast milk.

References.
1. Davies NM. Clinical pharmacokinetics of tiaprofenic acid and its enantiomers. *Clin Pharmacokinet* 1996; **31**: 331–47.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Surgam; *Cz.*: Surgam; Thialgin†; *Denm.*: Surgamyl; *Fin.*: Surgamyl†; *Fr.*: Flanid; Surgam; *Ger.*: Surgam; *Gr.*: Surgam; *Hung.*: Surgam; *Irl.*: Surgam†; *Ital.*: Surgamyl; *Mex.*: Surgam; *Neth.*: Surgam; *NZ*: Surgam; *Pol.*: Surgam; *Port.*: Surgam; *S.Afr.*: Surgam†; *Thai.*: Fengam†; Surgam; *Turk.*: Surgam; *UK*: Surgam; *Venez.*: Torpas.

Tiaramide Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro de tiaramida; NTA-194; Tiaperamide Hydrochloride; Tiaramida, hidrocloruro de; Tiaramide, Chlorhydrate de; Tiaramidi Hydrochloridum; Тиарамида Гидрохлорид.
5-Chloro-3-[2-[4-(2-hydroxyethyl)piperazin-1-yl]-2-oxoethyl] benzothiazolin-2-one hydrochloride.
$C_{15}H_{18}ClN_3O_3S$,HCl=392.3
CAS — 32527-55-2 (tiaramide); 35941-71-0 (tiaramide hydrochloride).
UNII — ITY1616X9T.

Pharmacopoeias. In *Jpn.*

Profile

Tiaramide hydrochloride is an NSAID (p. 102.3) that is given orally for the relief of pain and inflammation. A dose equivalent to 100 mg of the base may be given three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Solantal.

Tilidine Hydrochloride *(USAN, pINNM)*

Gö 1261-C; Hidrocloruro de tilidina; Tilidate Hydrochloride (BANM); Tilidiinihydrokloridihemihydraatti; Tilidina, hidrocloruro de; Tilidine, Chlorhydrate de; Tilidine (chlorhydrate de) hémihydraté; Tilidin-hydrochlorid hemihydrát; Tilidinhydroklorid hemihydrat; Tilidini Hydrochloridum; Tilidini Hydrochloridum Hemihydricum; Tilidino hidrochloridas hemihidratas; W-5759A; Тилидина Гидрохлорид.
(±)-Ethyl *trans*-2-dimethylamino-1-phenylcyclohex-3-ene-1-carboxylate hydrochloride hemihydrate.
$C_{17}H_{23}NO_2$,HCl,½H_2O=318.8
CAS — 20380-58-9 (tilidine); 27107-79-5 (anhydrous tilidine hydrochloride); 24357-97-9 (anhydrous +-trans-tilidine hydrochloride).
ATC — N02AX01.
ATC Vet — QN02AX01.
UNII — 4YI72J28N9.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Tilidine Hydrochloride Hemihydrate). A white or almost white, crystalline powder. A suitable antoxidant may be added. Freely soluble in water and in alcohol; very soluble in dichloromethane. Protect from light.

Uses and Administration

Tilidine hydrochloride is an opioid analgesic (p. 108.1). It is used in the control of moderate to severe pain.

Tilidine hydrochloride may be given in usual oral doses of up to 50 mg four times daily. It has been given as a suppository, or by intravenous, intramuscular, or subcutaneous injection. Tilidine has also been given as the phosphate in modified release tablets. As a deterrent to abuse combined oral preparations of tilidine hydrochloride with naloxone hydrochloride are available in some countries.

Dependence and Withdrawal

As for Opioid Analgesics in general, p. 109.1.

Adverse Effects, Treatment, and Precautions

As for Opioid Analgesics in general, p. 110.1.

Overdosage. Cyanosis, respiratory depression, and seizures developed in a 28-year-old woman after an overdose of a combination preparation of tilidine and naloxone.[1] The authors commented that the amount of naloxone included in the preparation, in order to prevent abuse, was insufficient to prevent respiratory depression after severe overdose.

1. Regenthal R, *et al.* Poisoning with tilidine and naloxone: toxicokinetic and clinical observations. *Hum Exp Toxicol* 1998; 17: 593–7.

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

Pharmacokinetics

Tilidine is absorbed from the gastrointestinal tract. It is metabolised and excreted in the urine mainly as metabolites nortilidine (nortilidate) and bisnortilidine (bisnortilidate). Nortilidine is responsible for the analgesic activity of tilidine.

References.

1. Vollmer K-O, *et al.* Pharmacokinetics of tilidine and metabolites in man. *Arzneimittelforschung* 1989; 39: 1283–8.
2. Seiler K-U, *et al.* Pharmacokinetics of tilidine in terminal renal failure. *J Clin Pharmacol* 2001; 41: 79–84.
3. Hajda JP, *et al.* Sequential first-pass metabolism of nortilidine: the active metabolite of the synthetic opioid drug tilidine. *J Clin Pharmacol* 2002; 42: 1257–61.
4. Brennscheidt U, *et al.* Pharmacokinetics of tilidine and naloxone in patients with severe hepatic impairment. *Arzneimittelforschung* 2007; 57: 106–11.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Tinalox; Valtran; *Ger.*: Andolor†; Celldolor†; Nalidin†; Tili Comp†; Tili-Puren†; Tilicomp; Tilidin comp†; Tilidin N†; Tilidin plus; Tilidin-saar†; Tilidin; Tilnalox†; Valoron N; *S.Afr.*: Valoron; *Switz.*: Valoron.

Tinoridine Hydrochloride *(rINNM)*

Hidrocloruro de tinoridina; Tienoridine Hydrochloride; Tinoridina, hidrocloruro de; Tinoridine, Chlorhydrate de; Tinoridini Hydrochloridum; Y-3642 (tinoridine); Тиноридина Гидрохлорид.

Ethyl 2-amino-6-benzyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxylate hydrochloride.

$C_{17}H_{20}N_2O_2S,HCl$=352.9

CAS — 24237-54-5 (tinoridine); 25913-34-2 (tinoridine hydrochloride).

UNII — 05IIB89IVA.

Profile

Tinoridine hydrochloride is an NSAID that has been used for pain and inflammation.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Indon.*: Nonflamin.

Tofacitinib *(USAN, pINN)*

CP-690550; Tasocitinib; Tofacitinibum; Тофацитиниб.

3-[(3*R*,4*R*)-4-Methyl-3-[methyl(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]piperidin-1-yl]-3-oxopropanenitrile.

$C_{16}H_{20}N_6O$=312.4

CAS — 477600-75-2.

ATC — L04AA29.

ATC Vet — QL04AA29.

UNII — 87LA6FU830.

Tofacitinib Citrate *(USAN, pINNM)*

Citrato de tofacitinib; CP-690550-10; Tasocitinib Citrate; Tofacitinib, Citrate de; Tofacitinibi Citras; Тофацитиниба Цитрат.

$C_{16}H_{20}N_6O,C_6H_8O_7$=504.5

CAS — 540737-29-9.

ATC — L04AA29.

ATC Vet — QL04AA29.

UNII — O1FF4DIV0D.

Uses and Administration

Tofacitinib is an orally active Janus tyrosine kinase (JAK) inhibitor that is selective for JAK1 and JAK3. It is used as a disease-modifying antirheumatic drug (DMARD) in the treatment of moderately to severely active rheumatoid arthritis (p. 13.2) in patients who have had an inadequate response to, or intolerance of, methotrexate. It may be used as monotherapy, or in combination with methotrexate or another non-biological DMARD.

Tofacitinib is given as the citrate although doses are expressed in terms of the base; tofacitinib citrate 8 mg is equivalent to about 5 mg of tofacitinib. The usual oral dose is the equivalent of 5 mg of tofacitinib twice daily.

If a potent cytochrome P450 isoenzyme CYP3A4 inhibitor, or a combination of moderate CYP3A4 and potent CYP2C19 inhibitors, must also be used, the dose should be reduced to 5 mg once daily.

The dose of tofacitinib should also be reduced in patients with hepatic or renal impairment (see below).

Regular monitoring of haematological parameters is recommended; tofacitinib therapy should be interrupted or withdrawn if blood counts fall below acceptable levels (see Monitoring, under Adverse Effects and Precautions, below).

Tofacitinib is also being investigated for the treatment of various other auto-immune or immune-mediated disorders including ankylosing spondylitis, psoriatic arthritis, psoriasis, Crohn's disease, and ulcerative colitis, and for the prevention of graft rejection.

References.

1. Anonymous. Tofacitinib. *Drugs R D* 2010; 10: 271–84. Correction. *ibid.* 2012; 12: 41–3. [dose]
2. Fleischmann R, *et al.* ORAL Solo Investigators. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. *N Engl J Med* 2012; 367: 495–507.
3. van Vollenhoven RF, *et al.* ORAL Standard Investigators. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. *N Engl J Med* 2012; 367: 508–19.
4. Sandborn WJ, *et al.* Study A3921063 Investigators. Tofacitinib, an oral Janus kinase inhibitor, in active ulcerative colitis. *N Engl J Med* 2012; 367: 616–24.
5. Papp KA, *et al.* Efficacy and safety of tofacitinib, an oral Janus kinase inhibitor, in the treatment of psoriasis: a phase 2b randomized placebo-controlled dose-ranging study. *Br J Dermatol* 2012; 167: 668–77.
6. Burmester GR, *et al.* ORAL Step Investigators. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. *Lancet* 2013; 381: 451–60.

Administration in hepatic and renal impairment. The oral dose of tofacitinib should be reduced to 5 mg once daily in patients with moderate hepatic, or moderate or severe renal, impairment; it should not be used in those with severe hepatic impairment due to a lack of data.

Adverse Effects and Precautions

The most commonly reported adverse effects with tofacitinib are upper respiratory-tract infections, headache, diarrhoea, and nasopharyngitis. Serious and sometimes fatal infections caused by bacterial, mycobacterial, invasive fungal, or viral pathogens, such as pneumonia, cellulitis, herpes zoster, and urinary-tract infections may occur. Opportunistic infections such as tuberculosis, cryptococcus, oesophageal candidiasis, pneumocystosis, multidermatomal herpes zoster, CMV, and BK virus have also been reported. Disseminated disease may develop, particularly in patients also taking other immunomodulators such as methotrexate or corticosteroids. Tofacitinib should not be given to patients with active, including localised, infections; it should be used with caution in those with chronic or recurrent infection, exposure to tuberculosis, a history of serious or opportunistic infection, or underlying conditions that may predispose to infection, or who have resided or travelled in areas of endemic tuberculosis or mycoses. Patients should be evaluated for latent or active tuberculosis before starting therapy; if evidence of latent tuberculosis is found, standard chemoprophylaxis should be started before giving tofacitinib. Patients should be monitored for signs and symptoms of any infection during and after treatment with tofacitinib; treatment should be interrupted until the infection is controlled. Reactivation of viral infections, such as herpes zoster, has also been reported.

Tofacitinib has been associated with an increased incidence of malignancies, including lymphomas; care is advocated in patients with a history of malignancy. Post-transplant lymphoproliferative disorder associated with the Epstein-Barr virus has been reported in renal transplant patients also taking immunosuppressants.

Gastrointestinal perforation has been reported and tofacitinib should be used with caution in patients with an increased risk, such as those with a history of diverticulitis.

Blood disorders such as lymphocytosis followed by lymphocytopenia, neutropenia, and anaemia have been reported (see also Monitoring, below); impaired hepatic and renal function, and increases in serum cholesterol levels have also been noted.

Monitoring. Blood counts should be performed before the start of, and during, tofacitinib therapy.

Tofacitinib therapy should *not be started* in patients with any of the following baseline counts:

- haemoglobin < 90 g/litre
- lymphocyte < 500 cells/mm³
- neutrophil (ANC) < 1000 cells/mm³

Therapy should be *interrupted* (and restarted when values normalise) in patients who develop:

- haemoglobin < 80 g/litre or > 20 g/litre decrease
- persistent ANC of 500 to 1000 cells/mm³

Therapy should be *withdrawn* in patients who develop:

- lymphocyte < 500 cells/mm³
- ANC < 500 cells/mm³

Interactions

Live vaccines should not be given with tofacitinib as its effect on vaccine efficacy or the risk of infection transmission is unknown. Tofacitinib should not be given with biological disease-modifying antirheumatic drugs (DMARDs) or other potent immunosuppressants.

The use of tofacitinib with a potent cytochrome P450 isoenzyme CYP3A4 inhibitor, or with a combination of moderate CYP3A4 and potent CYP2C19 inhibitors, may increase exposure to tofacitinib; the dosage of tofacitinib should be reduced (see Uses and Administration, above). Conversely, use with a potent CYP3A4 inducer may decrease exposure to tofacitinib.

Pharmacokinetics

After oral doses of tofacitinib, peak plasma concentrations occur within 0.5 to 1 hour, with an absolute bioavailability of 74%. Protein binding is about 40%, mainly to albumin, and is distributed equally between red blood cells and plasma. The elimination half-life is about 3 hours and 70% of tofacitinib is eliminated via hepatic metabolism and 30% via renal excretion. Tofacitinib is metabolised mainly by the cytochrome P450 isoenzyme CYP3A4, and to a lesser extent by CYP2C19.

Studies in *animals* suggest that tofacitinib is distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Xeljanz; *USA*: Xeljanz.

Tolfenamic Acid *(BAN, rINN)*

Acide Tolfénamique; Ácido tolfenámico; Acidum Tolfenamicum; Kyselina tolfenamová; Tolfenaamihappo; Tolfenámico, ácido; Tolfenaminsäure; Tolfenaminsav; Tolfenamo rūgštis; Tolfenamsyra; Толфенамовая Кислота.

N-(3-Chloro-*o*-tolyl)anthranilic acid.

$C_{14}H_{12}ClNO_2$=261.7.

CAS — 13710-19-5.

ATC — M01AG02.

ATC Vet — QM01AG02.

UNII — 3G943U18KM.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Tolfenamic Acid). A white or slightly yellow crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol and in dichloromethane; soluble in dimethylformamide. It dissolves in dilute solutions of alkali hydroxides. Protect from light.

Uses and Administration

Tolfenamic acid, an anthranilic acid derivative related to mefenamic acid (p. 86.1), is an NSAID (p. 102.3). In the treatment of acute attacks of migraine tolfenamic acid is given in a usual oral dose of 200 mg when the first symptoms appear; if a satisfactory response is not obtained this dose may be repeated once after 1 to 2 hours. Tolfenamic acid has also been given for the relief of mild to moderate pain in disorders such as dysmenorrhoea, rheumatoid arthritis, or osteoarthritis in doses of 100 to 200 mg three times daily.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3.

Dysuria, most commonly in males and probably due to local irritation of the urethra by a metabolite, has been reported. Tremor, euphoria, and fatigue have also occurred. Tolfenamic acid is contra-indicated in patients with significant hepatic or renal impairment.

Breast feeding. Although tolfenamic acid is distributed into breast milk, the amount is considered by the *BNF* and licensed product information to be too small to be harmful to a breast-fed infant.

Effects on the lungs. Pulmonary infiltration has been associated with tolfenamic acid treatment in 6 patients.[1]

1. Strömberg C, *et al.* Pulmonary infiltrations induced by tolfenamic acid. *Lancet* 1987; ii: 685.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and

the Porphyria Centre Sweden, classifies tolfenamic acid as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 23/10/11)

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Pharmacokinetics

Tolfenamic acid is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur about 60 to 90 minutes after an oral dose. Tolfenamic acid is about 99% bound to plasma proteins. The plasma half-life is about 2 hours. Tolfenamic acid is metabolised in the liver; the metabolites and unchanged drug are conjugated with glucuronic acid. About 90% of an ingested dose is excreted in the urine and the remainder in the faeces. Tolfenamic acid is distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Flocur; *China*: Te Fen Ta (特芬它); *Cz.*: Migea†; *Denm.*: Migea; *Fin.*: Clotam; *Gr.*: Clotam; Gantil; Migea; Polmonin; Primactam; Purfalox; Tolfamic; Turbaund; *Norw.*: Migea; *Pol.*: Migea; *UK*: Clotam.

Tolmetin Sodium *(BANM, USAN, rINNM)*

McN-2559-21-98; McN-2559 (tolmetin); Natrii Tolmetinum; Tolmetina sódica; Tolmétine Sodique; Натрий Тольметин.

Sodium (1-methyl-5-*p*-toluoylpyrrol-2-yl)acetate dihydrate.

$C_{15}H_{14}NNaO_3,2H_2O$=315.3

CAS — 26171-23-3 (tolmetin); 35711-34-3 (anhydrous tolmetin sodium); 64490-92-2 (tolmetin sodium dihydrate).

ATC — M01AB03; M02AA21.

ATC Vet — QM01AB03; QM02AA21.

UNII — 02N1TZF99F.

Pharmacopoeias. In *US.*

USP 36: (Tolmetin Sodium). A light yellow to light orange crystalline powder. Freely soluble in water and in methyl alcohol; slightly soluble in alcohol; very slightly soluble in chloroform.

Uses and Administration

Tolmetin sodium is an NSAID (p. 102.3). It is used in musculoskeletal and joint disorders such as osteoarthritis and rheumatoid arthritis, including juvenile idiopathic arthritis. It is given orally as the sodium salt although doses are expressed in terms of the base; tolmetin sodium dihydrate 122.5 mg is equivalent to about 100 mg of tolmetin.

For the treatment of rheumatoid arthritis and osteoarthritis, the usual initial oral dose is the equivalent of 400 mg of tolmetin three times daily. Doses should be adjusted after 1 to 2 weeks according to response; maintenance doses of 600 mg to a maximum of 1800 mg daily in divided doses have been used.

For dosage details in children, see below.

Tolmetin as the free acid has been applied as a topical gel.

Administration in children. For the treatment of juvenile idiopathic arthritis in children aged 2 years and over, tolmetin sodium is given in initial oral doses equivalent to 20 mg/kg of tolmetin daily in three or four divided doses; maintenance doses of 15 mg/kg to a maximum of 30 mg/kg daily have been used.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p. 104.3.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were given tolmetin, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding. However, licensed product information recommends that tolmetin should be avoided in nursing mothers.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/11/07)

Effects on the blood. Case reports of agranulocytosis[1] and thrombocytopenia[2] associated with tolmetin.

1. Sakai J, Joseph MW. Tolmetin and agranulocytosis. *N Engl J Med* 1978; 298: 1203.
2. Lockhart JM. Tolmetin-induced thrombocytopenia. *Arthritis Rheum* 1982; 25: 1144–5.

Effects on the CNS. See Hypersensitivity, below.

Effects on the gastrointestinal tract. Erosive oesophagitis has been reported[1] in an 11-year-old child after ingestion of a dose of tolmetin while lying down and without drinking any water.

1. Palop V, *et al.* Tolmetin-induced esophageal ulceration. *Ann Pharmacother* 1997; 31: 929.

Effects on the kidneys. Interstitial nephritis[1] and nephrotic syndrome[2,3] have been reported in patients given tolmetin.

1. Katz SM, *et al.* Tolmetin: association with reversible renal failure and acute interstitial nephritis. *JAMA* 1981; 246: 243–5.
2. Chatterjee GP. Nephrotic syndrome induced by tolmetin. *JAMA* 1981; 246: 1589.
3. Tietjen DP. Recurrence and specificity of nephrotic syndrome due to tolmetin. *Am J Med* 1989; 87: 354–5.

Hypersensitivity. Anaphylactic shock,[1] urticaria and angioedema,[2] and aseptic meningitis[3] are among the hypersensitivity reactions reported in patients taking tolmetin.

1. Rosli AC, Knapp DE. Tolmetin-induced anaphylactoid reactions. *N Engl J Med* 1982; 307: 499–500.
2. Ponte CD, Wisman R. Tolmetin-induced urticaria/angioedema. *Drug Intell Clin Pharm* 1985; 19: 479–80.
3. Ruppert GB, Barth WF. Tolmetin-induced aseptic meningitis. *JAMA* 1981; 245: 67–8.

Interactions

For interactions associated with NSAIDs, see p. 107.3.

Pharmacokinetics

Tolmetin is almost completely absorbed from the gastrointestinal tract and peak plasma concentrations occur about 30 to 60 minutes after ingestion. It is extensively bound to plasma proteins (over 99%) and has a biphasic plasma half-life of about 1 to 2 hours and 5 hours, respectively. Tolmetin penetrates synovial fluid and very small amounts are distributed into breast milk. It is excreted in the urine as an inactive dicarboxylic acid metabolite and its glucuronide and as tolmetin glucuronide with small amounts of unchanged drug.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Tolectin; *Mex.*: Tolectin; *S. Afr.*: Tolectin†; *Spain*: Artrocaptin†; *Turk.*: Tolectin; *USA*: Tolectin.

Pharmacopoeial Preparations

USP 36: Tolmetin Sodium Capsules; Tolmetin Sodium Tablets.

Tramadol Hydrochloride

(BANM, USAN, rINNM)

CG-315; CG-315E; Hidrocloruro de tramadol; Tramadol, Chlorhydrate de; Tramadol, hidrocloruro de; Tramadol Hidroklorür; Tramadol-hidroklorid; Tramadol-hydrochlorid; Tramadolhydrochlorid; Tramadolhydroklorid; Tramadoli Hydrochloridum; Tramadolihydrokloridi; Tramadolio hidrochloridas; U-26225A; Трамадола Гидрохлорид.

(±)-*trans*-2-Dimethylaminomethyl-1-(3-methoxyphenyl) cyclohexanol hydrochloride.

$C_{16}H_{25}NO_2$,HCl=299.8

CAS — 27203-92-5 (tramadol); 22204-88-2 (tramadol hydrochloride); 36282-47-0 (tramadol hydrochloride).

ATC — N02AX02.

ATC Vet — QN02AX02.

UNII — 9N7R477WCK.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Tramadol Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water and in methyl alcohol; very slightly soluble in acetone. Protect from light.

USP 36: (Tramadol Hydrochloride). A white, crystalline powder. Freely soluble in water and methyl alcohol; very slightly soluble in acetone. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Incompatibility. Some manufacturers state that tramadol hydrochloride injection 50 mg/mL is incompatible with injections of diazepam, diclofenac sodium, flunitrazepam, glyceryl trinitrate, indometacin, midazolam, piroxicam, and phenylbutazone if mixed in the same syringe. A study[1] also found tramadol hydrochloride injection (diluted to 400 micrograms/mL) to be incompatible with aciclovir and clindamycin when mixed together.

1. Abanmy NO, *et al.* Compatibility of tramadol hydrochloride injection with selected drugs and solutions. *Am J Health-Syst Pharm* 2005; 62: 1299–1302.

Stability. Oral suspensions of tramadol hydrochloride 5 mg/mL, prepared by mixing crushed tablets with a strawberry syrup and *Ora-Plus* (1:1) or with *Ora-Sweet* and *Ora-Plus* (1:1) were found to be stable for at least 90 days when stored either in the refrigerator or at room temperature.[1] Oral suspensions containing tramadol hydrochloride 7.5 mg/mL and paracetamol 65 mg/mL, prepared by mixing the crushed tablets of a combination preparation with the above vehicles, were also found to be stable for at least 90 days when stored under similar conditions.[2]

1. Wagner DS, *et al.* Stability of oral liquid preparations of tramadol in strawberry syrup and a sugar-free vehicle. *Am J Health-Syst Pharm* 2003; 60: 1268–70.
2. Johnson CE, *et al.* Stability of tramadol hydrochloride–acetaminophen (Ultracet) in strawberry syrup and in a sugar-free vehicle. *Am J Health-Syst Pharm* 2004; 61: 54–7.

Uses and Administration

Tramadol hydrochloride is an opioid analgesic (p. 108.1). It also has noradrenergic and serotonergic properties that may contribute to its analgesic activity. Tramadol is used for moderate to severe pain.

Tramadol hydrochloride is given orally, intravenously, or rectally as a suppository. The intramuscular route has also been used. It may also be given by infusion or as part of a patient-controlled analgesia system.

Usual *oral* doses are 50 to 100 mg every 4 to 6 hours. Tramadol hydrochloride may also be given orally as a modified-release preparation once or twice daily. The total oral daily dosage should not exceed 400 mg. Usual doses may be used in elderly patients although in those aged over 75 years the elimination half-life is increased and a reduced dose may be required; the licensed product information for one US preparation (*Ultram*, *PriCara*) recommends a maximum dose of 300 mg daily in such patients while an increase in the dosage interval is often suggested in UK product information. Preparations containing tramadol hydrochloride with other analgesics such as paracetamol are also used.

When used *parenterally*, a dose of 50 to 100 mg may be given every 4 to 6 hours by intramuscular or intravenous injection over 2 to 3 minutes, or by intravenous infusion. For the treatment of postoperative pain, the initial dose is 100 mg followed by 50 mg every 10 to 20 minutes if necessary to a total maximum (including the initial dose) of 250 mg in the first hour. Thereafter, doses are 50 to 100 mg every 4 to 6 hours up to a total daily dose of 600 mg.

Usual *rectal* doses by suppository are 100 mg up to 4 times daily.

For details of doses in children and in patients with hepatic or renal impairment, see below and p. 140.1, respectively.

References.

1. Scott LJ, Perry CM. Tramadol: a review of its use in perioperative pain. *Drugs* 2000; 60: 139–76.
2. McClellan K, Scott LJ. Tramadol/paracetamol. *Drugs* 2003; 63: 1079–86. Correction. *ibid.*: 1636.
3. Grond S, Sablotzki A. Clinical pharmacology of tramadol. *Clin Pharmacokinet* 2004; 43: 879–923.
4. Leppert W, Luczak J. The role of tramadol in cancer pain treatment—a review. *Support Care Cancer* 2005; 13: 5–17.
5. Close BR. Tramadol: does it have a role in emergency medicine? *Emerg Med Australas* 2005; 17: 73–83.
6. Cepeda MS, *et al.* Tramadol for osteoarthritis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 26/06/08).
7. Duehmke RM, *et al.* Tramadol for neuropathic pain. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 26/06/08).
8. Keating GM. Tramadol sustained-release capsules. *Drugs* 2006; 66: 223–30.
9. Hair PI, *et al.* Tramadol extended-release tablets. *Drugs* 2006; 66: 2017–27.
10. Freeman R, *et al.* Randomized study of tramadol/acetaminophen versus placebo in painful diabetic peripheral neuropathy. *Curr Med Res Opin* 2007; 23: 147–61.

Administration in children. In the UK, tramadol hydrochloride is licensed for the management of moderate to severe pain in children 12 years of age and older; usual adult doses may be given (see above). However, in some other European countries it is licensed in younger children although the age range permitted can vary: for example, in *France*, a usual dose in those aged 3 years and over is 1 to 2 mg/kg orally, which may be repeated 3 or 4 times daily, whereas in *Germany*, similar doses are permitted in children as young as 1 year old. Tramadol has also been given parenterally to children in doses similar to those used orally.

Some references[1-4] on the use of tramadol in children.

1. Finkel JC, *et al.* An evaluation of the efficacy and tolerability of oral tramadol hydrochloride tablets for the treatment of postsurgical pain in children. *Anesth Analg* 2002; 94: 1469–73.
2. Demiraran Y, *et al.* A comparison of the postoperative analgesic efficacy of single-dose epidural tramadol versus morphine in children. *Br J Anaesth* 2005; 95: 510–13.
3. Bozkurt P. Use of tramadol in children. *Paediatr Anaesth* 2005; 15: 1041–7.
4. Chu Y-C, *et al.* Intraoperative administration of tramadol for postoperative nurse-controlled analgesia resulted in earlier awakening

The symbol † denotes a preparation no longer actively marketed

and less sedation than morphine in children after cardiac surgery. *Anesth Analg* 2006; 102: 1668–73.

Administration in hepatic or renal impairment. A dosage interval of 12 hours is recommended for tramadol usage in severe hepatic impairment; US licensed product information suggests that patients with cirrhosis should be given oral doses of 50 mg every 12 hours. The dosage interval should also be increased to 12 hours in patients with a creatinine clearance (CC) of less than 30 mL/minute; in the USA licensed product information suggests that the maximum oral dose should not exceed 200 mg daily in these patients. Tramadol should not be given to patients with more severe renal impairment (CC less than 10 mL/minute).

Dependence and Withdrawal

As for Opioid Analgesics, p. 109.1.

Tramadol may have lower potential for producing dependence than morphine.

A WHO expert committee[1] considered in 2003 that the available information on tramadol was not sufficient to warrant international control. Studies in *animals* indicated that tramadol produced little tolerance, had mild withdrawal symptoms, and a lower abuse potential than codeine and pentazocine. Subsequently, when reviewed in 2006, the committee[2] considered that, despite an increase in its use, tramadol continued to show a low level of abuse and concluded that there was not sufficient evidence to justify a further review.

Nevertheless, there have been reports[3-8] of dependence and abuse, particularly in opioid-dependent persons, and of withdrawal symptoms. In October 1996, the UK CSM[9] commented that since June 1994 they had received reports of drug dependence in 5 patients and withdrawal symptoms associated with tramadol in 28 patients, which corresponded to a reporting rate of about 1 in 6000. Doses in excess of the recommended maximum of 400 mg daily had been taken by 5 of the patients. The duration of treatment before onset of these effects ranged from 10 to 409 days (average 3 months). Withdrawal symptoms reported were typically those of opioid withdrawal in general. A more recent report from the Swedish Medical Products Agency[10] stated that between 1996 to 2005 they had received 71 reports of withdrawal symptoms associated with tramadol; treatment duration ranged from 1 week to over 3 years at daily doses of between 50 mg to 2 g.

1. WHO. WHO expert committee on drug dependence: thirty-third report. *WHO Tech Rep Ser 915* 2003. Also available at: http://libdoc.who.int/trs/WHO_TRS_915.pdf (accessed 26/06/08)
2. WHO. WHO expert committee on drug dependence: thirty-fourth report. *WHO Tech Rep Ser 942* 2006. Also available at: http://libdoc.who.int/trs/WHO_TRS_942_eng.pdf (accessed 26/06/08)
3. Rodriguez Villamañan JC, *et al.* Withdrawal syndrome after long-term treatment with tramadol. *Br J Gen Pract* 2000; 50: 406.
4. Yates WR, *et al.* Tramadol dependence with no history of substance abuse. *Am J Psychiatry* 2001; 158: 964.
5. Brinker A, *et al.* Abuse, dependence, or withdrawal associated with tramadol. *Am J Psychiatry* 2002; 159: 881.
6. Skipper GE, *et al.* Tramadol abuse and dependence among physicians. *JAMA* 2004; 292: 1818–19.
7. Soyka M, *et al.* Tramadol use and dependence in chronic noncancer pain patients. *Pharmacopsychiatry* 2004; 37: 191–2.
8. Ripamonti C, *et al.* Withdrawal syndrome after delayed tramadol intake. *Am J Psychiatry* 2004; 161: 2326–7.
9. CSM/MCA. Tramadol—(Zydol, Tramake and Zamadol). *Current Problems* 1996; 22: 11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023218&RevisionSelectionMethod=LatestReleased (accessed 26/06/08)
10. Läkemedelsverket (Medical Products Agency—Sweden). Utsättningsreaktioner av tramadol—ett större problem än förväntat? (issued 14th November, 2006). Available at: http://www.lakemedelsverket.se/Allanyheter/NYHETER-2006/Utsattningsreaktioner-av-tramadol-ett-storre-problem-an-forvantat-/ (accessed 02/08/10)

Adverse Effects and Treatment

As for Opioid Analgesics in general, p. 110.1.

Tramadol may produce fewer typical opioid adverse effects such as respiratory depression and constipation. In addition to hypotension, hypertension has occasionally occurred.

Deaths associated with tramadol use have been reported in patients with a history of emotional disturbances, suicidal ideation or attempted suicide, or misuse of CNS depressants such as alcohol and anxiolytics.

Effects on the CNS. The UK CSM[1] commented in February 1995 that since June 1994 they had received reports of 15 patients who had had *confusion* and/or *hallucinations* while taking tramadol. The majority of the reactions developed 1 to 7 days after starting treatment and in most patients resolved rapidly on withdrawal. It was noted that psychiatric reactions comprised about 10% of all reactions reported with tramadol.

In a later comment[2] in October 1996, the CSM noted that 27 reports of *convulsions* and one of worsening epilepsy had been received, which corresponded to a reporting rate of about 1 in 7000. Of the 5 patients receiving intravenous tramadol, 2 had been given doses equivalent to 1.45 and 4 g daily, well in excess of those recommended (see also Overdosage, below). Of the patients receiving oral tramadol, the majority were taking other drugs known to cause convulsions, including tricyclic antidepressants and SSRIs. A similar pattern has been reported in the USA[3] and Australia.[4-6]

A debilitating CNS-mediated reaction to an initial dose of tramadol has been described in a patient.[7] Symptoms, which lasted about 4 hours, included ataxia, dilatation of the pupils, numbness in all limbs, tremulousness, and dysphoria. Although the exact mechanism of the reaction was unknown, it was suggested that since the patient was an extensive metaboliser with very high activity of the cytochrome P450 isoenzyme CYP2D6, high concentrations of the active *O*-desmethyl metabolite were the cause. The patient recovered with no sequelae. It is possible that this represents a case of the *serotonin syndrome*, since tramadol is known to be associated with this condition, particularly at high doses or when given with other drugs that raise serotonin concentrations.[4]

1. CSM/MCA. Tramadol (Zydol)—psychiatric reactions. *Current Problems* 1995; 21: 2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015618&RevisionSelectionMethod=LatestReleased (accessed 26/06/08)
2. CSM/MCA. Tramadol—(Zydol, Tramake and Zamadol). *Current Problems* 1996; 22: 11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023218&RevisionSelectionMethod=LatestReleased (accessed 26/06/08)
3. Kahn LH, *et al.* Seizures reported with tramadol. *JAMA* 1997; 278: 1661.
4. Adverse Drug Reactions Advisory Committee (ADRAC). Tramadol—four years experience. *Aust Adverse Drug React Bull* 2003; 22: 1–2. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0302.pdf (accessed 26/06/08)
5. Labate A, *et al.* Tramadol and new-onset seizures. *Med J Aust* 2005; 182: 42–3.
6. Boyd IW. Tramadol and seizures. *Med J Aust* 2005; 182: 595–6.
7. Gleason PP, *et al.* Debilitating reaction following the initial dose of tramadol. *Ann Pharmacother* 1997; 31: 1150–2.

Effects on the respiratory system. Respiratory depression has been reported after tramadol infusion anaesthesia,[1] although in a postoperative study[2] tramadol had no significant respiratory depressant effect when equianalgesic doses of morphine, pentazocine, pethidine, piritramide, and tramadol were compared.

1. Paravicini D, *et al.* Tramadol-infusionsanaesthesie mit Substitution von Enfluran und differenten Lachgaskonzentrationen. *Anaesthesist* 1985; 34: 20–7.
2. Fechner R, *et al.* Clinical investigations on the effect of morphine, pentazocine, pethidine, piritramide and tramadol on respiration. *Anasth Intensivmed* 1985; 26: 126–32.

Overdosage. In a multicentre case series,[1] 126 cases of tramadol toxicity were reported between October 1995 and August 1996; of these, 87 involved exposure to tramadol alone. Common symptoms included lethargy, nausea, tachycardia, and agitation; seizures were also noted. Respiratory depression was seen in only 2 patients. The inhibitory effects of tramadol on monoamine reuptake, rather than its opioid effects, was considered to result in much of its toxicity. A similar pattern of toxicity has also been seen in a more recent report.[2] In 190 tramadol-only exposures reported between January 1999 and July 2001, the main symptoms of overdosage were CNS depression, nausea and vomiting, tachycardia, and seizures. Again, the incidence of respiratory depression was rare, with only 1 case reported.

1. Spiller HA, *et al.* Prospective multicenter evaluation of tramadol exposure. *J Toxicol Clin Toxicol* 1997; 35: 361–4.
2. Marquardt KA, *et al.* Tramadol exposures reported to statewide poison control system. *Ann Pharmacother* 2005; 39: 1039–44.

Precautions

As for Opioid Analgesics in general, p. 110.3.

Tramadol should not be given to patients who are suicidal or prone to addiction. It should be used with caution in those who use alcohol in excess, or suffer from emotional disturbance or depression. Tramadol should be used with care in patients with a history of epilepsy or those susceptible to seizures. See also Effects on the CNS under Adverse Effects, above.

Tramadol should also be used with caution in patients with renal or hepatic impairment and should be avoided if renal impairment is severe. Removal by haemodialysis is reported to be minimal at 7%.

Abuse. See under Dependence and Withdrawal, above.

Anaesthesia. Licensed product information warns against using tramadol during very light planes of general anaesthesia because of possible intra-operative awareness, although it may be used intra-operatively provided anaesthesia is maintained with a potent volatile or intravenous anaesthetic. Intra-operative awareness was reported in 65% of a group of 20 patients when used to provide analgesia during light general anaesthesia with nitrous oxide and intermittent enflurane.[1] However, in a study[2] of 51 patients given tramadol during stable light continuous isoflurane-nitrous oxide anaesthesia there was no clinically significant lightening of anaesthesia and others have commented that during extensive use of tramadol intraoperatively over several years, there had not been any incidence of recall in any patient treated at their clinic.[3]

1. Lehmann KA, *et al.* Zur Bedeutung von Tramadol als intraoperativem Analgetikum: eine randomisierte Doppelblindstudie im Vergleich zu Placebo. *Der Anaesthetist* 1985; 34: 11–19.
2. Coetzee JF, *et al.* Effect of tramadol on depth of anaesthesia. *Br J Anaesth* 1996; 76: 415–18.
3. Budd K. Tramadol. *Br J Anaesth* 1995; 75: 500.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tramadol as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 22/10/11)

Interactions

For interactions associated with opioid analgesics, see p. 111.2.

Carbamazepine is reported to diminish the analgesic activity of tramadol by reducing serum concentrations.

The risk of seizures is increased if tramadol is used with other drugs that have the potential to lower the seizure threshold. See also Effects on the CNS, above.

Tramadol inhibits reuptake of noradrenaline and serotonin and enhances serotonin release and there is the possibility that it may interact with other drugs that enhance monoaminergic neurotransmission including lithium, tricyclic antidepressants, triptans, and SSRIs, thereby increasing the risk of serotonin syndrome; it should not be given to patients receiving MAOIs or within 14 days of their discontinuation.

Metabolism of tramadol is mediated by the cytochrome P450 isoenzymes CYP2D6 and CYP3A4. Use with specific inhibitors of these enzymes may increase concentrations of tramadol and lower concentrations of its active metabolite. The clinical consequences of this effect are unclear although the risk of seizures or serotonin syndrome may be increased.

Anticoagulants. For reports of the effect of tramadol on oral anticoagulants, see Analgesics under Interactions of Warfarin, p. 1530.2.

Antidepressants. For reference to possible cases of serotonin syndrome associated with use of tramadol and *SSRIs*, see Opioid Analgesics under Interactions of Fluoxetine, p. 427.1.

5-HT$_3$-receptor antagonists. The pre-operative use of *ondansetron* has been noted to reduce the postoperative analgesic efficacy of tramadol.[1,2] In one study,[1] the cumulative dose of tramadol was up to 35% greater in those patients who also received ondansetron compared with those who received no antiemetic. In addition there was no difference in the incidence of postoperative nausea and vomiting between the two groups.

1. De Witte JL, *et al.* The analgesic efficacy of tramadol is impaired by concurrent administration of ondansetron. *Anesth Analg* 2001; 92: 1319–21.
2. Arcioni R, *et al.* Ondansetron inhibits the analgesic effects of tramadol: a possible 5-HT$_3$ spinal receptor involvement in acute pain in humans. *Anesth Analg* 2002; 94: 1553–7.

Pharmacokinetics

Tramadol is readily absorbed after oral doses but is subject to some first-pass metabolism. Mean absolute bioavailability is about 70 to 75% after oral use and 100% after intramuscular injection. Plasma protein binding is about 20%. Tramadol is metabolised by *N*- and *O*-demethylation via the cytochrome P450 isoenzymes CYP3A4 and CYP2D6 and glucuronidation or sulfation in the liver. The metabolite *O*-desmethyltramadol is pharmacologically active. Tramadol is excreted mainly in the urine as metabolites. Tramadol is widely distributed, crosses the placenta, and appears in small amounts in breast milk. The elimination half-life is about 6 hours.

References.

1. Karbu D, *et al.* Comparative pharmacokinetics of a once-daily tramadol extended-release tablet and an immediate-release reference product following single-dose and multiple-dose administration. *J Clin Pharmacol* 2010; 50: 544–53.

Children. References.

1. Murthy BVS, *et al.* Pharmacokinetics of tramadol in children after i.v. or caudal epidural administration. *Br J Anaesth* 2000; 84: 346–9.
2. Payne KA, *et al.* Pharmacokinetics of oral tramadol drops for postoperative pain relief in children aged 4 to 7 years—a pilot study. *Anesth Prog* 2003; 49: 109–12.
3. Zwaveling J, *et al.* Pharmacokinetics of rectal tramadol in postoperative paediatric patients. *Br J Anaesth* 2004; 93: 224–7.
4. Garrido MJ, *et al.* Population pharmacokinetic/pharmacodynamic modelling of the analgesic effects of tramadol in pediatrics. *Pharm Res* 2006; 23: 2014–23.
5. Saudan S, Habre W. Particularités pharmacologiques du tramadol chez l'enfant. *Ann Fr Anesth Reanim* 2007; 26: 560–3.

The elderly. Pharmacokinetic parameters in elderly patients were found to be similar to those in younger patients.[1]

1. Likar R, *et al.* Pharmacokinetic and pharmacodynamic properties of tramadol IR and SR in elderly patients: a prospective, age-group—controlled study. *Clin Ther* 2006; **28**: 2022–39.

Metabolism. Production of the active metabolite *O*-desmethyltramadol is dependent on the cytochrome P450 isoenzyme CYP2D6, which shows genetic polymorphism.[1,2] For a reference to a debilitating CNS-mediated reaction in a patient who was an extensive metaboliser with high CYP2D6 activity, see Effects on the CNS, p. 140.1.

1. Poulsen L, *et al.* The hypoalgesic effect of tramadol in relation to CYP2D6. *Clin Pharmacol Ther* 1996; **60**: 636–44.
2. Pedersen RS, *et al.* Enantioselective pharmacokinetics of tramadol in CYP2D6 extensive and poor metabolizers. *Eur J Clin Pharmacol* 2006; **62**: 513–21.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ana-Q; Calmador; Cloq; Nobligan; Trama-Klosidol; Tramal; Tramanovag; ***Austral.***: Durotram; Tradonal; Tramahexal; Tramal; Tramedo; Zydol; ***Austria***: Adamon; Contramal; Cromatodol; Noax Uno; Nobligan; Tradolan; Tramabene; Tramadolor; Tramal; Tramastad; Tramundal; ***Belg.***: Contramal; Doctramadol†; Dolzam; Tradonal; Tramium; ***Braz.***: Anangor; Dorless; Rapitram; Sensitram; Sylador; Timasen; Trabilin†; Tramaden; Tramadon; Tramal; Tramaliv; Zamadol; ***Canad.***: Durela; Ralivia; Tridural; Ultram; Zytram; ***Chile***: Manol; Minidol; Naxodol; Timarol; Tramal; Zaledor; Zodol; ***China***: An Tian (安田); Bei Pin (倍平); Bing Ning (冰宁); Da Ma Er (达吗尔); Feng Tong Ding (丰同叮); Hua Jie Wei (华搅威); Hua Qu (华曲); Jun Qing (君庆); Le Shi Pu Kang (乐施普康); Nao Tai (瑙泰); Qi Zhi (奇止); Qimaite (奇迈特); Qu Feng (曲芬); Qu Ming (区明); Qu Teng (曲腾); Qu Tong Kang (曲同康); Qutong (曲通); Rui Li Ping (瑞立平); Tai Mei Ding (泰美定); Ti Ma Er (替马尔); Tong Ting (通亭); Tramadolor (泰德洛); Tramal (舒敏); Tramcontin (奇曼丁); Xi Li Xi Meng (西利西蒙); Xiang Yang (祥阳); Yi Bang (宜邦); Yi Nuo Xing (依诺兴); Yin Jia (银加); Yu Tong (愈通); ***Cz.***: Mabron; Noax; Protradon; Tradef; Tralgit; Tramabene; Tramagit†; Tramal; Tramundin; ***Denm.***: Dolol; Gemadol; Mandolgin; Metracop†; Nobligan; Tadol; Tradolan; Tramium; ***Fin.***: Tradolan; Tramadin; Tramagetic†; Tramal; Trambo; Tramium; ***Fr.***: Biodalgic Contramal; Monoalgic; Monocrixo; Monotramal; Orozamudol; Takadol; Topalgic; Trasedal†; Zamudol; Zumalgic; ***Ger.***: Amadol†; Jutadol†; T-long†; Trama†; Tramabeta; Tramadoc†; Tramadolor†; Tramagit; Tramal; Tramundin; Travex One; ***Gr.***: Oxxalgan; Tradol; Tramal; ***Hong Kong***: Mabron†; Sefmal; Tramal†; Tramo; ***Hung.***: Adamon; Contramal; Ralgen; Tramadolor; Tramalgic; ***India***: Acema; Adamon; Admadol; Amtadol; Anatram; Arrestadol; Atdol; Avdol; Bestodol; Bolodol; Bramadol; Cadol; Cemadol; CG-Mac; Contramal; Cormadol; Cradol; Damol; Decotram; Didol; Dol; Doleira; Dolodol; Dolomed-T; Dolotram; Dolriz; Dols; Dolstar; Doltel; Domadol; E-Dol; Eltram; Formador; FS; Gemodol; Haledol; Idol; Ivydol; Kamadol; Kevtram; Lagesic; Leedol; Madol; Medol; Meridol; Midol; Neutram; Nictram; Nobligan; Novadol; Opi-OT; Opiate; Orchidol; Ospidol; Painadol; Painex; Tramacip; Tramazac; TRD-Contin; Urgendol; ***Indon.***: Andalpha†; Bellatram†; Camigesik; Centrasic; Contram; Corsadol; Dolana; Dolgesik; Dolocap; Dolsic; Forgesic; Kamadol; Katrasic; Nonalges; Nufapotram; Orasic; Pinorec; Radol; Seminac; Simatral; Tlusic; Tradosik; Tradyl; Tragesik; Tramal; Trasik; Traumasik†; Trunal; Tugesal; Zephanal; Zumatram; ***Irl.***: Biodol; By-Madol; Tradol; Tramake; Tramapine; Tramex†; Troxidol; Xymel; Zamadol†; Zydol; ***Israel***: Trabar†; Trama; Tramadex; Tramal; ***Ital.***: Adamon; Contramal; Fortradol; Prontalgin; Tradonal; Traflash; Tralodie; Tramalin; Tramamed; Unitrama; Unitramarim; ***Jpn***: Tramal; ***Malaysia***: Acugesic; Analab; Domadol; Mabron; Pengesic; Sefmal; Trabilin; Tracidol; Tramada; Tramox; Tramundin; ***Mex.***: Durodor†; Nobligan; Prontofort; Tradol; Tralic; Tramed; Trexol; Veldrol; ***Neth.***: Doltard†; Theradol; Tradonal; Tramagetic; Tramajuna; Tramal; Tramazela†; Tramelene†; ***Norw.***: Nobligan; Tramagetic; ***NZ***: Durotram; Tramal; Tramedo†; Zytram; ***Philipp.***: Amaryll; Clomadol; Dolmal; Dolotral; Dolpaz; Doltrahex; Gesidol; Mardol; Microdol; Milador; MNS; Mosepan; Pengesic; Peptrad; Plazadol; Radol; Siverol; TDL; Tolma†; Tracaine; Tradomal; Tradonal; Tramadin; Tramal; Tramid; Tramkor; Tramundin; Unitral; Vistra; Vitral; ***Pol.***: Adamon; Noax Uno; Oratram; Poltram; Tramahexal; Tramal; Tramcod†; Tramundin; Travictol; ***Port.***: Dolpar†; Gelotralib; Nobligan; Paxilfar; Tramal; Tramy†; Travex; Tridural; Zydol; Zytram†; ***Rus.***: Mabron (Маброн); Plazadol (Плазадол); Sintradon (Синтрадон)†; Tradol (Традол); Tramaklosidol (Трамаклосидол); Tramal (Трамал); Tramolin (Трамолин); ***S.Afr.***: Dolotram; Domadol; Nobligan; Tramahexal; Tramal; Tramaspen; Tramazac; Tramgesic; ***Singapore***: Acugesic; Mabron; Pengesic; Sefmal; Tradol; Tramal; Tramium†; ***Spain***: Adolonta; Ceparidin; Dolodol; Dolpar; Gelotradol; Nobligan†; Tloner; Tradonal; Zytram; ***Swed.***: Gemadol; Nobligan; Tiparol; Tradolan; Zamadol†; ***Switz.***: Dolotramine†; Ecodolor†; Trabar; Tradonal; Tramactil Uno; Tramal; Tramundin; ***Thai.***: Amanda; Ammitram†; Anadol; Analab; Mabron; Madol; Madola; Matradol; Millidol; Modsenal; Pacmadol; Paindol; Pharmadol; Ramadol; Rofy†; Sefmal; Tamolan; Tracine; Tradolgesic; Tradonal†; Tramada; Tramadil; Tramadon; Tramal; Tramamed; Tramax; Tramazac; Tramoda; Trasic; Traumed; Trosic; Vesnon; Volcidol; ***Turk.***: Contramal; Tramadolor; Ultramex; ***UK***: Dromadol†; Larapam; Mabron; Marol; Maxitram; Nobligan; Oldaram; Tilodol; Tradorec; Tramake; Tramquel; Tramulief; Zamadol; Zeridame; Zydol; ***Ukr.***: Tramalgin (Трамалгин)†; ***USA***: ConZip; Rybix; Ryzolt†; Ultram; ***Venez.***: Tramal.

Multi-ingredient Preparations. ***Arg.***: Calmador Plus; Cloq Plus; Trama-Klosidol Plus†; Tramacet; Tramal Plus; ***Austria***: Zaldiar; ***Belg.***: Pontalsic; Zaldiar; ***Braz.***: Paratram; Ultracet; ***Canad.***: Tramacet; ***Chile***: Analgex Sap; Cronus; Doloten; Minidol Plus; Naxodol Plus; Pramol†; Timarol-Par; Zafin; Zaldiar; Zaledor-P; ***China***: Keluoqu (克洛曲); Ultracet (及通安); ***Cz.***: Doreta; Partramec; Traparac; Zaldiar; ***Fr.***: Ixprim; Zaldiar; ***Ger.***: Dolevar†; Zaldiar; ***Gr.***: Zaldiar; ***Hong Kong***: Ultracet; ***Hung.***: Zaldiar; ***India***: Acema-P; Actidol-DP; Acuvin; Anatram-P; Anbrol; Arrestadol-P; Atdol Plus; Avdol-P; Bramadol-P; Cadol-P; Conac-PT; Cradol-P; Decotram-PD; Didol-D; Didol-P; Dolfen-P; Dolocet; Dols Plus; Dolwin-T; Domadol Plus; E-Dol Plus; Esgipyrin-T; Fentra; Freze; FS Plus; FS-D; Ibudol; Indolpara; Ingesic Forte; Kamadol-P; Kdol-P; Kevtram-DP; Kevtram-P; Leedol-P; Madol-P; Maxoflam-T; Meridol-D; Meridol; Miradol; Mortrin Compound; Movon-PT; Muzox; Neutram-P; Nictram Plus; Novadol-P; Novodol; Omodol; Opi-OT; Opiate-P; Opiate-PD; Oshdol; Osteodol; Otram; Painadol-P; Paratel-T; Tolydol; Tramacip Plus; Ultrazac; ***Indon.***: Patral; Ultracet; Zaldiar; ***Irl.***: Ixprim; ***Israel***: Zaldiar; ***Ital.***: Kolibri; Patrol; ***Jpn***: Tramcet; ***Malaysia***: Ultracet; ***Mex.***: Gammadol; Sinergix; Tramacet; Tremepen; Voydol-C; Zaldiar; ***Neth.***: Tilalgin†; Tramacet; Zaldiar; ***Philipp.***: Algesia; Cetodol; Cetra; Dolcet; ***Pol.***: Acutral; Doreta; Padolten; Poltram Combo; Zaldiar; ***Port.***: Tilalgin; Zaldiar; ***Rus.***: Forsodol (Форсодол); Zaldiar (Залдиар); ***S.Afr.***: Tramacet; ***Singapore***: Ultracet; ***Spain***: Pazital; Pontalsic; Zaldiar; ***Switz.***: Zaldiar; ***Thai.***: Ultracet; ***Turk.***: Zaldiar; ***UK***: Tramacet; ***Ukr.***: Zaldiar (Залдиар); ***USA***: Ultracet; ***Venez.***: Ultracet; Zaldiar.

Pharmacopoeial Preparations

BP 2014: Prolonged-release Tramadol Capsules; Prolonged-release Tramadol Tablets; Tramadol Capsules;
USP 36: Acetaminophen and Tramadol Hydrochloride Tablets; Tramadol Hydrochloride and Acetaminophen Oral Suspension; Tramadol Hydrochloride Extended-release Tablets; Tramadol Hydrochloride Oral Suspension; Tramadol Hydrochloride Tablets.

Trimeperidine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de trimeperidina; Promedol (trimeperidine); Promedolum (trimeperidine); Trimeperidina, hidrocloruro de; Trimépéridine, Chlorhydrate de; Trimeperidini Hydrochloridum; Тримеперидина Гидрохлорид.

1,2,5-Trimethyl-4-phenyl-4-piperidyl propionate hydrochloride.

$C_{17}H_{25}NO_2$,HCl=311.8

CAS — 64-39-1 (trimeperidine); 125-80-4 (trimeperidine hydrochloride).

Profile

Trimeperidine hydrochloride is an opioid analgesic (p. 108.1) with actions and uses similar to those of pethidine (p. 121.3).

Trolamine Salicylate *(pINNM)*

Salicilato de trietanolamina; Salicilato de trolamina; Trietanolamina, salicilato de; Triethanolamine Salicylate; Trolamine, Salicylate de; Trolamini Salicylas; Троламина Салицилат.

$C_{13}H_{21}NO_6$=287.3

CAS — 2174-16-5.

UNII — H8O40408HD.

Pharmacopoeias. In *US*.

USP 36: (Trolamine Salicylate). A compounded mixture of trolamine and salicylic acid in propylene glycol. pH of a 5% solution in water is between 6.5 and 7.5. Store in airtight containers in a cool place.

Profile

Trolamine salicylate is a salicylic acid derivative used similarly to methyl salicylate (p. 92.1) in topical rubefacient preparations in a concentration of 10 to 20% for the relief of muscular and rheumatic pain. It has also been used as a sunscreen.

Percutaneous absorption. In contrast to methyl salicylate, which undergoes considerable absorption and produces high subcutaneous and dermal concentrations of salicylic acid after application to intact skin, concentrations of salicylic acid after topical application of trolamine salicylate were substantially lower in tissue[1] and undetectable in serum.[2]

1. Cross SE, *et al.* Is there tissue penetration after application of topical salicylate formulations? *Lancet* 1997; **350**: 636.
2. Morra P, *et al.* Serum concentrations of salicylic acid following topically applied salicylate derivatives. *Ann Pharmacother* 1996; **30**: 935–40.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Dencorub Arthritis; Goanna Arthritis Cream; Metsal AR Analgesic; ***Canad.***: Actiflex†; Analgesic Cream; Aspercreme; Bengay Muscle Pain No Odor; Myoflex; Rub A-535 Antiphlogistine No Odour; ***Mex.***: Myoflex†; ***Singapore***: Metsal AR Analgesic; ***Spain***: Bexidermil; ***USA***: Analgesia Creme; Analgesic Creme; Aspercreme; Coppertone Tan Magnifier; Flex-Power Performance Sports; Mobisyl; Myoflex; Sportscreme; Tropical Blend Tan Magnifier.

Multi-ingredient Preparations. ***Austral.***: Metsal Analgesic; ***Canad.***: Rub A-535 Extra Strength Arthritis.

Ufenamate *(rINN)*

Butyl Flufenamate; Ufénamate; Ufenamato; Ufenamatum; Уфенамат.

Butyl *N*-(α,α,α-trifluoro-*m*-tolyl)anthranilate.

$C_{18}H_{18}F_3NO_2$=337.3

CAS — 67330-25-0.

UNII — 8Z7O7C1SLZ.

Profile

Ufenamate is an NSAID (p. 102.3) that has been used topically in inflammatory skin disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Combec; Fenazol.

Valdecoxib *(BAN, USAN, rINN)*

SC-65872; Valdécoxib; Valdecoxibum; Valdekoksib; Вальдекоксиб.

p-(5-Methyl-3-phenyl-4-isoxazolyl)benzenesulfonamide.

$C_{16}H_{14}N_2O_3S$=314.4

CAS — 181695-72-7.

ATC — M01AH03.

ATC Vet — QM01AH03.

UNII — 2919279Q3W.

Profile

Valdecoxib is an NSAID (p. 102.3) reported to be a selective inhibitor of cyclo-oxygenase-2 (COX-2). It was given orally in the treatment of osteoarthritis and rheumatoid arthritis, and for the pain of dysmenorrhoea. The risk of serious skin reactions with valdecoxib (see below), in addition to its cardiovascular adverse effects (see below), prompted its general withdrawal worldwide in April 2005.

Effects on the cardiovascular system. The short-term use of parecoxib and valdecoxib after coronary artery bypass graft surgery has been associated with an increased risk of adverse effects such as myocardial infarction, deep-vein thrombosis, pulmonary embolism, and stroke.[1] When compared with patients in the placebo group, the risk of such effects was almost 4 times greater in those who had received intravenous parecoxib for 3 days followed by oral valdecoxib for the next 7 days. Those patients who received oral valdecoxib only for 7 days postoperatively had a non-significant increase in risk for adverse cardiovascular effects.

The adverse cardiovascular effects associated with valdecoxib treatment were one of the reasons the drug was generally withdrawn in April 2005.

1. Nussmeier NA, *et al.* Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. *N Engl J Med* 2005; **352**: 1081–91.

Effects on the skin. Toxic epidermal necrolysis developed in a patient who took valdecoxib for 8 days, despite stopping the drug at the first signs of a rash and starting treatment with oral prednisolone;[1] the patient had a history of hypersensitivity to sulfonamides. Health Canada[2] noted in January 2004 that it had received 5 reports of serious cutaneous adverse reactions associated with valdecoxib over less than 1 year from marketing of the drug in December 2002. However, none of these were erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis although such reactions had been reported to other regulatory authorities. In December 2004, the EMEA[3] stated that it had received reports of all 3 reactions, as well as exfoliative dermatitis; most of them had occurred within the first 2 weeks of starting treatment and the incidence rate appeared greater for valdecoxib than other selective cyclo-oxygenase-2 (COX-2) inhibitors. The EMEA also noted that use of parecoxib (a prodrug of valdecoxib, see p. 119.3) had been associated with serious skin reactions.

The increased risk of serious skin reactions with valdecoxib treatment was one of the reasons the drug was generally withdrawn in April 2005.

1. Glasser DL, Burroughs SH. Valdecoxib-induced toxic epidermal necrolysis in a patient allergic to sulfa drugs. *Pharmacotherapy* 2003; 23: 551–3.
2. Health Canada. Valdecoxib (Bextra): severe cutaneous reactions. *Can Adverse React News* 2004; 14 (1): 1–2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v14n1-eng.pdf (accessed 29/08/08)
3. EMEA. EMEA public statement on valdecoxib (Bextra/Valdyn) and parecoxib sodium (Dynastat/Rayzon): cardiovascular risks in coronary artery bypass graft (CABG) surgery and serious adverse skin reactions (issued 15th December, 2004). Available at: http://www.emea.europa.eu/pdfs/human/press/pus/20480204en.pdf (accessed 29/08/08)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Bioval; Creval; Leap; Mobyle-V; Nizox; Osra; Oval; Valdiff; Valdixx; Valdone; Valus.

Multi-ingredient Preparations. *India*: Nizox-MR; Vectra-P.

Vedaprofen *(BAN, USAN, rINN)*

CERM-10202; PM-150; Vedaprofeeni; Védaprofène; Vedaprofeno; Vedaprofenum; Ведапрофен.

(±)-4-Cyclohexyl-α-methyl-1-naphthaleneacetic acid.

$C_{19}H_{22}O_2$=282.4

CAS — 71109-09-6.

ATC Vet — QM01AE90.

UNII — OKX88EO7OI.

Pharmacopoeias. In *Eur.* (see p. vii) for veterinary use only.

Ph. Eur. 8: (Vedaprofen for Veterinary Use; Vedaprofen BP (Vet) 2014). A white or almost white powder. Practically insoluble in water; soluble in methyl alcohol; freely soluble in acetone; it dissolves in dilute solutions of alkali hydroxides.

Profile

Vedaprofen, a propionic acid derivative, is an NSAID (p. 102.3) used in veterinary medicine for the treatment of inflammation and pain.

Viminol Hydroxybenzoate *(rINNM)*

Diviminol Hydroxybenzoate; Hidroxibenzoato de viminol; Viminol, hidroxibenzoato de; Viminol, Hydroxybenzoate de; Viminoli Hydroxybenzoas; Z-424 (viminol); Виминола Гидроксибензоат.

1-[1-(2-Chlorobenzyl)pyrrol-2-yl]-2-(di-sec-butyl)aminoethanol 4-hydroxybenzoate.

$C_{21}H_{31}ClN_2O.C_7H_6O_3$=501.1

CAS — 21363-18-8 (viminol); 21466-60-4 (viminol hydroxybenzoate); 23784-10-3 (viminol hydroxybenzoate).

ATC — N02BG05.

ATC Vet — QN02BG05.

Profile

Viminol hydroxybenzoate has analgesic and antipyretic properties. The equivalent of 400 mg daily of viminol has been given orally in divided doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Dividol; *Ital.*: Dividol.

Zaltoprofen *(rINN)*

CN-100; Zaltoprofène; Zaltoprofeno; Zaltoprofenum; ZC-102; Зальтопрофен.

(±)-10,11-Dihydro-α-methyl-10-oxodibenzo[*b*,*f*]thiepin-2-acetic acid.

$C_{17}H_{14}O_3S$=298.4

CAS — 89482-00-8.

UNII — H8635NG3PY.

NOTE. The names Borbit, Peleton, Peon, Salafapinon, Soleng, Soluirubin, and Zatferon have been used as trade marks for zaltoprofen.

Pharmacopoeias. In *Jpn.*

Profile

Zaltoprofen is an NSAID (p. 102.3) that has been given in an oral dose of 80 mg three times daily for pain and musculoskeletal and joint disorders.

References.
1. Ishizaki T, *et al.* Pharmacokinetic profile of a new nonsteroidal anti-inflammatory agent, CN-100, in humans. *Drug Invest* 1991; 3: 1–7.
2. Hatori M, Kokubun S. The long-term efficacy and tolerability of the new anti-inflammatory agent zaltoprofen in rheumatoid arthritis. *Curr Med Res Opin* 1998; 14: 79–87.
3. Hase K, *et al.* The effect of zaltoprofen on physiotherapy for limited shoulder movement in breast cancer patients: a single-blinded before-after trial. *Arch Phys Med Rehabil* 2006; 87: 1618–22.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Mex.*: Soleton.

Ziconotide *(USAN, rINN)*

CI-1009; SNX-111; ω-Conotoxin M VIIA; Ziconotida; Ziconotidum; Зиконотид.

L-Cysteinyl-L-lysylglycyl-L-lysylglycl-L-alanyl-L-lysyl-L-cystelnyl-L-seryl-L-arginyl-L-leucyl-L-methionyl-L-tyrosyl-L-α-aspartyl-L-cysteinyl-L-cysteinyl-L-threonylglycyl-L-seryl-L-cysteinyl-L-arginyl-L-serylglycyl-L-lysyl-L-cysteinamide cyclic(1→16), (8→20),(15→25)-tris(disulfide).

$C_{102}H_{172}N_{36}O_{32}S_7$=2639.1

CAS — 107452-89-1.

ATC — N02BG08.

ATC Vet — QN02BG08.

UNII — 7164C51O16.

Ziconotide Acetate *(rINNM)*

Acetato de ziconotida; Ziconotide, Acétate de; Ziconotidi Acetas; Зиконотида Ацетат.

$C_{102}H_{172}N_{36}O_{32}S_7$, $C_2H_4O_2$=2699.2

ATC — N02BG08.

ATC Vet — QN02BG08.

UNII — T2I226K69M.

Uses and Administration

Ziconotide is a synthetic form of a peptide derived from the venom of the cone shell *Conus magus* (a sea snail). It is reported to be an N-type (neurone-specific) calcium-channel blocker. Ziconotide is given as a continuous intrathecal infusion in the management of severe chronic pain in patients who are intolerant of or refractory to more conventional treatments (see Choice of Analgesic, p. 4.2).

Ziconotide is given intrathecally as the acetate; doses may be expressed in terms of the base or the acetate. In the EU, the initial licensed dose (expressed in terms of the base) is 2.4 micrograms daily adjusted according to response, in increments of up to 2.4 micrograms, to a maximum daily dose of 21.6 micrograms. It is recommended that the interval between dose increases is at least 2 days. In the USA, the initial licensed dose (expressed in terms of the acetate) should be no more than 2.4 micrograms daily, adjusted according to response. Dose increases of up to 2.4 micrograms two or three times a week are permitted, over a period of at least 3 weeks, up to a maximum daily dose of 19.2 micrograms.

References.
1. Wermeling D, *et al.* Pharmacokinetics and pharmacodynamics of intrathecal ziconotide in chronic pain patients. *J Clin Pharmacol* 2003; 43: 624–36.
2. Staats PS, *et al.* Intrathecal ziconotide in the treatment of refractory pain in patients with cancer or AIDS: a randomized controlled trial. *JAMA* 2004; 291: 63–70.
3. Rauck RL, *et al.* A randomized, double-blind, placebo-controlled study of intrathecal ziconotide in adults with severe chronic pain. *J Pain Symptom Manage* 2006; 31: 393–406.
4. Lynch SS, *et al.* Intrathecal ziconotide for refractory chronic pain. *Ann Pharmacother* 2006; 40: 1293–1300.
5. Lyseng-Williamson KA, Perry C. Ziconotide. *CNS Drugs* 2006; 20: 331–8.
6. Wallace MS, *et al.* Ziconotide 98-022 Study Group. Intrathecal ziconotide for severe chronic pain: safety and tolerability results of an open-label, long-term trial. *Anesth Analg* 2008; 106: 628–37.
7. Williams JA, *et al.* Ziconotide: an update and review. *Expert Opin Pharmacother* 2008; 9: 1575–83.
8. Vitale V, *et al.* Intrathecal therapy with ziconotide: clinical experience and considerations on its use. *Minerva Anestesiol* 2008; 74: 727–33.
9. Kapural L, *et al.* Intrathecal ziconotide for complex regional pain syndrome: seven case reports. *Pain Pract* 2009; 9: 296–303.
10. Rauck RL, *et al.* Intrathecal ziconotide for neuropathic pain: a review. *Pain Pract* 2009; 9: 327–37.
11. Kress HG, *et al.* Intrathecal therapy: what has changed with the introduction of ziconotide. *Pain Pract* 2009; 9: 338–47.
12. Schmidtko A, *et al.* Ziconotide for treatment of severe chronic pain. *Lancet* 2010; 375: 1569–77.

Adverse Effects and Precautions

The most common adverse effects reported with ziconotide have included dizziness, nausea and vomiting, nystagmus, abnormal gait, blurred vision, headache, elevated creatine kinase levels, and asthenia. Cognitive impairment, particularly confusion and impaired memory, is also very common, and typically develops after several weeks of treatment. Severe CNS symptoms such as hallucinations, paranoid reactions, speech disorders, aphasia, and decreased alertness may occur but convulsions, stroke, delirium, encephalopathy, and coma have been reported less commonly. Creatine kinase may be elevated, and monitoring of blood concentrations is recommended, but clinical myopathy or rhabdomyolysis is uncommon. Ziconotide may cause or exacerbate depression. Patients with a history of psychosis should not be treated with ziconotide.

References.
1. Penn RD, Paice JA. Adverse effects associated with the intrathecal administration of ziconotide. *Pain* 2000; 85: 291–6.

Effects on mental state. Suicidal ideation has been reported in 2 patients receiving intrathecal ziconotide for the severe chronic pain.[1] One patient committed suicide; the other, who had a history of depression, showed a moderate improvement in her depressive symptoms after stopping ziconotide.

1. Maier C, *et al.* Increased risk of suicide under intrathecal ziconotide treatment? — A warning. *Pain* 2011; 152: 235–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Prialt; *Cz.*: Prialt; *Denm.*: Prialt; *Fr.*: Prialt; *Ger.*: Prialt; *Gr.*: Prialt; *Hung.*: Prialt; *Irl.*: Prialt; *Ital.*: Prialt; *Neth.*: Prialt; *Norw.*: Prialt†; *Pol.*: Prialt; *Port.*: Prialt; *Spain*: Prialt; *Swed.*: Prialt; *Switz.*: Prialt; *UK*: Prialt; *USA*: Prialt.

Anthelmintics

This chapter describes the important helminth or worm infections that occur in man (see Table 1, p. 144) and the anthelmintics used to treat them.

Choice of Anthelmintic

Helminth infections are among the most common infections in man, affecting a large proportion of the world's population, mainly in tropical regions. In developing countries they pose a large threat to public health, and contribute to the prevalence of malnutrition, anaemia, eosinophilia, and pneumonia. Helminth infections causing severe morbidity include lymphatic filariasis (a cause of elephantiasis), onchocerciasis (river blindness), and schistosomiasis (bilharziasis). These infections can affect the majority of populations in endemic areas with major economic and social consequences. WHO is making strenuous efforts to control a number of these infections in endemic areas. Control of these infections in both individuals and populations depends not only on the use of chemotherapeutic agents but also on preventing transmission by advice on food preparation and hygiene, the provision of adequate sanitation and sewage treatment (especially where sewage is used as fertiliser), the provision of safe potable water supplies, and effective vector control.

The worms that cause infection in man generally fall either into the phylum Nematoda, which includes the nematodes or roundworms, or into the phylum Platyhelminthes, which includes the cestodes or tapeworms and the trematodes or flukes.

The **nematodes** (or roundworms) are a large group of worms, some of which are capable of producing infections in man. In many cases man is the primary (definitive) host but human infections caused by parasites for which animals are the primary hosts also occur. Nematodes do not generally multiply in man; strongyloidiasis is an exception as re-infection can occur without environmental re-exposure. Nematode infections are most common in warm, moist climates, but some species of nematode can tolerate cool or arid conditions and infective forms can persist in the environment for long periods. An understanding of the life cycle of the infective species is necessary for diagnostic tests to be made at appropriate times, usually to coincide with the infective stage of the cycle, and for the choice of appropriate control measures.

The nematode infections can be divided into filarial infections, intestinal infections, and tissue infections.

Filarial nematodes are endemic in large areas of the tropics and produce considerable morbidity. The adult worms may live for several years, releasing large numbers of motile embryos known as microfilariae into the blood or skin, depending on the species. Transmission is usually by biting insects, which form the intermediate host. In some endemic areas multiple infections with filarial nematodes are common.

Filarial nematode infections include:
- loiasis, p. 147.3
- lymphatic filariasis, p. 148.1
- mansonella infections, p. 148.2
- onchocerciasis, p. 148.3.

Intestinal nematode infections (roundworms) are very common especially in developing countries in the tropics and subtropics. Children are particularly at risk and these infections contribute to morbidity through malnutrition, vitamin deficiencies, diarrhoea, anaemia, and pneumonia. Poor sanitation and sewage disposal perpetuate infections with soil-borne nematodes. Often several different worm infections are endemic in the same region, resulting in mixed infections. When this occurs, broad-spectrum anthelmintics may be used to reduce the overall infection burden in the population (see under Ascariasis, p. 145.2).

Intestinal nematode infections include:
- angiostrongyliasis, p. 145.2
- ascariasis, p. 145.2
- capillariasis, p. 145.3
- enterobiasis, p. 146.3
- hookworm infections, p. 147.1
- strongyloidiasis, p. 149.2
- trichostrongyliasis, p. 150.1
- trichuriasis, p. 150.1.

The *tissue nematodes* represent a miscellaneous group causing a variety of pathological conditions in man. In cutaneous larva migrans and toxocariasis, the nematodes have a primary animal host and the human disease is caused by infection with infective larvae which do not subsequently mature in man. Trichinosis and gnathostomiasis affect some carnivorous animals and man is an incidental host. Syngamosis is mainly an infection of domestic fowl and wild birds although infection in man has been reported rarely. In dracunculiasis, man is the primary (definitive) host. Although these diseases are not generally fatal they cause a considerable degree of morbidity and treatment is complicated by the lack of effective, non-toxic systemic anthelmintics.

Tissue nematode infections include:
- angiostrongyliasis, p. 145.2
- cutaneous larva migrans, p. 145.3
- dracunculiasis, p. 146.2
- gnathostomiasis, p. 147.1
- syngamosis, p. 149.3
- toxocariasis, p. 149.3
- trichinosis, p. 150.1.

The **cestodes** (flatworms, segmented worms, or tapeworms) cause infection in man in most parts of the world. Man may be the primary host, harbouring the adult worm in the intestine, or an intermediate host carrying the larval form. With the exception of *Hymenolepis nana* the adult worms do not usually multiply within the same host. However, larval forms may be produced and, as with infection or ingestion of these forms, systemic infection may develop.

Cestode infections include:
- cysticercosis, p. 146.1
- diphyllobothriasis, p. 146.2
- echinococcosis, p. 146.3
- hymenolepiasis, p. 147.2
- taeniasis, p. 149.3.

Trematode (or fluke) infections are caused by parasitic worms of the class Trematoda. There are 4 categories of fluke which are pathogenic in man; the blood flukes *Schistosoma* spp., the intestinal flukes *Fasciolopsis, Heterophyes, Metagonimus,* and *Nanophyetus* spp., the liver flukes *Clonorchis, Fasciola,* and *Opisthorchis* spp., and the lung flukes *Paragonimus* spp. Symptoms are usually only seen in heavy infections and commonly include fever, pain, and eosinophilia.

Trematode infections include:
- intestinal fluke infections, p. 147.2
- liver fluke infections, p. 147.3
- lung fluke infections, p. 147.3
- schistosomiasis, p. 149.1.

Ancylostomiasis

For infections caused by *Ancylostoma duodenale* see under Hookworm Infections, p. 147.1. Larvae of *Ancylostoma* spp. (usually *A. braziliense* and *A. caninum*) are also a cause of cutaneous larva migrans (see p. 145.3).

Angiostrongyliasis

Angiostrongyliasis[1,2] is due to accidental infection with species of the animal nematode *Angiostrongylus*. Infection may cause eosinophilic meningitis or abdominal angiostrongyliasis depending on the infecting species:
- **eosinophilic meningitis** is due to infection with *A. cantonensis*, the rat lungworm. Humans are infected by eating raw or undercooked snails or slugs, crustaceans, or contaminated vegetables. Although cases have been reported worldwide, most cases have been reported from endemic areas such as south Asia, Australia, and the Pacific and Caribbean Islands. Clinical symptoms are caused by the presence of larvae in the brain and by local host reactions. The disease is generally self-limiting but a minority of patients may develop severe encephalitis, coma, and death. Eye involvement is very rare and causes permanent visual impairment and a wide range of ocular inflammations (such as retinitis or optic neuritis).
- **abdominal angiostrongyliasis** is caused by infection with *A. costaricensis*. Cases have been reported from Central and South America and it most commonly occurs in young children after ingestion of vegetables contaminated by infected slugs. Abdominal angiostrongyliasis mimics appendicitis, with eosinophilia.

No drug treatment has been proven to be effective for the treatment of angiostrongyliasis. However, most patients infected with either species have a self-limiting course and recover completely.[3] Treatment of *A. cantonensis* infection is controversial, but symptomatic treatment with analgesics and removal of CSF to relieve pressure in the brain is usually recommended.[1-4] Treatment with corticosteroids for 2 weeks has been reported to be beneficial[5] and is considered reasonable,[1,3] although some studies have not reported benefit.[3] Anthelmintics are usually not recommended because of their potential to exacerbate neurological symptoms by release of antigens after the death of the parasite,[2] however, an anthelmintic (preferably albendazole or alternatively mebendazole), with or without a corticosteroid, may reduce the duration of headaches in patients with meningitis.[1-4,6] Praziquantel with a corticosteroid has also been tried.[4] Surgical removal or laser therapy has been tried in patients with ocular angiostrongyliasis but did not improve the patients visual acuity;[2] corticosteroids may be given in those patients who have eosinophilic meningitis with ocular angiostrongyliasis or other ocular inflammations.[2]

1. Abramowicz M, ed. *Drugs for parasitic infections*. 3rd ed. New Rochelle NY: The Medical Letter, 2013.
2. Sawanyawisuth K, Sawanyawisuth K. Treatment of angiostrongyliasis. *Trans R Soc Trop Med Hyg* 2008; 102: 990–6.
3. Ramirez-Avila L, *et al*. Eosinophilic meningitis due to Angiostrongylus and Gnathostoma species. *Clin Infect Dis* 2009; 48: 322–7.
4. Wang QP, *et al*. Human angiostrongyliasis. *Lancet Infect Dis* 2008; 8: 621–30.
5. Chotmongkol V, *et al*. Corticosteroid treatment of eosinophilic meningitis. *Clin Infect Dis* 2000; 31: 660–2.
6. Chotmongkol V, *et al*. Treatment of eosinophilic meningitis with a combination of prednisolone and mebendazole. *Am J Trop Med Hyg* 2006; 74: 1122–4.

Ascariasis

Ascariasis is an infection caused by *Ascaris lumbricoides*, the common or giant roundworm. It is commonly found in the tropics and especially in rural areas. On ingestion of mature eggs the larvae hatch and penetrate the intestinal wall. They migrate in the bloodstream via the liver to the lungs where they enter the alveoli. The larvae then move up the bronchial tree and are swallowed. The mature adult develops in the intestines, and it has been estimated that gravid females are produced about 2 months after infection. Eggs are excreted in the faeces and can remain viable in

Table 1. Helminths: classification and diseases.

Group	Helminth	Common Name	Clinical infection
Nematodes (filarial)	*Brugia malayi*		lymphatic filariasis (Malayan, brugian)
	Brugia timori		lymphatic filariasis (Timorian, brugian)
	Loa loa	eye-worm	loiasis
	Mansonella spp.		Mansonella infections
	Onchocerca volvulus		onchocerciasis (river blindness)
	Wuchereria bancrofti		lymphatic filariasis (bancroftian)
Nematodes (intestinal)	*Ancylostoma duodenale*	Old World hookworm	ancylostomiasis
	Angiostrongylus costaricensis		angiostrongyliasis
	*Ascaris lumbricoides**	common roundworm, giant roundworm	ascariasis
	Capillaria philippinensis		capillariasis
	*Enterobius vermicularis**	threadworm, pinworm	enterobiasis
	Necator americanus	New World hookworm	necatoriasis
	Strongyloides stercoralis	sometimes called threadworm in USA	strongyloidiasis
	Trichostrongylus spp.		trichostrongyliasis
	*Trichuris trichiura**	whipworm	trichuriasis
Nematodes (tissue)	*Ancylostoma* spp. (usually *A. braziliense* and *A. canium*)	dog/cat hookworm	cutaneous larva migrans (creeping eruption)
	Angiostrongylus cantonensis		angiostrongyliasis
	Dracunculus medinensis	guinea-worm	dracunculiasis (dracontiasis)
	Gnathostoma spinigerum		gnathostomiasis
	Syngamus spp.	gapeworm	syngamosis
	Toxocara spp.*		toxocariasis (visceral larva migrans, ocular larva migrans)
	*Trichinella spiralis**		trichinosis (trichinellosis)
Cestodes (tapeworms)	*Diphyllobothrium latum*	broad fish tapeworm	diphyllobothriasis
	Echinococcus spp.		echinococcosis (hydatid disease)
	Hymenolepis nana	dwarf tapeworm	hymenolepiasis
	*Taenia saginata**	beef tapeworm	taeniasis
	*Taenia solium**	pork tapeworm	cysticercosis (larval form), taeniasis (adult worm)
Trematodes (flukes)	*Clonorchis sinensis*	Chinese liver fluke	clonorchiasis
	Fasciola hepatica	liver fluke	fascioliasis
	Fasciolopsis buski	intestinal fluke	fasciolopsiasis
	Heterophyes heterophyes	intestinal fluke	heterophyiasis
	Metagonimus yokogawi	intestinal fluke	metagonimiasis
	Nanophyetus salmincola	intestinal fluke	nanophyetiasis
	Opisthorchis spp.	liver fluke	opisthorchiasis
	Paragonimus spp.	oriental lung fluke	paragonimiasis
	Schistosoma spp.	blood fluke	schistosomiasis (bilharziasis)

NOTE: Infections due to worms marked with an asterisk may occur in temperate climates. Infections due to other worms are generally limited to tropical or localised areas, but may occur in travellers who have visited those areas.

moist soil for several years. The life span of the adult worm is 1 to 2 years.

Ascariasis may be asymptomatic or intestinal infection may produce anorexia, abdominal pain, and diarrhoea; nutritional deficiency may result. The pulmonary stage may result in pneumonitis and bronchospasm, often accompanied by eosinophilia. Heavy infections can cause intestinal or biliary obstruction. Migration of the worm from the small intestine can rarely cause serious ectopic infection of the genito-urinary tract, lungs, liver, or heart.

Treatment is with a benzimidazole carbamate derivative such as albendazole or mebendazole[1-3] with both drugs being equally highly effective. Pyrantel embonate[3] and levamisole are alternatives, while the potential of nitazoxanide for the treatment of ascariasis is being investigated.[1] Ivermectin has also been used.[2] Such broad-spectrum therapy can be useful if the patient is suffering from a mixed intestinal nematode infection. Drugs such as tiabendazole with little or no activity against *Ascaris* should be avoided for the initial treatment of mixed infections since they may stimulate the worm to migrate to a different body site.

Mass treatment programmes may be necessary in endemic areas to reduce the overall burden of disease.[1] WHO recommends[4] the use of albendazole or mebendazole or alternatively levamisole or pyrantel targeted at preschool and school-age children, women of child-bearing age (including pregnant women in the second and third trimesters and lactating women), and adults engaged in high-risk occupations for soil-transmitted helminthiasis, such as tea-pickers and miners. Children less than 1 year of age and women in the first trimester of pregnancy are excluded from such mass treatment programmes. The frequency of intervention should be determined by the prevalence and intensity of infection among school-age children.

1. Bethony J, *et al.* Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm. *Lancet* 2006; 367: 1521–32.
2. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.
3. Keiser J, Utzinger J. Efficacy of current drugs against soil-transmitted helminth infections: systematic review and meta-analysis. *JAMA* 2008; 299: 1937–48.
4. WHO. *Preventive chemotherapy in human helminthiasis: coordinated use of antihelminthic drugs in control interventions: a manual for health professionals and programme managers.* Geneva: WHO, 2006. Also available at: http://whqlibdoc.who.int/publications/2006/9241547103_eng.pdf (accessed 27/08/09)

Capillariasis

Capillariasis is caused by infection with *Capillaria philippinensis*, a nematode endemic in the Philippines and southern Thailand. Infection in man is through eating raw or undercooked freshwater fish containing infective larvae. The larvae mature in the intestines and the adults produce both eggs and infective larvae so that auto-infection occurs and heavy infections can result. Symptoms are mostly gastrointestinal, with abdominal pain, vomiting, and severe prolonged diarrhoea leading to cachexia and muscle wasting. The infection has a mortality rate of between 20 and 30% if untreated. Prolonged treatment with mebendazole for 20 days[1] for new cases and 30 days for relapsed cases or, alternatively, albendazole for 10 days,[1] is necessary. Single oral doses of mebendazole are given 4 times a year as part of mass treatment control programmes.

1. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.

Clonorchiasis

See under Liver Fluke Infections, p. 147.3.

Cutaneous larva migrans

Cutaneous larva migrans (creeping eruption)[1-4] occurs when man becomes accidentally infected with the larvae of animal hookworms, usually *Ancylostoma braziliense* or *A. caninum*, hookworms of cats and dogs. Other hookworms may also be involved or may cause other infections (see Hookworm Infections, p. 147.1).

Infection with *Gnathostoma spinigerum* or *Strongyloides stercoralis* can also cause cutaneous larva migrans (see Gnathostomiasis p. 147.1 and Strongyloidiasis, p. 149.2). Ocular and visceral larva migrans are features of toxocariasis (see p. 149.3) and gnathostomiasis.

The larvae penetrate the skin and then migrate causing characteristic trails in the skin sometimes with bullous lesions or folliculitis. This migration can persist for several months and can be a source of intense pruritus. Animal hookworm larvae cannot generally penetrate deeper tissues in humans, although there are rare reports of larvae migrating to the lungs causing eosinophilia and pulmonary symptoms. Secondary bacterial infections occur in about 8% of those infected.

Cutaneous larva migrans is a self-limiting condition and without any treatment, most cases will resolve within 2 to 8 weeks.[1,2] However, treatment with anthelmintics may shorten the disease course, ease pruritus and lead to resolution of skin tracks within 1 week. The drug of choice is ivermectin and cure rates after a single oral dose range from 77 to 100%.[4] If the initial treatment fails or the patient relapses, 1 or 2 repeat doses may be given.[2,4] Repeat treatments may also be required in hookworm folliculitis.[4] Oral albendazole daily for 3 to 5 days is an alternative;[1,4] treatment for 5 to 7 days showed cure rates of 92 to 100%.[4] Tiabendazole, given orally for 2 to 4 days, was formerly widely used; however, since both ivermectin and albendazole have better efficacy and less adverse events than tiabendazole, its use is not now recommended.[4] Albendazole (10%)[2] or tiabendazole (10 to 15%)[1,4] can also be applied topically 2 to 3 times a day for 5 to 10 days, but may be of limited value for multiple lesions and hookworm folliculitis.[1,4] Freezing with liquid nitrogen or carbon dioxide is not effective because the larva is usually located a few centimetres beyond the visible end of the trail.[1,2,4]

1. Caumes E. Treatment of cutaneous larva migrans. *Clin Infect Dis* 2000; 30: 811–14.
2. Hochedez P, Caumes E. Hookworm-related cutaneous larva migrans. *J Travel Med* 2007; 14: 326–33.
3. Bowman DD, *et al.* Hookworms of dogs and cats as agents of cutaneous larva migrans. *Trends Parasitol* 2010; 26: 162–7.
4. Heukelbach J, Feldmeier H. Epidemiological and clinical characteristics of hookworm-related cutaneous larva migrans. *Lancet Infect Dis* 2008; 8: 302–9.

Cysticercosis

Infection with the pork tapeworm, *Taenia solium* may result in taeniasis (intestinal infection with adult tapeworms—see p. 149.3) or cysticercosis (tissue infection with larval forms). Cysticercosis may develop after ingestion of *T. solium* eggs in food or water contaminated with infected human faecal material, or as a result of auto-infection in intestinal carriers of adult tapeworms. Ingested eggs release larvae that may penetrate the intestinal wall to be carried via the bloodstream to skeletal muscles, heart, eyes, brain, and spinal cord where they form encapsulated cysts (cysticerci). Human cysticercosis is associated with poverty and endemic in areas where hygiene is poor and sanitation inadequate.

Infection is typically subclinical, but symptoms may develop when the encysted larvae die and elicit an inflammatory reaction. Clinical features depend on the number, size, location, and stage of development of the cysticerci, as well as on the host's immune response. Cysts in the CNS (**neurocysticercosis**) may result in seizures and headaches, and are a common cause of epilepsy in endemic areas. Other symptoms include confusion, attention deficit, and ataxia. Hydrocephalus and intracranial hypertension may result from obstruction of CSF flow. Cysts in the spinal cord, eyes, or heart may also cause serious morbidity.

The need for and approach to **treatment** of neurocysticercosis differs depending on factors such as the location, stage of evolution, and number of cysts, as well as the degree of inflammation and severity of symptoms.[1,2] Seizures are managed with antiepileptics; these can usually be stopped once patients have been seizure-free for more than 2 years.[3]

The use of anthelmintics in the treatment of neurocysticercosis remains controversial.[3-6] Live cysticerci usually do not provoke seizures whereas dead or dying

parasites can elicit an inflammatory response, seizures, and transient neurological effects, hence treatment does not necessarily reduce seizure frequency. Patients with viable or degenerating parenchymal cysts and those with extraparenchymal cysts (such as subarachnoid cysts, including giant cysts and racemose forms) may, however, benefit from anthelmintics.[3,5,7] Anthelmintics are of little or no benefit in patients with inactive, calcified lesions, and are contra-indicated in patients with cysticercotic encephalitis as they may exacerbate intracranial hypertension.[3,4] A double-blind, placebo-controlled study in patients with seizures due to viable parenchymal cysts confirmed that albendazole therapy (with dexamethasone) was safe and decreased the burden of parasites and the number of generalised seizures.[8] Albendazole is now considered to be the drug of choice,[2,9,10] but praziquantel may also be used.[2,3,7,10] High doses of the chosen anthelmintic should be given for a minimum of 8 days, but those with extraparenchymal cysts may need longer and multiple treatment courses.[1,10]

Adjunctive corticosteroids are recommended for parenchymal infections[4] if there are many cysts, or if neurological symptoms or intracranial hypertension develop after starting treatment. Patients with subarachnoid cysticercosis should also be given adjunctive corticosteroids,[4] and some favour use in almost all patients.[2] However, use of corticosteroids with praziquantel may be complicated by a pharmacokinetic interaction— see Corticosteroids, under Interactions of Praziquantel p. 166.3 for further details. If hydrocephalus is present, surgical removal of cysts or ventricular shunting may be indicated.[2,3] Detailed consensus guidelines for the treatment of neurocysticercosis have been developed.[4]

Prevention of infection with *T. solium* is possible by avoiding ingestion of undercooked pork and food and water contaminated with human faeces. Ideally, prevention measures should include adequate sanitation, sewage treatment, and abattoir inspection. Those already infected with *T.solium* and their close contacts should be treated with anthelmintics in order to interrupt or reduce the cycle of direct person-to-person transmission. Universal or selected treatment of human taeniasis with praziquantel has significantly reduced the prevalence in areas where *T. solium* infection is endemic.[3,11]

1. Nash TE, *et al.* Treatment of neurocysticercosis: current status and future research needs. *Neurology* 2006; 67: 1120–7.
2. Ramírez-Zamora A, Alarcón T. Management of neurocysticercosis. *Neurol Res* 2010; 32: 229–37.
3. Takayanagui OM. Therapy for neurocysticercosis. *Expert Rev Neurother* 2004; 4: 129–39.
4. García HH, *et al.* Current consensus guidelines for treatment of neurocysticercosis. *Clin Microbiol Rev* 2002; 15: 747–56. Also available at: http://cmr.asm.org/cgi/reprint/15/4/747.pdf (accessed 09/08/07)
5. García HH, *et al.* Taenia solium cysticercosis. *Lancet* 2003; 362: 547–56.
6. Baird RA, *et al.* Evidence-based guideline: treatment of parenchymal neurocysticercosis: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 2013; 80: 1424–9.
7. Del Brutto OH, *et al.* Meta-analysis: cysticidal drugs for neurocysticercosis— albendazole and praziquantel. *Ann Intern Med* 2006; 145: 43–51.
8. Garcia HH, *et al.* A trial of antiparasitic treatment to reduce the rate of seizures due to cerebral cysticercosis. *N Engl J Med* 2004; 350: 249–58.
9. Abba K, *et al.* Anthelmintics for people with neurocysticercosis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2010 (accessed 22/07/10).
10. Abramowicz M, ed. *Drugs for parasitic infections*. 3rd ed. New Rochelle NY: The Medical Letter, 2013.
11. WHO. *Control of neurocysticercosis*. Geneva: WHO, 2003. Also available at: http://apps.who.int/gb/archive/pdf_files/WHA56/ea5610.pdf (accessed 29/07/10)

Diphyllobothriasis

Diphyllobothriasis[1,2] is an intestinal infection with the fish tapeworm *Diphyllobothrium latum* and other *Diphyllobothrium* spp. and is acquired in man through ingestion of raw, infected, freshwater fish. The infection is rarely symptomatic. However, because the adult worm competes for vitamin B_{12}, some patients may develop megaloblastic anaemia with its associated neurological symptoms. Concentrations of other vitamins may also be reduced. Occasionally, infection may cause acute abdominal pain and intestinal obstruction; rarely migration of proglottids (segments) can cause cholangitis or cholecystitis.

Treatment is with a single dose of praziquantel; niclosamide is an alternative.[3] Vitamin supplements should also be given to correct any deficiencies.

1. Llaguno MM, *et al. Diphyllobothrium latum* infection in a non-endemic country: case report. *Rev Soc Bras Med Trop* 2008; 41: 301–3.
2. Nakaji K, *et al.* Diphyllobothriasis. *Intern Med* 2009; 48: 1479.
3. Abramowicz M, ed. *Drugs for parasitic infections*. 3rd ed. New Rochelle NY: The Medical Letter, 2013.

Dracunculiasis

Dracunculiasis (dracontiasis, guinea-worm infection)[1-4] is caused by infection with the nematode *Dracunculus medinensis*. It has been endemic in parts of Africa and Asia, but attempts are being made to eradicate it and during 2010 only 1797 cases were reported, the majority from the Sudan and the remainder from Ethiopia, Mali, Chad, Ghana, and Niger. The disease is transmitted through drinking water containing water fleas (*Cyclops species*) that have ingested *Dracunculus* larvae. The larvae penetrate the intestinal mucosa and develop into adult worms in connective tissue. The adult female slowly migrates to the subcutaneous tissues causing intense pain, sometimes with non-specific symptoms such as fever and rash, and about 10 to 14 months later emerges through the skin, usually at the feet, producing oedema, a blister and eventually an ulcer; secondary bacterial infection is a common complication. Pain and symptoms decrease once the blister has ruptured. When the affected body part comes into contact with water the female worms release their larvae and set in motion a new life cycle.

The most effective method of controlling dracunculiasis is by provision of safe drinking water. The WHO eradication campaign is based on health education, and the provision of safe water by measures including water treatment with pesticides such as temefos and encouraging the use of domestic filters.

There is no effective direct drug therapy against any stage in man. The traditional treatment is removal of the adult worm by gentle traction sometimes over several weeks. Metronidazole or tiabendazole may provide symptomatic benefit in the management of dracunculiasis although they have no direct anthelmintic effect. They are thought to act by weakening the anchorage of the worms within the subcutaneous tissues, thus allowing them to be removed more quickly. However, treatment with mebendazole has been linked with aberrant migration of worms, which resulted in infections in places other than the lower limbs.

1. Greenaway C. Dracunculiasis (guinea worm disease). *CMAJ* 2004; 170: 495–500.
2. WHO. Eradicating guinea-worm disease. Available at: http://whqlibdoc.who.int/hq/2008/WHO_HTM_NTD_PCT_2008.1_eng.pdf (accessed 16/07/09)
3. CDC. Progress toward global eradication of dracunculiasis, January 2011–June 2012. *MMWR* 2012; 61: 854–7.
4. WHO. Monthly report on dracunculiasis cases, January–April 2013. *Wkly Epidem Rec* 2013; 88: 267–8.

Echinococcosis

Echinococcosis, or hydatid disease, in man is infection with the larval stage of the cestode *Echinococcus granulosus* or *E. multilocularis*. These two species cause distinct forms of the disease known as cystic echinococcosis and alveolar echinococcosis respectively. Various animals are involved in the transmission of the disease, man becoming infected through ingestion of eggs from contaminated faeces. The eggs hatch in the intestine and the embryos penetrate the intestinal wall and invade body organs, usually the liver. The embryo develops into a cyst which slowly increases in size and may remain intact for many years. Symptomatic infection usually only occurs when the cyst is large enough to cause obstruction or to compress adjacent structures, or if rupture occurs. Where possible, surgical removal of the intact cyst is the first line of treatment.

In **cystic echinococcosis**, drugs may be given locally or systemically before surgery to kill infective larvae within the cyst and reduce the risk of further infection. They are also given postoperatively if a cyst ruptures during surgery. Local injection of a larvicidal agent such as alcohol, cetrimide, or hypertonic saline has been used. Chemotherapy is also used as an adjunct or when surgery is not possible. The preferred drug for associated systemic treatment is albendazole. Mebendazole may be used, although due to poorer absorption from the gastrointestinal tract it is not as effective as albendazole and very high doses must be taken for several months. Praziquantel has also been reported to be effective, and may be combined with albendazole. Albendazole may be a suitable alternative to surgery as initial treatment in uncomplicated cases; use with cimetidine (to inhibit its metabolism) may increase its efficacy. Nitazoxanide has also been tried in disseminated disease.

A further option when surgery is not possible is the PAIR (puncture/aspiration/injection/re-aspiration) procedure which consists of ultrasound-guided cyst puncture followed by aspiration of the cyst fluid, local injection of alcohol or hypertonic saline into the cyst, and re-aspiration of the cyst contents. Concomitant chemotherapy is recommended.

E. multilocularis infection (**alveolar echinococcosis**) is more invasive and is characterised by a tumour-like infiltrative growth; it usually requires both surgery and long-term treatment with a benzimidazole, such as albendazole, although some lesions are inoperable when diagnosed, and patients have improved on albendazole alone. Prolonged treatment has proved larvicidal in some patients.

References.
1. Kumar A, Chattopadhyay TK. Management of hydatid disease of the liver. *Postgrad Med J* 1992; 68: 853–6.
2. Wen H, *et al.* Diagnosis and treatment of human hydatidosis. *Br J Clin Pharmacol* 1993; 35: 565–74.
3. WHO Informal Working Group on Echinococcosis. Guidelines for treatment of cystic and alveolar echinococcosis in humans. *Bull WHO* 1996; 74: 231–42. Also available at: http://whqlibdoc.who.int/bulletin/1996/Vol74-No3/bulletin_1996_74(3)_231-242.pdf (accessed 27/08/09)
4. Reuter S, *et al.* Benzimidazoles in the treatment of alveolar echinococcosis: a comparative study and review of the literature. *J Antimicrob Chemother* 2000; 46: 451–6.
5. Mcmanus DP, *et al.* Echinococcosis. *Lancet* 2003; 362: 1295–1304.
6. Smego RA, *et al.* Percutaneous aspiration-injection-reaspiration drainage plus albendazole or mebendazole for hepatic cystic echinococcosis: a meta-analysis. *Clin Infect Dis* 2003; 37: 1073–83.
7. Smego RA, Sebanego P. Treatment options for hepatic cystic echinococcosis. *Int J Infect Dis* 2005; 9: 69–76.
8. Abramowicz M, ed. *Drugs for parasitic infections*. 3rd ed. New Rochelle NY: The Medical Letter, 2013.
9. Junghanss T, *et al.* Clinical management of cystic echinococcosis: state of the art, problems, and perspectives. *Am J Trop Med Hyg* 2008; 79: 301–11.
10. Moro P, Schantz PM. Echinococcosis: a review. *Int J Infect Dis* 2009; 13: 125–33.
11. Kern P. Clinical features and treatment of alveolar echinococcosis. *Curr Opin Infect Dis* 2010; 23: 505–12.
12. Wen H, *et al.* Diagnosis and management against the complications of human cystic echinococcosis. *Front Med China* 2010; 4: 394–8.
13. Pérez-Molina JA, *et al.* Evaluation of nitazoxanide for the treatment of disseminated cystic echinococcosis: report of five cases and literature review. *Am J Trop Med Hyg* 2011; 84: 351–6.

Enterobiasis

Enterobiasis is an infection with *Enterobius vermicularis* (pinworm or threadworm), an intestinal nematode that occurs throughout the world. Infections are particularly common in school-aged children, in families or primary caregivers of infected children, and in institutionalised groups. It is an infection of the large intestine and transmission follows ingestion or inhalation of mature eggs. The larvae mature in the gut in about 2 months. Mature females do not release eggs into the gut contents but migrate to the anus at night and lay eggs on the perianal and perineal skin. Eggs become infective within 6 hours and may remain so for 20 days. Diagnosis is based on detecting eggs around the anus. The most common symptom is perianal itching but many infections are asymptomatic. Rarely, migration of the worm may lead to ectopic disease such as appendicitis or salpingitis. The adult worm has a life span of about 6 weeks and, if re-infection can be prevented, the infection is self-limiting.

Treatment is with a single dose of a benzimidazole carbamate derivative, such as albendazole or mebendazole, or with pyrantel embonate.[1] A second single dose is given 2 weeks later to eliminate possible re-infection. These drugs are also generally effective if the patient is suffering from a mixed intestinal nematode infection. Other anthelmintics used in enterobiasis include ivermectin, piperazine or pyrvinium embonate. While additional hygiene measures can reduce the rate of re-infection, treatment of the whole family with an anthelmintic at the same time as treating the index case is also recommended. In institutions, day care centers, and schools mass drug treatment during an outbreak can be successful. However, re-infection is still common and more than one course may be required.

1. Abramowicz M, ed. *Drugs for parasitic infections*. 3rd ed. New Rochelle NY: The Medical Letter, 2013.

Fascioliasis

See under Liver Fluke Infections, p. 147.3.

Fasciolopsiasis

See under Intestinal Fluke Infections, p. 147.2.

Gnathostomiasis

Gnathostomiasis[1-4] is a parasite infection with, in most cases, the larval form of the nematode *Gnathostoma spinigerum*, although other *Gnathostoma* spp. have been identified. It is endemic in parts of Southeast Asia (particularly Thailand and Japan), Central and South America, the Middle East, and Australia, but case reports are emerging from around the world. *G. spinigerum* inhabits the stomach of cats and dogs. Eggs shed in their faeces are ingested by freshwater crustaceans and hatch into larvae which are ingested by fish or other animals; humans usually acquire the infection by eating the raw or undercooked flesh of these secondary hosts or rarely through direct larval penetration.

Once ingested the larvae penetrate the gut wall (usually triggering generalised eosinophilia) and aggressively migrate through various tissues. Migration through the subcutaneous tissues to the skin causes intermittent, painful, migratory swellings (similar to cutaneous larva migrans, see p. 144.3). The visceral form involves migration into deeper tissues and internal organs to involve the lungs, eyes, ears, gastrointestinal and genito-urinary systems; rarely there is involvement of the CNS. Symptoms may recur for 10 to 12 years.

The preferred treatment of gnathostomiasis is surgical removal of the gnathostome but this is only possible when it is superficial and accessible. Albendazole or, alternatively, ivermectin, may be used;[1,2,4] multiple courses may be needed for some patients.[2] Albendazole appears to stimulate the larva to migrate outwards and may make it more

accessible to excision.[2] Treatment of neurological infection is mainly supportive; there is a risk that severe host reaction to the dying larvae may result from active treatment.[3]

1. Ligon BL. Gnathostomiasis: a review of a previously localized zoonosis now crossing numerous geographical boundaries. *Semin Pediatr Infect Dis* 2005; 16: 137–43.
2. Herman JS, Chiodini PL. Gnathostomiasis, another emerging imported disease. *Clin Microbiol Rev* 2009; 22: 484–92.
3. Ramirez-Avila L, *et al.* Eosinophilic meningitis due to Angiostrongylus and Gnathostoma species. *Clin Infect Dis* 2009; 48: 322–7.
4. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.

Heterophyiasis

See under Intestinal Fluke Infections, p. 147.2.

Hookworm infections

Infections with the hookworms *Ancylostoma duodenale* (ancylostomiasis) and *Necator americanus* (necatoriasis) are a major cause of iron-deficiency anaemia in large areas of the tropics and sub-tropics, especially in rural communities. Eggs deposited in warm moist soil hatch into larvae which develop further into the infective form. Infection is normally by penetration through the skin although it may be by ingestion. The larvae migrate to the lungs and are subsequently swallowed and mature to the adult form in the small intestine. Eggs appear in the faeces about 6 to 8 weeks after infection and the adult worm may live for several years. *A. duodenale* larvae are capable of remaining dormant in the tissues, only maturing to the adult when climatic conditions are favourable. Symptoms correspond to the stage of infection. Visitors to endemic areas may develop intense pruritus, erythema, and papulovesicular eruption at the site of infection, known as ground itch. Migration through the lungs during the first infection may cause pneumonitis and bronchospasm with accompanying eosinophilia. The main symptoms of intestinal infection are iron-deficiency anaemia and severe hypoalbuminaemia. In addition, abdominal pain, diarrhoea, and weight loss may occur.

Treatment is usually with a benzimidazole carbamate derivative such as mebendazole or albendazole,[1-3] and such broad-spectrum therapy can also be useful if the patient has a mixed intestinal nematode infection. Albendazole may be more effective than mebendazole.[4] Other anthelmintics used in hookworm infections include levamisole or pyrantel embonate,[2-4] but these may be less effective against *N. americanus* than against *A. duodenale*. Iron-deficiency anaemia caused by hookworm infections responds rapidly to oral iron therapy; folic acid supplements may be necessary in some patients.

Mass treatment programmes may be necessary in endemic areas to reduce the overall burden of infection.[2,5] WHO recommends[6] the use of albendazole or mebendazole or alternatively levamisole or pyrantel targeted at preschool and school-age children, women of child-bearing age (including pregnant women in the second and third trimesters and lactating women), and adults engaged in high-risk occupations for soil-transmitted helminthiasis, such as tea-pickers and miners. Children less than 1 year of age and women in the first trimester of pregnancy are excluded from such mass treatment programmes. The frequency of intervention should be determined by the prevalence and intensity of infection among school-age children.

1. Hotez PJ, *et al.* Hookworm infection. *N Engl J Med* 2004; 351: 799–807.
2. Bethony J, *et al.* Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm. *Lancet* 2006; 367: 1521–32.
3. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.
4. Keiser J, Utzinger J. Efficacy of current drugs against soil-transmitted helminth infections: systematic review and meta-analysis. *JAMA* 2008; 299: 1937–48.
5. Idris MA, *et al.* Effective control of hookworm infection in school children from Dhofar, Sultanate of Oman: a four-year experience with albendazole mass chemotherapy. *Acta Trop* 2001; 80: 139–43.
6. WHO. *Preventive chemotherapy in human helminthiasis: coordinated use of antihelminthic drugs in control interventions: a manual for health professionals and programme managers.* Geneva: WHO, 2006. Also available at: http://whqlibdoc.who.int/publications/2006/9241547103_eng.pdf (accessed 27/08/09)

Hymenolepiasis

Hymenolepiasis is an infection of the intestine with *Hymenolepis nana*, or dwarf tapeworm. Infection is acquired through ingestion of eggs in contaminated food or water or on hands and can be passed directly from person to person. It is more common in children. Clinical symptoms occur in heavy infections and include diarrhoea and abdominal pain. Treatment is with a single dose of praziquantel.[1-3] Nitazoxanide[1,3] and niclosamide[2,3] may be used as alternatives.

1. Juan JO, *et al.* Comparative clinical studies of nitazoxanide, albendazole and praziquantel in the treatment of ascariasis, trichuriasis and hymenolepiasis in children from Peru. *Trans R Soc Trop Med Hyg* 2002; 96: 193–6.
2. WHO. *WHO model formulary.* Geneva: WHO, 2008. Also available at: http://www.who.int/selection_medicines/list/WMF2008.pdf (accessed 27/08/09)
3. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.

Intestinal fluke infections

More than 65 species of flukes are known to infect the human gastrointestinal tract; the most well known intestinal fluke infections are **fasciolopsiasis** (caused by *Fasciolopsis buski*), **heterophyiasis**, (*Heterophyes heterophyes* and some other *Heterophyes* spp.), **metagonimiasis** (*Metagonimus yokogawai*), and **nanophyetiasis** (*Nanophyetus salmincola*). Fasciolopsiasis, heterophyiasis, and metagonimiasis are endemic in the Far East and Southeast Asia, and heterophyiasis is also common in the Middle East. Nanophyetiasis has occurred increasingly in the Pacific Northwest of the USA. Fasciolopsiasis is caused by the ingestion of infected aquatic plants, while undercooked or raw infected fish are the sources of *H. heterophyes, M. yokogawai,* and *N. salmincola* infections.

Fasciolopsiasis is usually asymptomatic, but heavy infections can cause diarrhoea, abdominal pain, and, rarely, intestinal obstruction and an allergic oedematous reaction. Metagonimiasis is also generally asymptomatic but may cause mild diarrhoea, while pain and mucous diarrhoea are common in heterophyiasis. Similar gastrointestinal symptoms plus eosinophilia occur in nanophyetiasis. Eggs of *M. yokogawai* and *H. heterophyes* may rarely penetrate the bowel wall and enter the bloodstream to be deposited in various organs, leading to serious complications such as heart failure or fatal embolism in the heart or brain.

Treatment of choice for intestinal fluke infections is with praziquantel;[1,2] triclabendazole is also effective. Niclosamide is effective against fasciolopsiasis and heterophyiasis infections.

1. WHO. Control of foodborne trematode infections. *WHO Tech Rep Ser 849* 1995. Available at: http://libdoc.who.int/trs/WHO_TRS_849_(part1).pdf and http://libdoc.who.int/trs/WHO_TRS_849_(part2).pdf (accessed 16/07/08)
2. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.

Liver fluke infections

Fasciola hepatica, F. gigantica, Opisthorchis viverrini, O. felineus, and *Clonorchis sinensis* are liver flukes transmitted by the ingestion of infected aquatic plants, grasses or water (*F. hepatica* and *F. gigantica*), or raw or undercooked fish (*Opisthorchis* spp., *C. sinensis*). **Fasciollasis** is mainly a disease of sheep and cattle and human infections may occur wherever these animals are raised, whereas **clonorchiasis** and **opisthorchiasis** are seen mainly in Southeast Asia and eastern Europe.

Fascioliasis in the acute phase is usually characterised by fever, gastrointestinal symptoms, pain due to liver enlargement, and marked eosinophilia, but these symptoms decline as the worms enter their final habitat in the bile ducts. Acute symptoms occur rarely with clonorchiasis and opisthorchiasis and infections tend to be asymptomatic for many years. Adult flukes live in the bile ducts and symptoms of biliary-tract obstruction appear after repeated or heavy infections with liver flukes. Cholangiocarcinoma (bile-duct cancer) is now generally accepted to be associated with liver fluke infection although its exact pathogenesis is unclear.

Praziquantel is used for the treatment of most liver fluke infections,[1,2] (except *Fasciola* infections) and triclabendazole is considered the treatment of choice for liver fluke infections caused by *Fasciola*.[2] Bithionol is more effective than praziquantel in fascioliasis and is an alternative to triclabendazole; dehydroemetine has also been used, and nitazoxanide[2] may be effective.

Praziquantel remains the treatment of choice for clonorchiasis and opisthorchiasis.[1,2] Albendazole is a suggested alternative for clonorchiasis.[2]

1. WHO. Control of foodborne trematode infections. *WHO Tech Rep Ser 849* 1995. Available at: http://libdoc.who.int/trs/WHO_TRS_849_(part1).pdf and http://libdoc.who.int/trs/WHO_TRS_849_(part2).pdf (accessed 16/07/08)
2. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.

Loiasis

Loiasis is an infection with the filarial nematode *Loa loa* (sometimes also known as the African eye worm) which occurs in areas of Central and West Africa. It is transmitted by the biting tabanid fly *Chrysops*. The infective larvae mature to adult worms which migrate through subcutaneous tissues and occasionally the subconjunctiva. Symptoms include pruritus, swelling, and pain, with occasional subcutaneous swellings, often on the arms or legs, that are characteristic of the disease. Passage of a worm through the subconjunctiva produces intense conjunctivitis. Eosinophilia may be severe, especially in visitors from non-endemic areas. Other complications include renal disease, endomyocardial fibrosis, encephalopathy, and peripheral neuropathy.

Diethylcarbamazine is used for treatment;[1,2] it is effective against the microfilariae, larval forms, and a proportion of adult worms. In some cases, treatment has been associated with acute encephalitis, particularly in patients with heavy microfilaraemia. It has been assumed that this is related to blockage of capillaries in the brain and meninges and for this reason small doses of diethylcarbamazine are given initially, with a corticosteroid and antihistamine, gradually increasing to full therapeutic doses over several days. However this does not eliminate the risk of encephalitis entirely and the role of the microfilariae in this syndrome has been questioned. Albendazole may be useful where diethylcarbamazine is ineffective or cannot be used, but repeated courses may be needed.[1] Mebendazole has also been used.[2] Some consider that ivermectin could be used[1,2] but, as with diethylcarbamazine, there is concern over its potential neurotoxic effects in patients with heavy microfilaraemia; this is also a potential problem where ivermectin is distributed for mass treatment of onchocerciasis (p. 148.3) in areas co-endemic for both diseases.

Diethylcarbamazine is also used for prophylaxis[1,2] but it has been suggested that it should be reserved for subjects at high risk of exposure. Vector control is regarded as impractical and methods aimed at reducing contact with the vector such as window screens and protective clothing are recommended.

1. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.
2. Padgett JJ, Jacobsen KH. Loiasis: African eye worm. *Trans R Soc Trop Med Hyg* 2008; 102: 983–9.

Lung fluke infections

The lung fluke infection **paragonimiasis** is caused by *Paragonimus* spp., commonly *P. westermani,* and occurs in Asia, Africa, and Central or South America. The disease is transmitted by the ingestion of raw infected freshwater crabs or crayfish, or from drinking infected water.

The flukes mature in the lungs where they cause local necrosis, haemorrhage, inflammation, and fibrosis. Symptoms of paragonimiasis include fever, pain, and chest complaints, but most light to moderate infections are asymptomatic. The worms may also develop at other sites, particularly the brain where they can cause epilepsy, symptoms of cerebral tumours, or cerebral embolism, which may be fatal.

Treatment is with praziquantel or bithionol[1] (though the latter is less often used because of more frequent adverse effects). Triclabendazole is considered effective and well tolerated.[1,2] Corticosteroids should be given with praziquantel for cerebral paragonimiasis.

1. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.
2. WHO. *WHO model formulary.* Geneva: WHO, 2008. Also available at: http://www.who.int/selection_medicines/list/WMF2008.pdf (accessed 27/08/09)

Lymphatic filariasis

Lymphatic filariasis[1] is a parasitic disease caused by filarial nematodes. The three species of filariae that cause lymphatic filariasis are *Wuchereria bancrofti* (bancroftian filariasis), *Brugia malayi,* and *B. timori* (brugian filariasis, also known as Malayan and Timorian filariasis respectively). Adult worms produce larvae (microfilariae) which enter the peripheral bloodstream and through mosquito vectors infective larvae may be transmitted from person to person. The larvae migrate from the skin to the lymphatic system where they mature into adult worms that may live for several years. Development of lymphatic filariasis requires multiple bites from infected mosquitoes over a prolonged period of time (months to years); consequently, people living in endemic areas are at greatest risk of developing the disease.

Filarial infection is usually contracted in childhood and most infections are initially asymptomatic, although nearly all those infected will have some degree of subclinical lymphatic and kidney damage. Infection may remain occult or species- and body-site-dependent symptoms may follow.

- Acute inflammatory reactions to immature and dead or dying adult worms in the lymphatic system are referred to as *adenolymphangitis,* and are characterised by episodic attacks of fever, malaise, and inflammation of the inguinal lymph nodes, testis, and spermatic cord, and focal lymphoedema. These acute episodes usually resolve spontaneously after about a week, but can recur several times a year.
- *Chronic filariasis* may develop 10 to 15 years after initial symptoms and results from recurrent inflammation with subsequent damage to the lymphatic system, leading to impaired lymph drainage and lymphoedema. Manifestations include mild to massive enlargement of the legs, arms, breasts, or genitals (testicular hydrocele or swelling of the vulva), chyluria, and elephantiasis (grossly swollen limbs with thickened, hard, rough, and fissured

skin). Lymphangitis may result from secondary bacterial infections.

- *Occult filariasis* refers to filarial infection in which microfilariae are not detected in the peripheral blood but may be found in other body fluids and tissues. It is rare and is thought to result from a hypersensitivity reaction to filarial antigens. Clinical manifestations include tropical pulmonary eosinophilia, glomerulopathies, endomyocardial fibrosis, filarial arthritis, and filarial granulomas in the breast.

There is no entirely satisfactory **treatment** for individuals with lymphatic filariasis. Current treatments are effective against microfilariae, and thus prevent disease transmission, but have little or no effect on the adult worms and do not halt the progression of symptoms once the disease has developed.

Diethylcarbamazine removes circulating microfilariae and is partially effective against the adult worm and is considered the treatment of choice.[2] Treatment may trigger acute lymphangitis, and diethylcarbamazine should not be given during an acute episode as it may cause further worm death and thus exacerbate the inflammatory response.

Ivermectin is only active against microfilariae and is mainly used in areas also endemic for onchocerciasis or loiasis.

Albendazole plus either of these two drugs is considered to increase their efficacy and such combinations are recommended for mass treatment programmes.[3] However, systematic reviews of randomised studies[4,5] found insufficient evidence to either confirm or reject the observation that albendazole with diethylcarbamazine or ivermectin is more effective than either drug given alone.

Secondary infections with bacteria and fungi occur in poorly vascularised tissues and therefore rigorous hygiene, skin care, physiotherapy, and other measures to promote lymph flow in the affected areas are recommended; in some cases antimicrobials are needed. Large hydroceles and scrotal elephantiasis are generally not reversible with drug therapy and usually require surgical intervention after a treatment course with diethylcarbamazine.

Tropical pulmonary eosinophilia responds to a 3-week course of diethylcarbamazine but patients may relapse and require re-treatment. Filarial arthritis responds rapidly to treatment with diethylcarbamazine.

Filaria have been shown to contain *Wolbachia* **endobacteria** which are essential for larval development and adult worm fertility and viability. This symbiotic dependency has provided a new approach in the treatment of filariasis. In patients infected with *W. bancrofti* oral doxycycline for 4, 6, or, 8 weeks has resulted in a reduction in adult worms and prolonged reduction in microfilaraemia,[1,6] while a 3-week course of oral doxycycline followed by a single dose of ivermectin plus albendazole 4 months after the start of treatment, was found to be more effective in inducing long-term clearance of microfilariae than standard treatment with ivermectin plus albendazole, but was insufficient to kill adult worms.[7] In patients infected with *B. malayi* a 6-week course of oral doxycycline, either alone or followed by a single dose of diethylcarbamazine plus albendazole 4 months later, significantly reduced *Wolbachia* levels and led to a decrease in microfilaraemia that was sustained for at least 1 year after treatment.[8] Doxycycline may also prevent or ameliorate serious adverse effects to standard antifilarial treatment.[7,8]

In communities where lymphatic filariasis is endemic **mass treatment** of the entire community is the basis of the Global Programme to Eliminate Lymphatic Filariasis.[3] The primary goal is to eliminate microfilariae from the blood of infected individuals thereby interrupting transmission. The programme recommends a single dose of 2 drugs (albendazole plus either diethylcarbamazine or ivermectin) given once-yearly for 4 to 6 years.[3,4] Albendazole plus ivermectin is used in areas where onchocerciasis or loiasis are also endemic. Pregnant women, lactating women in the first week after birth, children under 90 cm in height (or weighing less than about 15 kg), and the severely ill are excluded from mass treatment programmes in areas where ivermectin and albendazole are used. In areas where diethylcarbamazine and albendazole are used, pregnant women, children under 2 years of age, and the severely ill are excluded.[9] An alternative approach is the use of diethylcarbamazine-medicated salt for 6 to 12 months throughout the community at risk.

Ongoing **vector control** should be carried out before or during peak transmission season, in order to consolidate the effects of mass chemotherapy. People living in or visiting endemic areas are advised to sleep under a mosquito net and use mosquito repellent on exposed skin between dusk and dawn.

1. Taylor MJ, *et al.* Lymphatic filariasis and onchocerciasis. *Lancet* 2010; 376: 1175–85.
2. Cox FEG, *et al.* (eds). *Topley and Wilson's microbiology and microbial infections: parasitology.* 10th ed. London: Hodder Arnold, 2005.
3. WHO. *Eliminate filariasis: attack poverty—a green light from the Global Alliance.* Geneva: WHO, 2000. Also available at: http://whqlibdoc.who.int/hq/2000/WHO_CDS_CPE_CEE_2000.5.pdf (accessed 03/08/07)
4. Tisch DJ, *et al.* Mass chemotherapy options to control lymphatic filariasis: a systematic review. *Lancet Infect Dis* 2005; 5: 514–23.
5. Addiss D, *et al.* International Filariasis Review Group. Albendazole for lymphatic filariasis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 02/10/06).
6. Taylor MJ, *et al.* Macrofilaricidal activity after doxycycline treatment of Wuchereria bancrofti: a double-blind, randomised placebo-controlled trial. *Lancet* 2005; 365: 2116–21.
7. Turner JD, *et al.* A randomized, double-blind clinical trial of a 3-week course of doxycycline plus albendazole and ivermectin for the treatment of Wuchereria bancrofti infection. *Clin Infect Dis* 2006; 42: 1081–9.
8. Supali T, *et al.* Doxycycline treatment of Brugia malayi-infected persons reduces microfilaremia and adverse reactions after diethylcarbamazine and albendazole treatment. *Clin Infect Dis* 2008; 46: 1385–93.
9. WHO. *Preventive chemotherapy in human helminthiasis: coordinated use of antihelminthic drugs in control interventions: a manual for health professionals and programme managers.* Geneva: WHO, 2006. Also available at: http://whqlibdoc.who.int/publications/2006/9241547103_eng.pdf (accessed 11/09/09)

Mansonella infections

Infections with the filarial nematodes *Mansonella perstans*, *M. ozzardi*, and *M. streptocerca* are generally asymptomatic but symptoms including malaise, fever, joint pain, and meningeal symptoms have been described. Infection is transmitted by biting midges and flies.

Treatment varies according to the infecting species. A single oral dose of ivermectin has been suggested for *M. ozzardi* infections; diethylcarbamazine is ineffective.[1] *M. streptocerca* infections may be treated with diethylcarbamazine or ivermectin; diethylcarbamazine is active against the adult worms and microfilariae, while ivermectin is only effective against microfilariae.[1] Although diethylcarbamazine is generally recommended as a first-line drug for the treatment of *M. perstans* infection, this infection is generally considered to be relatively refractory to treatment with conventional antifilarial drugs and multiple treatments are needed to eliminate the infection.[2] Ivermectin and mebendazole have also been found to be ineffective for *M. perstans*.[1] A combination of mebendazole plus diethylcarbamazine was reported to be more effective than each drug given alone.[2] Tiabendazole has been tried but was found to be less effective than either mebendazole or diethylcarbamazine.[2]

Filaria have been shown to contain *Wolbachia* **endobacteria**, which are essential for larval development and adult worm fertility and viability. This symbiotic dependency has provided a new approach in the treatment of filariasis. In patients infected with *M. perstans*, daily oral doxycycline for 6 weeks resulted in significant reductions in microfilaraemia at 12 months and continued suppression 36 months after treatment.[3]

1. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.
2. Bregani ER, *et al.* Comparison of different anthelmintic drug regimens against Mansonella perstans filariasis. *Trans R Soc Trop Med Hyg* 2006; 100: 458–63.
3. Coulibaly YI, *et al.* A randomized trial of doxycycline for *Mansonella perstans* infection. *N Engl J Med* 2009; 361: 1448–58.

Metagonimiasis

See under Intestinal Fluke Infections, p. 146.2.

Nanophyetiasis

See under Intestinal Fluke Infections, p. 146.2.

Necatoriasis

For infections caused by *Necator americanus* see under Hookworm Infections, p. 146.1.

Onchocerciasis

Onchocerciasis (river blindness) is a parasitic disease caused by infection with the filarial nematode *Onchocerca volvulus*.[1,2] It is endemic in large areas of West and Central Africa, areas of Latin America, and Yemen. It is particularly prevalent near fast flowing rivers, the breeding ground of the blackfly which is the vector of the parasite. After infection, the larvae mature into adult worms in fibrous nodules, usually in the subcutaneous tissue. The adult female worms release large numbers of microfilariae which migrate from the nodules into other tissues, most notably the skin and the eyes. Death of microfilariae in the eyes causes severe inflammation and scarring that may lead to lesions in the eyes and impaired vision. There is some evidence that antigens released from symbiotic *Wolbachia* bacteria within the microfilariae also play a role.[3–5] Repeated infection over several years may result in irreversible blindness. In the skin the dying microfilariae trigger a subcutaneous inflammatory response that causes intense itching. Over time the skin becomes swollen and thickened (lizard skin) and may lose some of its elasticity and pigment (leopard skin).

Onchocerciasis is controlled either by treating the infected patient, thereby reducing the transmission of the infection from the human host to the vector, or by interrupting the transmission from vector to human. The drug of choice for the **treatment** of onchocerciasis is ivermectin.[4–7] A single oral dose of ivermectin rapidly eliminates microfilariae from the skin and more gradually eliminates them from the cornea and anterior chamber of the eye.[6] It has little effect on the adult worms although it suppresses release of microfilariae for several cycles. Ivermectin therefore only controls the disease; it does not cure or eradicate it. Control of the disease in endemic areas relies upon the use of ivermectin every 12 months in Africa (and every 6 months in Central and South America) and this may be combined with vector control (see below). Because the adult worms live for about 15 years, treatment will need to be continued for many years. Ivermectin is donated by *Merck* through the Mectizan Expert Committee (MEC) for human use in *community-wide mass treatment programmes* in all countries in which onchocerciasis is endemic, where it is given to all but pregnant women, breast-feeding mothers of recently born babies, children weighing less than 15 kg (equivalent to about 90 cm in height), and those unable to walk or otherwise seriously ill.[8,9] For further details, see under Ivermectin, p. 157.1. Increasing the frequency of the standard doses of ivermectin to every 3 months appears to increase efficacy compared with annual treatments.[10] Evidence from Ghana suggests that ivermectin-resistant populations of parasites are emerging and that its ability to suppress skin microfilariae repopulation is reduced over time in some communities.[11]

In areas where onchocerciasis and loiasis are co-endemic, care should be taken because ivermectin may cause serious adverse effects, including encephalopathy, in some patients with high *Loa loa* microfilaraemias (see Incidence of Adverse Effects, under Ivermectin, p. 158.1). The Mectizan Expert Committee and the Technical Consultative Committee[12] have implemented recommendations for ivermectin mass treatment programmes of onchocerciasis in areas co-endemic for loiasis.

Before the introduction of ivermectin in 1988, diethylcarbamazine was the usual treatment for onchocerciasis, but it is no longer recommended by WHO.[6] The major limitations to its use are the severe allergic reaction (the Mazzotti reaction) associated with its microfilaricidal action, aggravation of existing ocular lesions or precipitation of new ones, and the need to give repeated courses of treatment for continued suppression of the disease.[6] Suramin has also been used in the treatment of onchocerciasis and is effective against adult worms.[6] However, its use is restricted because of its toxicity.[1] Moxidectin is an anthelmintic used in veterinary medicine and is currently being evaluated for human use.[2,13] Amocarzine has also been evaluated in onchocerciasis.[6]

Recently it has been shown that adult worms contain *Wolbachia* **endobacteria**, which are essential for adult worm fertility and viability. This symbiotic dependency on *Wolbachia* has provided a new approach in the treatment of onchocerciasis. Treatment with oral doxycycline daily for 6 weeks has been shown to sterilise adult worms for the 4-month study period.[14] When given with a single dose of ivermectin, embryogenesis is interrupted for at least 18 months.[15] The long doxycycline treatment regimen is not suitable for mass treatment programmes, but it may be used with ivermectin for treatment of patients who permanently leave an endemic area.

In non-endemic areas ivermectin may be given every 3 to 6 months depending on the recurrence of symptoms or presence of microfilariae.

Vector control with larvicides, continued for the life span of an adult worm, is used to interrupt the transmission of infection and was the main strategy for onchocerciasis control before the introduction of ivermectin. However, despite initial success fly re-invasion became a problem, as the flight range of the vector was longer than expected.[16]

1. Stingl P. Onchocerciasis: developments in diagnosis, treatment and control. *Int J Dermatol* 2009; 48: 393–6.
2. Taylor MJ, *et al.* Lymphatic filariasis and onchocerciasis. *Lancet* 2010; 376: 1175–85.
3. Saint André A, *et al.* The role of endosymbiotic Wolbachia bacteria in the pathogenesis of river blindness. *Science* 2002; 295: 1892–5.
4. Hoerauf A, *et al.* Onchocerciasis. *BMJ* 2003; 326: 207–10.
5. Udall DN. Recent updates on onchocerciasis: diagnosis and treatment. *Clin Infect Dis* 2007; 44: 53–60.
6. WHO. Onchocerciasis and its control: report of a WHO expert committee on onchocerciasis control. *WHO Tech Rep Ser 852* 1995. Also available at: http://libdoc.who.int/trs/WHO_TRS_852.pdf (accessed 03/10/07)
7. WHO. Onchocerciasis (river blindness). Available at: http://www.who.int/blindness/partnerships/onchocerciasis_home/en/index.html (accessed 15/06/06)
8. Pond B. Distribution of ivermectin by health workers. *Lancet* 1990; 335: 1539.
9. WHO. *Preventive chemotherapy in human helminthiasis: coordinated use of antihelminthic drugs in control interventions: a manual for health professionals and programme managers.* Geneva: WHO, 2006. Also available at: http://whqlibdoc.who.int/publications/2006/9241547103_eng.pdf (accessed 09/09/09)
10. Gardon J, *et al.* Effects of standard and high doses of ivermectin on adult worms of Onchocerca volvulus: a randomised controlled trial. *Lancet* 2002; 360: 203–10.
11. Osei-Atweneboana MY, *et al.* Prevalence and intensity of Onchocerca volvulus infection and efficacy of ivermectin in endemic communities in Ghana: a two-phase epidemiological study. *Lancet* 2007; 369: 2021–9.
12. The Mectizan Expert Committee and Technical Consultative Committee. Recommendations for the treatment of onchocerciasis with Mectizan in areas co-endemic for onchocerciasis and loiasis. 2004.

Available at: http://www.mectizan.org/sites/default/files/EnglishMECTCCLoaRecs-June04_1.pdf (accessed 29/07/10)
13. Cotreau MM, *et al.* The antiparasitic moxidectin: safety, tolerability, and pharmacokinetics in humans. *J Clin Pharmacol* 2003; 43: 1108–15.
14. Hoerauf A, *et al.* Endosymbiotic bacteria in worms as targets for a novel chemotherapy in filariasis. *Lancet* 2000; 355: 1242–3.
15. Hoerauf A, *et al.* Depletion of wolbachia endobacteria in Onchocerca volvulus by doxycycline and microfilaridermia after ivermectin treatment. *Lancet* 2001; 357: 1415–6.
16. Thylefors B, Alleman M. Towards the elimination of onchocerciasis. *Ann Trop Med Parasitol* 2006; 100: 733–46.

Opisthorchiasis

See under Liver Fluke Infections, p. 146.2.

Paragonimiasis

See under Lung Fluke Infections, p. 146.3.

Schistosomiasis

Schistosomiasis (bilharziasis) is a parasitic infection caused by *Schistosoma* spp., largely *S. mansoni*, *S. japonicum*, and *S. haematobium*, and to a lesser extent *S. intercalatum* and *S. mekongi*. The disease is seen mainly in Africa, Asia, South America, and the Caribbean, where it is a hazard to individuals exposed to fresh water containing the intermediate host, infected freshwater snails.

Free-swimming cercariae are released from the snail and penetrate human skin causing a pruritic papular rash in sensitised individuals (swimmer's itch). Parasites mature in the lungs and liver within about 6 weeks, then migrate to the blood vessels, the bladder, or intestines. Mature female worms produce eggs which are excreted in urine or stools, or become lodged in tissues, and immunological reaction to these eggs results in disease. The acute reaction to egg deposition has been termed Katayama fever, a self-limiting but sometimes fatal illness resembling serum sickness and most frequently seen in *S. japonicum* infection. The chronic phase of infection is often asymptomatic for many years, but usually results in granuloma formation and fibrosis in tissues where eggs are deposited, such as the liver, lungs, intestines, or urinary tract, the site depending on the infecting species.

Praziquantel is used for the **treatment** of chronic schistosomiasis[1-5] and is effective against all species of schistosomes. Metrifonate and oxamniquine have been used as alternatives against *S. haematobium*[1,2] and *S. mansoni*[1,3,4] respectively. The artemisinins have been found to be effective against immature schistosomes in laboratory studies[2] and artemisinin derivatives used alone or with praziquantel are under investigation for *S. mansoni*,[6,7] *S. haematobium*,[8] and *S. japonica*[9] infections. However, results from these studies are variable and a systematic review[2] on the use of drugs to treat *S. haematobium* found that evidence of benefit with artemisinins was inconclusive. Mefloquine plus artesunate, given orally once daily for 3 days, was found to be effective against *S. haematobium* infection in children; high cure rates and egg reduction rates were also seen in those coinfected with *S. mansoni*.[10]

Mass treatment programmes may be necessary in endemic areas to reduce the overall burden of disease. WHO recommends[11] the use of praziquantel targeted at school-age children, adults considered to be at risk (including pregnant and lactating women or those engaged in high-risk occupations involving contact with infested water), and entire communities living in endemic areas. Children less than 4 years of age or 94 cm in height are excluded from such mass treatment programmes. The frequency of intervention should be determined by the prevalence of infection or of visible haematuria (for *S. haematobium* only) among school-age children.

Niclosamide is used as a molluscicide for the treatment of water in schistosomiasis control programmes. Copper sulfate or sodium pentachlorophenate have also been used but to a lesser extent.

Schistosomiasis vaccines are in development.

1. WHO. The control of schistosomiasis: second report of the WHO expert committee. *WHO Tech Rep Ser 830* 1993. Available at: http://libdoc.who.int/trs/WHO_TRS_830.pdf (accessed 16/07/08)
2. Danso-Appiah A, *et al.* Drugs for treating urinary schistosomiasis. Available in The Cochrane Database of Systematic Reviews: Issue 3. Chichester: John Wiley; 2008 (accessed 09/09/09).
3. Saconato H, Atallah AN. Interventions for treating schistosomiasis mansoni. Available in The Cochrane Database of Systematic Reviews: Issue 3. Chichester: John Wiley; 1999 (accessed 06/05/11).
4. Ross AGP, *et al.* Schistosomiasis. *N Engl J Med* 2002; 346: 1212–20.
5. Gryseels B, *et al.* Human schistosomiasis. *Lancet* 2006; 368: 1106–18.
6. De Clercq D, *et al.* Efficacy of artesunate against Schistosoma mansoni infections in Richard Toll, Senegal. *Trans R Soc Trop Med Hyg* 2000; 94: 90–1.
7. Utzinger J, *et al.* Oral artemether for prevention of Schistosoma mansoni infection: randomised controlled trial. *Lancet* 2000; 355: 1320–5.
8. Borrmann S, *et al.* Artesunate and praziquantel for the treatment of Schistosoma haematobium infections: a double-blind, randomized, placebo-controlled study. *J Infect Dis* 2001; 184: 1363–6.
9. Hou XY, *et al.* A randomized, double-blind, placebo-controlled trial of safety and efficacy of combined praziquantel and artemether treatment for acute schistosomiasis japonica in China. *Bull WHO* 2008; 86: 788–95.
10. Keiser J, *et al.* Efficacy and safety of mefloquine, artesunate, mefloquine-artesunate, and praziquantel against *Schistosoma haematobium*: randomized, exploratory open-label trial. *Clin Infect Dis* 2010; 50: 1205–13.
11. WHO. *Preventive chemotherapy in human helminthiasis: coordinated use of antihelminthic drugs in control interventions: a manual for health professionals and programme managers.* Geneva: WHO, 2006. Also available at: http://whqlibdoc.who.int/publications/2006/9241547103_eng.pdf (accessed 09/09/09)

Strongyloidiasis

Strongyloidiasis[1,2] is an infection of the small intestine caused by *Strongyloides stercoralis*, known as threadworm in the USA. It generally occurs in the tropics and subtropics and can also occur in some areas of South and East Europe, Japan, and the USA. Infective larvae penetrate the skin, migrate to the lungs, move up the bronchial tree to be swallowed, and finally penetrate the mucosa of the small intestine where they mature. Eggs are deposited about 28 days after initial infection. These hatch before leaving the gastrointestinal tract, and can cause autoinfection, particularly in immunocompromised patients. Larvae reaching the soil can either mature into free-living adults or remain in an infective larval stage.

Infection may be asymptomatic, but commonly patients have symptoms relating to the stages of infection. Penetration of larvae through the skin causes intense pruritus and an erythematous rash. The rash may follow the course of migration and is one of the causes of cutaneous larva migrans (p. 144.3). An inflammatory response to migration through the lungs may be seen and may include pneumonitis and bronchospasm. In heavy infections, which are most common in immunocompromised patients as a result of autoinfection, massive pulmonary invasion can occur resulting in fatal alveolar haemorrhage. Abdominal symptoms include colicky pain, diarrhoea, and vomiting, leading to nutritional deficiencies and weight loss. Eosinophilia may also be present. Disseminated disease may occur in immunocompromised patients (including transplant patients[3]) and produce severe pulmonary and abdominal symptoms, shock, encephalopathy, meningitis, and Gram-negative septicaemia. Since strongyloidiasis is commonly fatal in these patients, vulnerable patients from endemic areas should be screened regularly and treated promptly at the first sign of infection.

Ivermectin is considered to be the treatment of choice.[1,2,4] Tiabendazole was widely used, and still is in some countries, but albendazole is more effective and better tolerated. Mebendazole has also been suggested but it must be given for longer periods than albendazole since it has only a limited effect on migrating larvae. These broad-spectrum anthelmintics (except tiabendazole) are also useful if the patient is suffering from a mixed intestinal nematode infection.

1. Segarra-Newnham M. Manifestations, diagnosis, and treatment of Strongyloides stercoralis infection. *Ann Pharmacother* 2007; 41: 1992–2001.
2. Greaves D, *et al.* Strongyloides stercoralis infection. *BMJ* 2013; 347: f4610.
3. Roxby AC, *et al.* Strongyloidiasis in transplant patients. *Clin Infect Dis* 2009; 49: 1411–23.
4. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.

Syngamosis

Syngamosis, or gapeworm infection, is caused by *Syngamus* and *Mammomonogamus* spp. and is mainly an infection of domestic fowl and wild birds and mammals, although infection in man has been reported very rarely.[1-6] Man may become infected by eating foods contaminated with infective larvae which penetrate the intestinal wall and migrate to the lungs, where they mature into adult worms. The major symptom is cough, due to irritation of the bronchi and increased mucus production. The infection may be confused with asthma. Tiabendazole and mebendazole have been used successfully to treat the infection in man.

1. Timmons RF, *et al.* Infection of the respiratory tract with Mammomanogamus (Syngamus) laryngeus: a new case in Largo, Florida, and a summary of previously reported cases. *Am Rev Respir Dis* 1983; 128: 566–9.
2. Gardiner CH, Schantz PM. Mammomonogamus infection in a human: report of a case. *Am J Trop Med Hyg* 1983; 32: 995–7.
3. Leers WD, *et al.* Syngamosis, an unusual cause of asthma: the first reported case in Canada. *Can Med Assoc J* 1985; 132: 269–70.
4. Nosanchuk JS, *et al.* Case report of and description of parasite in Mammomonogamus laryngeus (human syngamosis) infection. *J Clin Microbiol* 1995; 33: 998–1000.
5. Turner P, *et al.* A case of human syngamosis. *Travel Med Infect Dis* 2003; 1: 231–3.
6. Castaño JC, *et al.* Reporte del primer caso humano de infección parasitaria por Mammomonogamus laryngeus en Colombia. *Biomedica* 2006; 26: 337–41.

Taeniasis

Taeniasis is an infection of the intestine with beef tapeworm, *Taenia saginata*, or pork tapeworm, *T. solium*, acquired through ingestion of contaminated raw or undercooked meat. The larval form of *T. solium* can cause the systemic infection cysticercosis (see p. 144.3).

Infection with the adult worm usually produces symptoms only when the worm reaches a size that can cause obstruction or related problems. Segments of the worm containing eggs may be excreted in the faeces so maintaining the cycle of reproduction. Treatment is with a single dose of praziquantel,[1] which has the advantage of also being active, in higher doses, against the larval form of *T. solium*. Niclosamide is also effective[1] but is only active against adult worms.

1. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.

Toxocariasis

Toxocariasis[1] is infection with the larval form of *Toxocara canis* or, less commonly, *T. cati*. The adult worms live in the intestines of dogs and cats respectively, and man becomes infected when eggs excreted in animal faeces are ingested. Once ingested the eggs hatch and the larvae migrate from the intestine to other organs, most commonly the liver, lung, and eye. Most infections are asymptomatic but two clinical syndromes, ocular larva migrans and visceral larva migrans, can occur, usually in children.

Ocular larva migrans occurs when larvae invade the eye causing a granuloma which may impair vision and can cause blindness. There is no specific treatment.[2] Anthelmintics such as albendazole or tiabendazole, corticosteroids, ocular surgery, and laser photocoagulation have been used but assessment of their efficacy is difficult because of the variable natural course of the disease.

The clinical symptoms of visceral larva migrans depend upon the organs involved but commonly include cough, wheezing, fever, and hepatomegaly. Encephalitis and seizures may occur and there is usually eosinophilia. Acute infection normally resolves without treatment.[3] However, severe or prolonged infections may be treated with albendazole;[4] diethylcarbamazine,[5] mebendazole, or tiabendazole have also been used.[1,4]

1. Despommier D. Toxocariasis: clinical aspects, epidemiology, medical ecology, and molecular aspects. *Clin Microbiol Rev* 2003; 16: 265–72.
2. Shields JA. Ocular toxocariasis: a review. *Surv Ophthalmol* 1984; 28: 361–81.
3. Gillespie SH. Human toxocariasis. *Commun Dis Rep* 1993; 3: R140–R143.
4. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.
5. WHO. *WHO model formulary.* Geneva: WHO, 2008. Available at: http://www.who.int/selection_medicines/list/WMF2008.pdf (accessed 19/11/09)

Trichinosis

Trichinosis[1] (trichinellosis or trichiniasis) is an infection caused by nematodes of the genus *Trichinella*, most commonly *Trichinella spiralis*. Man becomes infected through ingestion of raw or undercooked meat, usually pork, containing infective larvae. The larvae mature into adult worms in the small intestine and the mature females deposit larvae that migrate in the blood to skeletal muscle and sometimes to the myocardium. Symptoms usually occur only in heavy infections. Invasion of the intestines by the maturing adult worms can cause diarrhoea, abdominal pain, and vomiting followed about a week later by hypersensitivity reactions to the migrating larvae. These may include eosinophilia, fever, muscle pain, periorbital oedema and, more rarely, encephalitis, myocarditis, or pneumonia which may be fatal.

Treatment with anthelmintic drugs should be started as early as possible to kill the adult worms in the small intestine and thereby prevent the further release of larvae and subsequent muscular invasion.[1] Once the larvae have become established in skeletal muscle treatment may not completely eliminate the infection and associated symptoms. Albendazole or alternatively mebendazole are considered to be the anthelmintics of choice;[1,2] tiabendazole has also been used.[3] Pyrantel embonate may be given to pregnant women and children, although it is only effective against worms in the gut.[1] A corticosteroid should be given for severe hypersensitivity reactions.[1,2,4] If treatment is not started within the first few days of infection, repeated courses of treatment may be required.[1]

1. Gottstein B, *et al.* Epidemiology, diagnosis, treatment, and control of trichinellosis. *Clin Microbiol Rev* 2009; 22: 127–45.
2. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.
3. Watt G, *et al.* Blinded, placebo-controlled trial of antiparasitic drugs for trichinosis myositis. *J Infect Dis* 2000; 182: 371–4.
4. Shimoni Z, *et al.* The use of prednisone in the treatment of trichinellosis. *Isr Med Assoc J* 2007; 9: 537–9.

Trichostrongyliasis

Trichostrongyliasis is an infection of the small intestine caused by *Trichostrongylus* spp. including *T. colubriformis*. *Trichostrongylus* spp. are normally parasites of herbivores, but infections in man have been found. They have a similar life cycle to *Ancylostoma duodenale* (see Hookworm Infections, p. 146.1). Pyrantel embonate, albendazole, or mebendazole are recommended for the treatment of trichostrongyliasis.[1] Successful treatment with ivermectin has occurred in areas where widespread use of

benzimidazole carbamate derivatives in grazing animals has led to resistance to these drugs.[2]

1. Abramowicz M, ed. *Drugs for parasitic infections*. 3rd ed. New Rochelle NY: The Medical Letter, 2013.
2. Ralph A, *et al.* Abdominal pain and eosinophilia in suburban goat keepers. *Med J Aust* 2006; 184: 467–9. Correction. *ibid.*; 185: 49. [title]

Trichuriasis

Trichuriasis is an infection of the large intestine with *Trichuris trichiura*, sometimes known as whipworm. Distribution is worldwide, but most infections occur in the tropics and subtropics. Eggs are excreted in the faeces and can remain viable in the soil for extended periods. Under optimum conditions the eggs become infective in about 2 to 4 weeks. After ingestion, larvae are released from the eggs and develop within the wall of the small intestine for about 3 to 10 days, before migrating to the lumen of the large intestine where they remain attached to the mucosal lining. Eggs are detectable in the faeces about 1 to 3 months after infection. Trichuriasis is often asymptomatic, but heavy infection can result in anaemia, diarrhoea, and rectal prolapse.

Treatment is with a benzimidazole carbamate derivative such as albendazole or mebendazole[1-3] and such broad-spectrum therapy can be useful if the patient is suffering from a mixed intestinal nematode infection. Ivermectin[2] and nitazoxanide[4] are alternatives and addition of ivermectin to treatment with either albendazole or mebendazole has been shown to improve cure and egg reduction rates.[5] However, a systematic review[3] considered the treatment of trichuriasis to be unsatisfactory with current drugs.

Mass treatment programmes may be necessary in endemic areas to reduce the overall burden of disease. WHO recommends[6] the use of albendazole or mebendazole or alternatively levamisole or pyrantel targeted at preschool and school-age children, women of child-bearing age (including pregnant women in the second and third trimesters and lactating women), and adults engaged in high-risk occupations for soil-transmitted helminthiasis, such as tea-pickers and miners. Children less than 1 year of age and women in the first trimester of pregnancy are excluded from such mass treatment programmes. The frequency of intervention should be determined by the prevalence and intensity of infection among school-age children.

1. Bethony J, *et al.* Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm. *Lancet* 2006; 367: 1521–32.
2. Abramowicz M, ed. *Drugs for parasitic infections*. 3rd ed. New Rochelle NY: The Medical Letter, 2013.
3. Keiser J, Utzinger J. Efficacy of current drugs against soil-transmitted helminth infections: systematic review and meta-analysis. *JAMA* 2008; 299: 1937–48.
4. Juan JO, *et al.* Comparative clinical studies of nitazoxanide, albendazole and praziquantel in the treatment of ascariasis, trichuriasis and hymenolepiasis in children from Peru. *Trans R Soc Trop Med Hyg* 2002; 96: 193–6.
5. Knopp S, *et al.* Albendazole and mebendazole administered alone or in combination with ivermectin against *Trichuris trichiura*: a randomized controlled trial. *Clin Infect Dis* 2010; 51: 1420–8.
6. WHO. *Preventive chemotherapy in human helminthiasis: coordinated use of antihelminthic drugs in control interventions: a manual for health professionals and programme managers*. Geneva: WHO, 2006. Also available at: http://whqlibdoc.who.int/publications/2006/9241547103_eng.pdf (accessed 09/09/09)

Abamectin *(USAN, rINN)*

Abaimectin; Abamectina; Abamectine; Abamectinum; Abamektyna; MK-0936; Абамектин.

A mixture of abamectin component B_{1a} and abamectin component B_{1b}.

CAS — 65195-55-3 (component B_{1a}); 65195-56-4 (component B_{1b}).

ATC Vet — QP54AA02.

UNII — 5U8924T11H (abamectin); K54ZMM929K (abamectin component B_{1a}); W8DT67027W (abamectin component B_{1b}).

Profile

Abamectin is an avermectin anthelmintic used in veterinary medicine for nematode infections. It is also used as a systemic veterinary ectoparasiticide.

References.
1. Soyuncu S, *et al.* Abamectin intoxication with coma and hypotension. *Clin Toxicol* 2007; 45: 299–300.

Albendazole *(BAN, USAN, rINN)*

Albendatsoli; Albendazol; Albendazolas; Albendazolo; Albendazolum; SKF-62979; Альбендазол; Албендазол.

Methyl 5-propylthio-1*H*-benzimidazol-2-ylcarbamate

$C_{12}H_{15}N_3O_2S$=265.3

CAS — 54965-21-8.

ATC — P02CA03.

ATC Vet — QP52AC11.

UNII — F4216019LN.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 8: (Albendazole). A white to faintly yellowish powder. Practically insoluble in water and in alcohol; very slightly soluble in dichloromethane; freely soluble in anhydrous formic acid. Protect from light.

USP 36: (Albendazole). A white to faintly yellowish powder. Practically insoluble in water and in alcohol; very slightly soluble in ether and in dichloromethane; freely soluble in anhydrous formic acid. Store in airtight containers.

Uses and Administration

Albendazole is a benzimidazole carbamate anthelmintic structurally related to mebendazole (p. 160.1) and with similar activity. It is used in relatively high doses in the treatment of the cestode infections cysticercosis and echinococcosis (hydatid disease). In some countries albendazole is used in the treatment of single and mixed intestinal nematode infections including ascariasis, enterobiasis, hookworm, strongyloidiasis, and trichuriasis. It may also be used in the treatment of angiostrongyliasis, capillariasis, gnathostomiasis, and trichostrongyliasis. Albendazole may be effective in the treatment of the tissue nematode infections cutaneous larva migrans, toxocariasis, and trichinosis and has been tried in loiasis, and, with other anthelmintics, in mass treatment programmes in areas where lymphatic filariasis is endemic. It may be given as an alternative to praziquantel in the treatment of liver fluke infections caused by *Clonorchis sinensis*. For discussions of these infections and their treatment, see under Choice of Anthelmintic (p. 143.1), and under the individual headings below.

In the treatment of **echinococcosis**, albendazole is given orally with meals in a dose of 400 mg twice daily for 28 days for patients weighing over 60 kg. A dose of 15 mg/kg daily in two divided doses (to a maximum total daily dose of 800 mg) is used for patients weighing less than 60 kg. For cystic echinococcosis, the 28-day course is repeated after 14 days without treatment to a total of 3 treatment cycles. For alveolar echinococcosis, cycles of 28 days of treatment followed by 14 days without treatment may need to continue for months or years.

In the treatment of **neurocysticercosis**, US licensed product information recommends doses of albendazole for parenchymal cysts similar to the doses used in echinococcosis (see above); the recommended duration of treatment is 8 to 30 days. Expert opinion also favours similar doses of 15 mg/kg daily but with a duration of treatment of only 8 days for parenchymal disease and about 1 month for extraparenchymal disease, such as subarachnoid, ventricular, and spinal cord cysticercosis. For further information on dosage regimens, see Cysticercosis, p. 151.1.

Albendazole is given orally, usually as a single dose, in the treatment of single or mixed **intestinal nematode infections**. The usual dose for those with ascariasis, enterobiasis, hookworm infections, or trichuriasis is 400 mg as a single dose; a 3-day course of treatment is needed for heavier infections with trichuriasis. In enterobiasis, the dose may be repeated in 2 to 4 weeks. For *mass treatment* control programmes against ascariasis, hookworm infections, and trichuriasis, a dose of 400 mg is given as a single dose once or twice a year depending on the prevalence and intensity of infection among school-age children. In strongyloidiasis, 400 mg is given once or twice daily for 3 consecutive days; this may be repeated after 3 weeks if necessary.

In the treatment of **clonorchiasis**, albendazole is given orally with meals in a dose of 10 mg/kg daily for 7 days.

Albendazole has also been used to treat **giardiasis** (p. 923.2): suggested oral doses are 400 mg daily for 5 days.

For details of doses in children, see p. 150.3.

Administration in children. Albendazole may be given orally to children for the treatment of single or mixed intestinal nematode infections and for cestode infections such as neurocysticercosis and echinococcosis.

For nematode infections the following doses are recommended:

- for **ascariasis, enterobiasis, hookworm infections, and trichostrongyliasis** children from 12 months to 2 years of age may be given 200 mg as a single dose and those more than 2 years of age may be given 400 mg as a single dose. For enterobiasis infections the dose should be repeated after 14 to 28 days
- for **capillariasis** children from 2 years of age may be given a dose of 400 mg daily for 10 days
- for **strongyloidiasis** children from 2 years of age may be given a dose of 400 mg once or twice daily for 3 days; the dose may be repeated after 3 weeks if necessary
- for **trichuriasis** children from 12 months to 2 years of age may be given 200 mg as a single dose for moderate infections; for more severe infections an initial dose of 200 mg is given followed by 100 mg twice daily for 3 days. Those more than 2 years of age may be given 400 mg as a single dose for moderate infections; for more severe infections the usual dose is 400 mg daily for 3 days

For *mass treatment* control programmes against ascariasis, hookworm infections, and trichuriasis, children from 12 to 23 months of age may be given a single dose of 200 mg, while those 2 years of age or older may be given a single dose of 400 mg. Doses are given once or twice a year depending on the prevalence and intensity of infection among school-age children.

For cestode infections the following doses are recommended:

- for **echinococcosis** children from 2 years of age may be given a dose of 7.5 mg/kg twice daily (to a maximum daily dose of 800 mg) for 28 days; the 28-day course is repeated after 14 days without treatment to a total of 2 to 3 treatment cycles
- for **neurocysticercosis** children may be given a dose of 15 mg/kg daily in 2 divided doses (to a maximum daily dose of 800 mg) for 8 to 30 days; treatment may be repeated if necessary

Ascariasis. Albendazole is used as an alternative to mebendazole in the treatment of ascariasis (p. 143.3). Both drugs are equally highly effective with a cure rate greater than 98% reported for albendazole in one study.[1]

1. Albonico M, *et al.* A randomized controlled trial comparing mebendazole and albendazole against Ascaris, Trichuris and hookworm infections. *Trans R Soc Trop Med Hyg* 1994; 88: 585–9.

Capillariasis. Albendazole in an oral dose of 400 mg daily for 10 days has been suggested[1] as an alternative to mebendazole for the treatment of capillariasis (p. 144.2).

1. Abramowicz M, ed. *Drugs for parasitic infections*. 3rd ed. New Rochelle NY: The Medical Letter, 2013.

Cutaneous larva migrans. Albendazole has been reported[1-4] to be effective in the treatment of cutaneous larva migrans (p. 144.3) and is an alternative to tiabendazole or ivermectin. Albendazole, generally in an oral dose of 400 mg daily for three to five days,[1,2,5] has alleviated the discomfort of cutaneous larva migrans; treatment for seven days may be more effective and has not been associated with an increased incidence of adverse effects.[4] A single dose of 400 mg has also been effective.[3] An ointment containing albendazole 10%, applied 3 times daily for 10 days, was reported to be effective in treating cutaneous larva migrans in 2 young children.[6]

1. Jones SK, *et al.* Oral albendazole for the treatment of cutaneous larva migrans. *Br J Dermatol* 1990; 122: 99–101.
2. Sanguigni S, *et al.* Albendazole in the therapy of cutaneous larva migrans. *Trans R Soc Trop Med Hyg* 1990; 84: 831.
3. Orihuela AR, Torres JR. Single dose of albendazole in the treatment of cutaneous larva migrans. *Arch Dermatol* 1990; 126: 398–9.
4. Veraldi S, Rizzitelli G. Effectiveness of a new therapeutic regimen with albendazole in cutaneous larva migrans. *Eur J Dermatol* 1999; 9: 352–3.
5. Heukelbach J, Feldmeier H. Epidemiological and clinical characteristics of hookworm-related cutaneous larva migrans. *Lancet Infect Dis* 2008; 8: 302–9.
6. Caumes E. Efficacy of albendazole ointment on cutaneous larva migrans in 2 young children. *Clin Infect Dis* 2004; 38: 1647–8.

Cysticercosis. The use of anthelmintics in the treatment of neurocysticercosis (see Cysticercosis, p. 144.3) remains controversial, but if indicated oral albendazole is considered to be the drug of choice.[1-3] The dose of albendazole originally used was the same as that used in echinococcosis, typically about 15 mg/kg daily orally for 1 month. There is now some evidence that shorter courses of treatment may be appropriate in some forms of neurocysticercosis. A study[4] confirmed that a 10-day course of albendazole 400 mg twice daily, with dexamethasone, was safe and decreased the burden of parasites and the number of generalised seizures in patients with viable parenchymal cysts. Albendazole has also been reported to be effective for extraparenchymal infection, such as subarachnoid, ventricular,[2,5,6] and spinal cord cysticercosis,[2] but the longer treatment period of 1 month with a dose of 15 mg/kg daily is usually used; multiple courses may be needed.[7] Alternatively, a higher dose of albendazole for a shorter time may be considered. A study[5] of 36 patients with subarachnoid and intraventricular cysticercosis found that 30 mg/kg daily for 8 days was safe and more effective than 15 mg/kg daily for 8 days, both regimens being given with corticosteroids. For patients with solitary cysticercus granuloma a dose of 15 mg/kg daily, in 2 to 3 divided doses (with or without corticosteroids), for 1 to 2 weeks has been recommended.[8]

1. Sotelo J, Jung H. Pharmacokinetic optimisation of the treatment of neurocysticercosis. *Clin Pharmacokinet* 1998; 34: 503–15.
2. Takayanagui OM. Therapy for neurocysticercosis. *Expert Rev Neurother* 2004; 4: 129–39.
3. Del Brutto OH, *et al.* Meta-analysis: cysticidal drugs for neurocysticercosis: albendazole and praziquantel. *Ann Intern Med* 2006; 145: 43–51.
4. Garcia HH, *et al.* A trial of antiparasitic treatment to reduce the rate of seizures due to cerebral cysticercosis. *N Engl J Med* 2004; 350: 249–58.

5. Góngora-Rivera F, *et al.* Albendazole trial at 15 or 30 mg/kg/day for subarachnoid and intraventricular cysticercosis. *Neurology* 2006; **66**: 436–8.
6. Proaño JV, *et al.* Medical treatment for neurocysticercosis characterized by giant subarachnoid cysts. *N Engl J Med* 2001; **345**: 879–85.
7. Nash TE, *et al.* Treatment of neurocysticercosis: current status and future research needs. *Neurology* 2006; **67**: 1120–7.
8. Singh G, *et al.* A diagnostic and therapeutic scheme for a solitary cysticercus granuloma. *Neurology* 2010; **75**: 2236–45.

Echinococcosis. Albendazole is used in the treatment of echinococcosis (p. 145.2) as an adjunct to, or instead of, surgery. It is generally preferred to mebendazole.

References.

1. Teggi A, *et al.* Therapy of human hydatid disease with mebendazole and albendazole. *Antimicrob Agents Chemother* 1993; **37**: 1679–84.
2. Gil-Grande LA, *et al.* Randomised controlled trial of efficacy of albendazole in intra-abdominal hydatid disease. *Lancet* 1993; **342**: 1269–72.
3. Wen H, *et al.* Initial observation on albendazole in combination with cimetidine for the treatment of human cystic echinococcosis. *Ann Trop Med Parasitol* 1994; **88**: 49–52.
4. Wen H, *et al.* Albendazole chemotherapy for human cystic and alveolar echinococcosis in north-western China. *Trans R Soc Trop Med Hyg* 1994; **88**: 340–3.
5. Liu Y, *et al.* Continuous long-term albendazole therapy in intraabdominal cystic echinococcosis. *Chin Med J (Engl)* 2000; **113**: 827–32.
6. Keshmiri M, *et al.* Albendazole versus placebo in treatment of echinococcosis. *Trans R Soc Trop Med Hyg* 2001; **95**: 190–4.
7. Falagas ME, Blizlotis IA. Albendazole for the treatment of human echinococcosis: a review of comparative clinical trials. *Am J Med Sci* 2007; **334**: 171–9.

Giardiasis. Albendazole has been tried in the treatment of giardiasis (p. 923.2) with variable results; however, a meta-analysis[1] of 8 studies suggested that an oral dose of 400 mg once daily for 5 days was as effective as, and better tolerated than, standard treatment with metronidazole.

1. Solaymani-Mohammadi S, *et al.* A meta-analysis of the effectiveness of albendazole compared with metronidazole as treatments for infections with *Giardia duodenalis*. *PLoS Negl Trop Dis* 2010; **4**: e682.

Gnathostomiasis. Albendazole has been reported to be effective in the treatment of gnathostomiasis (p. 145.3). Oral doses of 400 mg once or twice daily have been given for 2 or 3 weeks.[1–4]

1. Kraivichian P, *et al.* Albendazole for the treatment of human gnathostomiasis. *Trans R Soc Trop Med Hyg* 1992; **86**: 418–21.
2. Suntharasamai P, *et al.* Albendazole stimulates outward migration of Gnathostoma spinigerum to the dermis in man. *Southeast Asian J Trop Med Public Health* 1992; **23**: 716–22.
3. Nontasut P, *et al.* Comparison of ivermectin and albendazole treatment for gnathostomiasis. *Southeast Asian J Trop Med Public Health* 2000; **31**: 374–7.
4. Abramowicz M, ed. *Drugs for parasitic infections*. 3rd ed. New Rochelle NY: The Medical Letter, 2013.

Hookworm infections. Hookworm infections (p. 146.1) are commonly treated with benzimidazole carbamates such as albendazole. In 77 patients with light necatoriasis (*Necator americanus* infection) albendazole, in a single 400-mg dose, produced an 84% cure rate and an 82% reduction in egg count in those patients not cured.[1] In another study,[2] although the cure rate was only 56.8% after a single 400-mg dose of albendazole this was superior to treatment with mebendazole which had a cure rate of 22.4%. A further study[3] comparing albendazole with mebendazole and pyrantel in the treatment of necatoriasis also found albendazole to be the most effective.

Albendazole is given in mass treatment programmes to reduce the overall burden of infection.[1,4]

1. Nahmias J, *et al.* Evaluation of albendazole, pyrantel, bephenium, pyrantel-praziquantel and pyrantel-bephenium for single-dose mass treatment of necatoriasis. *Ann Trop Med Parasitol* 1989; **83**: 625–9.
2. Albonico M, *et al.* A randomized controlled trial comparing mebendazole and albendazole against Ascaris, Trichuris and hookworm infections. *Trans R Soc Trop Med Hyg* 1994; **88**: 585–9.
3. Sacko M, *et al.* Comparison of the efficacy of mebendazole, albendazole and pyrantel in treatment of human hookworm infections in the southern region of Mali, West Africa. *Trans R Soc Trop Med Hyg* 1999; **93**: 195–203.
4. Idris MA, *et al.* Effective control of hookworm infection in school children from Dhofar, Sultanate of Oman: a four-year experience with albendazole mass chemotherapy. *Acta Trop* 2001; **80**: 139–43.

Loiasis. Albendazole has been given[1–3] to reduce microfilariasis in patients infected with *Loa loa* (see Loiasis, p. 146.2). It may be a useful alternative drug in those patients with a heavy or dense microfilarial load who are at risk for serious adverse effects from diethylcarbamazine[4] or where diethylcarbamazine is ineffective or cannot be used.[5] An [oral] dose of 200 mg twice daily for 3 weeks is usually given.[4]; repeat courses may be necessary.[5]

1. Klion AD, *et al.* Albendazole in human loiasis: results of a double-blind, placebo-controlled trial. *J Infect Dis* 1993; **168**: 202–6.
2. Klion AD, *et al.* Albendazole therapy for loiasis refractory to diethylcarbamazine treatment. *Clin Infect Dis* 1999; **29**: 680–2.
3. Tabi TE, *et al.* Human loiasis in a Cameroonian village: a double-blind, placebo-controlled, crossover clinical trial of a three-day albendazole regimen. *Am J Trop Med Hyg* 2004; **71**: 211–15.
4. Padgett JJ, Jacobsen KH. Loiasis: African eye worm. *Trans R Soc Trop Med Hyg* 2008; **102**: 983–9.
5. Abramowicz M, ed. *Drugs for parasitic infections*. 3rd ed. New Rochelle NY: The Medical Letter, 2013.

Lymphatic filariasis. Although the evidence for such use is relatively weak,[1,2] albendazole is used in the management of lymphatic filariasis (p. 146.3). In endemic areas mass treatment of the entire population (excluding neonates, pregnant women, and debilitated individuals) with appropriate drugs can reduce the intensity of transmission and the incidence of disease. The Global Programme to eliminate Lymphatic Filariasis launched by WHO, with other international agencies, advocates a single oral dose of albendazole 400 mg with either a single oral dose of ivermectin 150 to 200 micrograms/kg (if there is co-endemic loiasis or onchocerciasis) or with a single oral dose of diethylcarbamazine 6 mg/kg (if there is no co-endemic loiasis or onchocerciasis); these doses are given once each year for at least 5 years. Higher doses of albendazole and ivermectin (800 mg and 400 micrograms/kg respectively) given twice a year for 2 years, to 25 residents of an area of high *Wuchereria bancrofti* endemicity in Mali, were found to be more effective in reducing microfilarial levels than the standard annual dose regimen recommended by WHO. Higher-dose and/or more frequent treatment regimens could therefore potentially reduce the time necessary to interrupt transmission.[3]

1. Addiss D, *et al.* International Filariasis Review Group. Albendazole for lymphatic filariasis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 16/10/09).
2. Horton J. The development of albendazole for lymphatic filariasis. *Ann Trop Med Parasitol* 2009; **103** (suppl 1): S33–S40.
3. Dembele B, *et al.* Use of high-dose, twice-yearly albendazole and ivermectin to suppress *Wuchereria bancrofti* microfilarial levels. *Clin Infect Dis* 2010; **51**: 1229–35.

Microsporidiosis. Albendazole has been tried[1–6] in the treatment of the protozoal infection microsporidiosis (p. 925.3) in patients with AIDS. Albendazole has also been used empirically in the treatment of HIV-associated infections and complications (p. 960.3).

1. Blanshard C, *et al.* Treatment of intestinal microsporidiosis with albendazole in patients with AIDS. *AIDS* 1992; **6**: 311–13.
2. Dieterich DT, *et al.* Treatment with albendazole for intestinal disease due to Enterocytozoon bieneusi in patients with AIDS. *J Infect Dis* 1994; **169**: 178–82.
3. Franzen C, *et al.* Intestinal microsporidiosis with Septata intestinalis in a patient with AIDS—response to albendazole. *J Infect* 1995; **31**: 237–9.
4. Dore GJ, *et al.* Disseminated microsporidiosis due to Septata intestinalis in nine patients infected with the human immunodeficiency virus: response to therapy with albendazole. *Clin Infect Dis* 1995; **21**: 70–6.
5. Molina J-M, *et al.* Albendazole for treatment and prophylaxis of microsporidiosis due Encephalitozoon intestinalis in patients with AIDS: a randomized double-blind controlled trial. *J Infect Dis* 1998; **177**: 1373–7.
6. Tremoulet AH, *et al.* Albendazole therapy for Microsporidium diarrhea in immunocompetent Costa Rican children. *Pediatr Infect Dis J* 2004; **23**: 915–18.

Strongyloidiasis. Albendazole is generally preferred to tiabendazole or mebendazole in the treatment of strongyloidiasis (p. 148.2) although ivermectin is now generally considered to be the drug of choice. Both drugs have been used together in disseminated disease.

References.

1. Rossignol JF, Maisonneuve H. Albendazole: placebo-controlled study in 870 patients with intestinal helminthiasis. *Trans R Soc Trop Med Hyg* 1983; **77**: 707–11.
2. Chanthavanich P, *et al.* Repeated doses of albendazole against strongyloidiasis in Thai children. *Southeast Asian J Trop Med Public Health* 1989; **20**: 221–6.
3. Mojon M, Nielsen PB. Treatment of Strongyloides stercoralis with albendazole: a cure rate of 86 per cent. *Zentralbl Bakteriol Mikrobiol Hyg [A]* 1987; **263**: 619–24.
4. Archibald LK, *et al.* Albendazole is effective treatment for chronic strongyloidiasis. *Q J Med* 1993; **86**: 191–5.
5. Pornsuriyasak P, *et al.* Disseminated strongyloidiasis successfully treated with extended duration ivermectin combined with albendazole: a case report of intractable strongyloidiasis. *Southeast Asian J Trop Med Public Health* 2004; **35**: 531–4.
6. Singthong S, *et al.* Randomized comparative trial of two high-dose albendazole regimens for uncomplicated human strongyloidiasis. *Southeast Asian J Trop Med Public Health* 2006; **37** (suppl 3): 32–4.

Toxocariasis. Albendazole is one of the drugs that might be used for the treatment of toxocariasis (p. 148.3) but published controlled studies are mostly lacking. In a small study[1] it produced improvement similar to that achieved with tiabendazole but with fewer problems. An oral dose of 400 mg twice daily for 5 days has been recommended,[2,3] although the optimum duration of therapy is unknown and some would treat for 20 days.[3] In those with severe symptoms or eye involvement treatment may need to be extended; adjunctive corticosteroid treatment may also be necessary.[3]

1. Stürchler D, *et al.* Thiabendazole vs albendazole in treatment of toxocariasis: a clinical trial. *Ann Trop Med Parasitol* 1989; **83**: 473–8.
2. Despommier D. Toxocariasis: clinical aspects, epidemiology, medical ecology, and molecular aspects. *Clin Microbiol Rev* 2003; **16**: 265–72.
3. Abramowicz M, ed. *Drugs for parasitic infections*. 3rd ed. New Rochelle NY: The Medical Letter, 2013.

Trichinosis. Albendazole may be effective in the treatment of trichinosis (p. 148.3). A retrospective study in 44 patients with trichinosis comparing albendazole treatment with tiabendazole found that, while the two drugs were of comparable efficacy, albendazole was the better tolerated.[1] An oral dose of 400 mg twice daily for 8 to 14 days has been recommended.[2] Albendazole has been used to treat a patient infected with *Trichinella pseudospiralis*, an organism related to *T. spiralis*, the usual cause of trichinosis.[3]

1. Cabié A, *et al.* Albendazole versus thiabendazole as therapy for trichinosis: a retrospective study. *Clin Infect Dis* 1996; **22**: 1033–5.
2. Gottstein B, *et al.* Epidemiology, diagnosis, treatment, and control of trichinellosis. *Clin Microbiol Rev* 2009; **22**: 127–45.
3. Andrews JRH, *et al.* Trichinella pseudospiralis in humans: description of a case and its treatment. *Trans R Soc Trop Med Hyg* 1994; **88**: 200–3.

Trichostrongyliasis. Albendazole in a single oral dose of 400 mg has been suggested[1] as an alternative to pyrantel embonate or mebendazole in the treatment of trichostrongyliasis (p. 148.3).

1. Abramowicz M, ed. *Drugs for parasitic infections*. 3rd ed. New Rochelle NY: The Medical Letter, 2013.

Trichuriasis. Oral albendazole is used in the treatment of trichuriasis (p. 149.1). It is normally given in a single dose and is often used in mixed intestinal nematode infections. However, it has been reported[1–3] that in children with mixed intestinal worm infections single doses of albendazole are ineffective in eliminating *Trichuris trichiura* and multiple doses are required to produce worthwhile reductions in egg production. Treatment for 3 days has been used for heavier infections[4] (but for a suggestion that such regimens may be associated with impaired growth in less heavily infected children, see Effects on Growth under Adverse Effects, p. 152.1). Combined use of albendazole with ivermectin may prove useful.[5] A systematic review[4] however considered that all current regimens for the treatment of trichuriasis were unsatisfactory.

1. Hall A, Anwar KS. Albendazole and infections with Trichuris trichiura and Giardia intestinalis. *Southeast Asian J Trop Med Public Health* 1991; **22**: 84–7.
2. Hall A, Nahar Q. Albendazole and infections with Ascaris lumbricoides and Trichuris trichiura in children in Bangladesh. *Trans R Soc Trop Med Hyg* 1994; **88**: 110–12.
3. Albonico M, *et al.* A randomized controlled trial comparing mebendazole and albendazole against Ascaris, Trichuris and hookworm infections. *Trans R Soc Trop Med Hyg* 1994; **88**: 585–9.
4. Abramowicz M, ed. *Drugs for parasitic infections*. 3rd ed. New Rochelle NY: The Medical Letter, 2013.
5. Ismail MM, Jayakody RL. Efficacy of albendazole and its combinations with ivermectin or diethylcarbamazine (DEC) in the treatment of Trichuris trichiura infections in Sri Lanka. *Ann Trop Med Parasitol* 1999; **93**: 501–4.
6. Keiser J, Utzinger J. Efficacy of current drugs against soil-transmitted helminth infections: systematic review and meta-analysis. *JAMA* 2008; **299**: 1937–48.

Adverse Effects and Precautions

As for Mebendazole, p. 160.3.

Adverse effects are usually mild and resolve without treatment. However, in patients being treated for echinococcosis (hydatid disease), albendazole has caused mild to moderate increases of liver enzyme values in about 16% of patients; hepatitis and acute liver failure have also been reported. Leucopenia has occurred in less than 1% of patients; while agranulocytosis, aplastic anaemia, neutropenia, or thrombocytopenia are rare, deaths due to granulocytopenia and pancytopenia have been reported. Patients with liver disease, including hepatic echinococcosis, appear to be at increased risk of bone marrow suppression and in these patients blood cell counts and liver function should be closely monitored.

Patients being treated for neurocysticercosis should be given corticosteroids to prevent cerebral hypertensive episodes during the first week of therapy. Anticonvulsant therapy also may be necessary. Albendazole may cause irreparable damage when used to treat ocular or spinal cysts, even when corticosteroids are given, and an ophthalmic examination should be performed before treatment to exclude intra-ocular cysts.

Incidence of adverse effects. Although *high-dose* therapy with albendazole for the treatment of cystic echinococcosis (hydatid disease) was generally well-tolerated, the following adverse reactions were reported in the first phase of WHO-coordinated studies[1] involving 30 patients: raised serum-transaminase levels (2 patients), reduced leucocyte counts (1 patient), gastrointestinal symptoms (1 patient), allergic conditions (1 patient), and loss of hair (1 patient). Treatment was stopped in a further patient with alveolar echinococcosis because of depressed bone-marrow activity. In the second phase of these studies,[2] of 109 patients given albendazole for cystic echinococcosis, 20 had adverse effects; similar findings were reported with mebendazole. The range of effects with albendazole was: elevation of transaminases (5 patients), abdominal pain and other gastrointestinal symptoms (7 patients), severe headache (4 patients), loss of hair (2 patients), leucopenia (2 patients), fever and fatigue (1 patient), thrombocytopenia (1 patient), and urticaria and itching (1 patient). Albendazole had to be withdrawn in 5 patients because of adverse effects, although in 3 the withdrawal was only temporary.

1. Davis A, *et al.* Multicentre clinical trials of benzimidazolecarbamates in human echinococcosis. *Bull WHO* 1986; **64**: 383–8.

2. Davis A, *et al.* Multicentre clinical trials of benzimidazolecarbamates in human cystic echinococcosis (phase 2). *Bull WHO* 1989; 67: 503–8.

Breast feeding. The results of a study[1] in 33 women given a single oral 400-mg dose of albendazole suggested that albendazole and its active metabolite attained low concentrations in breast milk. The authors considered that albendazole was unlikely to be harmful to breast-fed infants.

1. Abdel-tawab AM, *et al.* Albendazole and its metabolites in the breast milk of lactating women following a single oral dose of albendazole. *Br J Clin Pharmacol* 2009; 68: 737–42.

Effects on growth. A multiple-dose regimen of albendazole in children with asymptomatic trichuriasis has been reported to be associated with impaired growth in those with low levels of infection.[1] However it was considered that this should not prevent the use of single doses in mass treatment programmes.[2]

1. Forrester JE, *et al.* Randomised trial of albendazole and pyrantel in symptomless trichuriasis in children. *Lancet* 1998; 352: 1103–8.
2. Winstanley P. Albendazole for mass treatment of asymptomatic trichuris infections. *Lancet* 1998; 352: 1080–1.

Effects on the liver. In a series of 40 patients given albendazole for echinococcosis, 7 developed abnormalities in liver function tests during therapy.[1] Six had a hepatocellular type of abnormality attributable to albendazole; the seventh had cholestatic jaundice which was probably not due to albendazole. See also Incidence of Adverse Effects, p. 150.3 for reports of raised serum-transaminase levels.

Albendazole should only be used in the treatment of echinococcosis if there is constant medical supervision with regular monitoring of serum-transaminase concentrations and of leucocyte and platelet counts. Patients with liver damage should be treated with reduced doses of benzimidazole carbamates, if at all.[2]

1. Morris DL, Smith PG. Albendazole in hydatid disease—hepatocellular toxicity. *Trans R Soc Trop Med Hyg* 1987; 81: 343–4.
2. Davis A, *et al.* Multicentre clinical trials of benzimidazolecarbamates in human cystic echinococcosis (phase 2). *Bull WHO* 1989; 67: 503–8.

Pregnancy. Albendazole is teratogenic in some *animals* and there are no adequate and well controlled studies in human pregnancy. Albendazole is therefore usually contra-indicated during pregnancy and US licensed product information cautions against becoming pregnant while taking albendazole or within one month of completing treatment.

For reference to a study of women given albendazole with ivermectin during the second trimester of pregnancy, see p. 158.2.

Interactions

Anthelmintics. The plasma concentration of albendazole sulfoxide has been increased by *praziquantel*,[1] although the practical consequences of this were considered uncertain. A later study[2] in healthy subjects indicated that plasma concentrations of (+) and (-) enantiomers of albendazole sulfoxide were increased by about 260 and 360% respectively, albendazole sulfone by some 190%, and (-)-(*R*)-praziquantel by about 65%, when albendazole and praziquantel were given together. Although this raised the possibility of increased efficacy from the combination, the magnitude of the changes suggested that increased adverse effects might be a problem, and dose adjustment might be needed.[2]

1. Homeida M, *et al.* Pharmacokinetic interaction between praziquantel and albendazole in Sudanese men. *Ann Trop Med Parasitol* 1994; 88: 551–9.
2. Lima RM, *et al.* Albendazole-praziquantel interaction in healthy volunteers: kinetic disposition, metabolism and enantioselectivity. *Br J Clin Pharmacol* 2011; 71: 528–35.

Antiepileptics. *Phenytoin, carbamazepine,* and *phenobarbital* appear to induce the oxidative metabolism of albendazole via the cytochrome P450 isoenzyme CYP3A by roughly the same extent, resulting in significantly reduced concentrations of albendazole sulfoxide. This interaction is likely to be clinically significant when albendazole is used to treat systemic worm infections, and increased doses of albendazole would be needed.[1] The interaction is probably not clinically significant when albendazole is used for intestinal worm infections.

1. Lanchote VL, *et al.* Pharmacokinetic interaction between albendazole sulfoxide enantiomers and antiepileptic drugs in patients with neurocysticercosis. *Ther Drug Monit* 2002; 24: 338–45.

Corticosteroids. Plasma concentrations of the active metabolite of albendazole (albendazole sulfoxide) were reported to be raised by about 50% in a study in 8 patients receiving *dexamethasone*.[1]

1. Jung H, *et al.* Dexamethasone increases plasma levels of albendazole. *J Neurol* 1990; 237: 279–80.

Gastrointestinal drugs. Concentrations of albendazole sulfoxide have been found to be raised in bile and hydatid cyst fluid when albendazole was given with *cimetidine*, which may increase efficacy in the treatment of echinococcosis.[1]

1. Wen H, *et al.* Initial observation on albendazole in combination with cimetidine for the treatment of human cystic echinococcosis. *Ann Trop Med Parasitol* 1994; 88: 49–52.

Pharmacokinetics

Absorption of albendazole from the gastrointestinal tract is poor but may be enhanced by a fatty meal. Albendazole rapidly undergoes extensive first-pass metabolism. Its principal metabolite albendazole sulfoxide has anthelmintic activity and a plasma half-life of about 8.5 hours. Albendazole sulfoxide is widely distributed throughout the body including into the bile and the CSF. It is about 70% bound to plasma protein. Albendazole sulfoxide is eliminated in the bile; only a small amount appears to be excreted in the urine.

References.

1. Marriner SE, *et al.* Pharmacokinetics of albendazole in man. *Eur J Clin Pharmacol* 1986; 30: 705–8.
2. Morris DL, *et al.* Penetration of albendazole sulphoxide into hydatid cysts. *Gut* 1987; 28: 75–80.
3. Steiger U, *et al.* Albendazole treatment of echinococcosis in humans: effects on microsomal metabolism and drug tolerance. *Clin Pharmacol Ther* 1990; 47: 347–53.
4. Jung H, *et al.* Clinical pharmacokinetics of albendazole in patients with brain cysticercosis. *J Clin Pharmacol* 1992; 32: 28–31.
5. Jung H, *et al.* Clinical pharmacokinetics of albendazole in children with neurocysticercosis. *Am J Ther* 1997; 4: 23–6.
6. Dayan AD. Albendazole, mebendazole and praziquantel: review of non-clinical toxicity and pharmacokinetics. *Acta Trop* 2003; 86: 141–59.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Vastus; Vermizole; ***Austral.***: Eskazole; Zentel; ***Austria***: Eskazole; ***Braz.***: Alba-3; Albel; Albendrox; Albendy; Albentel; Albenzonil; Albezin; Alin; Benzol; Imavermil†; Mebenix; Monozol; Neo Bendazol; Parasin; Parazol; Vermiclase; Vermital; Zentel; Zolben; ***Chile***: Ceprazol†; Vermoil; Zentel; ***China***: Abentel (阿西苯); Zentel (肠虫清); ***Cz.***: Zentel†; ***Fr.***: Eskazole; Zentel; ***Ger.***: Eskazole; ***Gr.***: Albendol; Eskazole; Zentel; ***India***: ABD; Abide; ABZ; Abzole; AH-1; Al; Albacos; Albamaa; Albasym; Albazole; Albekon; Albendol; Albent; Albenzole; Albesan; Albest; Albestar; Albex; Albezole; Albol; Albosym; Alboven; Albrodo; Alenda; Alio; Alminth; Altec Alworm; Alzad; Alzol; Anthel; Antiworm; Ariban; Asibend; Atbend; Aviband; Avizole; Band; Bandy; Banthel; Bendex; Bendol; Benrod; Benzys; Biwom; C-Band; C-Bend; C-Trop; Cidazole; Combantrin-A; Conthel; Cuwarm; Dazo; Dispel; E-Bend; Ebex; Ejectil; Elbend; Eleben; Elminex; Emanthal†; Enbenol; Foben; Gekare; Getrid; Janbol; Klraza; Lupibend; Milibend; Morband; N-Bend; NBWorm; Nemaban; Nemofex; Nemozole; Noworm; Nubend; Oben; Odal; Olban; Olworm; Omnitel; Zentel; ***Israel***: Eskazole; ***Ital.***: Zentel; ***Malaysia***: Albendol†; Almex; Champs D-Worms; Mesin-C; Thelban; Vemizol; Zendal; Zenmex; Zentel; Zoben; ***Mex.***: Albensil†; Aldamin; Alfazol; Bendapar†; Bradelmin; Dazocan; Dazolin; Dezabil; Digezanol; Entoplus†; Eskazole; Euralben; Gascop; Helmisons†; Ilides; Kolexan; Loveral†; Lumbrifar; Lurdex; Olbendital†; Rivazol; Serbendazol; Synparyn; Tenibex†; Veranzol†; Vermin Plus; Vermisen; Zelfin; Zenaxin; Zentel; ***Neth.***: Eskazole; ***Philipp.***: Adazol; Alzel; Benzol; Zentel; ***Pol.***: Zentel; ***Port.***: Zentel; ***Rus.***: Nemozole (Немозол); Sanoxal (Саноксал); ***S.Afr.***: Bendex; Wormadole; Zentel; ***Singapore***: Albendol; Alzental; Zentel; ***Spain***: Eskazole; ***Switz.***: Zentel; ***Thai.***: Abentel†; Albatel; Alben-Hero; Alben-VC; Alben; Albenda; Albenz; Albezol; Alda; Aldazole; Alfuca; Alzol; Antheda†; Benyad; CB-400; Falben; Fatel; Gendazel; Labenda; Leo-400†; Manozide; Mesin; Mycotel†; Prodazole; San-San; Vermixide; Vetoben; Zeben; Zela; Zentel; Zenzera; ***Turk.***: Andazol; ***UAE***: Albenda; ***Ukr.***: Aldazole (Альдазол); Vormil (Вормил); Zentel (Зентел); ***USA***: Albenza; ***Venez.***: Albezol; Albicar; Bevindazol; Helal; Sostril; Taron; Vendazol; Zentel.

Multi-ingredient Preparations. ***India***: Ablaze-IM; ABZ Plus; Albacos-IR; Albosym-IR; Alvect; Anthel-UP; Ariban Plus; Ascapil A; Bandy Plus; Benrod-I; Benzole; D-Worm; Ectin-A; Elect-A; Elminova; Eradix; Eris Plus; Getrid-I; Hymin Plus; Hymin; Imectin Forte; Ivecop-AB; Ivercid-A; Iverzole; Ivoral; Kaybend; Kidi; Macbi Plus; Networm; ***Mex.***: C Cobistal; Farmiver; Oxal; ***Thai.***: Albemed.

Pharmacopoeial Preparations
USP 36: Albendazole Tablets.

Trivalent Antimony Compounds

Compuestos de antimonio trivalente; Трехвалентные Соединения Сурьмы.

Antimony Potassium Tartrate

Antim. Pot. Tart; Antimónico potásico, tartrato; Antimonium Tartaricum; Antymonu potasu winian; Brechweinstein; Kalii Stibyli Tartras; Potassium Antimonyltartrate; Stibii et Kalii Tartras; Tartar Emetic; Tartarus Stibiatus; Антимонил-тартрат Калия.

Dipotassium bis[μ-[2,3-dihydroxybutanedioato(4-)-O^1,O^2:O^3,O^4]]-diantimonate(2-) trihydrate; Dipotassium bis[μ-tartrato(4-)]diantimonate(2-) trihydrate.
$C_8H_4K_2O_{12}Sb_2.3H_2O$=667.9
CAS — 11071-15-1 (anhydrous antimony potassium tartrate); 28300-74-5 (antimony potassium tartrate trihydrate).
UNII — DL6QZ476V3.

Pharmacopoeias. In *US.*

USP 36: (Antimony Potassium Tartrate). Odourless, colourless, transparent crystals or white powder. The crystals effloresce on exposure to air and do not readily rehydrate even on exposure to high humidity. Soluble 1 in 12 of water, 1 in 3 of boiling water, and 1 in 15 of glycerol; insoluble in alcohol. Its solutions are acid to litmus.

Antimony Sodium Tartrate

Antim. Sod. Tart.; Antimónico sódico, tartrato; Sodium Antimonyltartrate; Stibium Natrium Tartaricum; Антимонил-тартрат Натрия.
Disodium bis[μ-[2,3-dihydroxybutanedioato(4-)-O^1,O^2:O^3,O^4]] diantimonate(2-); Disodium bis[μ-[L-(+)-tartrato(4-)]]diantimonate(2-).
$C_8H_4Na_2O_{12}Sb_2$=581.6
CAS — 34521-09-0.
UNII — 3KUI0LP48L.

Pharmacopoeias. In *Int.* (as $C_4H_4NaO_7Sb$ = 308.8) and *US.*

USP 36: (Antimony Sodium Tartrate). Odourless, colourless, transparent crystals or white powder. The crystals effloresce on exposure to air. Freely soluble in water; insoluble in alcohol.

Sodium Stibocaptate *(BAN, rINN)*

Antimony Sodium Dimercaptosuccinate; Estibocaptato de sodio; Natrii Stibocaptas; Ro-4-1544/6; Sb-58; Stibocaptate; Stibocaptate de Sodium; TWSb/6; Натрия Стибокаптат.
Antimony sodium *meso*-2,3-dimercaptosuccinate. The formula varies from $C_{12}H_{11}NaO_{12}S_6Sb_2$ = 806.1 to $C_{12}H_6Na_6O_{12}S_6Sb_2$ = 916.0.
CAS — 3064-61-7 ($C_{12}H_6Na_6O_{12}S_6Sb_2$).
UNII — VFV49ULL8Q.

Stibophen

Estibofeno; Fouadin; Stibophenum; Стибофен.
Bis[4,5-dihydroxybenzene-1,3-disulphonato(4-)-O^4,O^5]antimonate(5-) pentasodium heptahydrate.
$C_{12}H_4Na_5O_{16}S_4Sb.7H_2O$=895.2
CAS — 15489-16-4 (stibophen heptahydrate).
ATC — P02BX03.

Uses and Administration

Trivalent antimony compounds were used in the treatment of the protozoal infection leishmaniasis until the advent of the less toxic pentavalent compounds. They continued to be used in the treatment of schistosomiasis, but have now been superseded by less toxic and more easily given drugs such as praziquantel.

Antimony sodium tartrate was formerly used as an emetic. The sodium tartrate and potassium tartrate have also been used as expectorants.

Adverse Effects and Treatment

Trivalent antimony compounds are more toxic than pentavalent antimonials such as sodium stibogluconate, possibly because they are excreted much more slowly. The most serious adverse effects are on the heart and liver. There are invariably ECG changes during treatment, but hypotension, bradycardia, and cardiac arrhythmias are more serious. Sudden death or cardiovascular collapse may occur at any time. Elevated liver enzyme values are common; liver damage with hepatic failure and death is more likely in patients with pre-existing hepatic disease.

Adverse effects immediately after intravenous use of trivalent antimonials, in particular the tartrates, have included coughing, chest pain, pain in the arms, vomiting, abdominal pain, fainting, and collapse, especially after rapid injection. Extravasation during injection is extremely painful because of tissue damage. An anaphylactoid reaction characterised by an urticarial rash, husky voice, and collapse has been reported after the sixth or seventh intravenous injection of a course of treatment.

Many less immediate adverse effects have occurred including gastrointestinal disturbances, muscular and joint pains, arthritis, pneumonia, dyspnoea, headache, dizziness, weakness, pruritus, rashes, facial oedema, fever, haemolytic anaemia, and kidney damage.

Large oral doses of antimony compounds have an emetic action. Continuous treatment with small doses of antimony

may give rise to symptoms of subacute poisoning similar to those of chronic arsenical poisoning.

Treatment of severe poisoning with antimony compounds is similar to that for arsenic poisoning (p. 2449.1); dimercaprol may be of benefit.

References.

1. Stemmer KL. Pharmacology and toxicology of heavy metals: antimony. *Pharmacol Ther* 1976; 1: 157–60.

Precautions

Trivalent antimony therapy has generally been superseded by less toxic treatment. It is contra-indicated in the presence of lung, heart, liver, or kidney disease. Intravenous injections should be given very slowly and stopped if coughing, vomiting, or substernal pain occurs; extravasation should be avoided.

Some antimony compounds such as the tartrates cause severe pain and tissue necrosis and should not be given by intramuscular or subcutaneous injection.

Breast feeding. The American Academy of Pediatrics[1] states that there have been no reports of any clinical effect on the infant associated with the use of antimony by breast-feeding mothers, and that therefore it may be considered to be usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 02/06/04)

Glucose-6-phosphate dehydrogenase deficiency. In the event of trivalent antimony compounds being used, patients with G6PD deficiency should be excluded. WHO lists stibophen[1] among the anthelmintics to be avoided in patients with this deficiency.

1. WHO. Glucose-6-phosphate dehydrogenase deficiency. *Bull WHO* 1989; 67: 601–11.

Pharmacokinetics

Antimony compounds are poorly absorbed from the gastrointestinal tract. They are slowly excreted, mainly in the urine, after parenteral doses. Antimony accumulates in the body during treatment and persists for several months afterwards. Trivalent antimony has a greater affinity for cell proteins than for plasma proteins.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Port.*: Stodal; *Thai.*: Brown Mixture; Mist Tussis.

Homoeopathic Preparations. *Austral.*: Allergy Relief; Childrens Cough Relief; Respatona Chesty Cough & Nasal Congestion; *Austria*: Bronchalis-Heel; Pneumodoron Nr 2; Tartephedreel; Tonsan chronisch; *Canad.*: Acne; Brocosin; Bronkeel†; Calnor†; Cou Complex†; Cough Syrup with Honey†; Hylands Cough; Hylands Formula CS; Stodal; *Cz.*: Bronchalis-Heel; *Fr.*: Boripharm No 12†; Cetraria Complexe No 61; Homeogene 14†; Homeogrippe†; Ipeca Compose; Pulmo-Drainol†; Stodal; Stodal; *Ger.*: Bomarthros Harpagophytum Complex; Bronchiselect; Cefasulfon N†; Eupatorium N Oligoplex; Pneumodoron 2; Rheuma-Hevert; Rheuma-Hevert; Roth's RKT Tropfen; Rufebran bronchot; Vomistop; *Hung.*: Bronchalis-Heel; Stodal; *Neth.*: Bronchalis; Stodal; *Rus.*: Атма (Atma); Stodal (Стодаль); *S.Afr.*: Pneumodoron 2†; *Switz.*: Bronchalis-Heel; Stodal; *Ukr.*: Атма (Атма); Stodal (Стодаль).

Betanaphthol

2-Naftol; β-Naftol; 2-Naftoli; 2-Naftolo; Naphthol; Бета-нафтол.
Naphth-2-ol.
$C_{10}H_8O$=144.2
CAS — 135-19-3.
UNII — P2Z71CIK5H.

Pharmacopoeias. In *Pol.* and *Swiss.*

Profile

Betanaphthol was formerly used as an anthelmintic in hookworm and tapeworm infections, but it has been superseded by less toxic and more efficient drugs.

Betanaphthol has a potent parasiticidal effect and has been used topically in the treatment of scabies, ringworm, and other skin diseases.

Betanaphthyl benzoate has been used in preparations for the treatment of gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Hekabetol.

Bithionol *(BAN, rINN)*

Bithionololum; Bithionolum; Bitionol; Bitionolol; Bitionololi; Битионол.
2,2'-Thiobis(4,6-dichlorophenol).
$C_{12}H_6Cl_4O_2S$=356.0
CAS — 97-18-7.
ATC — D10AB01; P02BX01.
ATC Vet — QD10AB01; QP52AG07.
UNII — AMT77LS62O.

Pharmacopoeias. *Fr.* includes bithionol oxide for veterinary use.

Uses and Administration

Bithionol is a chlorinated bis-phenol with bactericidal and anthelmintic properties. It is active against most trematodes (flukes). Bithionol is used in preference to praziquantel in fascioliasis as an alternative to triclabendazole (see Liver Fluke Infections, p. 146.2). It is also used in paragonimiasis (see Lung Fluke Infections, p. 146.3) as an alternative to praziquantel. It may be given in an oral dose of 30 to 50 mg/kg on alternate days for 10 to 15 doses. Shorter regimens have been used.

Bithionol was formerly used topically as a bactericide but this use has declined because of photosensitivity reactions.

Adverse Effects

Adverse effects in patients taking oral bithionol include anorexia, nausea, vomiting, abdominal discomfort, diarrhoea, salivation, dizziness, headache, and rashes.

Photosensitivity reactions have occurred in persons using soap containing bithionol. Cross-sensitisation with other halogenated disinfectants has also occurred.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Fonergine.

Bromofenofos *(rINN)*

Bromfenofos; Bromofenofós; Bromofénofos; Bromofenofosum; Bromophenophos; Bromphenphos; Бромофенофос.
3,3',5,5'-Tetrabromo-2,2'-biphenyldiolmono(dihydrogen phosphate).
$C_{12}H_7Br_4O_5P$=581.8
CAS — 21466-07-9.
ATC Vet — QP52AB02.
UNII — XTH861Q3CR.

Profile

Bromofenofos is a bisphenol derivative used as an anthelmintic in veterinary medicine for the treatment of fluke infections.

Cambendazole *(BAN, USAN, rINN)*

Cambendazol; Cambendazolum; MK-905; Камбендазол.
Isopropyl 2-(thiazol-4-yl)-1*H*-benzimidazol-5-ylcarbamate.
$C_{14}H_{14}N_4O_2S$=302.4
CAS — 26097-80-3.
ATC Vet — QP52AC08.
UNII — 079X63S3DU.

Profile

Cambendazole is a benzimidazole carbamate anthelmintic structurally related to tiabendazole (p. 168.1). It is used in the treatment of strongyloidiasis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Cambem.

Multi-ingredient Preparations. *Braz.*: Exelmin.

Chenopodium Oil

Aceite de quenopodio; Aetheroleum Chenopodii; Esencia de Quenopodio Vermifuga; Oil of American Wormseed; Wurmsamenöl; Маревое Масло; Амброзиевое Масло.
CAS — 8006-99-3.
UNII — 3009681U6R.

Profile

Chenopodium oil is distilled with steam from the fresh flowering and fruiting plants, excluding roots, of *Chenopodium ambrosioides* var. *anthelminticum*. It contains ascaridole and was formerly used as an anthelmintic for the expulsion of roundworms (*Ascaris*) and hookworms. It is toxic and has caused many fatalities.

Handling. Chenopodium oil may explode when heated.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Fr.*: Cina Complexe No 55†.

Clorsulon *(BAN, USAN, rINN)*

Clorsulón; Clorsulone; Clorsulonum; MK-401; Клорсулон.
4-Amino-6-(trichlorovinyl)benzene-1,3-disulphonamide.
$C_8H_8Cl_3N_3O_4S_2$=380.6
CAS — 60200-06-8.
UNII — EG1ZDO6LRD.

Pharmacopoeias. In *US* for veterinary use only.

USP 36: (Clorsulon). A white to off-white powder. Slightly soluble in water; freely soluble in acetonitrile and in methyl alcohol; very slightly soluble in dichloromethane.

Profile

Clorsulon is a sulfonamide anthelmintic used in veterinary medicine for the treatment of liver fluke infections.

Closantel *(BAN, USAN, rINN)*

Closantelum; R-31520; Клозантел.
5'-Chloro-4'-(4-chloro-α-cyanobenzyl)-3,5-di-iodosalicyl-o-toluidide.
$C_{22}H_{14}Cl_2I_2N_2O_2$=663.1
CAS — 57808-65-8.
ATC Vet — QP52AG09.
UNII — EUL532EI54.

Closantel Sodium *(BANM, rINNM)*

Closantel sódico; Closantel Sodique; Closantelum natricum; Klosanteelinatrium; Klosantel sodná sůl; Klosantelnatrium; Natrii Closantelum; R-34828; Натрий Клозантел.
$C_{22}H_{14}Cl_2I_2N_2O_2Na$=686.1
UNII — 0ZBS9YC04P (anhydrous closantel sodium); 181924887F (closantel sodium dihydrate).

Pharmacopoeias. In *Eur.* (see p. vii) as the dihydrate for veterinary use.

Ph. Eur. 8: (Closantel Sodium Dihydrate for Veterinary Use; Closantel Sodium Dihydrate BP(Vet) 2014). A yellow, slightly hygroscopic, powder. It exhibits polymorphism. Very slightly soluble in water; freely soluble in alcohol; soluble in methyl alcohol. Store in airtight containers. Protect from light.

Profile

Closantel is an anthelmintic used in veterinary medicine for the treatment of fluke and nematode infections.

Effects on the eyes. Loss of eyesight was reported in 11 women who received closantel (Flukiver) in mistake for a gynaecological product.[1] Sight was restored after closantel was stopped but incapacitating eye pain remained.

1. t Hoen E, *et al.* Harmful human use of donated veterinary drug. *Lancet* 1993; 342: 308–9.

Diamfenetide *(BAN, rINN)*

Diamfenetida; Diamfénétide; Diamfenetidum; Diamphenethide; Диамфенетид.
β,β'-Oxybis(aceto-*p*-phenetidide).
$C_{20}H_{24}N_2O_5$=372.4
CAS — 36141-82-9.
UNII — U4TFJ7GB6T.

Profile

Diamfenetide is an anthelmintic that has been used in veterinary medicine for the control of fascioliasis in sheep.

Dichlorophen *(BAN, rINN)*

Dichlorofeen; Dichlorophène; Dichlorophenum; Diclorofeno; Di-phenthane-70; G-4; Дихлорофен.
2,2'-Methylenebis(4-chlorophenol).
$C_{13}H_{10}Cl_2O_2$=269.1
CAS — 97-23-4.
ATC — P02DX02.

ATC Vet — QP52AG01.
UNII — T1J0JOU64O.

Pharmacopoeias. In *Br.* and *Fr.*

BP 2014: (Dichlorophen). A white or slightly cream-coloured powder with a not more than slightly phenolic odour. Practically insoluble in water; freely soluble in alcohol; very soluble in ether.

Profile

Dichlorophen is an anthelmintic that was used in the treatment of infection by tapeworms but has been superseded by praziquantel or niclosamide.

Dichlorophen also has antifungal and antibacterial activity and has been used topically in the treatment of fungal infections and as a germicide in soaps and cosmetics.

Hypersensitivity. Dichlorophen is used for its antibacterial and antifungal properties in various manufactured products and there is a report[1] of a patient whose eczema of the hands and face and vesicular-bullous lesions of the feet were associated with the presence of dichlorophen in the leather of her shoes. It was of note that the appearance of the reaction to dichlorophen in patch testing was delayed for 10 days.

1. Barbuzza O, *et al.* Late patch test reaction to dichlorophene. *J Investig Allergol Clin Immunol* 2008; **18**: 317–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *UK*: Mycota.

Pharmacopoeial Preparations
BP 2014: Dichlorophen Tablets.

Diethylcarbamazine Citrate

(BANM, rINNM)

Citrato de dietilcarbamazina; Diethylcarbam. Cit.; Diethylcarbamazindihydrogencitrat; Diethylcarbamazine Acid Citrate; Diéthylcarbamazine, citrate de; Diethylcarbamazini Citras; Diethylkarbamazin-citrát; Dietilcarbamazina, citrato de; Dietilkarbamazin-citrát; Dietilkarbamazino citratas; Dietylkarbamazincitrat; Dietyylikarbamatsiinisitraatti; Ditrazini Citras; RP-3799; Диэтилкарбамазина Цитрат.

NN-Diethyl-4-methylpiperazine-1-carboxamide dihydrogen citrate.

$C_{10}H_{21}N_3O,C_6H_8O_7$=391.4

CAS — 90-89-1 (diethylcarbamazine); 1642-54-2 (diethylcarbamazine citrate).

ATC — P02CB02.

UNII — OS1Z389K8S.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Diethylcarbamazine Citrate). A white or almost white, crystalline, slightly hygroscopic powder. Very soluble in water; soluble in alcohol; practically insoluble in acetone. Store in airtight containers.

USP 36: (Diethylcarbamazine Citrate). A white, crystalline, slightly hygroscopic powder, odourless or has a slight odour. Very soluble in water; sparingly soluble in alcohol; practically insoluble in acetone, in chloroform, and in ether. Store in airtight containers.

Uses and Administration

Diethylcarbamazine is an anthelmintic used in the treatment of lymphatic filariasis due to *Wuchereria bancrofti* (bancroftian filariasis), *Brugia malayi*, or *B. timori* (both known as brugian filariasis and as Malayan and Timorian filariasis respectively). It is also used in the treatment of loiasis due to *Loa loa* and toxocariasis (visceral larva migrans). Diethylcarbamazine is active against both the microfilariae and adult worms of *W. bancrofti*, *B. malayi*, and *Loa loa*, but only against the microfilariae of *Onchocerca volvulus*. It was used in onchocerciasis due to *O. volvulus* before ivermectin became available. It has been tried in *Mansonella* infections and may be most effective against *M. streptocerca*. For discussions of these infections and their treatment, see under Choice of Anthelmintic, p. 143.1, and under the individual headings below.

Diethylcarbamazine is usually given orally as the citrate.

In the treatment of **lymphatic filariasis** caused by *W. bancrofti* a total cumulative dose of 72 mg/kg is usually recommended; half this dose is usually effective in *B. malayi* and *B. timori* infections. To reduce the incidence and severity of hypersensitivity reactions due to the destruction of microfilariae an initial dose of 1 mg/kg is given and then gradually increased over 2 to 3 days to 6 mg/kg daily (preferably in divided doses) for 12 days. However, adverse effects of diethylcarbamazine may be reduced, without loss of efficacy, by giving a single dose of 6 mg/kg at weekly or monthly intervals. In areas where lymphatic filariasis is endemic, *mass treatment* campaigns can reduce the intensity of transmission and incidence of disease. Diethylcarbamazine may also be used in the form of medicated salt to control lymphatic filariasis. For further details, see p. 154.3.

In the treatment of **loiasis** diethylcarbamazine citrate 6 to 9 mg/kg daily in 3 divided doses for 21 days has been given. In heavy infections rapid killing of microfilariae can cause severe adverse effects including encephalitis and treatment should start with very small doses, increasing gradually over 3 days. A corticosteroid has been given concurrently. In the prophylaxis of loiasis, a dose of 300 mg weekly is recommended by WHO.

In the treatment of **toxocariasis** diethylcarbamazine citrate 6 mg/kg daily in 2 divided doses for 21 days may be given. Diethylcarbamazine is considered by some to be the treatment of choice while others do not recommend its use due to high rates of allergic reactions induced by dying larvae. To reduce the intensity of these reactions WHO suggests starting treatment at a dose of 1 mg/kg twice daily and increasing gradually to 3 mg/kg twice daily.

For details of doses in children, see p. 154.3.

Administration. Diethylcarbamazine was first used as the chloride, but was subsequently produced as the dihydrogen citrate which contains only half its weight as base. In reporting doses it was therefore important to indicate whether they referred to a specific salt or to the base; unless otherwise stated, it could generally be assumed that the dose referred to the citrate.[1]

1. WHO. Lymphatic filariasis: fourth report of the WHO expert committee on filariasis. *WHO Tech Rep Ser 702* 1984. Available at: http://libdoc.who.int/trs/WHO_TRS_702.pdf (accessed 16/07/08)

Administration in children. Diethylcarbamazine citrate may be given orally to children for the treatment of lymphatic filariasis, loiasis and toxocariasis (visceral larva migrans).

For the treatment of **lymphatic filariasis** US experts[1] consider that children may be given the same dose as for adults (see above), while WHO recommends that children under 10 years of age be given half the usual adult dose.[2]

For the treatment of **loiasis** *US* experts consider that children may be given a dose of 9 mg/kg daily in 3 divided doses for 21 days; treatment should start with very small doses, increasing gradually over 3 days.[1] *No* dose recommendation is given by WHO.[2]

For the treatment of **toxocariasis** WHO considers that children may be given the same dose as for adults (see above).[2]

1. Abramowicz M, ed. *Drugs for parasitic infections*. 3rd ed. New Rochelle NY: The Medical Letter,2013.
2. WHO. *WHO model formulary*. Geneva: WHO, 2008. Available at: http://www.who.int/selection_medicines/list/WMF2008.pdf (accessed 19/11/09)

Loiasis. Diethylcarbamazine is the main drug used in the management of loiasis (p. 146.2).

References.
1. Nutman TB, *et al.* Loa loa infection in temporary residents of endemic regions: recognition of a hyperresponsive syndrome with characteristic clinical manifestations. *J Infect Dis* 1986; **154**: 10–18.
2. Nutman TB, *et al.* Diethylcarbamazine prophylaxis for human loiasis: results of a double-blind study. *N Engl J Med* 1988; **319**: 752–6.
3. Nutman TB, Ottesen EA. Diethylcarbamazine and human loiasis. *N Engl J Med* 1989; **320**: 320.
4. Kilon AD, *et al.* Effectiveness of diethylcarbamazine in treating loiasis acquired by expatriate visitors to endemic regions: long-term follow-up. *J Infect Dis* 1994; **169**: 604–10.

Lymphatic filariasis. Diethylcarbamazine is used in the management of lymphatic filariasis (p. 146.3). In endemic areas *mass treatment* of the entire population (excluding neonates, pregnant women, and debilitated individuals) can reduce the intensity of transmission and the incidence of disease. In countries where there is no co-endemic loiasis or onchocerciasis, the Global Programme to Eliminate Lymphatic Filariasis launched by WHO with other international agencies, advocates a single oral dose of diethylcarbamazine citrate 6 mg/kg with a single oral dose of albendazole 400 mg, given once each year for at least 5 years. If diethylcarbamazine-medicated salt is to be employed then intake of salt needs to be on a daily basis for 6 to 12 months.

Mansonella infections. Diethylcarbamazine given orally at a dose of 6 mg/kg daily in 3 divided doses for 12 days,[1] is one of the drugs that has been suggested for the treatment of infections with *Mansonella streptocerca* (p. 147.2).

1. Abramowicz M, ed. *Drugs for parasitic infections*. 3rd ed. New Rochelle NY: The Medical Letter,2013.

Adverse Effects

Mild to moderate adverse effects are common but the incidence of serious adverse effects is very low. Adverse effects may be more severe and common in those with a high parasite burden. Commonly reported adverse effects include fever, dizziness, drowsiness, headache, malaise, microscopic haematuria, myalgia, nausea, and vomiting.

Hypersensitivity reactions arise from the death of the microfilariae. These can be serious, especially in onchocerciasis where there may also be sight-threatening ocular toxicity; fatalities have been reported. Encephalitis may be exacerbated in patients with loiasis and fatalities have occurred; those with very high microfilaria counts are at increased risk.

Reactions occurring during diethylcarbamazine treatment of **lymphatic filariasis** are basically of 2 types: pharmacological dose-dependent responses and a response of the infected host to the destruction and death of parasites.[1]

- Reactions of the first type include weakness, dizziness, lethargy, anorexia, and nausea. They begin within 1 to 2 hours of taking diethylcarbamazine, and persist for a few hours.
- Reactions of the second type are less likely to occur and are less severe in bancroftian than in brugian filariasis. They may be systemic or local, both with or without fever.

Systemic reactions may occur a few hours after the first oral dose of diethylcarbamazine and generally do not last for more than 3 days. They include headache, aches in other parts of the body, joint pain, dizziness, anorexia, malaise, transient haematuria, allergic reactions, vomiting, and sometimes attacks of bronchial asthma in asthmatic patients. Fever and systemic reactions are positively associated with microfilaraemia. Systemic reactions are reduced if diethylcarbamazine is given in spaced doses or in repeated small doses. They eventually cease spontaneously and interruption of treatment is rarely necessary; symptomatic treatment with antipyretics or analgesics may be helpful.

Local reactions tend to occur later in the course of treatment and last longer; they also disappear spontaneously and interruption of treatment is not necessary. Local reactions include lymphadenitis, abscess, ulceration, and transient lymphoedema; funiculitis and epididymitis may also occur in bancroftian filariasis.

It has been suggested that the release of interleukin-6 may be implicated in diethylcarbamazine's adverse effects in patients with lymphatic filariasis.[2]

In most patients with **onchocerciasis**, the microfilaricidal activity of diethylcarbamazine leads to a series of events with dermal, ocular, and systemic components, known as the *Mazzotti reaction*, within minutes to hours after its use.[3]

- Clinical manifestations can be severe, dangerous, and debilitating. Systemic reactions include increased itching, rash, headache, aching muscles, joint pain, painful swollen and tender lymph nodes, fever, tachycardia and hypotension, and vertigo. Most patients have eye discomfort in the first few hours after diethylcarbamazine treatment. Punctate keratitis can develop as can optic neuritis and visual field loss.

WHO no longer recommends the use of diethylcarbamazine in onchocerciasis as safer alternatives exist.

1. WHO. Lymphatic filariasis: the disease and its control: fifth report of the WHO expert committee on filariasis. *WHO Tech Rep Ser 821* 1992. Also available at: http://libdoc.who.int/trs/WHO_TRS_821.pdf (accessed 19/11/09)
2. Yazdanbakhsh M, *et al.* Serum interleukin-6 levels and adverse reactions to diethylcarbamazine in lymphatic filariasis. *J Infect Dis* 1992; **166**: 453–4.
3. WHO. WHO expert committee on onchocerciasis: third report. *WHO Tech Rep Ser 752* 1987. Also available at: http://libdoc.who.int/trs/WHO_TRS_752_(part1).pdf (accessed 19/11/09)

Precautions

Treatment with diethylcarbamazine should be closely supervised since hypersensitivity reactions are common and may be severe, especially in patients with onchocerciasis or loiasis. Diets that promote the alkalinisation of the urine may increase the elimination half-life of diethylcarbamazine (see also Pharmacokinetics, p. 155.1); dose reductions may be needed. Patients with onchocerciasis should be monitored for eye changes. (The use of diethylcarbamazine to treat onchocerciasis is no longer recommended.) In patients with heavy *Loa loa* infection there is a small risk of encephalopathy and diethylcarbamazine should be stopped at the first sign of cerebral involvement.

Infants, pregnant women, the elderly, and the debilitated, especially those with cardiac or renal disease, are normally excluded when diethylcarbamazine is used in mass treatment schedules.

Pregnancy. Pregnant women are normally excluded when diethylcarbamazine is used in mass treatment schedules.

Animal studies[1] suggest that the uterine hypermotility induced by diethylcarbamazine is mediated via prostaglan-

din synthesis; this might explain the mechanism of the abortifacient action previously reported.[2]

1. Joseph CA, Dixon PAF. Possible prostaglandin-mediated effect of diethylcarbamazine on rat uterine contractility. *J Pharm Pharmacol* 1984; 36: 281–2.
2. Subbu VSV, Biswas AR. Ecbolic effect of diethyl carbamazine. *Indian J Med Res* 1971; 59: 646–7.

Renal impairment. For a study on the effects of renal impairment on the pharmacokinetics of diethylcarbamazine, see under Pharmacokinetics, p. 155.2.

Pharmacokinetics

Diethylcarbamazine is readily absorbed from the gastrointestinal tract and also through the skin and conjunctiva. It is not significantly bound to plasma protein. It is widely distributed in tissues and is mainly excreted in the urine unchanged and as the *N*-oxide metabolite. Urinary excretion and hence plasma half-life is dependent on urinary pH, with a shorter half-life in acidic urine. About 5% of a dose is eliminated in the faeces.

Disposition. A pharmacokinetic study in 6 patients with onchocerciasis[1] indicated that diethylcarbamazine is absorbed quickly and almost completely from the gastrointestinal tract, and is eliminated largely as unchanged drug in urine, with relatively small amounts being excreted as the N_7-oxide metabolite. After a single radioactively labelled oral dose of diethylcarbamazine citrate 500 micrograms/kg given as an aqueous solution, peak plasma concentrations of 100 to 150 nanograms/mL were achieved in 1 to 2 hours, followed by a sharp decline, then a marked secondary rise 3 to 6 hours after dosing, followed by a steady decline. The half-life ranged from 9 to 13 hours. Urinary excretion of diethylcarbamazine and diethylcarbamazine *N*-oxide was complete within 96 hours; between 4 and 5% of the dose was recovered in the faeces. Disposition was similar in 5 healthy subjects given a single 50-mg tablet of diethylcarbamazine citrate. Peak plasma concentrations were initially 80 to 200 nanograms/mL, with a secondary rise 3 to 9 hours after dosing, the terminal half-life ranged from 5 to 13 hours, and urinary excretion of unchanged diethylcarbamazine and the *N*-oxide was complete within 48 hours.

When an alkaline urinary pH was maintained, the elimination half-life of diethylcarbamazine and the area under the plasma concentration versus time curve were significantly increased compared with when an acidic urinary pH was maintained.[2]

1. Edwards G, *et al.* Diethylcarbamazine disposition in patients with onchocerciasis. *Clin Pharmacol Ther* 1981; 30: 551–7.
2. Edwards G, *et al.* The effect of variations in urinary pH on the pharmacokinetics of diethylcarbamazine. *Br J Clin Pharmacol* 1981; 12: 807–12.

Renal impairment. Results in patients with chronic renal impairment and in healthy subjects, given a single 50-mg oral dose of diethylcarbamazine citrate, indicated that the plasma half-life of diethylcarbamazine is prolonged and its 24-hour urinary excretion considerably reduced in those with moderate and severe degrees of renal impairment.[1] Mean plasma half-lives in 7 patients with severe renal impairment (creatinine clearance less than 25 mL/minute), in 5 patients with moderate renal impairment (creatinine clearance between 25 and 60 mL/minute), and in 4 healthy subjects, were 15.1, 7.7, and 2.7 hours, respectively. The patient with the longest plasma half-life of 32 hours did not have the poorest renal function, but it was considered likely that the abnormally slow elimination of diethylcarbamazine was due to the high urinary pH (7) resulting from sodium bicarbonate therapy. A further patient with a half-life longer than expected also had a less acidic urine.

1. Adjepon-Yamoah KK, *et al.* The effect of renal disease on the pharmacokinetics of diethylcarbamazine in man. *Br J Clin Pharmacol* 1982; 13: 829–34.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Notezine; *Gr.*: Notezine; *India*: Banocide; Decet; Dicarb; Hetrazan; *Thai.*: Diethizine.

Multi-ingredient Preparations. *India*: Carbamyl; Carcet; Decet-BD; Decet-OD; Dicarb Inga; Esnopil; Flary-Forte; Unicarbazan.

Pharmacopoeial Preparations
BP 2014: Diethylcarbamazine Tablets;
USP 36: Diethylcarbamazine Citrate Tablets.

Disophenol

Disofenol.
2,6-Diiodo-4-nitrophenol.
$C_6H_3I_2NO_3$=390.9
CAS — 305-85-1.
UNII — 39S5ZJ6SYN.

Profile

Disophenol is an anthelmintic used in veterinary medicine for the treatment of hookworm and gapeworm infections.

Doramectin *(BAN, USAN, rINN)*

Doramectina; Doramectine; Doramectinum; Doramektiini; Doramektin; UK-67994; Дорамектин.
CAS — 117704-25-3.
ATC Vet — QP54AA03.
UNII — KGD7A54H5P.

Profile

Doramectin is an avermectin anthelmintic used in veterinary medicine for nematode infections. It is also used as a systemic veterinary ectoparasiticide.

Embelia

Vidang; Виданга.
CAS — 550-24-3 (embelic acid).
UNII — YA87U85J0D (Embelia ribes); *X1Q40X9I5L* (Embelia ribes *fruit*).

Profile

Embelia consists of the dried fruits of *Embelia ribes* and *E. robusta* (= *E. tsjeriamcottam*) (Myrsinaceae), containing about 2.5% of embelic acid (embelin). It has been used in India and other Asian countries for the expulsion of tapeworms.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Hung.*: Herbadict; *India*: Happy'tizer†; *Ukr.*: Trypsidan (Трипсидан)†.

Eprinomectin *(USAN, rINN)*

Eprinomectina; Éprinomectine; Eprinomectinum; Eprinomektiini; Eprinomektin; MK-397; Эприномектин.
A mixture of eprinomectin component B_{1a} and eprinomectin component B_{1b}.
CAS — 159628-36-1 (eprinomectin); 123997-26-2 (eprinomectin); 133305-88-1 (component B_{1a}); 133305-89-2 (component B_{1b}).
ATC Vet — QP54AA04.
UNII — 75KP30FD8O (eprinomectin); 00OY54D31C (eprinomectin component B_{1a}); 31OML2QZ0Q (eprinomectin component B_{1b}).

Pharmacopoeias. In *US*.

USP 36: (Eprinomectin). Eprinomectin is a mixture of component B_{1a}($C_{50}H_{75}NO_{14}$ = 914.1) and component B_{1b} ($C_{49}H_{73}NO_{14}$ = 900.1). It contains not less than 90% of component B_{1a} and not less than 95% of components B_{1a} and B_{1b}, calculated on the anhydrous, solvent-free, and antoxidant-free basis. Antoxidants may be added. A white to off-white powder. Insoluble in cold water. Store in airtight containers at 2 degrees to 8 degrees.

Profile

Eprinomectin is an avermectin anthelmintic used in veterinary medicine for nematode infections. It is also used as a systemic veterinary ectoparasiticide.

Epsiprantel *(BAN, rINN)*

BRL-38705; Epsipranteeli; Epsiprantelum; Эпсипрантел.
2-Cyclohexylcarbonyl-1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-*a*][2]benzazepin-4-one.
$C_{20}H_{26}N_2O_2$=326.4
CAS — 98123-83-2.
ATC Vet — QP52AA04.
UNII — 0C1SPQ0FSR.

Profile

Epsiprantel is an anthelmintic closely related to praziquantel. It is used in veterinary medicine.

Febantel *(BAN, USAN, rINN)*

Bay-Vh-5757; Bay-h-5757; Febanteeli; Fébantel; Febantelum; Фебантел.
2'-[2,3-Bis(methoxycarbonyl)guanidino]-5'-phenylthio-2-methoxyacetanilide; Dimethyl (2-[2-(2-methoxyacetamido)-4-(phenylthio)phenyl]imidocarbonyl)dicarbamate.
$C_{30}H_{22}N_4O_6S$=446.5
CAS — 58306-30-2.
ATC Vet — QP52AC05.
UNII — S75C401OS1.

NOTE. The name Avicas has been used as a trade mark for febantel.

Pharmacopoeias. In *Eur.* (see p. vii) for veterinary use only.

Ph. Eur. 8: (Febantel for Veterinary Use; Febantel BP(Vet) 2014). A white or almost white, crystalline powder. It exhibits polymorphism. Practically insoluble in water; slightly soluble in dehydrated alcohol; soluble in acetone.

Profile

Febantel is a prodrug that is converted to fenbendazole (see p. 156.1). It is an anthelmintic used in veterinary medicine for the treatment of nematode infections of the gastrointestinal tract and lungs and in tapeworm infections.

Fenbendazole *(BAN, USAN, rINN)*

Fenbendatsoli; Fenbendazol; Fenbendazolum; Hoe-881V; Фенбендазол.
Methyl 5-phenylthio-1*H*-benzimidazol-2-ylcarbamate.
$C_{15}H_{13}N_3O_2S$=299.3
CAS — 43210-67-9.
ATC — P02CA06.
ATC Vet — QP52AC13.
UNII — 621BVT9M36.

NOTE. The names Beaphar, Fenzol, Granofen, Norworm and Panacur have been used as trade marks for fenbendazole.

Pharmacopoeias. In *Eur.* (see p. vii) and *US* for veterinary use only.

Ph. Eur. 8: (Fenbendazole for Veterinary Use; Fenbendazole BP(Vet) 2014). A white or almost white powder. Practically insoluble in water; sparingly soluble in dimethylformamide; very slightly soluble in methyl alcohol. Protect from light.

USP 36: (Fenbendazole). A white to off-white powder. Practically insoluble in water; sparingly soluble in dimethylformamide; very slightly soluble in methyl alcohol. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Profile

Fenbendazole is a benzimidazole carbamate anthelmintic structurally related to mebendazole (p. 160.1). It is used in veterinary medicine for the treatment of nematode infections of the gastrointestinal tract and lungs and in tapeworm infections.

Flubendazole *(BAN, USAN, rINN)*

Flubendatsoli; Flubendazol; Flubendazolas; Flubendazolum; Fluoromebendazole; R-17889; Флубендазол.
Methyl 5-(4-fluorobenzoyl)-1*H*-benzimidazol-2-ylcarbamate.
$C_{16}H_{12}FN_3O_3$=313.3
CAS — 31430-15-6.
ATC — P02CA05.
ATC Vet — QP52AC12.
UNII — R8M46911LR.

NOTE. The names Flubenol, Flubenvet, and Solubenol have been used as trade marks for flubendazole.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Flubendazole). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water, in alcohol, and in dichloromethane. Protect from light.

Profile

Flubendazole, a benzimidazole carbamate anthelmintic, is an analogue of mebendazole (p. 160.1) and has similar actions and uses.

For the treatment of enterobiasis in adults and children, flubendazole 100 mg is given as a single oral dose, repeated after 2 to 3 weeks. For ascariasis, hookworm infections, and trichuriasis 100 mg is given twice daily for 3 days. For discussions of these infections and their treatment, see under Choice of Anthelmintic, p. 143.1.

It is also used in veterinary medicine for the treatment of nematode and tapeworm infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Flumoxal; *Fr.*: Fluvermal; *Port.*: Fluvermal; Teniverme; *Spain*: Flicum†; *Venez.*: Fluvermox.

Haloxon *(BAN, rINN)*

Haloxón; Haloxone; Haloxonum; Галоксон.

Bis(2-chloroethyl) 3-chloro-4-methylcoumarin-7-yl phosphate.

$C_{14}H_{14}Cl_3O_6P$=415.6

CAS — 321-55-1.

ATC Vet — QP52AB04.

UNII — T8KXA37068.

Profile

Haloxon is an organophosphorus compound (see Organophosphorus Insecticides, p. 2158.3) used as an anthelmintic in veterinary medicine.

Hygromycin B

Higromicina B; Hygromycine B; Гигромицин Б.

O-6-Amino-6-deoxy-L-glycero-D-galacto-heptopyranosylidene-(1→2-3)-*O*-β-D-talopyranosyl-(1→5)-2-deoxy-*N*^{3}-methyl-D-streptamine.

$C_{20}H_{37}N_3O_{13}$=527.5

CAS — 31282-04-9.

UNII — 3XQ2233B0B.

Profile

Hygromycin B is used as a feed additive in veterinary practice; use over several weeks is moderately effective in controlling gastrointestinal roundworms in pigs and poultry.

Ivermectin *(BAN, USAN, rINN)*

Ivermectina; Ivermectine; Ivermectinum; Ivermektiini; Ivermektin; Ivermektinas; Ивермектин.

CAS — 70288-86-7 (ivermectin); 71827-03-7 (component B_{1a}); 70209-81-3 (component B_{1b}).

ATC — P02CF01.

ATC Vet — QP54AA01; QS02QA03.

UNII — 8883YP2R6D (ivermectin); 91Y2202OUW (ivermectin component H_2B_{1a}); 0W28CYI3TU (ivermectin component H_2B_{1b}).

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Ivermectin). A mixture of ivermectin component H_2B_{1a} (5-*O*-demethyl-22,23-dihydroavermectin A_{1a}; $C_{48}H_{74}O_{14}$=875.1) and ivermectin component H_2B_{1b} (5-*O*-demethyl-25-de(1-methylpropyl)-25-(1-methylethyl)-22,23-dihydroavermectin A_{1a}; $C_{47}H_{72}O_{14}$=861.1).

A white or yellowish-white, slightly hygroscopic, crystalline powder. Practically insoluble in water; soluble in alcohol; freely soluble in dichloromethane. Store in airtight containers.

USP 36: (Ivermectin). A mixture of component H_2B_{1a} (5-*O*-demethyl-22,23-dihydro-avermectin A_{1a}; $C_{48}H_{74}O_{14}$=875.1) and component H_2B_{1b} (5-*O*-demethyl-25-de(1-methylpropyl)-22,23-dihydro-25-(1-methylethyl)-avermectin A_{1a}; $C_{47}H_{72}O_{14}$=861.1). It may contain small amounts of suitable antoxidant and chelating agents.

A white to yellowish-white, slightly hygroscopic, crystalline powder. Practically insoluble in water and in petroleum spirit; soluble in acetone and in acetonitrile; freely soluble in dichloromethane and in methyl alcohol. Store in airtight containers at a temperature of 2 degrees to 8 degrees. Where the use of an antoxidant is allowed, store at 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Ivermectin is a semisynthetic derivative of one of the avermectins, a group of macrocyclic lactones produced by *Streptomyces avermitilis*.

It has a microfilaricidal action in onchocerciasis and reduces the microfilarial load without the toxicity seen with diethylcarbamazine. Ivermectin also has a microfilaricidal action in lymphatic filariasis and is used in endemic areas as part of a mass treatment regimen. Ivermectin is active in some other worm infections. It is used in the treatment of strongyloidiasis and has been tried in some *Mansonella* infections. For details of these infections and their treatment, see under Choice of Anthelmintic, p. 143.1, and under the individual headings below. It is used topically in the treatment of head pediculosis (see also p. 157.2).

In the treatment of **onchocerciasis**, a single oral dose of ivermectin, based roughly on 150 micrograms/kg may be given to patients weighing more than 15 kg; re-treatment is usually required, and is given after an interval of at least 3 months. For mass treatment in infected areas (see p. 157.1) the dose is given annually or every 6 months. No food should be taken for 2 hours before or after the dose. Similar or slightly higher doses, plus a dose of albendazole, are advocated by WHO in the mass treatment of **lymphatic filariasis** (see p. 157.1 for details).

For the treatment of **strongyloidiasis**, ivermectin 200 micrograms/kg as a single oral dose, or daily on two consecutive days, is given to patients weighing more than 15 kg.

Ivermectin is used in the treatment of **head pediculosis** as a single topical application of a 0.5% lotion in adults and children from 6 months of age. It should be applied to dry hair, left on for 10 minutes and then washed out.

Reviews.

1. Ottesen EA, Campbell WC. Ivermectin in human medicine. *J Antimicrob Chemother* 1994; 34: 195–203.
2. Ōmura S. Ivermectin: 25 years and still going strong. *Int J Antimicrob Agents* 2008; 31: 91–8.

Administration in children. Ivermectin may be given orally to children weighing more than 15 kg and over 5 years of age, for the management of onchocerciasis and lymphatic filariasis and also for the treatment of strongyloidiasis. Doses used are the same by weight as those used for adults (see above).

Cutaneous larva migrans. There are some reports[1-5] of ivermectin being effective in the treatment of cutaneous larva migrans (p. 144.3). An oral dose of 200 micrograms/kg daily for 1 to 2 days has been recommended.[6]

1. Caumes E, *et al.* Efficacy of ivermectin in the therapy of cutaneous larva migrans. *Arch Dermatol* 1992; 128: 994–5.
2. Caumes E, *et al.* A randomized trial of ivermectin versus albendazole for the treatment of cutaneous larva migrans. *Am J Trop Med Hyg* 1993; 49: 641–4.
3. Bouchaud O, *et al.* Cutaneous larva migrans in travelers: a prospective study, with assessment of therapy with ivermectin. *Clin Infect Dis* 2000; 31: 493–8. Correction. *Ibid.* 2001; 32: 523.
4. del Mar Sáez-De-Ocariz M, *et al.* Treatment of 18 children with scabies or cutaneous larva migrans using ivermectin. *Clin Exp Dermatol* 2002; 27: 264–7.
5. Senba Y, *et al.* Case of creeping disease treated with ivermectin. *J Dermatol* 2009; 36: 86–9.
6. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.

Intestinal nematode infections. Ivermectin activity has been seen in man against *Ascaris lumbricoides*, *Strongyloides stercoralis*, and *Trichuris trichiura*;[1] although some have failed to detect activity against *Trichuris*,[2] ivermectin given with albendazole in doses similar to those recommended for mass treatment in the management of lymphatic filariasis (see p. 157.1), has been studied for the treatment of trichuriasis (p. 149.1) and may prove useful in areas where soil-transmitted worm infections and lymphatic filariasis are public health problems.[3] A randomised, controlled study in 548 school children in Zanzibar[4] found that single oral doses of ivermectin (200 micrograms/kg) plus either albendazole (400 mg) or mebendazole (500 mg) improved cure and egg reduction rates against *T. trichiura*. The highest cure and egg reduction rates were achieved with ivermectin plus mebendazole (55 and 97% respectively), while lower rates were seen with ivermectin plus albendazole (38% cure rate and 91% egg reduction rate). Roundworm expulsion has also been reported as a 'side-effect' of ivermectin when used in community-based treatment of onchocerciasis.[5] In a controlled study,[6] single oral doses of ivermectin 150 or 200 micrograms/kg produced cure rates of 94% in strongyloidiasis (see p. 157.3) and above 67% in ascariasis, trichuriasis, and enterobiasis. Although some activity has been seen against *Necator americanus*,[1] cure rates for hookworm were considered unsatisfactory.[6]

1. Freedman DO, *et al.* The efficacy of ivermectin in the chemotherapy of gastrointestinal helminthiasis in humans. *J Infect Dis* 1989; 159: 1151–3.
2. Whitworth JAG, *et al.* A field study of the effect of ivermectin on intestinal helminths in man. *Trans R Soc Trop Med Hyg* 1991; 85: 232–4.
3. Belizario VY, *et al.* A comparison of the efficacy of single doses of albendazole, ivermectin, and diethylcarbamazine alone or in combinations against Ascaris and Trichuris spp. *Bull WHO* 2003; 81: 35–42.
4. Knopp S, *et al.* Albendazole and mebendazole administered alone or in combination with ivermectin against *Trichuris trichiura*: a randomized controlled trial. *Clin Infect Dis* 2010; 51: 1420–8.
5. Whitworth JAG, *et al.* Community-based treatment with ivermectin. *Lancet* 1988; II: 97–8.
6. Naquira C, *et al.* Ivermectin for human strongyloidiasis and other intestinal helminths. *Am J Trop Med Hyg* 1989; 40: 304–9.

Loiasis. There is evidence of reduced microfilaraemia after ivermectin treatment[1-5] in patients with loiasis (p. 146.2), but concern exists over its potential for neurotoxicity in patients with a high microfilarial burden.[6,7] There is some evidence[8] that a genetic predisposition to altered distribution of ivermectin may be a co-factor for the development of serious adverse events in patients with high numbers of microfilaria. Low-dose regimens (about 25 micrograms/kg) have been investigated[9] but did not seem to offer much advantage in reducing neurotoxicity.

1. Martin-Prevel Y, *et al.* Reduction of microfilaraemia with single high-dose of ivermectin in loiasis. *Lancet* 1993; 342: 442.
2. Ranque S, *et al.* Decreased prevalence and intensity of Loa loa infection in a community treated with ivermectin every three months for two years. *Trans R Soc Trop Med Hyg* 1996; 90: 429–30.
3. Duong TH, *et al.* Reduced Loa loa microfilaria count ten to twelve months after a single dose of ivermectin. *Trans R Soc Trop Med Hyg* 1997; 91: 592–3.
4. Gardon J, *et al.* Marked decrease in Loa loa microfilaraemia six and twelve months after a single dose of ivermectin. *Trans R Soc Trop Med Hyg* 1997; 91: 593–4.
5. Chippaux J-P, *et al.* Impact of repeated large scale ivermectin treatments on the transmission of Loa loa. *Trans R Soc Trop Med Hyg* 1998; 92: 454–8.
6. Anonymous. Encephalitis following treatment of loiasis. *WHO Drug Inf* 1991; 5: 113–14.
7. Gardon J, *et al.* Serious reactions after mass treatment of onchocerciasis with ivermectin in an area endemic for Loa loa infection. *Lancet* 1997; 350: 18–22.
8. Bourguinat C, *et al.* Analysis of the mdr-1 gene in patients co-infected with *Onchocerca volvulus* and *Loa loa* who experienced a post-ivermectin serious adverse event. *Am J Trop Med Hyg* 2010; 83: 28–32.
9. Kamgno J, *et al.* Randomized, controlled, double-blind trial with ivermectin on Loa loa microfilaraemia: efficacy of a low dose (~25 μ g/kg) versus current standard dose (150 μ g/kg). *Trans R Soc Trop Med Hyg* 2007; 101: 777–85.

Lymphatic filariasis. Ivermectin is used in the management of lymphatic filariasis (p. 146.3). In endemic areas mass treatment of the entire population (excluding neonates, pregnant women, and debilitated individuals) can reduce the intensity of transmission and the incidence of disease. In countries where there is co-endemic loiasis or onchocerciasis, the Global Programme to Eliminate Lymphatic Filariasis launched by WHO, with other international agencies, advocates a single oral dose of ivermectin 150 to 200 micrograms/kg with a single oral dose of albendazole 400 mg given once each year for at least 5 years.

Higher doses of albendazole and ivermectin (800 mg and 400 micrograms/kg respectively) given twice a year for 2 years, to 25 residents of an area of high *Wuchereria bancrofti* endemicity in Mali, were found to be more effective in reducing microfilarial levels than the standard annual dose regimen recommended by WHO. Higher-dose and/or more frequent treatment regimens could therefore potentially reduce the time necessary to interrupt transmission.[1]

1. Dembele B, *et al.* Use of high-dose, twice-yearly albendazole and ivermectin to suppress *Wuchereria bancrofti* microfilarial levels. *Clin Infect Dis* 2010; 51: 1229–35.

Malaria. It has been suggested that ivermectin, given as part of mass treatment programs for filarial infections, may also kill malarial mosquitos when they bite treated patients, resulting in a reduction in malaria transmission.[1,2]

1. Kobylinski KC, *et al.* Ivermectin mass drug administration to humans disrupts malaria parasite transmission in Senegalese villages. *Am J Trop Med Hyg* 2011; 85: 3–5.
2. Tanne JH. Antiparasite drug ivermectin cuts mosquito numbers by 80%. *BMJ* 2011; 343: d4355.

Mansonella infections. The response of *Mansonella* infections (p. 147.2) to ivermectin depends on the species. It may be effective against *Mansonella ozzardi*, but studies in *M. perstans* infection have not shown ivermectin to produce a substantial reduction in microfilaraemia,[1,2] even used with albendazole.[3,4] A good response to a single oral dose of 150 micrograms/kg of ivermectin has been reported in infections with *M. streptocerca*.[5,6]

1. Van den Enden E, *et al.* Treatment failure of a single high dose of ivermectin for Mansonella perstans filariasis. *Trans R Soc Trop Med Hyg* 1993; 87: 90.
2. Schulz-Key H, *et al.* Efficacy of ivermectin in the treatment of concomitant Mansonella perstans infections in onchocerciasis patients. *Trans R Soc Trop Med Hyg* 1993; 87: 227–9.
3. Asio SM, *et al.* Mansonella perstans: safety and efficacy of ivermectin alone, albendazole alone and the two drugs in combination. *Ann Trop Med Parasitol* 2009; 103: 31–7.
4. Asio SM, *et al.* A randomised, double-blind field trial of ivermectin alone and in combination with albendazole for the treatment of Mansonella perstans infections in Uganda. *Trans R Soc Trop Med Hyg* 2009; 103: 274–9.
5. Fischer P, *et al.* Treatment of human Mansonella streptocerca infection with ivermectin. *Trop Med Int Health* 1997; 2: 191–9.
6. Fischer P, *et al.* Long-term suppression of Mansonella streptocerca microfilariae after treatment with ivermectin. *J Infect Dis* 1999; 180: 1403–5.

Onchocerciasis. Ivermectin has a microfilaricidal action against *Onchocerca volvulus* and is the main drug used in the control of onchocerciasis (p. 147.2). A single oral dose rapidly eliminates microfilariae from the skin, with maximum effect after 1 to 2 months,[1] and gradually eliminates them from the cornea and anterior chamber of the eye.[2] Ivermectin has little effect on the adult worms but does suppress the release of microfilariae from the adult worm for several cycles which accounts for its prolonged activity. Ivermectin therefore only controls the disease; it does not cure or eradicate it. Its action against *O. volvulus* has been attributed to a GABA-agonist effect. Studies have also

indicated that ivermectin inhibits the transmission of microfilariae by reducing their uptake from man by the insect vector.[3-6]

Ivermectin is donated by *Merck* through the Mectizan Expert Committee (MEC) for human use in community-wide mass treatment programmes in all countries in which onchocerciasis is endemic, where it is given at a standard oral dose of 150 micrograms/kg once or twice a year to all but pregnant women, breast-feeding mothers of recently born babies, children weighing less than 15 kg, and those unable to walk or otherwise seriously ill.[7] The adult worms live for about 15 years, therefore treatment will need to be continued for many years. Several studies have confirmed the long-term safety and efficacy of such programmes.[8-12] Studies have reported that increasing the frequency of the standard doses of ivermectin to every 3 or 6 months appears to increase efficacy compared with annual treatments[13,14] and that 3-monthly regimens may also reduce risk of adverse effects.[14,15] No additional benefit was noted by increasing the dose of ivermectin to 400 or 800 micrograms/kg given either 3-monthly or annually.

In non-endemic areas, repeated doses may be necessary to reduce recurrence; a study in the UK found that patients given three doses at monthly intervals had fewer relapses at 6 months than patients who received a single dose, but relapses were nevertheless seen in 50% of patients at 12 months.[16]

The ocular microfilarial load can be safely reduced by ivermectin[2,17] and early lesions of the anterior segment of the eye have improved.[17] A reduction in the incidence[18] and progression[19] of optic nerve damage has also been reported, but the effect on posterior segment disease is less certain.[20] A systematic review of 5 placebo-controlled studies, with data from 3810 individuals, found no statistically significant difference between ivermectin and placebo groups for preventing visual acuity loss.[21] Improvements in skin lesions have been reported.[22]

1. Basáñez MG, *et al.* Effect of single-dose ivermectin on Onchocerca volvulus: a systematic review and meta-analysis. *Lancet Infect Dis* 2008; 8: 310–22.
2. Newland HS, *et al.* Effect of single-dose ivermectin therapy on human Onchocerca volvulus infection with onchocercal ocular involvement. *Br J Ophthalmol* 1988; 72: 561–9.
3. Taylor HR, *et al.* Impact of mass treatment of onchocerciasis with ivermectin on the transmission of infection. *Science* 1990; 250: 116–18.
4. Trpis M, *et al.* Effect of mass treatment of a human population with ivermectin on transmission of Onchocerca volvulus by Simulium yahense in Liberia, West Africa. *Am J Trop Med Hyg* 1990; 42: 148–56.
5. Chavasse DC, *et al.* Low level ivermectin coverage and the transmission of onchocerciasis. *Trans R Soc Trop Med Hyg* 1995; 89: 534–7.
6. Boussinesq M, *et al.* Onchocerca volvulus: striking decrease in transmission in the Vina valley (Cameroon) after eight annual large scale ivermectin treatments. *Trans R Soc Trop Med Hyg* 1997; 91: 82–6.
7. Pond B. Distribution of ivermectin by health workers. *Lancet* 1990; 335: 1539.
8. De Sole G, *et al.* Adverse reactions after large-scale treatment of onchocerciasis with ivermectin: combined results from eight community trials. *Bull WHO* 1989; 67: 707–19.
9. Pacqué M, *et al.* Safety of and compliance with community-based ivermectin therapy. *Lancet* 1990; 335: 1377–80.
10. Pacqué M, *et al.* Community-based treatment of onchocerciasis with ivermectin: safety, efficacy, and acceptability of yearly treatment. *J Infect Dis* 1991; 163: 381–5.
11. Steel C, *et al.* Immunologic responses to repeated ivermectin treatment in patients with onchocerciasis. *J Infect Dis* 1991; 164: 581–7.
12. Whitworth JAG, *et al.* A community trial of ivermectin for onchocerciasis in Sierra Leone: clinical and parasitological responses to four doses given at six-monthly interval. *Trans R Soc Trop Med Hyg* 1992; 86: 277–80.
13. Greene BM, *et al.* A comparison of 6-, 12-, and 24-monthly dosing with ivermectin for treatment of onchocerciasis. *J Infect Dis* 1991; 163: 376–80.
14. Gardon J, *et al.* Effects of standard and high doses of ivermectin on adult worms of Onchocerca volvulus: a randomised controlled trial. *Lancet* 2002; 360: 203–10.
15. Kamgno J, *et al.* Adverse systemic reactions to treatment of onchocerciasis with ivermectin at normal and high doses given annually or three-monthly. *Trans R Soc Trop Med Hyg* 2004; 98: 496–504.
16. Churchill DR, *et al.* A trial of a three-dose regimen of ivermectin for the treatment of patients with onchocerciasis in the UK. *Trans R Soc Trop Med Hyg* 1994; 88: 242.
17. Dadzie KY, *et al.* Changes in ocular onchocerciasis after two rounds of community-based ivermectin treatment in a holo-endemic onchocerciasis focus. *Trans R Soc Trop Med Hyg* 1991; 85: 267–71.
18. Abiose A, *et al.* Reduction in incidence of optic nerve disease with annual ivermectin to control onchocerciasis. *Lancet* 1993; 341: 130–4.
19. Cousens SN, *et al.* Impact of annual dosing with ivermectin on progression of onchocercal visual field loss. *Bull WHO* 1997; 75: 229–36.
20. Whitworth JAG, *et al.* Effects of repeated doses of ivermectin on ocular onchocerciasis: community-based trial in Sierra Lione. *Lancet* 1991; 338: 1100–1103.
21. Ejere H, *et al.* Ivermectin for onchocercal eye disease (river blindness). Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2001 (accessed 29/07/07).
22. Pacqué M, *et al.* Improvements in severe onchocercal skin disease after a single dose of ivermectin. *Am J Med* 1991; 90: 590–4.

Scabies and pediculosis. Scabies (p. 2148.1) is usually treated with a topically applied acaricide. However, a single oral dose of ivermectin has been reported to be effective.[1-3] In a study of 11 patients with uncomplicated scabies, a single oral dose of ivermectin 200 micrograms/kg was effective in curing infection after 4 weeks. In a group of 11 patients, also infected with HIV, scabies was cured in 8 after 2 weeks.[1] Two of the remaining 3 patients received a second dose of ivermectin which cured the scabies infection by the fourth week. Ivermectin does not sterilise the scabies eggs and in order to kill newly hatched mites a second dose of ivermectin is recommended, given at least 7 days after the first dose.[4] A single oral dose of ivermectin 150 micrograms/kg was partially effective in an outbreak of scabies in 1153 Tanzanian patients.[5] A systematic review[3] on the treatment of scabies found that oral ivermectin was less effective than topical permethrin, but appeared to be as effective as topical benzyl benzoate and more effective than topical lindane. However, a randomised, open-label study[6] found that one or two applications of 12.5% benzyl benzoate, each left on for 24 hours, were more effective than a single oral dose of ivermectin of 150 to 200 micrograms/kg; bacterial superinfection also occurred more often in those given ivermectin than in those treated with benzyl benzoate.

Crusted (Norwegian) scabies has also been reported to be effectively treated by a single oral dose of 12 mg of ivermectin in addition to topical application of 3% salicylic acid ointment in 2 patients; the treatment was effective in under one week.[2] A single oral dose of ivermectin 200 micrograms/kg was effective for crusted scabies in a 2-year-old infant who had contracted the disease following long-term corticosteroid use.[7] Ivermectin has also been successfully used in a small number of patients with treatment-resistant scabies.[8]

Ivermectin has also been investigated[9] as a possible treatment for pediculosis (p. 2147.3) although, again, topically applied insecticides are the usual method of control. A study *in vitro* and in *animals* showed that ivermectin killed nymphs and females of the human body louse (*Pediculus humanus humanus*). Ivermectin was known to be effective against other louse species that infect a range of *animals*.[10] Ivermectin has also been shown to be effective against head lice: two oral doses of 400 micrograms/kg at an interval of 7 days were more effective than applications of malathion 0.5% in a controlled double-blind study in patients with refractory infestations.[11] A 0.5% topical lotion has been licensed in the USA for the treatment of head pediculosis (see Uses and Administration, p. 155.1).

1. Meinking TL, *et al.* The treatment of scabies with ivermectin. *N Engl J Med* 1995; 333: 26–30.
2. Aubin F, Humbert P. Ivermectin for crusted (Norwegian) scabies. *N Engl J Med* 1995; 332: 612.
3. Strong M, Johnstone PW. Interventions for treating scabies. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 21/08/09).
4. Currie BJ, McCarthy JS. Permethrin and ivermectin for scabies. *N Engl J Med* 2010; 362: 717–25.
5. Leppard B, Naburi AE. The use of ivermectin in controlling an outbreak of scabies in a prison. *Br J Dermatol* 2000; 143: 520–3.
6. Ly F, *et al.* Ivermectin versus benzyl benzoate applied once or twice to treat human scabies in Dakar, Senegal: a randomized controlled trial. *Bull WHO* 2009; 87: 424–30.
7. Marlière V, *et al.* Crusted (Norwegian) scabies induced by use of topical corticosteroids and treated successfully with ivermectin. *J Pediatr* 1999; 135: 122–4.
8. Cook AM, Romanelli F. Ivermectin for the treatment of resistant scabies. *Ann Pharmacother* 2003; 37: 279–81.
9. Foucault C, *et al.* Oral ivermectin in the treatment of body lice. *J Infect Dis* 2006; 193: 474–6.
10. Mumcuoglu KY, *et al.* Systemic activity of ivermectin on the human body louse (Anoplura: Pediculidae). *J Med Entomol* 1990; 27: 72–5.
11. Chosidow O, *et al.* Oral ivermectin versus malathion lotion for difficult-to-treat head lice. *N Engl J Med* 2010; 362: 896–905. Correction. *ibid.*; 1647.

Strongyloidiasis. Ivermectin is effective in the treatment of strongyloidiasis (p. 148.2) and is considered by some authorities to be the drug of choice. Subcutaneous use has been investigated in patients with severe, disseminated disease.

References.

1. Naquira C, *et al.* Ivermectin for human strongyloidiasis and other intestinal helminths. *Am J Trop Med Hyg* 1989; 40: 304–9.
2. Wijesundera M de S, Sanmuganathan PS. Ivermectin therapy in chronic strongyloidiasis. *Trans R Soc Trop Med Hyg* 1992; 86: 291.
3. Lyagoubi M, *et al.* Chronic persistent strongyloidiasis cured by ivermectin. *Trans R Soc Trop Med Hyg* 1992; 86: 541.
4. Datry A, *et al.* Treatment of Strongyloides stercoralis infection with ivermectin compared with albendazole: results of an open study of 60 cases. *Trans R Soc Trop Med Hyg* 1994; 88: 344–5.
5. Gann PH, *et al.* A randomized trial of single- and two-dose ivermectin versus thiabendazole for treatment of strongyloidiasis. *J Infect Dis* 1994; 169: 1076–9.
6. Marti H, *et al.* A comparative trial of a single-dose ivermectin versus three days of albendazole for treatment of Strongyloides stercoralis and other soil-transmitted helminth infections in children. *Am J Trop Med Hyg* 1996; 55: 477–81.
7. Igual-Adell R, *et al.* Efficacy and safety of ivermectin and thiabendazole in the treatment of strongyloidiasis. *Expert Opin Pharmacother* 2004; 5: 2615–9.
8. Marty FM, *et al.* Treatment of human disseminated strongyloidiasis with a parenteral veterinary formulation of ivermectin. *Clin Infect Dis* 2005; 41: e5–e8.
9. Pacanowski J, *et al.* Subcutaneous ivermectin as a safe salvage therapy in Strongyloides stercoralis hyperinfection syndrome: a case report. *Am J Trop Med Hyg* 2005; 73: 122–4.
10. Salluh JI, *et al.* Successful use of parenteral ivermectin in an immunosuppressed patient with disseminated strongyloidiasis and septic shock. *Intensive Care Med* 2005; 31: 1292.
11. Hauber HP, *et al.* Fatal outcome of a hyperinfection syndrome despite successful eradication of Strongyloides with subcutaneous ivermectin. *Infection* 2005; 33: 383–6.
12. Turner SA, *et al.* Parenteral administration of ivermectin in a patient with disseminated strongyloidiasis. *Am J Trop Med Hyg* 2005; 73: 911–4.
13. Leung V, *et al.* Case report: failure of subcutaneous ivermectin in treating Strongyloides hyperinfection. *Am J Trop Med Hyg* 2008; 79: 853–5.
14. Lichtenberger P, *et al.* Hyperinfection strongyloidiasis in a liver transplant recipient treated with parenteral ivermectin. *Transpl Infect Dis* 2009; 11: 137–42.

Trichostrongyliasis. For mention of the use of ivermectin in *Trichostrongylus* infections, see p. 148.3.

Adverse Effects and Precautions

The adverse effects reported with ivermectin in patients with filariasis are generally consistent with a mild Mazzotti reaction arising from its effect on microfilariae. They include fever, pruritus, rashes, arthralgia, myalgia, asthenia, orthostatic hypotension, tachycardia, oedema, lymphadenopathy, gastrointestinal symptoms, sore throat, cough, and headache. The effects tend to be transient and if treatment is required they respond to analgesics and antihistamines.

Ivermectin may cause mild ocular irritation. Somnolence, transient eosinophilia, and raised liver enzyme values have also been reported.

Ivermectin is not recommended during pregnancy. Mass treatment is generally withheld from pregnant women (see Pregnancy, p. 158.2), children under 15 kg, and the seriously ill.

Incidence of adverse effects. Some studies have shown quite a high incidence of adverse effects with ivermectin and have associated the effects with the severity of infection.[1-3] However, in none of these studies were the reactions considered to be life-threatening and only symptomatic treatment was required. The severity, incidence, and duration of adverse reactions was reported to be reduced after repeated annual doses.[4]

When larger groups of patients were considered in the Onchocerciasis Control Programme (OCP) in West Africa, a much lower incidence of adverse reactions was seen in patients given ivermectin for the first time[5] and when treatment was repeated a year later that incidence was reduced even further. The results from several studies in this programme[6] showed 93 severe reactions in 50 929 patients (1.83%), most of the reactions being orthostatic hypotension or dizziness (53). In a 3-year randomised, double-blind, controlled study of ivermectin for onchocerciasis control in 572 patients,[7] 3-monthly treatment with the standard dose of 150 micrograms/kg was associated with a reduced risk of adverse reactions, especially oedema, pruritus, and back pain, when compared with the same dose given annually. Higher doses of 400 then 800 micrograms/kg, given either 3-monthly or annually, were associated with subjective ocular problems.

Another study[8] found 22 severe reactions in 17 877 patients treated for onchocerciasis in an area also endemic for *Loa loa* infection, and showed a relationship to heavy *L. loa* microfilaraemia. The Mectizan Expert Committee and the Technical Consultative Committee have reported the incidence of encephalopathy after ivermectin treatment of onchocerciasis in *Loa loa* endemic areas to be less than 1 case in 10 000 treatments[9] and have implemented recommendations for ivermectin mass treatment programmes of onchocerciasis in areas co-endemic for loiasis to reduce the risk of serious adverse events, especially in areas where the population is ivermectin naive.

Some supervision is considered necessary after doses of ivermectin;[2,6] the OCP recommendation[6] is for resident nurses to monitor patients for a period of 36 hours after treatment, whatever the level of endemicity. However, the incidence of adverse reactions reported after repeated doses appears to be lower than after the first dose and the need for supervision on re-treatment has been questioned.[10]

Neurotoxicity seen in some breeds of *dogs* has not been seen in *cattle* or *horses*[11] and nor was it reported in man in the above studies. Another potential concern was the prolongation of prothrombin times seen in 28 patients given ivermectin,[12] but others have not confirmed this effect[13] or seen any bleeding disorders.[14]

There has been some concern over the use of ivermectin to treat scabies in elderly patients after a report suggesting a possible link to an increased incidence of death among a cohort of 47 patients.[15] It has, however, been argued that no such association has been seen in other populations of elderly patients and that the statistical methods used by the original authors were deficient.[16-18] There was no evidence of an increase in death rate associated with ivermectin in a community-based study in Papua New Guinea of diethylcarbamazine with or without ivermectin for lymphatic filariasis.[19]

1. Kumaraswami V, *et al.* Ivermectin for the treatment of Wuchereria bancrofti filariasis: efficacy and adverse reactions. *JAMA* 1988; 259: 3150–3.
2. Rothova A, *et al.* Side-effects of ivermectin in treatment of onchocerciasis. *Lancet* 1989; i: 1439–41.
3. Zea-Flores R, *et al.* Adverse reactions after community treatment of onchocerciasis with ivermectin in Guatemala. *Trans R Soc Trop Med Hyg* 1992; 86: 663–6.

4. Burnham GM. Adverse reactions to ivermectin treatment for onchocerciasis: results of a placebo-controlled, double-blind trial in Malawi. *Trans R Soc Trop Med Hyg* 1993; 87: 313–17.
5. De Sole G, *et al.* Lack of adverse reactions in ivermectin treatment of onchocerciasis. *Lancet* 1990; 335: 1106–7.
6. De Sole G, *et al.* Adverse reactions after large-scale treatment of onchocerciasis with ivermectin: combined results from eight community trials. *Bull WHO* 1989; 67: 707–19.
7. Kamgno J,*et al.* Adverse systemic reactions to treatment of onchocerciasis with ivermectin at normal and high doses given annually or three-monthly. *Trans R Soc Trop Med Hyg* 2004; 98: 496–504.
8. Gardon J, *et al.* Serious reactions after mass treatment of onchocerciasis with ivermectin in an area endemic for Loa loa infection. *Lancet* 1997; 350: 18–22.
9. The Mectizan Expert Committee and The Technical Consultative Committee. Recommendations for the treatment of onchocerciasis with Mectizan in areas co-endemic for onchocerciasis and loiasis. 2004. Available at: http://www.mectizan.org/sites/default/files/EnglishMECTCCLoaRecs-June04_1.pdf (accessed 29/07/10)
10. Whitworth JAG, *et al.* A community trial of ivermectin for onchocerciasis in Sierra Leone: adverse reactions after the first five treatment rounds. *Trans R Soc Trop Med Hyg* 1991; 85: 501–5.
11. WHO. WHO expert committee on onchocerciasis: third report. *WHO Tech Rep Ser 752* 1987. Available at: http://libdoc.who.int/trs/WHO_TRS_752_(part1).pdf and http://libdoc.who.int/trs/WHO_TRS_752_(part2).pdf (accessed 16/07/08)
12. Homeida MMA, *et al.* Prolongation of prothrombin time with ivermectin. *Lancet* 1988; i: 1346–7.
13. Richards FO, *et al.* Ivermectin and prothrombin time. *Lancet* 1989; i: 1139–40.
14. Pacque MC, *et al.* Ivermectin and prothrombin time. *Lancet* 1989; i: 1140.
15. Barkwell R, Shields S. Deaths associated with ivermectin treatment of scabies. *Lancet* 1997; 349: 1144–5.
16. Diazgranados JA, Costa JL. Deaths after ivermectin treatment. *Lancet* 1997; 349: 1698.
17. Reintjes R, Hoek C. Deaths associated with ivermectin for scabies. *Lancet* 1997; 350: 215.
18. Coyne PE, Addiss DG. Deaths associated with ivermectin for scabies. *Lancet* 1997; 350: 215–16.
19. Alexander NDE, *et al.* Absence of ivermectin-associated excess deaths. *Trans R Soc Trop Med Hyg* 1998; 92: 342.

Breast feeding. Mean ivermectin concentrations in the breast milk of 4 healthy women who had been given a standard dose of ivermectin were 14.13 nanograms/mL.[1] It was considered that in view of this low concentration the precaution of excluding breast-feeding mothers from ivermectin mass treatment programmes should be reconsidered. Some authorities have recommended that ivermectin should not be given to mothers who are breast feeding until the infant is at least one week old. The American Academy of Pediatrics states that, since no adverse effects have been seen in breast-fed infants whose mothers were receiving ivermectin, it may be considered to be usually compatible with breast feeding.[2]

1. Ogbuokiri JE, *et al.* Ivermectin levels in human breast milk. *Eur J Clin Pharmacol* 1994; 46: 89–90.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 02/06/04)

Encephalopathy. For information on encephalopathy after ivermectin treatment of onchocerciasis in *Loa loa* endemic areas, see Incidence of Adverse Effects, p. 156.3.

Pregnancy. Ivermectin is teratogenic in *animals* and there are no adequate and well controlled studies in human pregnancy. Ivermectin treatment is therefore usually contra-indicated during pregnancy and pregnant women should be excluded from mass treatment schedules with ivermectin. However, women not yet diagnosed as pregnant or unwilling to admit their pregnancy have been treated. An assessment[1] of 203 pregnancy outcomes in women who had taken ivermectin during pregnancy, mostly during the first 12 weeks, found that the rates of major congenital malformation, miscarriage, and still-birth associated with ivermectin were similar to those in untreated mothers. In another study, 110 women also inadvertently given ivermectin during pregnancy had a similar lack of adverse effect on pregnancy outcome;[2] it was considered that avoiding the use of ivermectin in women once they were known to be pregnant should be adequate precaution. An open-label study[3] in women in the second trimester of pregnancy who were given ivermectin alone or with albendazole did not note any significant effect on birth weight, prematurity, congenital abnormality, or neonatal mortality.

1. Pacqué M, *et al.* Pregnancy outcome after inadvertent ivermectin treatment during community-based distribution. *Lancet* 1990; 336: 1486–9.
2. Chippaux J-P, *et al.* Absence of any adverse effect of inadvertent ivermectin treatment during pregnancy. *Trans R Soc Trop Med Hyg* 1993; 87: 318.
3. Ndyomugyenyi R, *et al.* Efficacy of ivermectin and albendazole alone and in combination for treatment of soil-transmitted helminths in pregnancy and adverse events: a randomized open label controlled intervention trial in Masindi district, western Uganda. *Am J Trop Med Hyg* 2008; 79: 856–63.

Pharmacokinetics

Ivermectin is absorbed after oral doses and peak plasma concentrations occur after about 4 hours. Ivermectin is reported to be about 93% bound to plasma proteins and has a plasma elimination half-life of about 12 hours. It undergoes metabolism in the liver, mainly via the cytochrome P450 isoenzyme CYP3A4. It is excreted largely as metabolites over a period of about 2 weeks, chiefly in the faeces, with less than 1% appearing in the urine and less than 2% in breast milk (see also Breast Feeding, above).

References.
1. González Canga A, *et al.* The pharmacokinetics and interactions of ivermectin in humans—a mini-review. *AAPS J* 2008; 10: 42–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Dermoper IV; Dermopero; Detebencil; Ivertal; Securo; *Austral.*: Stromectol; *Braz.*: Ivermec; Leverctin; Plurimec; Revectina; Vermectil; *Chile*: Kaonol; Mediderm†; *Fr.*: Mectizan†; Stromectol; *Gr.*: Stromectol; *India*: Ectin; Ectover; Elect; Ifact; Imectin; Ivecop; Iver-Sol; Ivercid; Iversan; Iverstar; Ivor; Ivori; Macbi; Mectin; *Jpn*: Stromectol; *Mex.*: Ivexterm; *Neth.*: Stromectol; *NZ*: Stromectol; *Singapore*: Stromectol; *Thai.*: Vermectin; *USA*: Mectizan; Sklice; Stromectol.

Multi-ingredient Preparations. *India*: Ablaze-IM; ABZ Plus; Albacos-IR; Albosym-IR; Alvect; Anthel-UP; Ariban Plus; Ascapil A; Bandy Plus; Benrod-I; Benzole; Ectin-A; Elect-A; Eris Plus; Getrid-I; Hymin Plus; Imectin Forte; Ivecop-AB; Ivercid-A; Iverzole; Ivoral; Kldi; Macbi Plus; Networm.

Pharmacopoeial Preparations
USP 36: Ivermectin and Pyrantel Pamoate Tablets; Ivermectin Tablets.

Levamisole *(BAN, rINN)*

Levamisol; Lévamisole; Levamisoli; Levamisolo; Levamisolum; Levamizol; Левамизол

(*S*)-2,3,5,6-Tetrahydro-6-phenylimidazo[2,1-*b*][1,3]thiazole.

$C_{11}H_{12}N_2S$=204.3

CAS — 14769-73-4.

ATC — P02CE01.

ATC Vet — QP52AE01.

UNII — 2880D3468G.

Pharmacopoeias. In *Eur.* (see p. vii) for veterinary use only.

Ph. Eur. 8: (Levamisole for Veterinary Use; Levamisole BP (Vet) 2014). A white or almost white powder. It exhibits polymorphism. Slightly soluble in water; freely soluble in alcohol and in methyl alcohol. Store in airtight containers. Protect from light.

Levamisole Hydrochloride *(BANM, USAN, rINNM)*

Cloridrato de Levamizol; Hidrocloruro de levamisol; ICI-59623; Levamisol, hidrocloruro de; Lévamisole, Chlorhydrate de; Levamisol-hydrochlorid; Levamisolhydrochlorid; Levamisolhydroklorid; Levamisoli Hydrochloridum; Levamisolihydrokloridi; Levamizol-hidroklorid; Levamizolio hidrochloridas; Lewamizolu chlorowodorek; NSC-177023; R-12564; RP-20605; *l*-Tetramisole Hydrochloride; Левамизола Гидрохлорид.

$C_{11}H_{12}N_2S.HCl$=240.7

CAS — 16595-80-5.

ATC — P02CE01.

UNII — DL9055K809.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 8: (Levamisole Hydrochloride). A white to almost white crystalline powder. Freely soluble in water; soluble in alcohol; slightly soluble in dichloromethane. A 5% solution in water has a pH of 3.0 to 4.5. Protect from light.

USP 36: (Levamisole Hydrochloride). A white or almost white crystalline powder. Freely soluble in water; soluble in alcohol; slightly soluble in dichloromethane; practically insoluble in ether. pH of a 5% solution in water is between 3.0 and 4.5. Protect from light.

Uses and Administration

Levamisole hydrochloride is the active laevo-isomer of tetramisole hydrochloride. It is used as an anthelmintic and has been used as an adjuvant in malignant disease. It has also been tried in several conditions where its stimulant effect on the depressed immune response might be useful.

Levamisole is active against intestinal nematodes and appears to act by paralysing susceptible worms which are subsequently eliminated from the intestines. In particular, levamisole is effective in the treatment of ascariasis (p. 143.3). It is also used in hookworm infections (p. 146.1).

Doses of levamisole hydrochloride are expressed in terms of the equivalent amount of levamisole. Levamisole hydrochloride 1.18 g is equivalent to about 1 g of levamisole. The usual dose for adults and children in **ascariasis** is 2.5 mg/kg of levamisole orally as a single dose. For **hookworm** infection (ancylostomiasis) or for **mixed ascariasis-hookworm** infections, both adults and children may be given 2.5 mg/kg as a single dose, repeated after 7 days in cases of severe hookworm infection.

Levamisole influences host defences by modulating cell-mediated immune responses; it restores depressed T-cell functions and has been described as an immunostimulant, although stimulation above normal levels does not seem to occur. It has been tried in many disorders, including bacterial and viral infections and rheumatic disorders, although in these conditions results have not been encouraging.

Levamisole has also been used as an adjunct in patients with malignant disease, although it is not clear that any response is due to its action on the immune system. Adjuvant treatment with levamisole and fluorouracil has been given to reduce recurrence after resection of adenocarcinoma of the colon with regional lymph node involvement (but see Malignant Neoplasms, p. 159.1).

Reviews.
1. Amery WKP, Bruynseels JPJM. Levamisole, the story and the lessons. *Int J Immunopharmacol* 1992; 14: 481–6.
2. Scheinfeld N, *et al.* Levamisole in dermatology: a review. *Am J Clin Dermatol* 2004; 5: 97–104.

Administration in children. Levamisole may be given orally to children for the treatment of ascariasis, hookworm infections, and mixed ascariasis and hookworm infections. Doses used are the same by weight as those used for adults (see above).

Hepatitis B. The CDC recommends that all dialysis patients be vaccinated against hepatitis B virus (HBV) because their potential exposure to blood, frequent transfusions, and sharing of dialysis equipment increases their risk of blood-borne viruses such as hepatitis B. However, the immune response to hepatitis B vaccination is impaired among those with chronic kidney disease. Levamisole is an immune modulator and meta-analyses[1,2] have shown that it has significant benefit as an adjuvant to HBV vaccination for upregulation of defective immune function in patients with chronic renal insufficiency.

1. Alavian SM, Tabatabaei SV. Effects of oral levamisole as an adjuvant to hepatitis B vaccine in adults with end-stage renal disease: a meta-analysis of controlled clinical trials. *Clin Ther* 2010; 32: 1–10.
2. Fabrizi F, *et al.* Meta-analysis: levamisole improves the immune response to hepatitis B vaccine in dialysis patients. *Aliment Pharmacol Ther* 2010; 32: 756–62.

Malignant neoplasms. Levamisole has been tried in the adjuvant treatment of various malignant neoplasms[1,2] with conflicting results. Based on the results of early adjuvant studies,[3-5] levamisole was formerly used with fluorouracil in patients with colorectal cancer, particularly in the USA. However, adjuvant levamisole alone was no more effective than placebo in 1 study,[6] and more recent studies have indicated that levamisole is no more effective than placebo when added to fluorouracil,[7] or to fluorouracil plus folinic acid.[8] For current management of colorectal cancer see p. 706.3.

1. Spreafico F. Use of levamisole in cancer patients. *Drugs* 1980; 20: 105–16.
2. Amery WK, Butterworth BS. Review/commentary: the dosage regimen of levamisole in cancer: is it related to efficacy and safety? *Int J Immunopharmacol* 1983; 5: 1–9.
3. Laurie JA, *et al.* Surgical adjuvant therapy of large-bowel carcinoma: an evaluation of levamisole and the combination of levamisole and fluorouracil: the North Central Cancer Treatment Group and the Mayo Clinic. *J Clin Oncol* 1989; 7: 1447–56.
4. Moertel CG, *et al.* Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *N Engl J Med* 1990; 322: 352–8.
5. Moertel CG, *et al.* Fluorouracil plus levamisole as effective adjuvant therapy after resection of stage III colon carcinoma: a final report. *Ann Intern Med* 1995; 122: 321–6.
6. Chlebowski RT, *et al.* Long-term survival following levamisole or placebo adjuvant treatment of colorectal cancer: a Western Cancer Study Group trial. *Oncology* 1988; 45: 141–3.
7. QUASAR Collaborative Group. Comparison of fluorouracil with additional levamisole, higher-dose folinic acid, or both, as adjuvant chemotherapy for colorectal cancer: a randomised trial. *Lancet* 2000; 355: 1588–96.
8. Wolmark N, *et al.* Clinical trial to assess the relative efficacy of fluorouracil and leucovorin, fluorouracil and levamisole, and fluorouracil, leucovorin, and levamisole in patients with Dukes' B and C carcinoma of the colon: results from National Surgical Adjuvant Breast and Bowel Project C-04. *J Clin Oncol* 1999; 17: 3553–9.

Mouth ulceration. Levamisole might be beneficial in severe mouth ulceration (p. 1814.2) but is limited by its adverse effects. A review[1] of its use in recurrent aphthous stomatitis indicated that beneficial results have been reported with levamisole in open studies, but results of double-blind studies have been conflicting. Nevertheless, there have been patients with severe recurrent aphthous stomatitis refractory to all other modes of treatment who have responded to levamisole. Dosage has been with 150 mg daily in divided doses given for 3 days at the first sign of ulceration, followed by 11 days without treatment, repeated as necessary. A small controlled study[2] indicated that it was ineffective in the prevention of recurrent aphthous stomatitis.

1. Miller MF. Use of levamisole in recurrent aphthous stomatitis. *Drugs* 1980; 20: 131–6.

2. Weckx LLM, *et al.* Levamisol não previne lesões de estomatite aftosa recorrente: um ensaio clínico randomizado, duplo-cego e controlado por placebo. *Rev Assoc Med Bras* 2009; 55: 132–8.

Renal disorders. In a randomised double-blind study, children with frequently relapsing corticosteroid-sensitive and corticosteroid-dependent nephrotic syndrome were given placebo or levamisole 2.5 mg/kg on alternate days and corticosteroid therapy was gradually withdrawn.[1] Of 31 children being treated with levamisole, 14 were still in remission 112 days after the start of the study compared with 4 of 30 receiving placebo. An evaluation of 3 randomised, controlled studies,[2] including this study, found that levamisole reduces the risk of relapse during treatment but no conclusion could be reached on its corticosteroid-sparing effect. There have been similar reports of adjunctive use in children with nephrotic syndrome,[3-7] but its place in therapy remains unknown. For a discussion of the treatment of glomerular kidney disorders, including the nephrotic syndrome, see p. 1604.3.

1. British Association for Paediatric Nephrology. Levamisole for corticosteroid-dependent nephrotic syndrome in childhood. *Lancet* 1991; 337: 1555–7.
2. Davin JC, Merkus MP. Levamisole in steroid-sensitive nephrotic syndrome of childhood: the lost paradise? *Pediatr Nephrol* 2005; 20: 10–4.
3. Donia AF, *et al.* Levamisole: adjunctive therapy in steroid dependent minimal change nephrotic children. *Pediatr Nephrol* 2002; 17: 355–8.
4. Pu LS, *et al.* Levamisole in steroid-sensitive nephrotic syndrome children with frequent relapses and/or steroid dependency: comparison of daily and every-other-day usage. *Nephron Clin Pract* 2004; 97: c137–c141.
5. Sümegi V, *et al.* Long-term effects of levamisole treatment in childhood nephrotic syndrome. *Pediatr Nephrol* 2004; 19: 1354–60.
6. Al-Saran K, *et al.* Experience with levamisole in frequently relapsing, steroid-dependent nephrotic syndrome. *Pediatr Nephrol* 2006; 21: 201–5.
7. Boyer O, *et al.* Short- and long-term efficacy of levamisole as adjunctive therapy in childhood nephrotic syndrome. *Pediatr Nephrol* 2008; 23: 575–80.

Vitiligo. In a study[1] involving 36 patients with limited slow-spreading vitiligo, response to levamisole treatment occurred in 34 within 2 to 4 months. Patients received 150 mg of oral levamisole daily on 2 consecutive days each week. Patients who were additionally treated with topical fluocinolone or clobetasol had higher rates of repigmentation. A later controlled study[2] involving 43 patients reported less benefit.

The usual treatment of vitiligo is discussed under Pigmentation Disorders, p. 1687.2.

1. Pasricha JS, Khera V. Effect of prolonged treatment with levamisole on vitiligo with limited and slow-spreading disease. *Int J Dermatol* 1994; 33: 584–7.
2. Agarwal S, *et al.* A randomized placebo-controlled double-blind study of levamisole in the treatment of limited and slowly spreading vitiligo. *Br J Dermatol* 2005; 153: 163–6.

Adverse Effects

When levamisole is used as an immunostimulant and given for longer periods, adverse effects are more frequent and diverse and, in common with other immunomodulators, may sometimes result from exacerbation of the primary underlying disease. Adverse effects associated especially with the more prolonged use of levamisole have included: hypersensitivity reactions such as fever, a flu-like syndrome, arthralgia, muscle pain, rashes, and cutaneous vasculitis; CNS effects including headache, insomnia, dizziness, and convulsions; haematological abnormalities such as agranulocytosis, leucopenia, and thrombocytopenia; and gastrointestinal disturbances, including an abnormal taste in the mouth. In many countries levamisole has been withdrawn from the market and is rarely used as an immunomodulator because of its severe adverse effects such as agranulocytosis and vasculitis. Levamisole has been added to cocaine as an adulterant and there are reports of these adverse effects among cocaine users (see under Abuse, p. 159.3).

Levamisole is, however, still available in some countries for the treatment of worm infections. When given in single doses for the treatment of ascariasis or other worm infections, levamisole is generally well tolerated and adverse effects are usually limited to nausea, vomiting, diarrhoea, abdominal pain, dizziness, and headache.

Incidence of adverse effects. In a review[1] (by the manufacturers) of 46 controlled studies in which 2635 cancer patients received adjuvant levamisole treatment, most patients received levamisole on 3 consecutive days every 2 weeks (1102 patients) or on 2 consecutive days every week (1156 patients), usually in a daily dose of 150 mg. Levamisole caused several adverse effects, such as rash, nausea, vomiting, and a metallic or bitter taste in the mouth, which although troublesome were relatively trivial and often regressed during therapy or disappeared on cessation of therapy. A total of 38 patients developed agranulocytosis and of these 36 had received weekly treatment. Several contracted possible life-threatening infections and 2 died of septic shock.

1. Amery WK, Butterworth BS. Review/commentary: the dosage regimen of levamisole in cancer: is it related to efficacy and safety? *Int J Immunopharmacol* 1983; 5: 1–9.

Effects on the endocrine system. Rechallenge confirmed that levamisole was responsible for inappropriate antidiuretic hormone syndrome in a patient receiving levamisole with fluorouracil.[1]

1. Tweedy CR, *et al.* Levamisole-induced syndrome of inappropriate antidiuretic hormone. *N Engl J Med* 1992; 326: 1164.

Effects on the liver. Elevated aspartate aminotransferase concentrations in 2 of 11 patients given levamisole for recurrent pyoderma suggested liver toxicity, a very rarely occurring adverse effect.[1] In a later report, liver enzyme concentrations were raised in a 14-year-old boy treated with levamisole for minimal change nephrotic syndrome.[2]

1. Papageorgiou P, *et al.* Levamisole in chronic pyoderma. *J Clin Lab Immunol* 1982; 8: 121–7.
2. Bulugahapitiya DTD. Liver toxicity in a nephrotic patient treated with levamisole. *Arch Dis Child* 1997; 76: 289.

Effects on the nervous system. Reports[1,2] of inflammatory leukoencephalopathy were associated with the use of fluorouracil and levamisole in 4 patients being treated for adenocarcinoma of the colon. Active demyelination was found in 2 patients.[1] Clinical improvement occurred when chemotherapy was stopped; 3 patients were treated with corticosteroids.[1] A similar syndrome has been reported in a patient with a history of hepatitis C given levamisole alone.[3]

1. Hook CC, *et al.* Multifocal inflammatory leukoencephalopathy with 5-fluorouracil and levamisole. *Ann Neurol* 1992; 31: 262–7.
2. Kimmel DW, Schutt AJ. Multifocal leukoencephalopathy: occurrence during 5-fluorouracil and levamisole therapy and resolution after discontinuation of chemotherapy. *Mayo Clin Proc* 1993; 68: 363–5.
3. Lucia P, *et al.* Multifocal leucoencephalopathy induced by levamisole. *Lancet* 1996; 348: 1450.

Precautions

The use of levamisole should be avoided in patients with pre-existing blood disorders. Patients given levamisole with fluorouracil should undergo appropriate monitoring of haematological and hepatic function.

Abuse. Cases of severe neutropenia and agranulocytosis associated with abuse of cocaine tainted with levamisole have been reported.[1,2] Necrotising vasculitides,[3] including retiform purpura[4] have been associated with abuse of such mixtures.[3] Fatalities have been reported.[5]

The purpose of adulterating cocaine with levamisole is unclear, but it is thought that it might be linked to a report of metabolism of levamisole to aminorex in racehorses. Aminorex and related compounds (specifically its analogue 4-methylaminorex) have high abuse potential because of their amfetamine-like pharmacological activity. Similar metabolism has since been reported in humans.[6]

1. Knowles L, *et al.* Levamisole tainted cocaine causing severe neutropenia in Alberta and British Columbia. *Harm Reduct J* 2009; 6: 30.
2. CDC. Agranulocytosis associated with cocaine use — four states, March 2008–November 2009. *MMWR* 2009; 58: 1381–5. Also available at: http://www.cdc.gov/mmwr/PDF/wk/mm5849.pdf (accessed 18/05/10)
3. Bradford M, *et al.* Bilateral necrosis of earlobes and cheeks: another complication of cocaine contaminated with levamisole. *Ann Intern Med* 2010; 152: 758–9.
4. Geller L, *et al.* Retiform purpura: a new stigmata of illicit drug use? *Dermatol Online J* 2011; 17: 7.
5. Duflou JA, *et al.* Levamisole as an adulterant in a cocaine overdose fatality. *Med J Aust* 2010; 192: 724.
6. Bertol E, *et al.* Determination of aminorex in human urine samples by GC-MS after use of levamisole. *J Pharm Biomed Anal* 2011; 55: 1186–9.

Rheumatoid arthritis. The presence of HLA B27 in seropositive rheumatoid arthritis is an important predisposing factor to the development of agranulocytosis with levamisole; it is recommended that the use of levamisole in this group should be avoided.[1]

1. Mielants H, Veys EM. A study of the hematological side effects of levamisole in rheumatoid arthritis with recommendations. *J Rheumatol* 1978; 5 (suppl 4): 77–83.

Sjögren's syndrome. A study was stopped after adverse effects appeared in 9 of 10 patients with rheumatoid arthritis and Sjögren's syndrome while receiving levamisole.[1] Levamisole should be given with caution, if at all, to patients with Sjögren's syndrome.

1. Balint G, *et al.* Sjögren's syndrome: a contraindication to levamisole treatment? *BMJ* 1977; 2: 1386–7.

Interactions

Alcohol. US licensed product information states that levamisole can produce a disulfiram-like reaction with *alcohol*.

Anticoagulants. For an increase in the activity of *warfarin* when given with levamisole and fluorouracil, see Interactions, Levamisole, under Warfarin, p. 1534.2.

Antiepileptics. For increased *phenytoin* concentrations when given with levamisole and fluorouracil, see Interactions, Antineoplastics, under Phenytoin, p. 544.1.

Pharmacokinetics

Levamisole is rapidly absorbed from the gastrointestinal tract and peak plasma concentrations occur within 1.5 to 2 hours. It is extensively metabolised in the liver. The plasma half-life for levamisole is 3 to 4 hours and for the metabolites is 16 hours. It is excreted mainly in the urine as metabolites and a small proportion in the faeces. About 70% of a dose is excreted in the urine over 3 days, with about 5% as unchanged levamisole.

References.

1. Luyckx M, *et al.* Pharmacokinetics of levamisole in healthy subjects and cancer patients. *Eur J Drug Metab Pharmacokinet* 1982; 7: 247–54.
2. Kouassi E, *et al.* Novel assay and pharmacokinetics of levamisole and p-hydroxylevamisole in human plasma and urine. *Biopharm Drug Dispos* 1986; 7: 71–89.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Levam; Meglum; *Braz.*: Ascaridil; *Gr.*: Ergamisol†; *Hong Kong*: Decaris; *Hung.*: Decaris; *India*: Dewormis; Dicaris; L-Vin; Levomol; Vermisol; Vizole†; *Indon.*: Askamex†; *Israel*: Ergamisol†; *Mex.*: Decaris; *Rus.*: Decaris (Декарис); *S.Afr.*: Ergamisol†; *Turk.*: Helmazol; Paraks; Sitraks; *Ukr.*: Decaris (Декарис).

Multi-ingredient Preparations. *China*: Hai Mi Ke (海密克); *India*: Eradix; Exit.

Pharmacopoeial Preparations

USP 36: Levamisole Hydrochloride Tablets.

Male Fern

Almindelig Mangeløv; Aspidium; Echter Wurmfarn; Erdei Pajzsika; Falguera Mascle; Farnwurzel; Felce Maschio; Feto Macho; Filix Mas; Fougère Mâle; Helecho Macho; Kapraď Samec; Kelminis Papartis; Kivikkoalvejuuri; Maarja-sõnajalg; Mannetjesvaren; Nerecznica Samcza; Ormetelg; Rhizoma Filicis Maris; Stóriburkni; Träjon; Щитовник Мужской.

CAS — 114-42-1 (flavaspidic acid).

ATC Herb — HP02DW5002 (Dryopteris filix-mas: *rhizome*). *UNII — 584YXJ3H6L* (Dryopteris filix-mas); *V4770BG68I* (Dryopteris filix-mas *leaf*); *C0ZK0RRF5X* (Dryopteris filix-mas *root*).

Pharmacopoeias. In *Chin.*

Profile

Male fern consists of the rhizome, frond-bases, and apical bud of *Dryopteris filix-mas* agg. (Polypodiaceae), collected late in the autumn, divested of the roots and dead portions and carefully dried, retaining the internal green colour. It contains not less than 1.5% of filicin. During storage the green colour of the interior gradually disappears, often after a lapse of 6 months, and such material is unfit for medicinal use.

Filicin is the mixture of ether-soluble substances obtained from male fern. Its activity is chiefly due to flavaspidic acid, a phloroglucinol derivative.

Male fern has anthelmintic properties and was formerly used as male fern extract (aspidium oleoresin) for the expulsion of tapeworms. However, male fern is highly toxic and has been superseded by other drugs.

Adverse effects include headache, nausea and vomiting, severe abdominal cramp, diarrhoea, dyspnoea, albuminuria, hyperbilirubinaemia, dizziness, tremors, convulsions, visual disturbances including blindness (possibly permanent), stimulation of uterine muscle, coma, respiratory failure, bradycardia, and cardiac failure. Fatalities have occurred.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Digestodoron; *Ger.*: Digestodoron; *S.Afr.*: Digestodoron†.

Homoeopathic Preparations. *Fr.*: Digestodoron; *Ger.*: Agaricus comp Phosphorus; Chelidonium comp; Phonix Thuja-Lachesis spag; Phonix Urtica-Arsenicum spag; *UK*: Digestodoron.

Mebendazole *(BAN, USAN, rINN)*

Mebendatsoli; Mebendazol; Mebendazolas; Mébendazole; Mebendazolum; R-17635; Мебендазол.

Methyl 5-benzoyl-1*H*-benzimidazol-2-ylcarbamate.

$C_{16}H_{13}N_3O_3$=295.3

CAS — 31431-39-7.

ATC — P02CA01.

ATC Vet — QP52AC09.

UNII — 81G6I5V05I.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 8: (Mebendazole). A white or almost white powder. It shows polymorphism. Practically insoluble in water, in alcohol, and in dichloromethane. Protect from light.

USP 36: (Mebendazole). A white to slightly yellow, almost odourless, powder. Practically insoluble in water, in alcohol, in chloroform, in ether, and in dilute mineral acids; freely soluble in formic acid.

Uses and Administration

Mebendazole, a benzimidazole carbamate derivative, is an anthelmintic with activity against most nematodes and some other worms; activity against some larval stages and ova has also been shown. It inhibits or destroys cytoplasmic microtubules in the worm's intestinal or absorptive cells. Inhibition of glucose uptake and depletion of glycogen stores follow as do other inhibitory effects leading to death of the worm within several days.

Mebendazole, being poorly absorbed from the gastrointestinal tract, is used mainly in the treatment of the intestinal nematode infections ascariasis (roundworm infection), enterobiasis (pinworm or threadworm infections), hookworm (ancylostomiasis and necatoriasis), and **trichuriasis** (whipworm infection); it is useful in mixed infections. During treatment with mebendazole, migration of worms with expulsion through the mouth and nose has occurred in some patients heavily infected with *Ascaris*. Mebendazole is also used in the treatment of capillariasis and trichostrongyliasis and has been used in strongyloidiasis. Other nematode infections which may respond to mebendazole are infection with the filarial nematode *Mansonella perstans*, and the tissue infections toxocariasis and trichinosis. Mebendazole has also been tried in high doses in the treatment of echinococcosis (hydatid disease). For discussions of these infections and their treatment, see under Choice of Anthelmintic, p. 143.1, and under the individual headings below.

Mebendazole is given orally. The usual dose for adults and children aged over 2 years with **enterobiasis** is 100 mg as a single dose, repeated if necessary after 2 to 3 weeks; for **ascariasis, hookworm infections**, and trichuriasis the usual dose in adults and children over 1 year is 100 mg twice daily for 3 days, although a single dose of 500 mg may be effective and this dose is also used in *mass treatment* programmes for hookworm infections and trichuriasis. For mass treatment control programmes against ascariasis, hookworm infections, and trichuriasis a dose of 500 mg is given as a single dose once or twice a year depending on the prevalence and intensity of infection among school-age children. For the treatment of **capillariasis** in adults and children over 2 years of age, mebendazole is given in a dose of 200 mg twice daily for 20 days; for *mass treatment* control programmes a dose of 500 mg is given as a single dose 4 times a year.

Administration in children. Mebendazole may be given orally to children for the treatment of intestinal nematode infections, including ascariasis, capillariasis, enterobiasis, hookworm infections, trichostrongyliasis, and trichuriasis. Doses used are the same as those used for adults (see above).

Although licensed product information indicates that mebendazole should not be given to children under 2 years of age, there have been no reports of toxicity or adverse effects when used in this group of children.[1] After a review of human and animal toxicological data, WHO concluded that there were no reasons to exclude children as young as 12 months from treatment with benzimidazoles, such as mebendazole and albendazole, and they recommend that children from one year of age should be included in systematic de-worming programmes;[2] doses given are the same as those used for adults.[3]

1. Montresor A, *et al.* Is the exclusion of children under 24 months from anthelmintic treatment justifiable? *Trans R Soc Trop Med Hyg* 2002; **96**: 197–9.
2. Anonymous. Benzimidazoles: use in children. *WHO Drug Inf* 2003; **17**: 29–30.
3. WHO. *Preventive chemotherapy in human helminthiasis: coordinated use of antihelminthic drugs in control interventions: a manual for health professionals and programme managers*. Geneva: WHO, 2006. Also available at: http://whqlibdoc.who.int/publications/2006/9241547103_eng.pdf (accessed 27/08/09)

Angiostrongyliasis. Mebendazole was formerly used for the treatment of angiostrongyliasis (p. 143.3) but current opinion is that there is no convincing evidence to support its use.

Echinococcosis. Mebendazole has been used[1-9] in echinococcosis (p. 145.2), but albendazole is generally preferred. The usual oral dose of mebendazole in cystic echinococcosis is 40 to 50 mg/kg daily for at least 3 to 6 months.[8] A similar dose is used as an adjuvant to surgery. For alveolar echinococcosis, the dose is adjusted after 4 weeks to produce a plasma concentration of at least 250 nanomoles/litre (74 nanograms/mL), although adults should not be given more than 6 g daily. Treatment is continued for at least 2 years after radical surgery, or indefinitely in inoperable cases.

1. Ammann RW, *et al.* Recurrence rate after discontinuation of long-term mebendazole therapy in alveolar echinococcosis (preliminary results). *Am J Trop Med Hyg* 1990; **43**: 506–15.
2. Messaritakis J, *et al.* High mebendazole doses in pulmonary and hepatic hydatid disease. *Arch Dis Child* 1991; **66**: 532–3.
3. Teggi A, *et al.* Therapy of human hydatid disease with mebendazole and albendazole. *Antimicrob Agents Chemother* 1993; **37**: 1679–84.
4. Gökmen A, *et al.* Treatment of hydatid disease in childhood with mebendazole. *Eur Respir J* 1993; **6**: 253–7.
5. Ammann RW, *et al.* Effect of chemotherapy on the larval mass and the long-term course of alveolar echinococcosis. *Hepatology* 1994; **19**: 735–42.
6. Erdinçler P, *et al.* The role of mebendazole in the surgical treatment of central nervous system hydatid disease. *Br J Neurosurg* 1997; **11**: 116–20.
7. Vutova K, *et al.* Effect of mebendazole on human cystic echinococcosis: the role of dosage and treatment duration. *Ann Trop Med Parasitol* 1999; **93**: 357–65.
8. WHO Informal Working Group on Echinococcosis. Guidelines for treatment of cystic and alveolar echinococcosis in humans. *Bull WHO* 1996; **74**: 231–42.
9. Smego RA, *et al.* Percutaneous aspiration-injection-reaspiration drainage plus albendazole or mebendazole for hepatic cystic echinococcosis: a meta-analysis. *Clin Infect Dis* 2003; **37**: 1073–83.

Giardiasis. For mention of the use of mebendazole for the treatment of giardiasis, see p. 923.2.

Loiasis. In those patients with a heavy or dense microfilarial load who are at risk for serious adverse effects from diethylcarbamazine, alternative drugs such as mebendazole have been given. An [oral] dose of 300 mg daily for several weeks was effective in slowly decreasing the microfilarial load.[1]

1. Padgett JJ, Jacobsen KH. Loiasis: African eye worm. *Trans R Soc Trop Med Hyg* 2008; **102**: 983–9.

Mansonella infections. Mebendazole, given orally at a dose of 100 mg twice daily for 30 days, is one of the drugs that has been suggested for the treatment of infections with *Mansonella perstans* (p. 147.2). Some patients have responded to mebendazole with levamisole,[1,2] diethylcarbamazine,[3] or to mebendazole alone.[3,4]

1. Maertens K, Wery M. Effect of mebendazole and levamisole on Onchocerca volvulus and Dipetalonema perstans. *Trans R Soc Trop Med Hyg* 1975; **69**: 359–60.
2. Bernberg HC, *et al.* The combined treatment with levamisole and mebendazole for a perstans-like filarial infection in Rhodesia. *Trans R Soc Trop Med Hyg* 1979; **73**: 233–4.
3. Bregani ER, *et al.* Comparison of different anthelmintic drug regimens against Mansonella perstans filariasis. *Trans R Soc Trop Med Hyg* 2006; **100**: 458–63.
4. Wahlgren M, Frolov I. Treatment of Dipetalonema perstans infections with mebendazole. *Trans R Soc Trop Med Hyg* 1983; **77**: 422–3.

Strongyloidiasis. Mebendazole has been used for the treatment of strongyloidiasis (p. 148.2), but needs to be given for longer periods than albendazole to control autoinfection, so that, of the two, albendazole is preferred.[1-3]

1. Wilson KH, Kauffman CA. Persistent Strongyloides stercoralis in a blind loop of the bowel: successful treatment with mebendazole. *Arch Intern Med* 1983; **143**: 357–8.
2. Mravak S, *et al.* Treatment of strongyloidiasis with mebendazole. *Acta Trop (Basel)* 1983; **40**: 93–4.
3. Pelletier LL, Baker CB. Treatment failures following mebendazole therapy for chronic strongyloidiasis. *J Infect Dis* 1987; **156**: 532–3.

Syngamosis. Mebendazole has been used successfully[1] to treat syngamosis (p. 148.2).

1. Timmons RF, *et al.* Infection of the respiratory tract with Mammomanogamus (Syngamus) laryngeus: a new case in Largo, Florida, and a summary of previously reported cases. *Am Rev Respir Dis* 1983; **128**: 566–9.

Toxocariasis. Mebendazole has been used in the treatment of toxocariasis (p. 148.3). In comparative studies, mebendazole has been reported to produce similar improvements to those obtained with tiabendazole[1] and with diethylcarbamazine,[2] in each case with a lower incidence of adverse effects. An oral dose of 100 to 200 mg twice daily for 5 days has been recommended, however, the optimum duration of therapy is unknown and some would treat for 20 days.[3]

1. Magnaval JF, Charlet JP. Efficacité comparée du thiabendazole et du mébendazole dans le traitement de la toxocarose. *Therapie* 1987; **42**: 541–4.
2. Magnaval J-F. Comparative efficacy of diethylcarbamazine and mebendazole for the treatment of human toxocariasis. *Parasitology* 1995; **110**: 529–33.
3. Abramowicz M, ed. *Drugs for parasitic infections*. 3rd ed. New Rochelle NY: The Medical Letter,2013.

Trichinosis. Mebendazole is used for the treatment of trichinosis (p. 148.3) in some countries. An oral dose of 200 to 400 mg three times a day for 3 days followed by 400 to 500 mg three times a day for 10 days has been recommended.[1]

1. Gottstein B, *et al.* Epidemiology, diagnosis, treatment, and control of trichinellosis. *Clin Microbiol Rev* 2009; **22**: 127–45.

Adverse Effects

Since mebendazole is poorly absorbed from the gastrointestinal tract at the usual therapeutic doses, adverse effects have generally been restricted to gastrointestinal disturbances, such as transient abdominal pain and diarrhoea, and have tended to occur in patients being treated for heavy intestinal infection. Headache and dizziness have been reported. Adverse effects have been reported more frequently with the high doses tried in echinococcosis and have included allergic reactions, raised liver enzyme values, alopecia, and bone marrow depression.

Incidence of adverse effects. In the first phase[1] of WHO-coordinated multicentre studies on the treatment of echinococcosis (hydatid disease) involving *Echinococcus granulosus* or *E. multilocularis*, the most frequent adverse effects in the 139 patients given *high-dose* mebendazole, generally for 3 months, were reduced leucocyte count (25 patients), gastrointestinal symptoms (22 patients), and raised serum-transaminase values (22 patients). Other adverse effects were allergic conditions such as fever and skin reactions (4 patients), CNS symptoms including headache (6 patients), and loss of hair (7 patients). Seven patients stopped treatment because of adverse effects.

The second phase of studies[2] compared albendazole with mebendazole in more prolonged high-dosage schedules for cystic *E. granulosus* infection. Adverse effects were similar to those reported with the first phase. However, in the first phase the allergic consequences of the 14 ruptured lung cysts and the 4 ruptured liver cysts that occurred with mebendazole were not reported. In the second phase, 2 patients suffered anaphylactic shock as a result of rupture of a lung cyst and a cyst in the abdominal cavity. These 2 patients were withdrawn from mebendazole treatment, as were another 4 patients as a consequence of their adverse reactions, although in 3 the withdrawal was only temporary.

Although albendazole is preferred to mebendazole in the treatment of echinococcosis, if either drug is used there should be constant medical supervision with regular monitoring of serum-transaminase concentrations and of leucocyte and platelet counts. Patients with liver damage should be treated with reduced doses of benzimidazole carbamates, if at all.[2]

1. Davis A, *et al.* Multicentre clinical trials of benzimidazolecarbamates in human echinococcosis. *Bull WHO* 1986; **64**: 383–8.
2. Davis A, *et al.* Multicentre clinical trials of benzimidazolecarbamates in human cystic echinococcosis (phase 2). *Bull WHO* 1989; **67**: 503–8.

Overdosage. Respiratory arrest and tachyarrhythmia associated with continuous convulsions were reported[1] in an 8-week-old infant after accidental poisoning with mebendazole. Treatment by exchange transfusion and anticonvulsants was successful.

1. el Kalla S, Menon NS. Mebendazole poisoning in infancy. *Ann Trop Paediatr* 1990; **10**: 313–14.

Precautions

Patients given high doses of mebendazole, such as those with echinococcosis, should be supervised closely with blood counts and liver function being monitored; such high-dose therapy may be inappropriate in those with hepatic impairment (see under Incidence of Adverse Effects, above).

Monitoring drug concentrations. In a retrospective analysis of patients given high doses of mebendazole for echinococcosis,[1] no relationship was found between dose and plasma concentration of mebendazole and considerable intra- and interindividual variation in plasma concentrations was seen, emphasising the need for repeated monitoring. Several patients appeared to have what were considered to be subtherapeutic plasma concentrations.

1. Luder PJ, *et al.* Treatment of hydatid disease with high oral doses of mebendazole: long-term follow-up of plasma mebendazole levels and drug interactions. *Eur J Clin Pharmacol* 1986; **31**: 443–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mebendazole as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Pregnancy. Mebendazole is teratogenic in *rats* and there are no adequate and well controlled studies in human pregnancy. Mebendazole is therefore usually contra-indicated during pregnancy. However, US licensed product information notes that in a survey of a limited number of pregnant women who had inadvertently taken mebendazole during the first trimester, the incidence of malformation and spontaneous abortion was no greater than that seen in the general population. The UK *National Teratology Information Service* (UKTIS) also considers that

the available data on the use of mebendazole in pregnancy does not show a significantly increased risk of congenital malformations; the rate of abnormalities present in the collected data was higher than expected, however, no specific pattern of defects was seen. UKTIS suggests that mebendazole may be given after the first trimester of pregnancy for the treatment of pinworms if hygiene measures are ineffective; it may be also be given for the treatment of hookworm where the benefit of treatment, even during the first trimester, could outweigh any risks.[3] This latter recommendation is supported by a randomised, double-blind, study undertaken in Peru (in a highly hookworm-endemic area),[2] among 1042 women in their second trimester of pregnancy, which compared mebendazole (500 mg given as a single oral dose) plus iron supplementation with placebo plus iron supplementation. There were no statistically significant differences in the numbers of congenital malformations, spontaneous abortions, still-births, or premature deliveries seen between the groups. However, the frequency of very low birth-weight infants decreased in those given mebendazole.

1. National Teratology Information Service. Use of mebendazole in pregnancy (issued July 2011). Available at: http:// www.toxbase.org/upload/Pregnancy%20pdfs/Mebendazole%202011.pdf (accessed 20/08/13)
2. Larocque R, *et al.* A double-blind randomized controlled trial of antenatal mebendazole to reduce low birthweight in a hookworm-endemic area of Peru. *Trop Med Int Health* 2006; 11: 1485–95.

Interactions

Antiepileptics. *Phenytoin* or *carbamazepine* have been reported to lower plasma-mebendazole concentrations in patients receiving high doses for echinococcosis, presumably as a result of enzyme induction; *valproate* had no such effect.[1]

1. Luder PJ, *et al.* Treatment of hydatid disease with high oral doses of mebendazole: long-term follow-up of plasma mebendazole levels and drug interactions. *Eur J Clin Pharmacol* 1986; 31: 443–8.

Histamine H_2-antagonists. Plasma concentrations of mebendazole have been raised when the enzyme inhibitor *cimetidine* was also given, and this has resulted in the resolution of previously unresponsive hepatic hydatid cysts.[1]

1. Bekhti A, Pirotte J. Cimetidine increases serum mebendazole concentrations: implications for treatment of hepatic hydatid cysts. *Br J Clin Pharmacol* 1987; 24: 390–2.

Pharmacokinetics

Mebendazole is poorly absorbed from the gastrointestinal tract and undergoes extensive first-pass metabolism in the liver. Bioavailability after usual oral doses is therefore low but may be increased by taking mebendazole with a fatty meal. Peak plasma concentrations generally occur after 1.5 to 7.25 hours and show wide interpatient variation. The drug crosses the blood-brain barrier. Mebendazole, the conjugated forms of mebendazole, and its metabolites are excreted in the urine and bile. The apparent elimination half-life after an oral dose is 3 to 6 hours.

Mebendazole is highly protein bound (about 90 to 95%).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Dazomet; Helmint; Mebutar; Nemasole; Tesical; Tru M; ***Austral.***: Chemists Own De Worm; Combantrin-1 with Mebendazole; Vermox; ***Austria***: Pantelmin; ***Belg.***: Docmebenda†; Vermox; ***Braz.***: Belmirax; Ductelmin; Geophagol; Kindelmin†; Mebental; Medazol; Menbel; Moben†; Multizol; Necamin; Neo Mebend; Novelmin; Panfugan; Pantelmin; Pluriverm†; Probendazol†; Sirben; Vermiben; Vermoplex; Vermoral; Verzol; ***Canad.***: Vermox; ***Chile***: Diacor; ***China***: Vermox (安乐士); Cz.: Vermox; ***Denm.***: Vermox; ***Ger.***: Surfont; Vermox; ***Gr.***: Cecurin; Septinalis; Vermox; ***Hong Kong***: Mebenzole†; Vermox; ***Hung.***: Vermox; ***India***: Eben; Elmin; Helmintol; Idibend; Kit Kat; Lupimeb; Mebazole; Mebex; Mendazole; Neomex; Wormin; ***Indon.***: Gavox†; Vermox; ***Irl.***: Vermox; ***Israel***: Vermox; ***Ital.***: Vermox; ***Malaysia***: Quemox; Thelmox; Vermox; ***Mex.***: Amatol; Bensolmin; Bestelar; Daben; Diazolen; Edivertin; Exbenzol; Exteny; Panciadazol; Hedazol; L-Ombrix; Lumbicid; Meb-Overoid; Mebelmin†; Mebendicin; Mebensole; Mebentiasis; Mebentral; Nemapres; Panvermin†; Profenzol; Revapol†; Vermicol; Vermidil†; Vermin-Dazol; Vermox; Vertizole; ***Neth.***: Anti-Worm†; Kruidvat Anti-worm; Madicure; Trekpleister Anti-Worm; Vermox; ***Norw.***: Vermox; ***NZ***: Combantrin-1; Vermox; ***Philipp.***: Antiox; Helmacon; Wormex; ***Pol.***: Vermox; ***Port.***: Pantelmin; Toloxim; ***Rus.***: Vermox (Вермокс); Wormin (Вормин); ***S.Afr.***: Adco-Wormex; Cipex; D-Worm; Rioworm; Rolab-Anthex†; Vermox; Wormgo; Wormstop; ***Spain***: Lomper; Sufil; ***Swed.***: Vermox; ***Switz.***: Vermox; ***Thai.***: Alworm; Anti-Worm; Benda; Bendazole; Benfu†; Big-Ben; Drivermide; Fuben; Fugacar; Hero-Benson; KB Bendazole; Masaworm-1; Meba; Meben; Mebenda-P; Medazole; Quemox; Rid-O-Worm; Vagaka; Warca; Wormob†; ***Turk.***: Vermazol; Versid; ***UAE***: Mebzol; ***UK***: Boots Threadworm Tablets 2 Years Plus; Ovex; Pripsen†; Vermox; ***USA***: Vermox; ***Venez.***: Bendacor; Bendamen; Eprofil; Vermalon.

Multi-ingredient Preparations. *Arg.*: Aduar; Helmint Compuesto; Mebutar Compuesto; Tru Compuesto; ***Braz.***: Exelmin; Forverm†; Helmiben; Neovermin; Profium†; ***China***: Hai Mi Ke (海蜜克); ***India***: Exit; Mebex Plus; ***Mex.***: Amoebriz; Bensolmin Complex; Mebeciclol; Vermox-Plus; ***Ukr.***: Vermox (Вермокс).

Pharmacopoeial Preparations
USP 36: Mebendazole Tablets.

Melarsomine *(rINN)*

Melaminylthioarsenite; Melarsomina; Mélarsomine; Melarsominum; RM-110; Меларсомин.

Bis(2-aminoethyl) *p*-[(4,6-diamino-*s*-triazin-2-yl)amino]dithiobenzenearsonite.

$C_{13}H_{21}AsN_8S_2$=428.4

CAS — 128470-15-5 (melarsomine); 89141-50-4 (melarsomine dihydrochloride).

ATC Vet — QP51AD06.

UNII — 374GJ0S41A.

NOTE. The names Cymelarsan and Immiticide have been used as trade marks for melarsomine dihydrochloride.

Profile

Melarsomine is a trivalent arsenical derivative used in veterinary medicine for the control of canine heartworm (dirofilariasis).

Metrifonate *(BAN, rINN)*

Bayer-L-1359; DETF; Metrifonaat; Metrifonaatti; Metrifonat; Metrifonát; Metrifonatas; Métrifonate; Metrifonato; Metrifonatum; Metriphonate; Trichlorfon (USAN); Trichlorphon; Метрифонат.

Dimethyl 2,2,2-trichloro-1-hydroxyethylphosphonate.

$C_4H_8Cl_3O_4P$=257.4

CAS — 52-68-6.

ATC — P02BB01.

ATC Vet — QP52AB01; QP53AF02.

UNII — DBF2DG4G2K.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *US*.

Ph. Eur. 8: (Metrifonate). A white or almost white, crystalline powder. M.p. is between 76 degrees and 81 degrees. Freely soluble in water, in alcohol, and in acetone; very soluble in dichloromethane. Protect from light.

USP 36: (Metrifonate). A white crystalline powder. M.p. about 78 degrees with decomposition. Freely soluble in water, in alcohol, in acetone, in chloroform, in ether, and in benzene; very soluble in dichloromethane; very slightly soluble in hexane and in pentane. Decomposed by alkali. Store at a temperature not exceeding 25 degrees.

Uses and Administration

Metrifonate is an organophosphorus compound and is converted in the body to the active metabolite dichlorvos (p. 2152.3), an anticholinesterase.

Metrifonate has anthelmintic activity against *Schistosoma haematobium* and has been given orally as an alternative to praziquantel in the treatment of schistosomiasis due to *S. haematobium*. It has usually been given in three doses of 7.5 to 10 mg/kg at intervals of 2 weeks.

Metrifonate has also been used as an insecticide and is used in veterinary medicine as an ectoparasiticide and for the treatment of gastrointestinal roundworms.

Alzheimer's disease. Metrifonate, like some other cholinesterase inhibitors, has been tried in the treatment of Alzheimer's disease (see Dementia, p. 390.1). Clinical studies produced modest benefits but research was stopped after reports of muscle weakness, sometimes requiring respiratory support.[1]

1. López-Arrieta JM, Schneider L. Metrifonate for Alzheimer's disease. Available in The Cochrane Database of Systematic Reviews: Issue 2. Chichester: John Wiley; 2006 (accessed 23/07/10).

Schistosomiasis. While praziquantel is now the main treatment for schistosomiasis (p. 148.1), metrifonate has been given as an alternative for infection due to *Schistosoma haematobium*. Cure rates with standard doses in schistosomiasis control programmes ranged from 40 to more than 80%, with a reduction of more than 80% in egg counts among those not cured. Although praziquantel and metrifonate appeared to be of similar efficacy a systematic review failed to find studies comparing the two drugs when used in standard doses.[1] However, metrifonate's dosage schedule of 3 doses at intervals of 2 weeks has caused problems of patient compliance;[2] giving 5 mg/kg three times in one day has produced similar results to a standard dosage schedule.[3]

1. Danso-Appiah A, *et al.* Drugs for treating urinary schistosomiasis Available in The Cochrane Database of Systematic Reviews: Issue 3 Chichester: John Wiley; 2008 (accessed 29/07/10).
2. Aden Abdi Y, Gustafsson LL. Poor patient compliance reduces the efficacy of metrifonate treatment of *Schistosoma haematobium* in Somalia. *Eur J Clin Pharmacol* 1989; 36: 161–4.
3. Aden Abdi Y, Gustafsson LL. Field trial of the efficacy of a simplified and standard metrifonate treatments of *Schistosoma haematobium*. *Eur J Clin Pharmacol* 1989; 37: 371–4.

Adverse Effects, Treatment, and Precautions

Metrifonate is generally well tolerated, but may cause nausea, vomiting, abdominal pain, diarrhoea, headache, dizziness, and weakness.

It is an organophosphorus compound and because of its anticholinesterase properties depresses plasma-cholinesterase concentrations. For a description of the toxic effects of organophosphorus compounds and the treatment of acute poisoning, see Organophosphorus Insecticides, p. 2158.3. Atropine has been used to relieve cholinergic adverse effects without affecting metrifonate's activity against *Schistosoma haematobium*.

Anticholinesterase effects. Metrifonate depresses cholinesterase activity and there has been the occasional report of severe cholinergic adverse effects.[1] However, it does not usually give rise to troublesome effects at doses normally used, even though there may temporarily be almost complete inhibition of plasma cholinesterase and considerable inhibition of erythrocyte cholinesterase[2] (but see also under Alzheimer's Disease, above).

The environmental aspects of metrifonate usage have been considered by WHO.[3]

1. Jamnadas VP, Thomas JEP. Metriphonate and organophosphate poisoning. *Cent Afr J Med* 1979; 25: 130.
2. Pleština R, *et al.* Effect of metrifonate on blood cholinesterases in children during the treatment of schistosomiasis. *Bull WHO* 1972; 46: 747–59.
3. WHO. Trichlorfon. *Environmental Health Criteria 132*. Geneva: WHO, 1992. Available at: http://www.inchem.org/documents/ehc/ehc/ehc132.htm (accessed 16/07/08)

Handling. Bulk metrifonate is very toxic when inhaled, swallowed, or spilled on the skin. It can be removed from the skin by washing with soap and water. Contaminated material should be immersed in a 2% aqueous solution of sodium hydroxide for several hours.

Pregnancy. WHO reported[1] that metrifonate had not shown embryotoxicity or teratogenicity, but did not recommend the use of metrifonate in pregnant patients unless immediate intervention was essential. There has been a report of an infant born with massive hydrocephalus and a large meningomyelocele whose mother had been treated twice with metrifonate during the second month of pregnancy.[2] A possible link between congenital abnormalities and the use of metrifonate to eradicate fish parasites has also been postulated.[3]

1. WHO. The control of schistosomiasis: second report of the WHO expert committee. *WHO Tech Rep Ser 830* 1993. Available at: http://libdoc.who.int/trs/WHO_TRS_830.pdf (accessed 16/07/08)
2. Monson MH, Alexander K. Metrifonate in pregnancy. *Trans R Soc Trop Med Hyg* 1984; 78: 565.
3. Czeizel AE, *et al.* Environmental trichlorfon and cluster of congenital abnormalities. *Lancet* 1993; 341: 539–42.

Interactions

Patients treated with metrifonate should not be given depolarising neuromuscular blockers such as suxamethonium for at least 48 hours. The use of metrifonate should be avoided in those recently exposed to insecticides or other agricultural chemicals with anticholinesterase activity.

Pharmacokinetics

Metrifonate is absorbed after oral doses and some is converted to dichlorvos which is considered to be the active moiety. Plasma concentrations of dichlorvos are about 1% of those of metrifonate and peak concentrations of both substances occur within 2 hours. Excretion is via the kidney, mainly as glucuronides.

References.

1. Nordgren I, *et al.* Plasma levels of metrifonate and dichlorvos during treatment of schistosomiasis with Bilarcil. *Am J Trop Med Hyg* 1980; 29: 426–30.
2. Nordgren I, *et al.* Levels of metrifonate and dichlorvos in plasma and erythrocytes during treatment of schistosomiasis with Bilarcil. *Acta Pharmacol Toxicol (Copenh)* 1981; 49 (suppl V): 79–86.
3. Pettigrew LC, *et al.* Pharmacokinetics, pharmacodynamics, and safety of metrifonate in patients with Alzheimer's disease. *J Clin Pharmacol* 1998; 38: 236–45.

Milbemycin Oxime

CGA-179246; Milbemicina oxima; Milbemycinoxim; Мильбемицин Оксим.

A mixture of milbemycin A_4 5-oxime and milbemycin A_3 5-oxime.
CAS — 129496-10-2.
ATC Vet — QP54AB01.
UNII — 0502PUN0GT (milbemycin oxime); 053YPP1I9C (milbemycin A_3 5-oxime); 6ZWJ394628 (milbemycin A_4 5-oxime).

Profile

Milbemycin oxime is an anthelmintic used in veterinary medicine.

Morantel *(BAN, pINN)*

Moranteli; Morantelum; Морантел.
(*E*)-1,4,5,6-Tetrahydro-1-methyl-2-[2-(3-methyl-2-thienyl) vinyl]pyrimidine.
$C_{12}H_{16}N_2S$=220.3
CAS — 20574-50-9.
ATC Vet — QP52AF01.
UNII — 7NU031HAX5.

Morantel Citrate *(BANM, pINNM)*

Citrato de morantel; Morantel, Citrate de; Morantel, citrato de; Moranteli Citras; Морантела Цитрат.
$C_{12}H_{16}N_2S,C_6H_8O_7,H_2O$=430.5
CAS — 69525-81-1.
ATC Vet — QP52AF01.

NOTE. The name Exhelm has been used as a trade mark for morantel citrate.

Morantel Tartrate *(BANM, USAN, pINNM)*

CP-12009-18; Moranteelivetytartraatti; Morantel, hydrogénotartrate de; Morantel, Tartrate de; Morantel, tartrato de; Morantel-hidrogén-tartarát; Morantel-hydrogen-tartarát; Moranteli hydrogenotartras; Moranteli Tartras; Morantelvätetartrat; Tartrato de morantel; UK-2964-18; Морантела Тартрат.
$C_{12}H_{16}N_2S,C_4H_6O_6$=370.4
CAS — 26155-31-7.
ATC Vet — QP52AF01.
UNII — 5WF7E9QC3F.

Pharmacopoeias. In *Eur.* (see p. vii) and *US* for veterinary use only.

Ph. Eur. 8: (Morantel Hydrogen Tartrate for Veterinary Use; Morantel Tartrate BP(Vet) 2014). A white or pale yellow, crystalline powder. Very soluble in water and in alcohol; practically insoluble in ethyl acetate. A 1% solution in water has a pH of 3.3 to 3.9. Protect from light.

USP 36: (Morantel Tartrate). A white or pale yellow, crystalline powder. Very soluble in water and in alcohol; practically insoluble in ethyl acetate. pH of a 1% solution in water is between 2.8 and 3.9. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Profile

Morantel is an analogue of pyrantel. The citrate and the tartrate are used as anthelmintics in veterinary medicine for the treatment of gastrointestinal roundworms.

Moxidectin *(BAN, USAN, rINN)*

CL-301423; Moksidektiini; Moxidectina; Moxidectine; Moxidectinum; Moxidektin; Моксидектин.
(6*R*,15*S*)-5-*O*-Demethyl-28-deoxy-25-[(*E*)-1,3-dimethylbut-1-enyl]-6,28-epoxy-23-oxomilbemycin B (*E*)-23-*O*-methyloxime.
$C_{37}H_{53}NO_8$=639.8
CAS — 113507-06-5.
ATC Vet — QP54AB02.
UNII — NGU5H31YO9.

NOTE. The names Cydectin, Equest, and Zermex have been used as trade marks for moxidectin.

Pharmacopoeias. In *Eur.* (see p. vii) and *US* for veterinary use.

Ph. Eur. 8: (Moxidectin for Veterinary Use). A white or pale yellow, amorphous powder. Practically insoluble in water; very soluble in alcohol; slightly soluble in hexane.

USP 36: (Moxidectin). A white to pale yellow powder. Practically insoluble in water; very soluble in alcohol; slightly soluble in hexane. Store at a temperature of 2 degrees to 8 degrees. Protect from light.

Profile

Moxidectin is an anthelmintic used in veterinary medicine. It is also used as a systemic veterinary ectoparasiticide and for the treatment of intestinal roundworms and lungworms. It is under investigation for the treatment of human onchocerciasis.

References.
1. Cotreau MM, *et al.* The antiparasitic moxidectin: safety, tolerability, and pharmacokinetics in humans. *J Clin Pharmacol* 2003; **43**: 1108–15.
2. Korth-Bradley JM, *et al.* Excretion of moxidectin into breast milk and pharmacokinetics in healthy lactating women. *Antimicrob Agents Chemother* 2011; **55**: 5200–4.

Naftalofos *(BAN, USAN, rINN)*

Bay-9002; E-9002; ENT-25567; Naftalofós; Naftalofosum; Naphthalophos; Phthalophos; S-940; Нафталофос.
Diethyl naphthalimido-oxyphosphonate.
$C_{16}H_{16}NO_6P$=349.3
CAS — 1491-41-4.
ATC Vet — QP52AB06.
UNII — H5IT2P8H5I.

Profile

Naftalofos is an organophosphorus compound (see Organophosphorus Insecticides, p. 2158.3) used as an anthelmintic in veterinary medicine.

Netobimin *(BAN, USAN, rINN)*

Netobimina; Nétobimine; Netobiminum; Sch-32481; Нетобимин.
2-[3-Methoxycarbonyl-2-[2-nitro-5-(propylthio)phenyl]guanidino]ethanesulphonic acid.
$C_{14}H_{20}N_4O_7S_2$=420.5
CAS — 88255-01-0.
ATC Vet — QP52AC06.
UNII — U30C54N3MU.

Profile

Netobimin is a prodrug that is converted to albendazole (p. 149.1). It is used in veterinary medicine for the treatment of nematode, tapeworm, and fluke infections.

Niclosamide *(BAN, USAN, rINN)*

Anhydrous Niclosamide; Bay-2353; Niclosamid; Niclosamida; Niclosamida Anidra; Niclosamide anhydre; Niclosamidum; Niclosamidum anhydricum; Niklosamid; Niklosamid, vattenfri; Niklosamidi; Niklosamidi, vedetön; Niklozamid; Niklozamid bezvodny; Niklozamidas, bevandenis; Niklozamit; Phenasale; Vízmentes niklozamid; Никлозамид.
2′,5-Dichloro-4′-nitrosalicylanilide; 5-Chloro-*N*-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide.
$C_{13}H_8Cl_2N_2O_4$=327.1
CAS — 50-65-7.
ATC — P02DA01.
ATC Vet — QP52AG03.
UNII — 8KK8CQ2K8G.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Int. permits the anhydrous substance or the monohydrate under the title Niclosamide.

Ph. Eur. 8: (Niclosamide, Anhydrous). Yellowish-white to yellowish, fine crystals. Practically insoluble in water; slightly soluble in dehydrated alcohol; sparingly soluble in acetone. Store in airtight containers. Protect from light.

Niclosamide Monohydrate *(BANM, rINNM)*

Niclosamid-Monohydrat; Niclosamida Mono-hidratada; Niclosamida monohidrato; Niclosamide Monohydraté; Niclosamidum monohydricum; Niklosamid monohydrát; Niklosamidimonohydraatti; Niklosamidmonohydrat; Niklozamidas monohidratas; Niklozamid-monohidrát; Никлозамид Моногидрат.
$C_{13}H_8Cl_2N_2O_4,H_2O$=345.1
ATC — P02DA01.
UNII — 20Z25R1145.

Pharmacopoeias. In *Eur.* (see p. vii).

Int. permits the monohydrate or the anhydrous substance under the title Niclosamide.

Ph. Eur. 8: (Niclosamide Monohydrate). Yellowish, fine crystals. Practically insoluble in water; slightly soluble in dehydrated alcohol; sparingly soluble in acetone. Protect from light.

Uses and Administration

Niclosamide is an anthelmintic that is active against most tapeworms, including the beef tapeworm (*Taenia saginata*), the pork tapeworm (*T. solium*), the fish tapeworm (*Diphyllobothrium latum*) and the dog tapeworm (*Dipylidium caninum*); it has also been given for infections with the dwarf tapeworm, *Hymenolepis nana*. For discussions of the treatment of tapeworm infections, see Diphyllobothriasis, p. 145.1, Hymenolepiasis, p. 146.1, and Taeniasis, p. 148.2. The activity of niclosamide against these worms appears to be due to inhibition of mitochondrial oxidative phosphorylation; anaerobic ATP production is also affected.

Niclosamide is given as tablets, which must be chewed thoroughly before swallowing and washed down with water.

For infections with pork tapeworm a single 2-g dose is given after a light breakfast. Niclosamide is not active against the larval form (cysticerci) and, although the risk of inducing cysticercosis appears to be theoretical, a laxative is given about 2 hours after the dose to expel the killed worms and minimise the possibility of the migration of ova of *T. solium* into the stomach; an antiemetic may also be given before treatment.

For infections with beef or fish tapeworms the 2-g dose of niclosamide may be divided, with 1 g taken after breakfast and 1 g an hour later.

In dwarf-tapeworm infections an initial dose of 2 g has been given on the first day followed by 1 g daily for 6 days.

Unless expulsion of the worm is aided by a laxative, portions are voided in a partially digested form after treatment with niclosamide; the scolex is rarely identifiable.

For details of doses in children, see p. 163.1.

In schistosomiasis (p. 148.1), niclosamide is used as a molluscicide in water-treatment control programmes.

Administration in children. Niclosamide may be given orally to children for the treatment of most tapeworm infections. Children 2 to 6 years of age are given half the usual adult dose; those under 2 years of age are given one-quarter the usual adult dose. Children over 6 years of age are given the usual adult dose (see above).

Malignant neoplasms. Studies in *animals* and *in vitro* have suggested[1,2] that niclosamide may have therapeutic potential as an antineoplastic.

1. Jin Y, *et al.* Antineoplastic mechanisms of niclosamide in acute myelogenous leukemia stem cells: inactivation of the NF-κB pathway and generation of reactive oxygen species. *Cancer Res* 2010; **70**: 2516–27.
2. Sack U, *et al.* Novel effect of antihelminthic niclosamide on S100A4-mediated metastatic progression in colon cancer. *J Natl Cancer Inst* 2011; **103**: 1018–36.

Vector control. Reference[1] to the use of niclosamide ethanolamine (sometimes referred to as clonitralide) as a molluscicide in the management of schistosomiasis.

1. Yang G-J, *et al.* Molluscicidal efficacies of different formulations of niclosamide: result of meta-analysis of Chinese literature. *Parasit Vectors* 2010; **3**: 84.

Adverse Effects and Precautions

Gastrointestinal disturbances may occur occasionally with niclosamide. Lightheadedness and pruritus have been reported less frequently.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies niclosamide as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 06/10/11)

Pharmacokinetics

Niclosamide is not significantly absorbed from the gastrointestinal tract.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Yomesan; *Braz.*: Atenase; *Fin.*: Kontal; *Fr.*: Tredemine; *Ger.*: Yomesan; *Gr.*: Tredemine; Yomesan†; *Hong Kong*: Leo-99†; *India*: Niclosan; *Israel*: Yomesan†; *Ital.*: Yomesan; *Mex.*: Overoid†; *Neth.*: Yomesan; *S. Afr.*: Yomesan; *Swed.*: Yomesan; *Thai.*: CB-99; Leo-99†; Mano-verm; Shors Mesan†; Sinchoni; Sinper-Tabs; Telmitin; Topida; Unicide†; Utosamide; Yomesan; *Turk.*: Yomesan; *UK*: Yomesan.

Multi-ingredient Preparations. *Thai.*: Anson; Heroanson; Taeniacide; Zenda.

Pharmacopoeial Preparations
BP 2014: Niclosamide Tablets.

Nitroscanate *(BAN, USAN, rINN)*

CGA-23654; Nitroscanato; Nitroscanatum; Nitroskanaatti; Nitroskanat; Нитросканат.
4-(4-Nitrophenoxy)phenyl isothiocyanate.
$C_{13}H_8N_2O_3S$=272.3
CAS — 19881-18-6.
ATC Vet — QP52AX01.
UNII — P4IE5B6D6U.

NOTE. The name Troscan has been used as a trade mark for nitroscanate.

Profile

Nitroscanate is an isothiocyanate anthelmintic used in veterinary medicine for the treatment of gastrointestinal roundworm and tapeworm infections.

Nitroxinil *(BAN, rINN)*

Nitroxinilo; Nitroxinilum; Nitroxynil; Нитроксинил.
4-Hydroxy-3-iodo-5-nitrobenzonitrile.
$C_7H_3IN_2O_3$=290.0
CAS — 1689-89-0 (nitroxinil); 27917-82-4 (nitroxinil eglumine).
ATC Vet — QP52AG08.
UNII — 9L0EXQ7125.

NOTE. The name Trodax has been used as a trade mark for nitroxinil.

Pharmacopoeias. In *BP(Vet)*. Also in *Fr.* for veterinary use only.

BP(Vet) 2014: (Nitroxinil). A yellow to yellowish brown powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in ether; it dissolves in solutions of alkali hydroxides. Protect from light.

Profile

Nitroxinil is an anthelmintic used in veterinary medicine for the treatment of fascioliasis and some gastrointestinal roundworms in cattle and sheep.

Oxamniquine *(BAN, USAN, rINN)*

Oksamnichina; Oxamniquina; Oxamniquinum; UK-4271; Оксамнихин.
1,2,3,4-Tetrahydro-2-isopropylaminomethyl-7-nitro-6-quinolylmethanol.
$C_{14}H_{21}N_3O_3$=279.3
CAS — 21738-42-1.
ATC — P02BA02.
ATC Vet — QP52AA02.
UNII — 0O977R722D.

Pharmacopoeias. In *Fr.* and *Int.*

Uses and Administration

Oxamniquine is an anthelmintic used in the treatment of schistosomiasis caused by *Schistosoma mansoni*, but not by other *Schistosoma* spp. It causes worms to shift from the mesenteric veins to the liver where the male worms are retained; the female worms return to the mesentery, but can no longer release eggs. Resistance may occur.

Oxamniquine is given orally, preferably after food. Dosage depends on the geographical origin of the infection and total doses range from 15 mg/kg as a single dose to 60 mg/kg given over 2 to 3 days. A single dose of 15 mg/kg is recommended in West Africa, South America, and the Caribbean Islands; in East and Central Africa and the Arabian peninsula this dose should be increased to 30 mg/kg in 2 divided doses. A total dose of 60 mg/kg given over 2 to 3 days is recommended for Egypt and southern Africa but some experts recommend a total dose of 40 to 60 mg/kg given over 2 to 3 days for all African countries. A single dose should not exceed 20 mg/kg.

Schistosomiasis. Oxamniquine is an alternative to praziquantel for the treatment of schistosomiasis (p. 148.1) due to *Schistosoma mansoni*, although resistance has occurred, particularly in South America,[1] and it is somewhat less effective than praziquantel.[2] After the appropriate therapeutic dose of oxamniquine, cure rates of at least 60%, and often more than 90%, can be expected. Egg excretion in those not cured will be reduced by over 80%, and usually by over 90%, one year after treatment.[3]

1. WHO. The control of schistosomiasis: second report of the WHO expert committee. *WHO Tech Rep Ser 830* 1993. Available at: http://libdoc.who.int/trs/WHO_TRS_830.pdf (accessed 16/07/08)
2. Ferrari ML, *et al.* Efficacy of oxamniquine and praziquantel in the treatment of Schistosoma mansoni infection: a controlled trial. *Bull WHO* 2003; 81: 190–6.
3. WHO: The control of schistosomiasis: report of a WHO expert committee. *WHO Tech Rep Ser 728* 1985. Available at: http://libdoc.who.int/trs/WHO_TRS_728.pdf (accessed 16/07/08)

Adverse Effects

Oxamniquine causes severe pain at the injection site when given intramuscularly and is no longer given by this route.

It is generally well tolerated after oral doses, although dizziness with or without drowsiness occurs in at least a third of patients, beginning up to 3 hours after a dose and usually lasting for up to 6 hours. Headache and gastrointestinal effects such as nausea, vomiting, and diarrhoea are also common.

Hypersensitivity reactions including urticaria, pruritic skin rashes, and fever may occur. Liver enzyme values have been raised transiently in some patients. Epileptiform convulsions have been reported, especially in patients with a history of convulsive disorders. Hallucinations and excitement have occurred rarely.

A reddish discoloration of urine, probably due to a metabolite of oxamniquine, has been reported.

Effects on body temperature. A review[1] in 1987 noted that although a modest post-treatment rise in temperature had been reported occasionally, fever was not a common adverse effect of oxamniquine, except in Egypt where it appeared to be characteristic. The cause was unknown. Increased immune complexes and excretion of antigens occurred in only half the cases, there was no evidence that Egyptian patients metabolised the drug differently to produce a pyrogenic metabolite, and the effect had not been seen in other areas where a similar high-dose regimen was used.[1]

1. Foster R. A review of clinical experience with oxamniquine. *Trans R Soc Trop Med Hyg* 1987; 81: 55–9.

Effects on the nervous system. In 37 patients with *Schistosoma mansoni* infection treated successfully with oxamniquine,[1] dizziness and drowsiness were most common, but the most significant adverse effect was the development of EEG abnormalities in 6 of 34 patients whose pretreatment EEG was normal. Of the 3 patients with pre-existing EEG abnormalities, 1 suffered a tonic-clonic seizure during therapy as previously reported.[2] 1 did not suffer seizures, and the third received phenytoin prophylaxis during oxamniquine therapy. It was considered prudent to give antiepileptics before starting oxamniquine in patients with a history of seizure disorder. After completion of this study, a patient with no history of seizures suffered a tonic-clonic seizure 2 hours after each of the second and third doses of oxamniquine.

The main neuropsychiatric adverse effects seen in 180 Brazilian patients with *Schistosoma mansoni* infection treated with single oral doses of oxamniquine were: drowsiness (50.6%), dizziness (41.1%), headache (16.1%), temporary amnesia (2.2%), behavioural disturbances (1.7%), chills (1.1%), and seizures (1.1%).[3] An EEG was performed before and after treatment in 20 patients; there were alterations in 3 but they were not associated with neuropsychiatric changes.

1. Krajden S, *et al.* Safety and toxicity of oxamniquine in the treatment of Schistosoma mansoni infections, with particular reference to electroencephalographic abnormalities. *Am J Trop Med Hyg* 1983; 32: 1344–6.
2. Keystone JS. Seizures and electroencephalograph changes associated with oxamniquine therapy. *Am J Trop Med Hyg* 1978; 27: 360–2.
3. de Carvalho SA, *et al.* Neurotoxicidade do oxamniquine no tratamento da infeção humana pelo Schistosoma mansoni. *Rev Inst Med Trop Sao Paulo* 1985; 27: 132–42.

Precautions

Oxamniquine should be used with caution in patients with epilepsy or a history of convulsive disorders. Patients should be warned that oxamniquine can cause dizziness or drowsiness and if affected they should not drive or operate machinery.

Pharmacokinetics

Oxamniquine is readily absorbed after oral doses and peak plasma concentrations occur after 1 to 3 hours. The plasma half-life is 1 to 2.5 hours.

It is extensively metabolised to inactive metabolites, mainly the 6-carboxy derivative, which are excreted in the urine. About 70% of a dose of oxamniquine is excreted as the 6-carboxy metabolite within 12 hours of a dose; traces of the 2-carboxy metabolite have also been detected in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Mansil.

Oxantel Embonate *(BANM, rINNM)*

CP-14445-16; Embonato de oxantel; Oxantel, Embonate d'; Oxantel, embonato de; Oxantel Pamoate (USAN); Oxanteli Embonas; Оксантела Эмбонат.

(*E*)-3-[2-(1,4,5,6-Tetrahydro-1-methylpyrimidin-2-yl)vinyl] phenol 4,4'-methylenebis(3-hydroxy-2-naphthoate).
$C_{13}H_{16}N_2O$,$C_{23}H_{16}O_6$=604.7
CAS — 36531-26-7 (oxantel); 68813-55-8 (oxantel embonate); 42408-84-4 (oxantel embonate).
ATC — P02CC02.
UNII — UPY1D732T0.

Profile

Oxantel is an analogue of pyrantel that has been used as the embonate in the treatment of trichuriasis. It is used with pyrantel embonate for various intestinal nematode infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Indon.*: Quantrel†; *Philipp.*: Quantrel; *Venez.*: Dualid; Quantrel.

Oxfendazole *(BAN, USAN, rINN)*

Oksfendatsoli; Oxfendazol; Oxfendazolum; RS-8858; Оксфендазол.
Methyl 5-phenylsulphinyl-1*H*-benzimidazol-2-ylcarbamate.
$C_{15}H_{13}N_3O_3S$=315.3
CAS — 53716-50-0.
ATC Vet — QP52AC02.
UNII — OMP2H17F9E.

NOTE. The names Bovex, Endoworm, and Parafend have been used as trade marks for oxfendazole.

Pharmacopoeias. In *Eur.* (see p. vii) and *US* for veterinary use only.

Ph. Eur. 8: (Oxfendazole for Veterinary Use; Oxfendazole BP(Vet) 2014). A white or almost white powder. It shows polymorphism. Practically insoluble in water; slightly soluble in alcohol and in dichloromethane. Protect from light.

USP 36: (Oxfendazole). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol and in dichloromethane. Protect from light.

Profile

Oxfendazole is a benzimidazole carbamate anthelmintic structurally related to mebendazole (p. 158.3). It is used in veterinary medicine for the treatment of nematode and tapeworm infections.

Oxibendazole *(BAN, USAN, rINN)*

Oxibendazol; Oxibendazolum; SKF-30310; Оксибендазол.
Methyl 5-propoxy-1*H*-benzimidazol-2-ylcarbamate.
$C_{12}H_{15}N_3O_3$=249.3
CAS — 20559-55-1.
ATC Vet — QP52AC07.
UNII — 022N12KJ0X.

NOTE. The name Anthelcide has been used as a trade mark for oxibendazole.

Profile

Oxibendazole is a benzimidazole carbamate anthelmintic structurally related to mebendazole (p. 158.3). It is used in veterinary medicine for the treatment of nematode infections.

Oxyclozanide *(BAN, rINN)*

ICI-46683; Oxiclozanida; Oxyclozanidum; Оксиклозанид.
3,3',5,5',6-Pentachloro-2'-hydroxysalicylanilide.
$C_{13}H_6Cl_5NO_3$=401.4
CAS — 2277-92-1.
ATC Vet — QP52AG06.
UNII — 1Q59G4876X.

NOTE. The name Zanil has been used as a trade mark for oxyclozanide.

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2014: (Oxyclozanide). A pale cream or cream-coloured powder. Very slightly soluble in water; soluble in alcohol; freely soluble in acetone; slightly soluble in chloroform.

Profile

Oxyclozanide is an anthelmintic used in veterinary medicine for the control of fascioliasis in cattle and sheep.

Piperazine

Piperatslini; Piperazin; Piperazina; Piperazinas; Pipérazine; Piperazinum; Piperazyna; Пиперазин.

$C_4H_{10}N_2$=86.14

CAS — 110-85-0.

ATC — P02CB01.

ATC Vet — QP52AH01.

UNII — 1RTM4PAL0V.

Pharmacopoeias. In *US.*

USP 36: (Piperazine). White to off-white lumps or flakes having an ammoniacal odour. Soluble in water and in alcohol; insoluble in ether. Store in airtight containers. Protect from light.

Piperazine Adipate

Piperatsiiniadipaatti; Piperaz. Adip.; Piperazina, adipato de; Piperazinadipat; Piperazin-adipát; Pipérazine, adipate de; Piperazini adipas; Piperazino adipatas; Piperazinum Adipicum; Пиперазина Адипат.

$C_4H_{10}N_2.C_6H_{10}O_4$=232.3

CAS — 142-88-1.

ATC — P02CB01.

UNII — V7P5P122LB.

Pharmacopoeias. In *Eur.* (see p. vii), *Int., Jpn,* and *Viet.*

In *US* for veterinary use only.

Ph. Eur. 8: (Piperazine Adipate). A white or almost white, crystalline powder. Soluble in water; practically insoluble in alcohol.

USP 36: (Piperazine Adipate). A white crystalline powder. Soluble in water; practically insoluble in alcohol.

Piperazine Citrate

Hydrous Tripiperazine Dicitrate; Piperatsiinisitraatti; Piperazina, citrato de; Piperazincitrat; Piperazin-citrát; Piperazin-citrát hydrát; Pipérazine, citrate de; Piperazini Citras; Piperazini Citras Hydricus; Piperazino citratas; Пиперазина Цитрат.

$(C_4H_{10}N_2)_3.2C_6H_8O_7.xH_2O$=642.7 (anhydrous substance)

CAS — 144-29-6 (anhydrous piperazine citrate); 41372-10-5 (piperazine citrate hydrate).

ATC — P02CB01.

UNII — 63KP7FXF2I.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int., US,* and *Viet.*

Ph. Eur. 8: (Piperazine Citrate). A white or almost white granular powder. It contains a variable amount of water. Freely soluble in water; practically insoluble in alcohol.

USP 36: (Piperazine Citrate). A white, crystalline powder having not more than a slight odour. Soluble in water; insoluble in alcohol and in ether. pH of a 10% solution in water is about 5.

Stability. A decrease in the content of piperazine [as citrate] in syrups on storage was attributed to interaction with fructose and glucose formed by hydrolysis of sucrose.[1] A syrup prepared with sorbitol lost no potency when stored at 25 degrees for 14 months.

1. Nielsen A, Reimer P. The stability of piperazine in syrup. *Arch Pharm Chemi (Sci)* 1975; 3: 73–8.

Piperazine Dihydrochloride

Пиперазина Дигидрохлорид.

$C_4H_{10}N_2.2HCl.xH_2O$=159.1 (anhydrous substance)

CAS — 142-64-3.

ATC — P02CB01.

UNII — 17VU4Z4W88.

Pharmacopoeias.

In *US* for veterinary use only.

USP 36: (Piperazine Dihydrochloride). A white crystalline powder. Soluble in water. A 5% solution in water has a pH of 3.0 to 3.4.

Piperazine Hydrate

Piperatsiinihydraatti; Piperazin Heksahidrat; Piperazin hexahydrát; Piperazin-Hexahydrat; Piperazina hexahidrato; Piperazinas hidratas; Piperazine Hexahydrate; Pipérazine, hydrate de; Piperazin-hidrát; Piperazinhydrat; Piperazini Hydras; Piperazinum Hexahydricum; Piperazinum Hydricum; Piperazyna uwodniona; Пиперазина Гидрат.

Piperazine hexahydrate.

$C_4H_{10}N_2.6H_2O$=194.2

CAS — 142-63-2.

ATC — P02CB01.

UNII — P3M07B8U64.

Pharmacopoeias. In *Eur.* (see p. vii) and *Viet.*

Ph. Eur. 8: (Piperazine Hydrate). Colourless deliquescent crystals. M.p. about 43 degrees. Freely soluble in water and in alcohol. A 5% solution in water has a pH of 10.5 to 12.0. Store in airtight containers. Protect from light.

Piperazine Phosphate

Piperazina, fosfato de; Piperazini Phosphas; Пиперазина Фосфат.

$C_4H_{10}N_2.H_3PO_4.H_2O$=202.1

CAS — 14538-56-8 (anhydrous piperazine phosphate); 18534-18-4 (piperazine phosphate monohydrate).

ATC — P02CB01.

UNII — 8T1F7T48FP.

Pharmacopoeias. In *Br., Chin., Jpn,* and *Viet.*

In *US* for veterinary use only.

BP 2014: (Piperazine Phosphate). A white odourless or almost odourless crystalline powder. Sparingly soluble in water; practically insoluble in alcohol. A 1% solution in water has a pH of 6.0 to 6.5.

USP 36: (Piperazine Phosphate). A white crystalline powder. Sparingly soluble in water; practically insoluble in alcohol. A 1% solution in water has a pH of 6.0 to 6.5. Store in airtight containers.

Uses and Administration

Piperazine is an anthelmintic effective against the intestinal nematodes *Ascaris lumbricoides* (roundworm) and *Enterobius vermicularis* (pinworm, threadworm), although other anthelmintics are usually preferred (see the discussions on the treatment of ascariasis and enterobiasis on p. 143.3 and p. 145.3). In roundworms piperazine produces a neuromuscular block leading to a flaccid muscle paralysis in susceptible worms, which are then easily dislodged by the movement of the gut and expelled in the faeces.

Piperazine is usually given as the citrate or phosphate, but the adipate may also be used. The dihydrochloride is used in veterinary practice. The dosage of the salts of piperazine is usually expressed in terms of piperazine hydrate; 100 mg of piperazine hydrate is equivalent to about 44.4 mg of piperazine, 120 mg of piperazine adipate, 125 mg of piperazine citrate (110 mg of anhydrous piperazine citrate), and to 104 mg of piperazine phosphate.

For the treatment of **ascariasis**, a single dose, repeated once after 14 days, has been used. In adults and children over 12 years of age, a dose equivalent to 4.5 g of piperazine hydrate is given orally.

For **enterobiasis**, piperazine has been given for 7 days. A second course after a 7-day interval may be required. Adults and children over 12 years of age are given the equivalent of 2.25 g of the hydrate once daily.

For details of doses in children, see p. 164.3.

Piperazine is also used as a preparation with senna in a single dose of 4 g of the phosphate for adults and children over 6 years of age, repeated after 14 days for enterobiasis, or repeated monthly if necessary for up to 3 months to treat and prevent ascariasis.

Administration in children. Piperazine may be given orally to children for the treatment of intestinal nematode infections, such as ascariasis (roundworm) and enterobiasis (pinworm and threadworm), although other anthelmintics are usually preferred.

For the treatment of **ascariasis**, a single dose equivalent to the following amount of piperazine hydrate is given, repeated once after 14 days:

- 9 to 12 years of age: 3.75 g
- 6 to 8 years of age: 3 g
- 4 to 5 years of age: 2.25 g
- 1 to 3 years of age: 1.5 g
- under 1 year of age (on medical advice only): 120 mg/kg has been suggested

For **enterobiasis**, piperazine has been given for 7 days in doses equivalent to the following amount of piperazine hydrate:

- 7 to 12 years of age: 1.5 g daily
- 4 to 6 years of age: 1.125 g daily
- 1 to 3 years of age: 750 mg daily
- under 1 year of age (on medical advice only): 45 to 75 mg/kg daily has been suggested

A second course of treatment after a 7-day interval may be required.

Adverse Effects

Serious adverse effects are rare with piperazine and generally indicate overdosage or impaired excretion. Nausea, vomiting, diarrhoea, abdominal pain, headache, rashes, and urticaria occasionally occur. Severe neurotoxicity and EEG abnormalities have been reported with symptoms including somnolence, dizziness, nystagmus, muscular incoordination ('worm wobble') and weakness, ataxia, paraesthesia, myoclonic contractions, choreiform movements, tremor, convulsions, and loss of reflexes.

Transient visual disturbances such as blurred vision have occurred occasionally and there were reports of cataract formation after treatment with piperazine although they do not appear to have been substantiated.

Hypersensitivity reactions such as bronchospasm, Stevens-Johnson syndrome, and angioedema have occurred in some individuals.

Piperazine has been taken off the market in some European countries because of general concern about its safety.[1] A study carried out in Sweden on 2 healthy subjects had indicated that mononitrosation of piperazine can occur in the stomach to produce the potential carcinogen *N*-mononitrosopiperazine; the more potent *N,N*-dinitrosopiperazine was not found.[2] However, the disease risk to man from such *N*-nitroso compounds has been questioned[3] and certainly reports of tumours associated with the use of piperazine have not been traced. Also, in the UK the CSM concluded that the incidence of serious adverse effects associated with piperazine was low and that, with appropriate pack warnings, piperazine products could remain as medicines available to the public through pharmacies.[1]

1. Anonymous. Data sheet changes for piperazine in pregnancy. *Pharm J* 1988; 240: 367.
2. Bellander BTD, *et al.* Nitrosation of piperazine in the stomach. *Lancet* 1981; ii: 372.
3. Tannenbaum SR. N-nitroso compounds: a perspective on human exposure. *Lancet* 1983; i: 629–32.

Abuse. Derivatives of piperazine have been developed and abused as 'designer drugs'—see Benzylpiperazine (p. 2318.1).

Effects on the blood. A 4-year-old African boy with G6PD deficiency developed haemolytic anaemia; no cause for the haemolysis was found except that 2 days previously he had taken *Pripsen* (piperazine and senna).[1] Severe thrombocytopenia with epistaxis and haemoptysis, which developed in a 61-year-old man after piperazine self-medication, was probably the result of sensitisation to piperazine 15 years earlier.[2]

1. Buchanan N, *et al.* G-6-PD deficiency and piperazine. *BMJ* 1971; 2: 110.
2. Cork MJ, *et al.* Pruritus ani, piperazine, and thrombocytopenia. *BMJ* 1990; 301: 1398.

Effects on the liver. A reaction resembling viral hepatitis occurred on 2 occasions in a 25-year-old woman after use of piperazine; it appeared to be a hypersensitivity reaction.[1]

1. Hamlyn AN, *et al.* Piperazine hepatitis. *Gastroenterology* 1976; 70: 1144–7.

Hypersensitivity. A patient had a serum-sickness-like illness associated with piperazine,[1] which was followed by a delayed hypersensitivity vasculitis. Occupational asthma related to exposure to piperazine citrate has also been reported.[2]

See also Effects on the Blood, above, and Effects on the Liver, above.

1. Balzan M, Cacciottolo JM. Hypersensitivity vasculitis associated with piperazine therapy. *Br J Dermatol* 1994; 131: 133–4.
2. Quirce S, *et al.* Occupational asthma due to piperazine citrate. *J Investig Allergol Clin Immunol* 2006; 16: 138–9.

Precautions

Piperazine is contra-indicated in patients with epilepsy or severe renal impairment and should be given with care to patients with neurological disturbances or mild to moderate renal impairment. It should also be avoided or given with extreme caution in patients with hepatic impairment.

Breast feeding. The UK licensed product information for *Pripsen* (piperazine and senna) states that piperazine is distributed into breast milk. Mothers should be advised to take a dose after breast feeding then not to breast feed for 8 hours during which period milk should be expressed and discarded at the regular feeding times.

Pregnancy. It has been reported that piperazine is teratogenic in *rabbits* and that there have been isolated reports of fetal malformations after clinical use, though no causal relationship has been established. Two infants with malformations have been described briefly:[1] one had bilateral hare lip, cleft palate, and anophthalmia; the other had an abnormality of one foot. Both mothers had taken *Pripsen* (piperazine and senna). UK licensed product information for *Pripsen* advises against use in pregnancy, especially during the first trimester, unless immediate treatment with piperazine is essential. However, the UK *National Teratology Information Service* notes that limited available data on the use of piperazine (with or without senna) in pregnancy does not show an increased risk of malformations or other adverse pregnancy outcomes and recom-

mends that treatment should not be withheld if clinically indicated.[2]

1. Leach FN. Management of threadworm infestation during pregnancy. *Arch Dis Child* 1990; 65: 399–400.
2. National Teratology Information Service. Use of piperazine in pregnancy (issued July 2011). Available at: http://www.toxbase.org/upload/Pregnancy%20pdfs/Piperazine%202011.pdf (accessed 11/08/11)

Interactions

The anthelmintic effects of piperazine and pyrantel may be antagonised when the two compounds are used together. The possibility that piperazine may enhance the adverse effects of phenothiazines such as chlorpromazine is discussed on p. 1053.2.

Pharmacokinetics

Piperazine is readily absorbed from the gastrointestinal tract and is excreted in the urine within 24 hours, partly as metabolites. The rate at which different individuals excrete piperazine has been reported to vary widely. It is distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Formule C34; *Fr.*: Vermifuge; *Gr.*: Oxyuran; *India*: Avizine; *Indon.*: Combicitrine; Piperacyl; *Ital.*: Citropiperazina; *Mex.*: Lu-Peracina; Overpon; Piperazil; Pipergress; Pirzinol; Verfid†; Vermin; *Port.*: Pipermel; Pipertox; *S.Afr.*: Padax; Pipralen†; Piprine; SB Tox Worm†; *Singapore*: Mei-Mei Worm; *Spain*: Mimedran†; Vermi; *Thai.*: Bompar; Sinpermine; Vermex†; *Turk.*: Asepar†; Askaripar; Helmicide; Helmipar; Oksiaskaril; Siropar; *Venez.*: Ciperina; Piperato; Piperazil; Piperdin; Piperzan; Verpirol.

Multi-ingredient Preparations. *Port.*: Biureol†; *UK*: Pripsen†.

Pharmacopoeial Preparations
BP 2014: Chewable Piperazine Phosphate Tablets; Piperazine Citrate Elixir; Piperazine Phosphate Tablets;
USP 36: Piperazine Citrate Syrup; Piperazine Citrate Tablets.

Pomegranate Bark

Casca da Romeira; Corteccia del Melograno; Corteza de Granado; Ecorce de Grenadier; Granado; Granati Cortex; Granatrinde; Pomegranate; Pomegranate Root Bark; Кора Гранатового Дерева.

UNII — O2ZT550U5E (Punica granatum); D9B634V4GP (Punica granatum flower); 56687D1Z4D (Punica granatum fruit); RS999V57DU (Punica granatum fruit rind); 995671U9KB (Punica granatum juice); O948615JXI (Punica granatum leaf); CLV24I3T1D (Punica granatum root bark); 7294Z34NS7 (Punica granatum seed).

Profile

Pomegranate bark, the dried bark of the stem and root of *Punica granatum* (Punicaceae) containing about 0.4 to 0.9% of alkaloids, has been used for the expulsion of tapeworms.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Hexaporine.

Multi-ingredient Preparations. *Chile*: Cellenergy; *Fr.*: Acyprost; *Ital.*: Pausanil; Rubis; *Switz.*: Padma Digestin; *USA*: Immunicare.

Homoeopathic Preparations. *Fr.*: Poconeol no 34.

Praziquantel *(BAN, USAN, rINN)*

EMBAY-8440; Pratsikvanteli; Prazicuantel; Prazikvantel; Prazikvantelis; Praziquantelum; Празиквантел.

2-Cyclohexylcarbonyl-1,2,3,6,7,11b-hexahydropyrazino[2,1-*a*]isoquinolin-4-one.

$C_{19}H_{24}N_2O_2$ = 312.4

CAS — 55268-74-1.
ATC — P02BA01.
ATC Vet — QP52AA01.
UNII — 6490C9U457.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US*.

Ph. Eur. 8: (Praziquantel). White or almost white crystalline powder. It exhibits polymorphism. Very slightly soluble in water; freely soluble in alcohol and in dichloromethane. Protect from light.

USP 36: (Praziquantel). A white or practically white crystalline powder; odourless or with a faint characteristic odour. Very slightly soluble in water; freely soluble in alcohol and in chloroform. Protect from light.

Uses and Administration

Praziquantel is an anthelmintic with a broad spectrum of activity against trematodes (flukes) including all species of *Schistosoma* pathogenic to man, and against cestodes (tapeworms). It is used in the treatment of cysticercosis, diphyllobothriasis, hymenolepiasis, schistosomiasis, taeniasis, and intestinal, liver, and lung fluke infections. For discussions of these infections and their treatment, see under Choice of Anthelmintic, p. 143.1, and under the individual headings below.

Praziquantel is given orally with food.

In the treatment of **schistosomiasis** in adults and children over 4 years it is given on one day as three doses of 20 mg/kg at intervals of 4 to 6 hours or it is given as a single dose of 40 to 60 mg/kg (but see p. 166.1).

Doses in adults and children over 4 years in liver and lung **fluke infections** are 25 mg/kg three times daily for two days or a single dose of 40 mg/kg. Similar doses may be used in intestinal fluke infections (see p. 165.3).

Praziquantel may be given as an oral single dose in the treatment of **tapeworm infections** in adults and children over 4 years of age. For the treatment of *Taenia saginata* and *T. solium* infections the recommended dose is 5 to 10 mg/kg, for *Hymenolepis nana* infections the dose is 15 to 25 mg/kg, and for *Diphyllobothrium latum* infections doses of 5 to 25 mg/kg have been suggested.

Praziquantel is used in adults and children over 4 years in the treatment of **neurocysticercosis** in a dose of 50 mg/kg daily in 3 divided doses for 14 days. An alternative regimen of 3 doses of 25 mg/kg every 2 hours has been proposed.

Reviews.

1. Pearson RD, Guerrant RL. Praziquantel: a major advance in anthelmintic therapy. *Ann Intern Med* 1983; 99: 195–8. Correction. *ibid.*; 574.
2. King CH, Mahmoud AAF. Drugs five years later: praziquantel. *Ann Intern Med* 1989; 110: 290–6.
3. Cioli D, Pica-Mattoccia L. Praziquantel. *Parasitol Res* 2003; 90 (suppl 1): S3–S9.
4. Ali BH. A short review of some pharmacological, therapeutic and toxicological properties of praziquantel in man and animals. *Pak J Pharm Sci* 2006; 19: 170–5.

Administration in children. Praziquantel may be given orally to children over 4 years of age for the treatment of trematode infections (including schistosomiasis) and cestode infections such as cysticercosis, diphyllobothriasis, hymenolepiasis, and taeniasis. Doses used are the same by weight as those used for adults (see above).

Although pre-school children are habitually excluded from schistosomiasis control programs, a study[1] involving 104 Zimbabwean children aged 1 to 5 years found that treatment of *Schistosoma haematobium* infection with a standard dose of praziquantel (40 mg/kg) was as safe and effective in this younger age group as in older children.

1. Mutapi F, *et al. Schistosoma haematobium* treatment in 1-5 year old children: safety and efficacy of the antihelminthic drug praziquantel. *PLoS Negl Trop Dis* 2011; 5: e1143.

Cysticercosis. Praziquantel is used in the treatment of neurocysticercosis (p. 144.3) although albendazole is also considered to be the drug of choice.

References.

1. Sotelo J, Jung H. Pharmacokinetic optimisation of the treatment of neurocysticercosis. *Clin Pharmacokinet* 1998; 34: 503–15.
2. Del Brutto OH, *et al.* Single-day praziquantel versus 1-week albendazole for neurocysticercosis. *Neurology* 1999; 52: 1079–81.
3. Del Brutto OH, *et al.* Meta-analysis: cysticidal drugs for neurocysticercosis: albendazole and praziquantel. *Ann Intern Med* 2006; 145: 43–51.

Echinococcosis. Praziquantel may be used as an adjunct to surgery in echinococcosis (p. 145.2). Praziquantel has been reported to possess a scolicidal effect *in vitro* and *in vivo* against *Echinococcus granulosus*, although it does not penetrate well into mature cysts.[1] There has been a report of the successful treatment of disseminated peritoneal hydatid disease with praziquantel and surgery.[2] In this case praziquantel was effective against the small cysts; 2 large cysts were removed surgically, one before praziquantel was started. However, activity in 9 other patients given praziquantel was disappointing.[3] A combination of praziquantel with albendazole may be more effective,[1,4] although better evidence is needed for firm recommendations.[1]

1. Bygott JM, Chiodini PL. Praziquantel: neglected drug? Ineffective treatment? Or therapeutic choice in cystic hydatid disease? *Acta Trop* 2009; 111: 95–101.
2. Henriksen T-H, *et al.* Treatment of disseminated peritoneal hydatid disease with praziquantel. *Lancet* 1989; i: 272.
3. Piens MA, *et al.* Praziquantel dans l'hydatidose humaine: évaluation par traitement médical pré-opératoire. *Bull Soc Pathol Exot Filiales* 1989; 82: 503–12.
4. Ayles HM, *et al.* A combined medical and surgical approach to hydatid disease: 12 years' experience at the Hospital for Tropical Diseases, London. *Ann R Coll Surg Engl* 2002; 84: 100–105.

Intestinal fluke infections. Praziquantel, given orally, is used in the treatment of intestinal fluke infections (p. 146.2). In the treatment of fasciolopsiasis, heterophyiasis, and metagonimiasis, the usual recommended dose is 25 mg/kg three times daily for one day.[1] However, a single dose of 25 mg/kg has also been recommended.[2] Single doses of 15 mg/kg, 25 mg/kg, or 40 mg/kg all yielded a cure rate of 100% in a study in 72 primary-school children in Thailand who were harbouring *Fasciolopsis buski*, suggesting that a single dose of 15 mg/kg at bedtime might be tried.[3] In another study, 9 patients infected with the trematode *Nanophyetus salmincola* were treated with praziquantel 20 mg/kg three times daily for one day and were negative for eggs in their stools 2 to 12 weeks later,[4] and this has become the usual recommended dose.[1]

1. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.
2. WHO. *WHO model formulary.* Geneva: WHO, 2008. Available at: http://www.who.int/selection_medicines/list/WMF2008.pdf (accessed 25/11/09)
3. Harinasuta T, *et al.* Efficacy of praziquantel on fasciolopsiasis. *Arzneimittelforschung* 1984; 34: 1214–15.
4. Fritsche TR, *et al.* Praziquantel for treatment of human Nanophyetus salmincola (Trogiotrema salmincola) infection. *J Infect Dis* 1989; 160: 896–9.

Liver fluke infections. Praziquantel given orally is the treatment of choice for clonorchiasis and opisthorchiasis; it has also been used in the treatment of fascioliasis (p. 146.2) although in this latter infection triclabendazole, or alternatively bithionol or nitazoxanide, are preferred.

Various studies have shown praziquantel to be effective in clonorchiasis[1-4] and opisthorchiasis,[5,6] although one study in opisthorchiasis[7] showed that re-infection was common despite praziquantel therapy, particularly in those with heavy initial infection. A study in Thailand[8] confirmed that mass treatment for opisthorchiasis with a single dose of praziquantel was beneficial, although it was suggested that ideally treatment should be given twice a year.

While praziquantel is not the drug of choice for fascioliasis, there has been a report[9] of successful treatment of a patient with severe infection. Subsequent studies[10-12] have, however, shown praziquantel to be of little benefit.

1. Soh C-J. Clonorchis sinensis: experimental and clinical studies with praziquantel in Korea. *Arzneimittelforschung* 1984; 34: 1156–9.
2. Chen C-Y, Hsieh W-C. Clonorchis sinensis: epidemiology in Taiwan and clinical experience with praziquantel. *Arzneimittelforschung* 1984; 34: 1160–2.
3. Kuang Q-H, *et al.* Clonorchiasis: treatment with praziquantel in 50 cases. *Arzneimittelforschung* 1984; 34: 1162–3.
4. Lee S-H. Large scale treatment of clonorchis sinensis infections with praziquantel under field conditions. *Arzneimittelforschung* 1984; 34: 1227–8.
5. Bunnag D, *et al.* Opisthorchis viverrini: clinical experience with praziquantel in hospital for tropical diseases. *Arzneimittelforschung* 1984; 34: 1173–4.
6. Ambroise-Thomas P, *et al.* Therapeutic results in opisthorchiasis with praziquantel in a reinfection-free environment in France. *Arzneimittelforschung* 1984; 34: 1177–9.
7. Upatham ES, *et al.* Rate of re-infection by Opisthorchis viverrini in an endemic northeast Thai community after chemotherapy. *Int J Parasitol* 1988; 18: 643–9.
8. Pungpak S, *et al.* Opisthorchis viverrini infection in Thailand: studies on the morbidity of the infection and resolution following praziquantel treatment. *Am J Trop Med Hyg* 1997; 56: 311–14.
9. Schiappacasse RH, *et al.* Successful treatment of severe infection with Fasciola hepatica with praziquantel. *J Infect Dis* 1985; 152: 1339–40.
10. Farag HF, *et al.* A short note on praziquantel in human fascioliasis. *J Trop Med Hyg* 1986; 89: 79–80.
11. Farid Z, *et al.* Unsuccessful use of praziquantel to treat acute fascioliasis in children. *J Infect Dis* 1986; 154: 920–1.
12. Farid Z, *et al.* Treatment of acute toxaemic fascioliasis. *Trans R Soc Trop Med Hyg* 1988; 82: 299.

Lung fluke infections. Praziquantel, given orally, is used in the treatment of the lung fluke infection paragonimiasis (p. 146.3).

References.

1. Vanijanonta S, *et al.* Paragonimus heterotremus and other Paragonimus spp. in Thailand: pathogenesis clinic and treatment. *Arzneimittelforschung* 1984; 34: 1186–8.
2. Pachucki CT, *et al.* American paragonimiasis treated with praziquantel. *N Engl J Med* 1984; 311: 582–3.
3. De NV, *et al.* Epidemiology, symptoms and treatment of paragonimiasis in Sin Ho district, Lai Chau province, Vietnam. *Southeast Asian J Trop Med Public Health* 2000; 31 (suppl 1): 26–30.

Schistosomiasis. Praziquantel is the main drug[1-4] used in the treatment of schistosomiasis (p. 148.1). It is effective against all species of schistosomes,[1] although the possibility of resistance remains a concern.[5-7] Oral doses are either 20 mg/kg given three times in one day or a single dose of 40 to 60 mg/kg. WHO considers[1] that in the field such a single-dose treatment will produce a cure rate of 60 to 90% with a reduction in egg count in those not cured of 90 to 95%. Good as such results are, a single dose or one day's sole treatment should not be considered to be all that is required to achieve a permanent cure or prevent re-infection, and any treatment plan should be reassessed after 6 or 12 months.[8,9] Such an approach with annual screening and targeted chemotherapy can provide, at least in some endemic areas, successful protection for children against intense infection and consequent hepatic disease.[9]

Several studies indicate that doses lower than those recommended above might be effective and in some control programmes 20 mg/kg might be enough for *S. haematobium*[10-12] or 30 mg/kg for *S. mansoni*.[10] The extent to which low doses contribute to resistance, as has been suggested with oxamniquine,[13] is unclear, but refractory infections

have been reported. A 4-day treatment course was needed to produce a complete cure in a patient who relapsed twice following standard one-day treatment regimens.[14] Hepatic impairment, specifically hepatic fibrosis, is a feature of some schistosomal infections and patients with such liver involvement have benefited from treatment with praziquantel.[9,15]

1. WHO. The control of schistosomiasis: second report of the WHO expert committee. *WHO Tech Rep Ser 830* 1993. Also available at: http://libdoc.who.int/trs/WHO_TRS_830.pdf (accessed 25/11/09)
2. Doenhoff MJ, Pica-Mattocia L. Praziquantel for the treatment of schistosomiasis: its use for control in areas with endemic disease and prospects for drug resistance. *Expert Rev Anti Infect Ther* 2006; 4: 199–210.
3. Doenhoff MJ, *et al.* Praziquantel: its use in control of schistosomiasis in sub-Saharan Africa and current research needs. *Parasitology* 2009; 136: 1825–35.
4. Dömling A, Khoury K. Praziquantel and schistosomiasis. *ChemMedChem* 2010; 5: 1420–34.
5. Doenhoff MJ, *et al.* Resistance of Schistosoma mansoni to praziquantel: is there a problem? *Trans R Soc Trop Med Hyg* 2002; 96: 465–9.
6. Doenhoff MJ, *et al.* Praziquantel: mechanisms of action, resistance and new derivatives for schistosomiasis. *Curr Opin Infect Dis* 2008; 21: 659–67.
7. Seto EY, *et al.* Human schistosomiasis resistance to praziquantel in china: should we be worried? *Am J Trop Med Hyg* 2011; 85: 74–82.
8. Anonymous. The chemotherapy of schistosomiasis control. *Bull WHO* 1986; 64: 23–5.
9. Anonymous. Mass treatment of schistosomiasis with praziquantel. *WHO Drug Inf* 1988; 2: 184–5.
10. Taylor P, *et al.* Efficacy of low doses of praziquantel for Schistosoma mansoni and S. haematobium. *J Trop Med Hyg* 1988; 91: 13–17.
11. King CH, *et al.* Dose-finding study for praziquantel therapy of Schistosoma haematobium in Coast Province, Kenya. *Am J Trop Med Hyg* 1989; 40: 507–13.
12. Hatz C, *et al.* Ultrasound scanning for detecting morbidity due to Schistosoma haematobium and its resolution following treatment with different doses of praziquantel. *Trans R Soc Trop Med Hyg* 1990; 84: 84–8.
13. Coles GC, *et al.* Tolerance of Kenyan Schistosoma mansoni to oxamniquine. *Trans R Soc Trop Med Hyg* 1987; 81: 782–5.
14. Murray-Smith SQ, *et al.* A case of refractory schistosomiasis. *Med J Aust* 1996; 165: 458.
15. Zwingenberger K, *et al.* Praziquantel in the treatment of hepatosplenic schistosomiasis: biochemical disease markers indicate deceleration of fibrogenesis and diminution of portal flow obstruction. *Trans R Soc Trop Med Hyg* 1990; 84: 252–6.

Taeniasis. Praziquantel is used in the treatment of taeniasis (p. 148.2). It has been studied in the mass control of taeniasis when a single dose of 5 mg/kg was used.[1]

Praziquantel is also effective against the larval form of *Taenia solium* and is used to treat neurocysticercosis (see p. 164.2).

1. Cruz M, *et al.* Operational studies on the control of Taenia solium taeniasis/cysticercosis in Ecuador. *Bull WHO* 1989; 67: 401–7.

Adverse Effects

Adverse effects with praziquantel may be common but are usually mild and transient. Headache, diarrhoea, dizziness, drowsiness, malaise, abdominal discomfort, nausea, and vomiting have been reported most frequently. Hypersensitivity reactions such as fever, urticaria, pruritic rashes, and eosinophilia can occur; they may be due to death of the infecting parasites. Raised liver enzyme values have been reported rarely.

Most patients with neurocysticercosis who are given praziquantel suffer CNS effects, including headache, hyperthermia, seizures, and intracranial hypertension, which are thought to result from an inflammatory response to dead and dying parasites in the CNS. Use with corticosteroids is advised in such patients.

Effects on the gastrointestinal tract. Colicky abdominal pain and bloody diarrhoea occurred in a small community in Zaire shortly after treatment for *Schistosoma mansoni* infection with single oral doses of praziquantel 40 mg/kg.[1] A similar syndrome has been reported in some patients with *Schistosoma japonicum* infection given praziquantel.[2] The abdominal pain occurring in these patients was very different from the mild abdominal discomfort much more commonly reported with praziquantel therapy.

1. Polderman AM, *et al.* Side effects of praziquantel in the treatment of Schistosoma mansoni in Maniema, Zaire. *Trans R Soc Trop Med Hyg* 1984; 78: 752–4.
2. Watt G, *et al.* Bloody diarrhoea after praziquantel therapy. *Trans R Soc Trop Med Hyg* 1986; 80: 345–6.

Effects on the nervous system. Adverse nervous system effects are common in patients with neurocysticercosis given praziquantel. Neurological symptoms have also been reported[1] with the much lower doses of praziquantel used in the treatment of taeniasis in a patient with undiagnosed neurocysticercosis.

1. Flisser A, *et al.* Neurological symptoms in occult neurocysticercosis after single taenicidal dose of praziquantel. *Lancet* 1993; 342: 748.

Hypersensitivity. A 35-year-old man developed sudden onset of pruritic urticaria over his entire body with dyspnoea, chest tightness, palpitation, dizziness, and vomiting 30 minutes after taking an oral dose of praziquantel for clonorchiasis. The patient had taken a dose of praziquantel 8 years ago, with no adverse effects, and was on no other drugs at the time of this episode. His symptoms resolved after gastric lavage, oxygen, and treatment with adrenaline, corticosteroids, and an antihistamine.[1]

1. Shen C, *et al.* A case of anaphylactic reaction to praziquantel treatment. *Am J Trop Med Hyg* 2007; 76: 603–5.

Precautions

Praziquantel should not be used in patients with ocular or spinal cysticercosis because of the risk of severe, irreversible eye damage or paralysis resulting from destruction of the parasite.

Patients should be warned that praziquantel may cause dizziness or drowsiness and if affected they should not drive or operate machinery during or for 24 hours after treatment.

Breast feeding. Praziquantel is distributed into breast milk at a concentration of about a quarter that of the maternal serum; US licensed product information advises that mothers should not breast feed during treatment or for 72 hours thereafter. For further information on WHO opinion on the use of praziquantel in breast feeding, see p. 166.2.

Pregnancy. In a review of 637 women given praziquantel in a mass distribution programme, 88 had had a single oral dose during pregnancy, including 37 in their first trimester. All pregnancies ended in full-term babies and there was no evidence of clinical abnormality. No difference was found in the rates of preterm delivery or abortion compared with a control group.[1] WHO opinion is that praziquantel may be considered the safest of all anthelmintic drugs and that the risks to pregnant women or unborn or nursing children from use of praziquantel are very small.[2] Praziquantel is the drug of choice in schistosomiasis and delaying treatment may in fact result in more serious outcomes. It therefore suggests that pregnant and lactating women may be given the drug and should be included in national de-worming programmes.[2]

1. Adam I, *et al.* Is praziquantel therapy safe during pregnancy? *Trans R Soc Trop Med Hyg* 2004; 98: 540–3.
2. Anonymous. Use of praziquantel in pregnant and lactating women. *WHO Drug Inf* 2003; 17: 29.

Interactions

Praziquantel is metabolised via various cytochrome P450 isoenzymes including CYP3A4 and therefore has the potential to interact with drugs that are inhibitors or inducers of such enzymes. Enzyme-inducing drugs such as carbamazepine, dexamethasone, phenobarbital, and phenytoin may decrease plasma concentrations of praziquantel. Conversely, enzyme inhibitors such as cimetidine, erythromycin, itraconazole, and ketoconazole may increase plasma concentrations of praziquantel.

Concomitant use of *rifampicin* and praziquantel should be avoided as rifampicin is a strong inducer of cytochrome P450 isoenzymes and may cause subtherapeutic concentrations of praziquantel. If treatment with praziquantel is essential, rifampicin should be stopped 4 weeks before starting praziquantel; treatment with rifampicin can be restarted one day after finishing praziquantel therapy.

Anthelmintics. For reference to an interaction between of *albendazole* and praziquantel, see p. 151.1.

Antibacterials. A study[1] in healthy subjects found that oral *rifampicin* decreased plasma concentrations after single and multiple doses of oral praziquantel to subtherapeutic levels.

1. Riddtid W, *et al.* Rifampin markedly decreases plasma concentrations of praziquantel in healthy volunteers. *Clin Pharmacol Ther* 2002; 72: 505–13.

Antiepileptics. *Carbamazepine* and *phenytoin* have been reported to reduce the bioavailability of praziquantel.[1]

1. Quinn DI, Day RO. Drug interactions of clinical importance: an updated guide. *Drug Safety* 1995; 12: 393–452.

Antifungals. A crossover study in 10 healthy subjects[1] suggested that the CYP3A4 and PgP inhibitor *ketoconazole* almost doubled exposure to, and mean peak plasma concentration of, praziquantel when both drugs were given together. It was suggested that standard doses of praziquantel should be halved when both drugs were given.

1. Riddtid W, *et al.* Pharmacokinetic interaction between ketoconazole and praziquantel in healthy volunteers. *J Clin Pharm Ther* 2007; 32: 585–93.

Antimalarials. *Chloroquine* has been reported to reduce the bioavailability of praziquantel.[1]

1. Masimirembwa CM, *et al.* The effect of chloroquine on the pharmacokinetics and metabolism of praziquantel in rats and in humans. *Biopharm Drug Dispos* 1994; 15: 33–43.

Corticosteroids. Corticosteroids may be used to reduce the inflammatory reactions that often occur within 2 to 3 days of starting cysticidal therapy. However, use is complicated by the fact that dexamethasone roughly halves the plasma concentration of praziquantel. It has therefore been suggested that when praziquantel is given in the 2-week treatment regimen, corticosteroids should not be given prophylactically but only if an inflammatory reaction develops. Dexamethasone is then given daily for 2 or 3 days and most of the treatment period will be free of pharmacokinetic interaction. When the short course praziquantel regimen is used (3 doses given 2 hours apart), the corticosteroid may be given prophylactically. The first dose of dexamethasone is given 4 hours after the last dose of praziquantel (when the concentration of praziquantel is starting to decrease and the pharmacological action is assumed to have been accomplished) and then daily for 2 to 3 days. No pharmacokinetic interaction would be expected at this point.[1]

1. Sotelo J, Jung H. Pharmacokinetic optimisation of the treatment of neurocysticercosis. *Clin Pharmacokinet* 1998; 34: 503–15.

Histamine H_2-antagonists. *Cimetidine* has been reported to increase praziquantel bioavailability.[1,2]

1. Metwally A, *et al.* Effect of cimetidine, bicarbonate and glucose on the bioavailability of different formulations of praziquantel. *Arzneimittelforschung* 1995; 45: 516–18.
2. Jung H, *et al.* Pharmacokinetic study of praziquantel administered alone and in combination with cimetidine in a single-day therapeutic regimen. *Antimicrob Agents Chemother* 1997; 41: 1256–9.

Pharmacokinetics

Praziquantel is rapidly absorbed after oral doses; more than 80% of a dose is reported to be absorbed. Peak plasma concentrations occur 1 to 4 hours after a dose, but there is a pronounced first-pass effect and praziquantel undergoes rapid and extensive metabolism in the liver, mainly via the cytochrome P450 isoenzymes CYP2B1 and CYP3A4, being hydroxylated to metabolites that are thought to be inactive. It is distributed into the CSF. The plasma elimination half-life of praziquantel is about 1 to 1.5 hours and that of the metabolites about 4 hours.

It is excreted in the urine, mainly as metabolites, about 80% of the dose being eliminated within 4 days and more than 90% of this in the first 24 hours.

Praziquantel is distributed into breast milk.

References.

1. Leopold G, *et al.* Clinical pharmacology in normal volunteers of praziquantel, a new drug against schistosomes and cestodes: an example of a complex study covering both tolerance and pharmacokinetics. *Eur J Clin Pharmacol* 1978; 14: 281–91.
2. Bühring KU, *et al.* Metabolism of praziquantel in man. *Eur J Drug Metab Pharmacokinet* 1978; 3: 179–90.
3. Patzschke K, *et al.* Serum concentrations and renal excretion in humans after oral administration of praziquantel—results of three determination methods. *Eur J Drug Metab Pharmacokinet* 1979; 3: 149–56.
4. Mandour M El M, *et al.* Pharmacokinetics of praziquantel in healthy volunteers and patients with schistosomiasis. *Trans R Soc Trop Med Hyg* 1990; 84: 389–93.
5. Godawska-Matysik A, Kieć-Kononowicz K. Biotransformation of „praziquantel by human cytochrome p450 3A4 (CYP 3A4). *Acta Pol Pharm* 2006; 63: 381–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Prazitral; *Austral.*: Biltricide; *Braz.*: Cestox; Cisticid; *Canad.*: Biltricide; *Chile*: Cesol; Cisticid; *Fr.*: Biltricide; *Ger.*: Biltricide; Cesol; Cysticide; *Gr.*: Biltricide; *Hong Kong*: Biltricide; *India*: Cest; Cysticide; Distocide; *Israel*: Biltricide†; *Mex.*: Cesol; Cisticid; Tecprazin; Teniken; Zifartel†; *Neth.*: Biltricide; *Rus.*: Azinox (Азинокс); Biltricid (Бильтрицид); *S.Afr.*: Biltricide†; Cysticide; *Singapore*: Distocide; *Thai.*: Mycotricide†; Opticide; Praquantel; Prasikon; Prazite; V Day Prazide; Wormicide; Zentozide; *Ukr.*: Biltricid (Бильтрицид); *USA*: Biltricide; *Venez.*: Cestox.

Pharmacopoeial Preparations

USP 36: Praziquantel Tablets.

Pyrantel Embonate *(BANM, rINNM)*

CP-10423-16; Embonato de pirantel; Pamoato de pirantel; Pirantel, embonato de; Pirantel Pamoat; Pirantel Pamoate; Pirantelio embonatas; Pyranteeliembonaatti; Pyrantel, embonate de; Pyrantel Pamoate (USAN); Pyrantelembonat; Pyrantel-embonat; Pyranteli Embonas; Pyrantelu embonian; Пирантела Эмбонат.

1,4,5,6-Tetrahydro-1-methyl-2-[(*E*)-2-(2-thienyl)vinyl]pyrimidine 4,4′-methylenebis(3-hydroxy-2-naphthoate).

$C_{11}H_{14}N_2S,C_{23}H_{16}O_6$=594.7

CAS — 15686-83-6 (pyrantel); 22204-24-6 (pyrantel embonate); 33401-94-4 (pyrantel tartrate).

ATC — P02CC01.

UNII — 81BK194Z5M.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Pyrantel Embonate). A pale yellow or yellow powder. Practically insoluble in water and in methyl alcohol; soluble in dimethyl sulfoxide. Protect from light.

USP 36: (Pyrantel Pamoate). A yellow to tan solid. Practically insoluble in water and in methyl alcohol; soluble

in dimethyl sulfoxide; slightly soluble in dimethylformamide. Protect from light.

Uses and Administration

Pyrantel embonate is an anthelmintic effective against intestinal nematodes including roundworms (*Ascaris lumbricoides*), threadworms or pinworms (*Enterobius vermicularis*), and *Trichostrongylus* spp., the tissue nematode *Trichinella spiralis*, and hookworms, although it is possibly less effective against *Necator americanus* hookworms than against *Ancylostoma duodenale*. Pyrantel embonate is one of the anthelmintics that may be used in the treatment of infections with these worms, as discussed under Choice of Anthelmintic, p. 143.1. It appears to act by paralysing susceptible worms which are then dislodged by peristaltic activity.

Pyrantel is given orally as the embonate, but doses are described in terms of the base. Pyrantel embonate 2.9 g is equivalent to about 1 g of pyrantel.

Single or mixed **Infections due to susceptible worms** may be treated with the equivalent of pyrantel 10 mg/kg as a single oral dose. **Ascariasis** occurring alone may only require 5 mg/kg; a single dose of 2.5 mg/kg given three or four times a year has been used in mass treatment programmes. In **necatoriasis**, 10 mg/kg daily for 3 or 4 days or 20 mg/kg daily for 2 days may be necessary. The response in **enterobiasis** may be improved by repeating the 10 mg/kg dose after 2 to 4 weeks. In **trichinosis**, a dose of 10 mg/kg daily for 5 days has been used.

Pyrantel tartrate has been used as a veterinary anthelmintic.

Administration in children. Doses of pyrantel embonate for the treatment of susceptible single or mixed worm infections in children are the same by weight as those for adults, see Uses and Administration, above.

Adverse Effects and Precautions

The adverse effects of pyrantel embonate are generally mild and transient. The most frequent are gastrointestinal effects such as nausea and vomiting, anorexia, abdominal pain, and diarrhoea. Other adverse effects reported include headache, dizziness, drowsiness, insomnia, rashes, and raised liver enzyme values.

Pyrantel embonate should be used with caution in patients with hepatic impairment.

Interactions

The anthelmintic effects of both pyrantel and piperazine may be antagonised when the two drugs are used together.

Pharmacokinetics

Due to its low water solubility only a small proportion of a dose of pyrantel embonate is absorbed from the gastrointestinal tract, thereby ensuring high concentrations of the drug in the intestinal lumen. The absorbed portion of the drug is partially metabolised by the liver. Up to about 7% is excreted as unchanged drug and metabolites in the urine but over half of the dose is excreted unchanged in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Anthel; Combantrin; Early Bird†; ***Austria***: Combantrin; ***Braz.***: Ascarical; ***Canad.***: Combantrin; Jaa Pyral; ***Chile***: Combantrin†; ***Fr.***: Combantrin; Helmintox; ***Ger.***: Helmex; ***Gr.***: Combantrin; ***Hong Kong***: Combantrin†; Pyrantin†; ***India***: Expent; Nemocid; Pa-Pa; ***Indon.***: Combantrin†; Konvermex†; Medicomtrin†; Piraska†; Proworm†; Upixon; ***Ital.***: Combantrin; ***Mex.***: Combantrin; Pirantrim; ***NZ***: Combantrin; ***Philipp.***: Combantrin; Gelminthic; ***Port.***: Combantrin; ***Rus.***: Helmintox (Гельминтокс); Nemocid (Немоцид); ***S.Afr.***: Combantrin†; ***Singapore***: Bearantel; ***Spain***: Lombriareu†; Trilombrin; ***Switz.***: Cobantril; ***Thai.***: Bantel; Pyrapam; Pyteldon; ***Turk.***: Kontil; Pirantrin; ***Ukr.***: Helmintox (Гельминтокс); ***USA***: Pin-Rid; Pin-X; Reese's Pinworm; ***Venez.***: Combantrin; Tamoa.

Multi-ingredient Preparations. ***India***: Mebex Plus; ***Indon.***: Quantrel†; ***Philipp.***: Quantrel; ***Venez.***: Dualid; Quantrel.

Pharmacopoeial Preparations
USP 36: Ivermectin and Pyrantel Pamoate Tablets; Pyrantel Pamoate Oral Suspension.

Pyrvinium Embonate *(rINNM)*

Embonato de pirvinio; Pirvinio, embonato de; Pirvinyum Pamoat; Pyrvinii Embonas; Pyrvinium, Embonate de; Pyrvinium Pamoate (BAN); Pyrvinium Pamoate; Viprynium Embonate; Viprynium Pamoate; Пирвиния Эмбонат.

Bis(6-dimethylamino-2-[2-(2,5-dimethyl-1-phenylpyrrol-3-yl)vinyl]-1-methylquinolinium) 4,4'-methylenebis(3-hydroxy-2-naphthoate).
$C_{52}H_{56}N_6C_{23}H_{14}O_6$=1151.4
CAS — 3546-41-6.
ATC — P02CX01.
UNII — 310X6584LW.

Pharmacopoeias. In *US.*

USP 36: (Pyrvinium Pamoate). A bright orange or orange-red to practically black crystalline powder. Practically insoluble in water and in ether; slightly soluble in chloroform and in methoxyethanol; freely soluble in glacial acetic acid; very slightly soluble in methyl alcohol. Store in airtight containers. Protect from light.

Uses and Administration

Pyrvinium embonate is an effective anthelmintic in the treatment of enterobiasis (p. 145.3), but has generally been superseded by other drugs.

Pyrvinium is given as the embonate but doses are described in terms of the base. Pyrvinium embonate 7.5 mg is equivalent to about 5 mg of pyrvinium.

It has been given orally in a single dose equivalent to pyrvinium 5 mg/kg, repeated after 2 to 3 weeks.

Adverse Effects

Pyrvinium occasionally causes nausea, vomiting, abdominal pain, and diarrhoea. Hypersensitivity reactions and photosensitivity have been reported. Headache may occur.

Pyrvinium stains the stools bright red and may stain clothing if vomiting occurs.

Pharmacokinetics

Pyrvinium embonate is not significantly absorbed from the gastrointestinal tract.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Tru; ***Braz.***: Pyr-Pam; Pyverm; ***Denm.***: Vanquin; ***Fin.***: Pyrvin; ***Fr.***: Povanyl; ***Ger.***: Molevac Pyrcon; ***Norw.***: Vanquin; ***Swed.***: Vanquin; ***Turk.***: Pirok.

Pharmacopoeial Preparations
USP 36: Pyrvinium Pamoate Oral Suspension; Pyrvinium Pamoate Tablets.

Rafoxanide *(BAN, USAN, rINN)*

MK-990; Rafoxanid; Rafoxanida; Rafoxanidum; Рафоксанид.
3'-Chloro-4'-(4-chlorophenoxy)-3,5-di-iodosalicylanilide.
$C_{19}H_{11}Cl_2I_2NO_3$=626.0
CAS — 22662-39-1.
ATC Vet — QP52AG05.
UNII — 22F4FLA7DH.

Profile

Rafoxanide is an anthelmintic used in veterinary medicine for the treatment of fascioliasis in cattle and sheep.

Santonin

Santoniini; Santonina; Santoninum; Santonin; Santonin.
(3*S*,3a*S*,5a*S*,9b*S*)-3a,5,5a,9b-Tetrahydro-3,5a,9-trimethylnaphtho[1,2-*b*]furan-2,8(3*H*,4*H*)-dione.
$C_{15}H_{18}O_3$=246.3
CAS — 481-06-1.
UNII — 1VL8J38ERO.

Pharmacopoeias. In *Jpn.*

Profile

Santonin is a crystalline lactone obtained from the dried unexpanded flowerheads of *Artemisia cina* (santonica, wormwood) and other species of *Artemisia* (Compositae). It was formerly used as an anthelmintic in the treatment of roundworm (*Ascaris*) infection, but has been superseded by other less toxic anthelmintics.

It is used as a flavour in food.

Selamectin *(BAN, USAN, rINN)*

Selamectina; Sélamectine; Selamectinum; Selamektiini; Selamektin; UK-124114; Селамектин.
(2a*E*,4*E*,5'*S*,6*S*,6'*S*,7*S*,8*E*,11*R*,13*R*,15*S*,17a*R*,20a*R*,20b*S*)-6'-Cyclohexyl-7-[(2,6-dideoxy-3-*O*-methyl-α-L-*arabino*-hexopyranosyl)oxy]-3',4',5',6,6',7,10,11,14,15,20a,20b-dodecahydro-20b-hydroxy-5',6,8,19-tetramethylspiro[11,15-methano-2*H*,13*H*,17*H*-furo[4,3,2-*p*,*q*][2,6]benzodioxacyclooctadecin-13,2'-[2*H*]pyran]-17,20(17a*H*)-dione 20-oxime.
$C_{43}H_{63}NO_{11}$=770.0
CAS — 165108-07-6.
ATC Vet — QP54AA05.
UNII — A2669OWX9N.

NOTE. The name Stronghold has been used as a trade mark for selamectin.

Pharmacopoeias. In *Eur.* (see p. vii) for veterinary use only.

Ph. Eur. 8: (Selamectin for Veterinary Use). A semisynthetic product derived from a fermentation product. A white or almost white, hygroscopic powder. Practically insoluble in water; soluble in acetone and in dichloromethane; freely soluble in isopropyl alcohol; sparingly soluble in methyl alcohol. Store in airtight containers.

Profile

Selamectin is an avermectin anthelmintic used in veterinary medicine as an ectoparasiticide and for the prophylaxis of gastrointestinal roundworms and heartworms.

Tetramisole Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de tetramisol; ICI-50627; McN-JR-8299-11; R-8299; Tetramisol, hidrocloruro de; Tétramisole, Chlorhydrate de; Tetramisoli Hydrochloridum; Тетрамизола Гидрохлорид.
(±)-2,3,5,6-Tetrahydro-6-phenylimidazo[2,1-*b*]thiazole hydrochloride.
$C_{11}H_{12}N_2S$,HCl=240.7
CAS — 5036-02-2 (tetramisole); 5086-74-8 (tetramisole hydrochloride).
UNII — 0NDK265MCV.

Pharmacopoeias. In *Fr.* for veterinary use only.

Profile

Tetramisole hydrochloride is an anthelmintic used in veterinary medicine for the control of nematode infections. It is a racemic mixture and the laevo-isomer, levamisole hydrochloride (p. 157.2), accounts for most of its activity.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***India***: Jetomisol-P.

Thiacetarsamide *(rINNM)*

Arsenamide; Thiacétarsamide; Thiacetarsamidum; Thioarsenite; Tiacetarsamida; Тиацетарсамид.
p-[Bis(carboxymethylmercapto)arsino]benzamide; 4-Carbamylphenyl bis[carboxymethylthio]arsenite.
$C_{11}H_{12}AsNO_5S_2$=377.3
CAS — 531-72-6.
ATC Vet — QP52AX08.
UNII — VMF4ELY9TZ.

Profile

Thiacetarsamide is an arsenical derivative used in veterinary medicine for canine heartworm.

Thiophanate *(BAN)*

Tiofanato; Тиофанат.
4,4'-*o*-Phenylenebis(ethyl 3-thioallophanate).
$C_{14}H_{18}N_4O_4S_2$=370.4
CAS — 23564-06-9.
ATC Vet — QP52AC04.
UNII — 5Q0Y96D5I8.

Profile

Thiophanate is a prodrug that is converted to the benzimidazole anthelmintic lobendazole. It has been used in veterinary medicine for the control of nematode infections.

Tiabendazole *(BAN, rINN)*

E233; MK-360; Thiabendazole (USAN); Thiabendazool; Tiabendatsoli; Tiabendazol; Tiabendazolas; Tiabendazolum; Тиабендазол.
2-(Thiazol-4-yl)-1*H*-benzimidazole.
$C_{10}H_7N_3S$=201.2

CAS — 148-79-8.
ATC — D01AC06; P02CA02.
ATC Vet — QD01AC06; QP52AC10.
UNII — N1Q45E87DT.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Tiabendazole). A white or almost white crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in dichloromethane; it dissolves in dilute mineral acids. Protect from light.

USP 36: (Thiabendazole). A white to practically white, odourless or practically odourless, powder. Practically insoluble in water; slightly soluble in alcohol and in acetone; very slightly soluble in chloroform and in ether.

Uses and Administration

Tiabendazole, a benzimidazole derivative, is an anthelmintic with activity against most nematode worms; activity against some larval stages and ova has also been shown. It is no longer marketed in many countries due to its toxicity and the availability of safer and more effective alternative drugs. The mode of action is not certain, but tiabendazole may inhibit the fumarate-reductase system of worms thereby interfering with their source of energy. Tiabendazole also has antifungal activity and is used commercially as a fungicide.

Tiabendazole has been used in the treatment of cutaneous larva migrans, dracunculiasis (guinea worm infection), strongyloidiasis, trichinosis, and toxocariasis. Tiabendazole is also active against some intestinal nematodes, but should not be used as primary therapy; the treatment of mixed infections including ascariasis is not recommended since tiabendazole may cause the worms to migrate to other body organs causing serious complications. For discussions of the treatment of the above infections see under Choice of Anthelmintic, p. 143.1, and under the individual headings below.

Tiabendazole is given orally, after meals, usually in a dose of 25 mg/kg twice daily for 2 or more days, the duration depending on the type of infection; the daily dose should not exceed 3 g. For those unable to tolerate 2 doses daily, 25 mg/kg may be given after the largest meal on day 1 and repeated 24 hours later after a similar meal on day 2. For mass treatment, a single dose of 50 mg/kg after the evening meal is suggested although the incidence of adverse effects may be higher than with 2 doses of 25 mg/kg.

In **cutaneous larva migrans**, 25 mg/kg may be given twice daily for 2 days, repeated after 2 days if necessary; topical treatment with a 10 to 15% suspension intended for oral use has also been advocated as an alternative or adjunct to oral treatment.

In **dracunculiasis**, 25 to 50 mg/kg may be given twice daily for one day; in massive infection a further 50 mg/kg may be given after 5 to 8 days.

In **strongyloidiasis**, 25 mg/kg may be given twice daily for 2 or 3 days or 50 mg/kg as a single dose; when the infection is disseminated treatment for at least 5 days may be necessary.

In **trichinosis**, 25 mg/kg may be given twice daily for 2 to 4 successive days.

In **toxocariasis**, 25 mg/kg may be given twice daily for 5 to 7 days.

Tiabendazole also has some antifungal activity. It is used as a fungicidal preservative for certain foods.

Dracunculiasis. Tiabendazole[1,2] has been used for symptomatic treatment of dracunculiasis (p. 145.1), although it has no direct anthelmintic effect. It is used to facilitate removal of the worm from subcutaneous tissues.

1. Muller R. Guinea worm disease: epidemiology, control, and treatment. *Bull WHO* 1979; **57**: 683–9.
2. Kale OO, *et al.* Controlled comparative trial of thiabendazole and metronidazole in the treatment of dracontiasis. *Ann Trop Med Parasitol* 1983; **77**: 151–7.

Strongyloidiasis. Tiabendazole has been used in the treatment of strongyloidiasis (p. 148.2), but albendazole or ivermectin are generally preferred.

References.
1. Grove DI. Treatment of strongyloidiasis with thiabendazole: an analysis of toxicity and effectiveness. *Trans R Soc Trop Med Hyg* 1982; **76**: 114–18.
2. Barnish G, Barker J. An intervention study using thiabendazole suspension against strongyloides fuelleborni-like infections in Papua New Guinea. *Trans R Soc Trop Med Hyg* 1987; **81**: 60–3.
3. Boken DJ, *et al.* Treatment of Strongyloides stercoralis hyperinfection syndrome with thiabendazole administered per rectum. *Clin Infect Dis* 1993; **16**: 123–6.
4. Gann PH, *et al.* A randomized trial of single- and two-dose ivermectin versus thiabendazole for treatment of strongyloidiasis. *J Infect Dis* 1994; **169**: 1076–9.
5. Pitisuttithum P, *et al.* A randomized comparative study of albendazole and thiabendazole in chronic strongyloidiasis. *Southeast Asian J Trop Med Public Health* 1995; **26**: 735–8.
6. Schaffel R, *et al.* Thiabendazole for the treatment of strongyloidiasis in patients with hematologic malignancies. *Clin Infect Dis* 2000; **31**: 821–2.

Syngamosis. Tiabendazole has been used successfully[1,2] to treat syngamosis (p. 148.2) when it has occurred in man.

1. Grell GAC, *et al.* Syngamus in a West Indian. *BMJ* 1978; **2**: 1464.
2. Leers W-D, *et al.* Syngamosis, an unusual case of asthma: the first reported case in Canada. *Can Med Assoc J* 1985; **132**: 269–70.

Adverse Effects

Dizziness and gastrointestinal disturbances, especially anorexia, nausea and vomiting, diarrhoea, and abdominal pain are common during treatment with tiabendazole. Other adverse effects occurring occasionally include pruritus, rashes, headache, fatigue, drowsiness, drying of mucous membranes, hyperglycaemia, disturbance of vision including colour vision, leucopenia, tinnitus, effects on the liver including cholestasis and parenchymal damage (in some cases severe and irreversible), enuresis, crystalluria, and bradycardia and hypotension. There have also been reports of erythema multiforme, fatal Stevens-Johnson syndrome, toxic epidermal necrolysis, convulsions, and effects on mental state.

Fever, chills, angioedema, and lymphadenopathy have been reported, but may represent allergic response to dead parasites rather than to tiabendazole.

The urine of some patients taking tiabendazole may have a characteristic odour similar to that after eating asparagus; it is attributed to the presence of a tiabendazole metabolite.

Effects on the salivary glands. Dry mouth with swollen parotid and salivary glands suggestive of the sicca complex preceded the development of cholestatic jaundice in a 17-year-old boy given tiabendazole.[1]

1. Davidson RN, *et al.* Intrahepatic cholestasis after thiabendazole. *Trans R Soc Trop Med Hyg* 1988; **82**: 620.

Hypersensitivity. Severe erythema multiforme developed in a patient 16 days after a course of tiabendazole.[1] Many of the lesions encircled pre-existing melanocytic naevi.

1. Humphreys F, Cox NH. Thiabendazole-induced erythema multiforme with lesions around melanocytic naevi. *Br J Dermatol* 1988; **118**: 855–6.

Precautions

Tiabendazole should be used with caution in patients with hepatic or renal impairment. Tiabendazole causes drowsiness in some patients and those affected should not drive or operate machinery.

Tiabendazole should not be used in mixed worm infections involving *Ascaris lumbricoides* as it can cause the latter to migrate; live worms have emerged through the mouth or nose.

Pregnancy. Tiabendazole is teratogenic in *mice* although there are no adequate and well controlled studies in human pregnancy.

Renal impairment. Tiabendazole and its 5-hydroxy metabolite did not accumulate in an anephric patient on haemodialysis and haemoperfusion who was treated for severe strongyloidiasis.[1] However, the potentially toxic conjugated glucuronide and sulfate metabolites did accumulate. The clearance of all 3 metabolites was poor by haemodialysis; haemoperfusion was much more efficient, although for rapid removal the haemoperfusion columns should be changed every hour.

1. Bauer L, *et al.* The pharmacokinetics of thiabendazole and its metabolites in an anephric patient undergoing hemodialysis and hemoperfusion. *J Clin Pharmacol* 1982; **22**: 276–80.

Interactions

Xanthines. For the effect of tiabendazole on serum concentrations of *theophylline*, see p. 1236.3.

Pharmacokinetics

Tiabendazole is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur after 1 to 2 hours. It is metabolised to 5-hydroxythiabendazole and excreted mainly in the urine as glucuronide or sulfate conjugates; about 90% is recovered in the urine within 48 hours of ingestion, but only 5% in the faeces. Absorption may occur from preparations applied to the skin or eyes.

References.
1. Tocco DJ, *et al.* Absorption, metabolism, and excretion of thiabendazole in man and laboratory animals. *Toxicol Appl Pharmacol* 1966; **9**: 31–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Foldan; *Austral.*: Mintezol†; *Braz.*: Benstatin; Foldan; Micosbel; Thiaben; Thiabose†; Thianax; Tiabiose; Tiadol; Tiaplex; *Chile*: Soldrin; *Gr.*: Mintezol; *Mex.*: Eprofil†; *USA*: Mintezol†.

Multi-ingredient Preparations. *Braz.*: Derms; Polderm Pomada†; Forverm†; Helmiben; Micoplex; Neovermin; Profium†; Thiabena.

Pharmacopoeial Preparations
BP 2014: Tiabendazole Tablets;
USP 36: Thiabendazole Oral Suspension; Thiabendazole Tablets.

Triclabendazole *(BAN, rINN)*

Triclabendazol; Triclabendazolum; Triklabendazol; Триклабендазол.

5-Chloro-6-(2,3-dichlorophenoxy)-2-(methylthio)benzimidazole.

$C_{14}H_9Cl_3N_2OS$=359.6

CAS — 68786-66-3.
ATC — P02BX04.
ATC Vet — QP52AC01.
UNII — 4784C8E03O.

Profile

Triclabendazole is a benzimidazole anthelmintic used for the treatment of the fluke infections, fasciliasis (p. 169.1) and paragonimiasis (p. 169.1). Adverse effects of triclabendazole are usually mild and often include abdominal and epigastric pain, headache, and sweating. Other adverse effects are nausea, vomiting, dizziness, cough, fever, urticaria, and pruritus; rash and leucopenia are uncommon.

For the treatment of **fasciolíasis** adults and children may be given a single oral dose of 10 mg/kg after food; if there has been previous treatment failure this may be followed by a second dose of 10 mg/kg after 12 to 24 hours. Children less than 4 years of age and pregnant or lactating women should be excluded from large-scale interventions, but may be given treatment in a clinical setting where they can be monitored. For the treatment of **paragonimiasis** WHO recommends that adults and children over 4 years of age be given a total daily oral dose of 20 mg/kg after food, in two divided doses.

Liver fluke infections. Although praziquantel is used to treat most food-borne trematode infections, it has little or no efficacy in fasciolíasis (p. 146.2) and triclabendazole is considered to be the drug of choice.[1,2] Several studies[3-8] have shown the efficacy of triclabendazole in fasciolíasis.

1. Keiser J, *et al.* Triclabendazole for the treatment of fascioliasis and paragonimiasis. *Expert Opin Invest Drugs* 2005; **14**: 1513–26.
2. Abramowicz M, ed. *Drugs for parasitic infections*. 3rd ed. New Rochelle NY: The Medical Letter, 2013.
3. Apt W, *et al.* Treatment of human chronic fascioliasis with triclabendazole: drug efficacy and serologic response. *Am J Trop Med Hyg* 1995; **52**: 532–5.
4. El-Karaksy H, *et al.* Human fasciolíasis in Egyptian children: successful treatment with triclabendazole. *J Trop Pediatr* 1999; **45**: 135–8.
5. Millán JC, *et al.* The efficacy and tolerability of triclabendazole in Cuban patients with latent and chronic Fasciola hepatica infection. *Am J Trop Med Hyg* 2000; **63**: 264–9.
6. Graham CS, *et al.* Imported Fasciola hepatica infection in the United States and treatment with triclabendazole. *Clin Infect Dis* 2001; **33**: 1–5.
7. Talaie H, *et al.* Randomized trial of a single, double and triple dose of 10 mg/kg of a human formulation of triclabendazole in patients with fasciolíasis. *Clin Exp Pharmacol Physiol* 2004; **31**: 777–82.
8. Marcos LA, *et al.* Natural history, clinicoradiologic correlates, and response to triclabendazole in acute massive fasciolíasis. *Am J Trop Med Hyg* 2008; **78**: 222–7.

Lung fluke infections. Although praziquantel is usually given as the drug of choice in the treatment of paragonimiasis (p. 146.3), triclabendazole is recommended as an alternative.[1] Encouraging results were reported from a pilot study of triclabendazole.[2] In an open comparative study[3] in 62 patients, a more rapid parasitological response was obtained with triclabendazole in oral doses of 5 mg/kg once daily for 3 days, 10 mg/kg twice on one day, or 10 mg/kg as a single dose, than with praziquantel. Clinical symptoms resolved at a comparable rate in all groups. A later study compared the two one-day regimens in 154 patients.[4] After 3 months, the cure rates (assessed by clearance of eggs from sputum) were 84.4% in those given a single dose of 10 mg/kg, and 90.9% in those given two such doses on the same day. In those who were still infected at 3 months, a second two-dose course resulted in complete parasitological clearance at 1 year.

1. Abramowicz M, ed. *Drugs for parasitic infections*. 3rd ed. New Rochelle NY: The Medical Letter, 2013.
2. Ripert C, *et al.* Therapeutic effect of triclabendazole in patients with paragonimiasis in Cameroon: a pilot study. *Trans R Soc Trop Med Hyg* 1992; **86**: 417.
3. Calvopiña M, *et al.* Treatment of human pulmonary paragonimiasis with triclabendazole: clinical tolerance and drug efficacy. *Trans R Soc Trop Med Hyg* 1998; **92**: 566–9.
4. Calvopiña M, *et al.* Comparison of two single-day regimens of triclabendazole for the treatment of human pulmonary paragonimiasis. *Trans R Soc Trop Med Hyg* 2003; **97**: 451–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Egaten; *Gr.*: Egaten.

The symbol † denotes a preparation no longer actively marketed

Antibacterials

This chapter includes antimicrobial drugs whose main use is the treatment and prophylaxis of bacterial infections. In practice the term 'antibiotics' is often, and in some instances erroneously, used to encompass all of these drugs. In *Martindale* the term antibacterial is preferred for the drugs in this chapter. The groups into which these drugs may be categorised are described p. 170.1. Antibacterials described elsewhere in *Martindale* include metronidazole (p. 938.1), nitazoxanide (p. 944.2), and tinidazole (p. 951.3), which, as well as being antiprotozoals, are used in the treatment of anaerobic bacterial infections.

Immunological approaches to the treatment and prophylaxis of bacterial infections are discussed under Vaccines Immunoglobulins and Antisera, p. 2373.1.

In addition, disinfectants and preservatives (p. 1731.1) are used to kill or inhibit the growth of micro-organisms.

Drug Groups

Although antibacterials are very diverse compounds they are often classified and discussed in groups. They may be classified according to their mode of action or spectrum of antimicrobial activity, but generally those with similar chemical structures are grouped together.

Aminoglycosides

The aminoglycosides are a closely related group of bactericidal antibacterials derived from bacteria of the order Actinomycetales or, more specifically, the genus *Streptomyces* (framycetin, kanamycin, neomycin, paromomycin, streptomycin, and tobramycin) and the genus *Micromonospora* (gentamicin and sisomicin). They are polycationic compounds that contain an aminocyclitol, usually 2-deoxystreptamine, or streptidine in streptomycin and related compounds, with cyclic amino-sugars attached by glycosidic linkages. Therefore, they have also been termed aminoglycosidic aminocyclitols. The sulfate salts are generally used.

The aminoglycosides have broadly similar toxicological features. Ototoxicity is a major limitation to their use; streptomycin and gentamicin are generally considered to be more toxic to the vestibular branch of the eighth cranial nerve and neomycin and kanamycin to be more toxic to the auditory branch. Other adverse effects common to the group include nephrotoxicity, neuromuscular blockade, and allergy, including cross-reactivity.

The pharmacokinetics of the aminoglycosides are very similar. Little is absorbed from the gastrointestinal tract but they are generally well distributed in the body after parenteral dosage although penetration into the CSF is poor. They are excreted unchanged in the urine by glomerular filtration.

The aminoglycosides have a similar antimicrobial spectrum and appear to act by interfering with bacterial protein synthesis, possibly by binding irreversibly to the 30S and to some extent the 50S portions of the bacterial ribosome. The manner in which they bring about cell death is not fully understood. They are most active against Gram-negative rods. *Staphylococcus aureus* is susceptible to the aminoglycosides but otherwise most Gram-positive bacteria, and also anaerobic bacteria, are naturally resistant. Aminoglycosides show enhanced activity with penicillins against some enterococci and streptococci. Bacterial resistance to streptomycin may occur by mutation, whereas with the other aminoglycosides it is usually associated with the plasmid-mediated production of inactivating enzymes which are capable of phosphorylation, acetylation, or adenylation. The aminoglycosides have a postantibiotic effect, that is antibacterial activity persisting after concentrations have dropped below minimum inhibitory concentrations.

Streptomycin was the first aminoglycoside to become available commercially and was isolated from a strain of *Streptomyces griseus* in 1944. Its use is now restricted mainly to the treatment of tuberculosis when it is always given with other antituberculous drugs because of the rapid development of resistance. *Dihydrostreptomycin*, a reduction product of streptomycin, is only rarely used because of its toxicity. The *neomycin* complex of antibacterials were the next to be isolated; neomycin itself is mainly a mixture of the B and C isomers; neomycin B is considered to be identical with *framycetin*. Because of their toxicity they are not given systemically. The related compound *paromomycin* (p. 945.3) also has antiprotozoal and anthelmintic properties and may be used in the treatment of intestinal amoebiasis, cestode infections, cryptosporidiosis, and leishmaniasis. *Kanamycin* is less toxic than neomycin and can be used systemically. Although it has been used in penicillin-resistant gonorrhoea, it is not active against *Pseudomonas aeruginosa* and has generally been replaced by gentamicin and other newer aminoglycosides.

Gentamicin was isolated from *Micromonospora purpurea* in 1963 and, being active against *Ps. aeruginosa* and *Serratia marcescens*, is widely used in the treatment of life-threatening infections. *Tobramycin* is one of several components of the nebramycin complex of aminoglycosides produced by *Streptomyces tenebrarius*. It has an antimicrobial spectrum very similar to that of gentamicin and is reported to be more active against *Ps. aeruginosa*. *Amikacin*, a

semisynthetic derivative of kanamycin, has a side-chain rendering it less susceptible to inactivating enzymes. It has a spectrum of activity like that of gentamicin but Gram-negative bacteria resistant to gentamicin, tobramycin, and kanamycin are often sensitive. *Sisomicin* is closely related structurally to gentamicin. *Netilmicin*, the *N*-ethyl derivative of sisomicin, may be active against some gentamicin-resistant strains of bacteria although not to the same extent as amikacin. Other aminoglycosides include *apramycin*, *arbekacin*, *astromicin*, *bekanamycin*, *dibekacin*, *etimicin*, *isepamicin*, and *micronomicin*.

Aminoglycosides should in general only be used for the treatment of serious infections because of their potential toxicity and antimicrobial spectrum. Doses must be carefully regulated to maintain plasma concentrations within the therapeutic range but avoid accumulation, especially in patients with renal impairment. Neomycin and framycetin, which are considered too toxic to be given parenterally, have been given orally to suppress the intestinal flora. The topical use of neomycin and gentamicin has been associated with allergic reactions and the emergence of resistant bacteria. Gentamicin or tobramycin are the drugs of choice in the treatment of life-threatening infections due to aminoglycoside-sensitive organisms and are often used with other antibacterials. With the continuing emergence of resistant strains, amikacin and netilmicin should be reserved for severe infections resistant to gentamicin and the other aminoglycosides.

Described in this chapter are

Antimycobacterials

The antimycobacterials are a miscellaneous group of antibacterials whose spectrum of activity includes *Mycobacterium* spp. and which are used in the treatment of tuberculosis, leprosy, and other mycobacterial infections. They include the rifamycins, also known as ansamycins or rifomycins, a group of antibacterials isolated from a strain of *Amycolatopsis mediterranei* (*Nocardia mediterranei*; *Streptomyces mediterranei*). The main antibacterial in this group, *rifampicin*, is a mainstay of regimens for the treatment of tuberculosis and leprosy, and is increasingly being used for other infections. The related drug *rifabutin* is also used in mycobacterial disease, especially nontuberculous mycobacterial infections due to *Mycobacterium avium* complex (MAC). Other rifamycins described in this chapter include *rifapentine*, *rifaximin* which is poorly absorbed and is mainly used for a local effect on the gastrointestinal tract, and *rifamycin sodium*, a rifamycin rarely used as it has been superseded by more effective drugs.

Another antimycobacterial widely used for tuberculosis is *isoniazid*, a derivative of isonicotinic acid; it is invariably used with other drugs to avoid or delay emergence of resistance. *Pyrazinamide*, a nicotinamide derivative, is also an important component of regimens for tuberculosis, while *ethambutol* and the aminoglycoside *streptomycin* are added when resistance to first-line drugs is likely. The thiosemicarbazone derivative *thioacetazone* is now less widely used in tuberculosis because of its toxicity and because more effective drugs are available, but is sometimes used in developing countries. Other drugs that have been used to treat tuberculosis including *aminosalicylic acid* and its salts, *bedaquiline fumarate*, *capreomycin*, *cycloserine*, *ethionamide*, *protionamide*, and *kanamycin* are regarded as secondary drugs and are reserved for patients in whom resistance or toxicity to first-line drugs is a problem. Delamanid is an imidazole derivative under investigation for multidrug-resistant tuberculosis.

The sulfones have been used since the 1940s in the treatment of leprosy, but the only one widely used now is *dapsone*, an important component of multidrug regimens. Its action is thought to involve inhibition of folate metabolism, similarly to the sulfonamides, and dapsone is also used for the prophylaxis of malaria and for prophylaxis and treatment of pneumocystis pneumonia. Also important in the treatment of leprosy is the phenazine dye *clofazimine*. Additionally, it has a role in the treatment of type 2 lepra reactions and has been used in other mycobacterial infections. The thioamides *ethionamide* and *protionamide* have been used in the treatment of leprosy and tuberculosis, but have generally been replaced by less toxic drugs, for example *clarithromycin*, *ofloxacin*, *minocycline*, or *pefloxacin*, in alternative antileprotic regimens.

Described in this chapter are

Cephalosporins and related beta lactams

The cephalosporins or cephem antibacterials are semisynthetic antibacterials derived from cephalosporin C, a natural antibacterial produced by the mould *Cephalosporium acremonium*. The active nucleus, 7-aminocephalosporanic acid, is very closely related to the penicillin nucleus, 6-aminopenicillanic acid, and consists of a beta-lactam ring fused with a 6-membered dihydrothiazine ring and having an acetoxymethyl group at position 3. Cephalosporin C has a side-chain at position 7 derived from D-α-aminoadipic acid. Chemical modification of positions 3 and 7 has resulted in a series of drugs with different characteristics. Substitution at the 7-amino group tends to affect antibacterial action whereas at position 3 it may have more of an effect on pharmacokinetic properties.

The cephalosporins are bactericidal and, like the penicillins, they act by inhibiting synthesis of the bacterial cell wall. The most widely used system of classification of cephalosporins is by generations and is based on the general features of their antibacterial activity, but may depend to some extent on when they were introduced. Succeeding generations generally have increasing activity against Gram-negative bacteria. *Cefalotin* was one of the first cephalosporins to become available and is representative of the **first-generation** cephalosporins. It has good activity against a wide spectrum of Gram-positive bacteria including penicillinase-producing, but not meticillin-resistant, staphylococci; enterococci are, however, resistant. Its activity against Gram-negative bacteria is modest. Cefalotin is not absorbed from the gastrointestinal tract and must be given parenterally although intramuscular dosage is painful. Cefalotin has generally been replaced by *cefazolin* or *cefradine*. *Cefaloridine* is now rarely used because of its nephrotoxicity. Cefradine is absorbed from the gastrointestinal tract and can be given both orally and by injection. *Cefadroxil*, *cefatrizine*, and *cefalexin* are all given orally. All of these drugs have a very similar spectrum of antimicrobial activity to cefalotin. *Cefaclor* is also given orally. It has similar activity to cefalotin against Gram-positive cocci, but because of its greater activity against Gram-negative bacteria, particularly *Haemophilus influenzae*, it is often classified as a second-generation drug. *Cefprozil* is an oral cephalosporin with a longer half-life than cefaclor.

Cefamandole was the first available **second-generation** cephalosporin. It has similar or slightly less activity than cefalotin against Gram-positive bacteria, but greater stability to hydrolysis by beta lactamases produced by Gram-negative bacteria and enhanced activity against many of the Enterobacteriaceae and *Haemophilus influenzae*. It is given parenterally. *Cefuroxime* has a similar spectrum of activity to cefamandole although it is even more resistant to hydrolysis by beta lactamases. It is given parenterally but, *cefuroxime axetil*, the acetoxyethyl ester of cefuroxime, is given orally. Other drugs classified as second-generation cephalosporins and given parenterally include *cefonicid*, *ceforanide*, and *cefotiam*; these all have spectra of activity similar to cefamandole. Cephamycins (see below) are also classified with second-generation cephalosporins.

The **third-generation** cephalosporins, sometimes referred to as **extended-spectrum** cephalosporins, are even more stable to hydrolysis by beta lactamases than cefamandole and cefuroxime. Compared with the earlier generations of cephalosporins they have a wider spectrum and greater potency of activity against Gram-negative organisms, including most clinically important Enterobacteriaceae. Their activity against Gram-positive organisms is said to be less than that of the first-generation drugs, but they are very active against streptococci. *Cefotaxime* was the first of this group to become available and it has relatively modest activity against *Pseudomonas aeruginosa*. *Cefmenoxime*, *cefodizime*, *ceftizoxime*, and *ceftriaxone* are all very similar to cefotaxime in their antimicrobial activity. These drugs are all given parenterally and differ mainly in their pharmacokinetic characteristics. *Cefixime* is a third-generation cephalosporin given orally; others include *cefdinir*, *cefetamet pivoxil*, *cefpodoxime proxetil*, and *ceftibuten*. *Ceftazidime* is typical of a group of parenteral third-generation cephalosporins with enhanced activity against *Ps. aeruginosa*. *Cefoperazone* is similar in its activity to ceftazidime. *Cefpiramide* is structurally related to cefoperazone and has comparable activity. Although *cefsulodin* is classified as a third-generation cephalosporin its activity against Gram-negative bacteria is confined to *Ps. aeruginosa*. *Latamoxef* is an **oxacephalosporin** which differs from the true cephalosporins in that the sulfur atom of the 7-aminocephalosporanic acid nucleus is replaced by an oxygen atom. It differs from cefotaxime mainly in its enhanced activity against *Bacteroides fragilis*.

The newer cephalosporins *cefepime* and *cefpirome* are generally considered to be **fourth-generation** because of their broad spectrum of activity. *Ceftobiprole* and *ceftaroline* are active against meticillin-resistant staphylococci, and are therefore sometimes termed **fifth-generation** cephalosporins.

The semisynthetic **cephamycins** are chemical modifications of cephamycin C, a beta-lactam antibacterial produced naturally by *Streptomyces* spp. They differ from the cephalosporins by the addition of a 7-α-methoxy group to the 7-aminocephalosporanic acid nucleus. Steric hindrance by this methoxy group is considered to be responsible for their greater stability to beta lactamases. For practical purposes they are generally classified with the second-generation cephalosporins, but are more active against anaerobic bacteria, especially *Bacteroides fragilis*. *Cefoxitin* was one of the first cephamycins available; *cefmetazole* and *cefotetan* have been introduced more recently. Another is *cefminox*. All these cephamycins must be given parenterally.

Imipenem was the first of the **carbapenem** group of antibacterials to become available; it is the *N*-formimidoyl derivative of thienamycin which is produced by *Streptomyces cattleya*. It is bactericidal, and, similarly to the cephalosporins, acts by inhibiting synthesis of the bacterial cell wall. It has a very broad spectrum of antimicrobial activity including Gram-positive and Gram-negative aerobic and anaerobic organisms; it has good activity against both *Ps. aeruginosa* and *B. fragilis*. Imipenem is given parenterally with cilastatin, a dehydropeptidase I inhibitor that inhibits the renal metabolism of imipenem. Similarly, the carbapenem panipenem is given with the renal protectant betamipron. Two other carbapenems, *ertapenem* and *meropenem*, are relatively stable to renal dehydropeptidase and can be used without such an inhibitor. Ertapenem has a narrower spectrum of activity than other carbapenems, including no activity against *Ps. aeruginosa*. *Doripenem* is a carbapenem claimed to have particular activity against *Ps. aeruginosa*.

The **monobactams** were first identified as monocyclic beta lactams isolated from bacteria; they are now produced synthetically. *Aztreonam* was the first commercially available monobactam. It is bactericidal with a similar action on bacterial cell-wall synthesis to the cephalosporins. Its antimicrobial activity, however, differs from imipenem and the newer cephalosporins in that it is restricted to Gram-negative aerobic organisms. It has good activity against *Ps. aeruginosa*. Aztreonam is given parenterally. Other monobactams include *carumonam*.

Carbacephems are structurally related to the cephalosporins, but the sulfur atom of the 7-aminocephalosporanic acid nucleus is replaced by a methylene group. *Loracarbef* is an oral carbacephem.

Described in this chapter are

Chloramphenicols

Chloramphenicol is an antibacterial which was first isolated from cultures of *Streptomyces venezuelae* in 1947 but is now produced synthetically. It has a relatively simple structure and is a derivative of dichloroacetic acid with a nitrobenzene moiety. Chloramphenicol was the first broad-spectrum antibacterial to be discovered; it acts by interfering with bacterial protein synthesis and is mainly bacteriostatic. Its range of activity is similar to that of tetracycline and includes Gram-positive and Gram-negative bacteria, Rickettsia spp., and Chlamydiaceae. The sensitivities of *Salmonella typhi*, *Haemophilus influenzae*, and *Bacteroides*

fragilis to chloramphenicol have dictated the principal indications for its use.

Shortly after its introduction chloramphenicol was found to have a serious and sometimes fatal depressant effect on the bone marrow. The 'grey syndrome', another potentially fatal adverse effect, was reported later in neonates. As a result of this toxicity the systemic use of chloramphenicol has been restricted in many countries; it should only be given when there is no suitable alternative and never for minor infections.

Chloramphenicol is active when given orally and, unlike most other antibacterials, it diffuses into the CSF even when the meninges are not inflamed. The majority of a dose is inactivated in the liver, only a small proportion appearing unchanged in the urine.

Chloramphenicol is widely used for typhoid fever, although resistance is a problem in some countries. For *Haemophilus influenzae* infections, especially meningitis, the emergence of ampicillin-resistant strains led to a reappraisal of the use of chloramphenicol, and suggestions that ampicillin and chloramphenicol should both be given empirically to patients with meningitis until the sensitivity of the infecting organisms was known, but the newer third-generation cephalosporins are increasingly preferred because of resistance. For proven *H. influenzae* meningitis, chloramphenicol is used as an alternative to the third-generation cephalosporins, which are now regarded as treatment of choice. Chloramphenicol is also effective against many anaerobic bacteria and may be valuable in such conditions as cerebral abscess where anaerobes such as *Bacteroides fragilis* are often involved, although metronidazole may be preferred.

Chloramphenicol sodium succinate is used parenterally and the palmitate is given orally. Ophthalmic and other topical preparations of chloramphenicol are used widely in some countries.

Thiamphenicol is a semisynthetic derivative of chloramphenicol in which the nitro group on the benzene ring has been replaced by a methylsulfonyl group, resulting, in general, in a loss of activity *in vitro*. It has been claimed that thiamphenicol is less toxic than chloramphenicol and there have been fewer reports of aplastic anaemia but reversible bone-marrow depression may occur more frequently. It is also less likely to cause the 'grey syndrome'. Unlike chloramphenicol, thiamphenicol is not metabolised in the liver to any extent and is excreted largely unchanged in the urine. It has been used similarly to chloramphenicol in some countries.

Azidamfenicol is another analogue of chloramphenicol that has been used topically in the treatment of eye infections.

Described in this chapter are

Azidamfenicol, p. 223.1
Chloramphenicol, p. 259.1
Florfenicol, p. 301.1
Thiamphenicol, p. 378.3

Glycopeptides

Vancomycin has a glycopeptide structure; it acts by interfering with bacterial cell wall synthesis and is very active against Gram-positive cocci. Intravenous vancomycin is reserved for the treatment of severe staphylococcal infections and for the treatment and prophylaxis of endocarditis when other antibacterials cannot be used, either because of patient sensitivity or bacterial resistance. It is the treatment of choice for infections caused by meticillin-resistant staphylococci. Vancomycin hydrochloride is poorly absorbed when taken orally; it is used in the treatment of pseudomembranous colitis. *Teicoplanin* is a glycopeptide with similar properties to vancomycin, but a longer duration of action. It can be given intramuscularly as well as intravenously. *Telavancin* also has similar properties to vancomycin and is given intravenously for complicated skin and skin structure infections and nosocomial pneumonia (including ventilator associated pneumonia) known or suspected to be caused by MRSA. *Ramoplanin* is under investigation, especially for the treatment of *Clostridium difficile*-associated diarrhoea. It has also been investigated for the prevention of infection due to vancomycin-resistant enterococci. Also under investigation are *dalbavancin* and *oritavancin*.

Described in this chapter are

Avoparcin, p. 223.1
Dalbavancin, p. 283.2
Norvancomycin, p. 336.2
Oritavancin, p. 338.1
Ramoplanin, p. 350.1
Teicoplanin, p. 371.3
Telavancin, p. 373.1
Vancomycin, p. 386.2

Lincosamides

Lincomycin is an antibacterial produced by a strain of *Streptomyces lincolnensis* and was first described in 1962; *clindamycin* is the 7-chloro-7-deoxy derivative of lincomycin.

Although not related structurally to erythromycin and the other macrolide antibacterials, the lincosamides have similar antimicrobial activity and act at the same site on the bacterial ribosome to suppress protein synthesis.

The lincosamides are bacteriostatic or bactericidal, depending on the concentration, and are active mainly against Gram-positive bacteria, and against *Bacteroides* spp. They also appear to have some antiprotozoal activity. Clindamycin and lincomycin have qualitatively similar activity but clindamycin is more active than lincomycin *in vitro*. Cross-resistance occurs between the lincosamides, macrolides, and streptogramins.

The lincosamides have been used, like erythromycin, as an alternative to penicillin, but reports of severe and sometimes fatal pseudomembranous colitis with lincomycin and clindamycin have led to the recommendation that they should only be used when there is no suitable alternative.

Both lincomycin and clindamycin can be given orally and parenterally, but clindamycin is much better absorbed from the gastrointestinal tract and less affected by the presence of food in the stomach. They both penetrate well into bone and have been used successfully in osteomyelitis. They have also been used topically in the treatment of acne vulgaris.

The main indication for the use of lincosamides is now in the treatment of severe anaerobic infections, although metronidazole (p. 938.2) or some beta lactams may be a more suitable choice in such infections. Clindamycin also has a role in the prophylaxis of endocarditis in penicillin-allergic patients and has been used, usually with other antiprotozoals, in babesiosis, chloroquine-resistant malaria, toxoplasmosis, and pneumocystis pneumonia.

Described in this chapter are

Clindamycin, p. 271.3
Lincomycin, p. 319.1
Pirlimycin, p. 343.3

Macrolides

The macrolides are a large group of antibacterials mainly derived from *Streptomyces* spp. and having a common macrocyclic lactone ring to which one or more sugars are attached. They are all weak bases and only slightly soluble in water. Their properties are very similar and in general they have low toxicity and a similar spectrum of antimicrobial activity with cross-resistance between individual members of the group. The macrolides are bacteriostatic or bactericidal, depending on the concentration and the type of micro-organism, and are thought to interfere with bacterial protein synthesis. Their antimicrobial spectrum is similar to that of benzylpenicillin but they are also active against such organisms as *Legionella pneumophila, Mycoplasma pneumoniae,* and some rickettsias, chlamydias, and chlamydophilas. Macrolides and related drugs have a postantibiotic effect: that is, antibacterial activity persists after concentrations have dropped below the minimum inhibitory concentration.

Erythromycin was discovered in 1952 and is the macrolide used most widely. It is destroyed by gastric acid and must therefore be given as enteric-coated formulations or as one of its more stable salts or esters such as the stearate or ethyl succinate. Hepatotoxicity has been reported after the use of erythromycin, most commonly as the estolate. Erythromycin lactobionate or gluceptate may be given intravenously. Cardiac arrhythmias have been reported occasionally after intravenous use. Erythromycin is used as an alternative to penicillin in many infections, especially in patients who are allergic to penicillin. It has similar uses to tetracycline in the treatment of infections due to *Mycoplasma pneumoniae* and *Chlamydia trachomatis*, and in acne vulgaris. It is also used in the treatment of infections caused by *Legionella pneumophila*.

More recently developed macrolides include *azithromycin, clarithromycin, dirithromycin,* and *roxithromycin*. These drugs all appear to have similar properties to erythromycin although they may differ in their pharmacokinetics. Clarithromycin and, to a lesser extent, azithromycin are more active than erythromycin against opportunistic mycobacteria such as *Mycobacterium avium* complex. Clarithromycin is also used in the treatment of leprosy and in regimens for the eradication of *Helicobacter pylori* in peptic ulcer disease. Both azithromycin and clarithromycin have activity against protozoa including *Toxoplasma gondii*.

Flurithromycin is another newer macrolide in use.

Other macrolides include *spiramycin*, which has been used extensively in Europe and has also been used in the treatment and prophylaxis of toxoplasmosis. It may be useful in the treatment of cryptosporidiosis.

Oleandomycin has been used orally and parenterally as the phosphate. Its ester, *troleandomycin*, is better absorbed from the gastrointestinal tract but, like erythromycin estolate, has proved hepatotoxic and more effective antibacterials are generally preferred. *Josamycin, kitasamycin, midecamycin,* and *rokitamycin* have been used in Europe and/or Japan. *Meleumycin* has been used in China.

Tilmicosin, tulathromycin, and *tylosin* are used in veterinary practice.

The **streptogramin** group of antibacterials are also derived from *Streptomyces* spp. and include *pristinamycin* and *virginiamycin*. They consist of two components that act synergistically and are therefore also known as synergistins. One of the components is structurally related to the macrolides, and they have a similar spectrum of antimicrobial activity to erythromycin. Semisynthetic derivatives such as *quinupristin/dalfopristin* may be useful in the treatment of infections with multidrug-resistant organisms including meticillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci.

Cross-resistance often occurs between the macrolides, lincosamides, and streptogramins. The **ketolide** antibacterials *telithromycin* and *cethromycin* are semisynthetic derivatives of erythromycin A that have been developed to overcome macrolide resistance in respiratory-tract pathogens.

Described in this chapter are

Azithromycin, p. 223.2
Cethromycin, p. 259.1
Clarithromycin, p. 268.2
Dirithromycin, p. 289.1
Erythromycin, p. 293.2
Flurithromycin, p. 302.2
Josamycin, p. 316.2
Kitasamycin, p. 317.2
Meleumycin, p. 323.2
Midecamycin, p. 326.3
Oleandomycin, p. 337.3
Pristinamycin, p. 346.1
Quinupristin/Dalfopristin, p. 349.1
Rokitamycin, p. 358.1
Roxithromycin, p. 358.2
Spiramycin, p. 360.3
Telithromycin, p. 373.3
Tilmicosin, p. 382.1
Troleandomycin, p. 385.2
Tulathromycin, p. 385.2
Tylosin, p. 385.3
Virginiamycin, p. 389.3

Penicillins

Penicillin was the first antibacterial to be used therapeutically and was originally obtained, as a mixture of penicillins known as F, G, X, and K, from the mould *Penicillium notatum*. Better yields were achieved using *P. chrysogenum* and benzylpenicillin (penicillin G) was selectively produced by adding the precursor phenylacetic acid to the fermentation medium. The term 'penicillin' is now used generically for the entire group of natural and semisynthetic penicillins. Penicillins are still widely used; they are generally well tolerated, apart from hypersensitivity reactions, and are usually bactericidal by virtue of their inhibitory action on the synthesis of the bacterial cell wall.

Penicillins all have the same ring structure and are monobasic acids that readily form salts and esters; 6-aminopenicillanic acid, the penicillin nucleus, consists of a fused thiazolidine ring and a beta-lactam ring with an amino group at the 6-position.

The earlier or so-called 'natural' penicillins were produced by adding different side-chain precursors to fermentations of the *Penicillium* mould; *benzylpenicillin*, with a phenylacetamido side-chain at the 6-position, and *phenoxymethylpenicillin* (penicillin V), with a phenoxyacetamido side-chain, were 2 of the first and are still widely used. Benzylpenicillin can be considered the parent compound of the penicillins and is active mainly against Gram-positive bacteria and *Neisseria* spp. It is inactivated by penicillinase-producing bacteria and because of its instability in gastric acid it is usually injected. Long-acting preparations include *procaine benzylpenicillin* and *benzathine benzylpenicillin*, which slowly release benzylpenicillin after injection. Phenoxymethylpenicillin is acid-stable and is therefore given orally but it is also inactivated by penicillinase. It is generally used for relatively mild infections.

When no side-chain precursor is added to the fermentation medium, 6-aminopenicillanic acid itself is obtained. A range of penicillins has been synthesised from 6-aminopenicillanic acid by substitution at the 6-amino position in an effort to improve on the instability of benzylpenicillin to gastric acid and penicillinases, to widen its antimicrobial spectrum, and to reduce its rapid rate of renal excretion. Phenoxypenicillins with an α-phenoxypropionamido (*pheneticillin*) or α-phenoxybutyramido (*propicillin*) side-chain are more stable to acid than benzylpenicillin but offer no advantage over phenoxymethylpenicillin.

Meticillin has a 2,6-dimethoxybenzamido group at the 6-position and was the first penicillin found to be resistant to destruction by staphylococcal penicillinase. However, it is not acid-resistant and has to be injected. The isoxazolyl penicillins, *cloxacillin, dicloxacillin, flucloxacillin,* and *oxacillin,* are resistant to penicillinase and gastric acid. They have very similar chemical structures and differ mainly in their absorption characteristics. *Nafcillin* is a similar penicillinase-resistant antibacterial but is irregularly absorbed when taken orally.

Ampicillin has a D(-)-α-aminophenylacetamido side-chain and a broader spectrum of activity than benzylpenicillin; although generally less active against Gram-positive bacteria, some Gram-negative organisms including *Escherichia coli, Haemophilus influenzae,* and *Salmonella* spp. are sensitive although resistance is being reported increasingly. *Pseudomonas* spp. are not sensitive. Ampicillin is acid-stable and can be given orally but is destroyed by penicillinase. Prodrugs such as *bacampicillin* and *pivampicillin* are also said to be better absorbed and are hydrolysed to ampicillin *in vivo*. *Amoxicillin,* with a D(-)-α-aminohydroxyphenylacetamido side-chain, only differs from ampicillin by the addition

of a hydroxyl group, but is better absorbed from the gastrointestinal tract.

Carbenicillin, with an α-carboxyphenylacetamido side-chain, has marked activity against *Pseudomonas aeruginosa* and some *Proteus* spp. but otherwise is generally less active than ampicillin. It has to be given by injection and large doses are required. *Carindacillin* is the indanyl ester of carbenicillin and is hydrolysed to carbenicillin *in vivo* when taken orally. *Sulbenicillin* has an α-phenylsulfoacetamido side-chain and *ticarcillin* an α-carboxythienylacetamido side-chain and both have similar activity to carbenicillin; ticarcillin is more active against *Ps. aeruginosa*. The ureidopenicillins *azlocillin* and *mezlocillin*, and the closely related drug *piperacillin* are more active than carbenicillin against *Ps. aeruginosa* and have a wider range of activity against Gram-negative bacteria.

Temocillin, a 6-α-methoxy derivative of ticarcillin, is resistant to many beta lactamases and is active against most Gram-negative aerobic bacteria, but not *Ps. aeruginosa*.

Mecillinam is a penicillanic acid derivative with a substituted amidino group in the 6-position. Unlike the 6-aminopenicillanic acid derivatives it is active mainly against Gram-negative bacteria, although *Ps. aeruginosa*, and *Bacteroides* spp. are considered resistant. Mecillinam itself is not active orally; it is given as *pivmecillinam*, which is hydrolysed to mecillinam on absorption.

The beta-lactamase inhibitors *clavulanic acid*, *sulbactam*, and *tazobactam* are used to extend the antimicrobial range of certain beta-lactam antibacterials.

Described in this chapter are

Quinolones

The quinolonecarboxylic acids, carboxyquinolones, or 4-quinolones are a group of synthetic antibacterials structurally related to nalidixic acid. The term 4-quinolone has been used as a generic name for the common 4-oxo-1,4-dihydroquinoline skeleton. Under this system nalidixic acid, a naphthyridene derivative, is an 8-aza-4-quinolone, cinoxacin, a cinnoline derivative, is a 2-aza-4-quinolone, and pipemidic and piromidic acids, pyrido-pyrimidine derivatives, are 6,8-diaza-4-quinolones.

Nalidixic acid is active against Gram-negative bacteria but has little activity against *Pseudomonas* and Gram-positive organisms. Because bactericidal concentrations can only be achieved in urine its use has generally been limited to the treatment of urinary-tract infections.

Modification of the structure of nalidixic acid has produced related antibacterials such as *oxolinic acid*, *cinoxacin*, and *rosoxacin*. Although some of these have a greater activity *in vitro* against Gram-negative organisms and activity against some Gram-positive organisms, none has been considered to represent a significant clinical advance over nalidixic acid; rosoxacin is only used in the treatment of gonorrhoea. Addition of a piperazinyl radical at position 7, as in *pipemidic acid*, appears to confer some activity against *Pseudomonas*. *Flumequine* was the first fluorinated 4-quinolone to be synthesised, but has no piperazinyl group. Addition of the 7-piperazinyl group and a fluorine atom at position 6 has produced a group of fluorinated piperazinyl quinolones or **fluoroquinolones** with a broader spectrum of activity than nalidixic acid and pharmacokinetic properties more suitable for the treatment of systemic infections. They include *ciprofloxacin*, *enoxacin*, *fleroxacin*, *gatifloxacin*, *gemifloxacin*, *levofloxacin*, *lomefloxacin*, *moxifloxacin*, *nadifloxacin*, *norfloxacin*, *ofloxacin*, *pazufloxacin*, *pefloxacin*, *rufloxacin*, and *sparfloxacin*. *Besifloxacin* is used topically. Several fluoroquinolones have been withdrawn because of toxicity including: *alatrofloxacin*, *clinafloxacin*, *grepafloxacin*, *temafloxacin*, and *trovafloxacin*. *Danofloxacin*, *enrofloxacin*, *ibafloxacin*, *marbofloxacin*, *orbifloxacin*, and *sarafloxacin* are used in veterinary practice. Development of *difloxacin* for human use was suspended because of the high incidence of adverse effects, but it is used in veterinary practice.

The fluoroquinolones are very active against aerobic Gram-negative bacilli and cocci including the Enterobacteriaceae, *Haemophilus influenzae*, *Moraxella catarrhalis* (*Branhamella catarrhalis*), and *Neisseria gonorrhoeae* and are also active against *Pseudomonas aeruginosa*. They are generally less active against Gram-positive organisms such as staphylococci and much less active against streptococci such as *Streptococcus pneumoniae*, although some fluoroquinolones now developed have increased activity against these organisms. They also have activity against mycobacteria, mycoplasmas, and rickettsias. Some, for example ofloxacin, have useful activity against *Chlamydia trachomatis*. Activity against anaerobic bacteria is generally poor. There is concern that the emergence of resistant strains of organisms may limit the usefulness of fluoroquinolones.

One disadvantage of the quinolone antibacterials is that they are generally not recommended for use in children, adolescents, and pregnant or breast-feeding women because of their propensity to cause joint erosions in immature *animals*.

Described in this chapter are

Sulfonamides and diaminopyrimidines

The sulfonamides are analogues of *p*-aminobenzoic acid. The first sulfonamide of clinical importance was *Prontosil*, an azo dye that is metabolised *in vivo* to *sulfanilamide*. It was synthesised in Germany in 1932. Many sulfonamides have since been synthesised; they differ only slightly in their antimicrobial activity, but vary in their pharmacokinetic properties. The sulfonamides have been classified according to their rate of excretion as short-, medium- or intermediate-, long-, and ultra-long-acting. The **short-acting** sulfonamides are excreted in the urine in high concentrations and have therefore been of particular use in the treatment of urinary-tract infections. The solubility in urine of earlier short-acting sulfonamides, such as *sulfapyridine*, and their acetyl metabolites is low and hence crystalluria has been reported frequently. Of the short-acting sulfonamides most commonly used, *sulfadiazine* also has low solubility in urine whereas *sulfadimidine* and *sulfafurazole* and their acetyl conjugates are very soluble. Three short-acting sulfonamides (triple sulfonamides) have been given together to reduce the risk of crystalluria, as the constituent sulfonamides can co-exist in solution in urine without affecting each other's solubility. Preparations of mixed sulfonamides have, however, generally been replaced by the more soluble sulfonamides. The **medium-acting** sulfonamides such as *sulfamethoxazole*, the **long-acting** sulfonamides such as *sulfadimethoxine*, *sulfamethoxypyridazine*, and *sulfametoxydiazine*, and the **ultra-long-acting** sulfonamides such as *sulfadoxine* and *sulfametopyrazine* do not attain such high concentrations in the urine and rarely cause crystalluria. Sulfonamides that are slowly excreted from the body do appear, however, to have been more commonly implicated in the development of reactions such as the Stevens-Johnson syndrome.

The sulfonamides are usually bacteriostatic, and interfere with folic acid synthesis of susceptible organisms; their broad spectrum of antimicrobial activity has, however, been limited by the development of resistance. The clinical use of sulfonamides has therefore been greatly reduced; in general they are indicated only in the treatment of urinary-tract infections and a few other disorders such as nocardiosis. Sulfonamides such as *sulfaguanidine*, *succinylsulfathiazole*, *phthalylsulfacetamide*, and *phthalylsulfathiazole* are poorly absorbed from the gastrointestinal tract and have been used for the treatment of gastrointestinal infections although they are now rarely indicated. *Sulfadiazine silver*, *sulfathiazole silver*, and *mafenide* are applied topically for their antibacterial action in patients with burns. *Sulfasalazine* (p. 1893.1), a conjugate of 5-aminosalicylic acid (mesalazine) and sulfapyridine, is used in the treatment of inflammatory bowel diseases and in rheumatoid arthritis.

Trimethoprim is a diaminopyrimidine that also inhibits folic acid synthesis but at a different stage in the metabolic pathway to that inhibited by the sulfonamides. It has a similar spectrum of antimicrobial activity to sulfonamides and often shows synergy *in vitro* with these drugs. Trimethoprim was initially available only in combination with sulfonamides, most commonly with sulfamethoxazole as co-trimoxazole. It is now used alone particularly in the treatment of infections of the urinary and respiratory tracts. Analogues of trimethoprim include *baquiloprim*, *brodimoprim*, *iclaprim*, *ormetoprim*, and *tetroxoprim*.

Co-trimoxazole generally replaced use of sulfonamides alone in the treatment of systemic infections, although its use has also been restricted in some countries and trimethoprim may be preferred. Co-trimoxazole is however indicated for pneumocystis pneumonia and nocardiosis and may be useful in protozoal infections such as toxoplasmosis. Other sulfonamides which have been combined with trimethoprim include sulfadiazine (as *co-trimazine*), sulfamethoxypyridazine, sulfametopyrazine, sulfametrole, and sulfamoxole (see *co-trifamole*). Sulfadiazine has been used with tetroxoprim (see *co-tetroxazine*).

Sulfonamides have also been used with pyrimethamine (p. 662.3) in the treatment or prophylaxis of some protozoal infections. Common combinations are sulfadoxine and pyrimethamine for malaria, and sulfadiazine and pyrimethamine for the treatment of toxoplasmosis.

Described in this chapter are

Tetracyclines

The tetracyclines are a group of antibacterials, originally derived from certain *Streptomyces* spp., having the same tetracyclic nucleus, naphthacene, and similar properties. Unlike the penicillins and aminoglycosides they are usually bacteriostatic at the concentrations achieved in the body but act similarly to the aminoglycosides by interfering with protein synthesis in susceptible organisms.

Tetracyclines all have a broad spectrum of activity which includes Gram-positive and Gram-negative bacteria, chlamydias and chlamydophilas, rickettsias, mycoplasmas, spirochaetes, some mycobacteria, and some protozoa, but the emergence of resistant strains and the development of other antimicrobials has often reduced their value. Adverse effects have also restricted their usefulness. Gastrointestinal disturbances are common and other important toxic effects include deposition in bones and teeth, precluding their use in pregnancy and young children; anti-anabolic effects, especially in patients with renal impairment; fatty changes in the liver; and photosensitivity, especially with demeclocycline. Allergic reactions are relatively uncommon. Because of these adverse effects tetracyclines should be avoided in pregnant women, children, and, apart from doxycycline and minocycline, patients with renal impairment.

The first tetracycline to be introduced was *chlortetracycline* in 1948 and, like chloramphenicol which was discovered at about the same time, it was found to have a broad spectrum of activity and to be active orally unlike benzylpenicillin or streptomycin, the only other antibacterials then in use. The discovery of chlortetracycline was followed closely by that of *oxytetracycline* and then *tetracycline*, a reduction product of chlortetracycline which may be produced semisynthetically. All three have very similar properties, although chlortetracycline is less well absorbed and oxytetracycline may cause less staining of teeth. *Demeclocycline*, demethylated chlortetracycline, has a longer half-life than tetracycline but is more often associated with phototoxic reactions. It has been used with some success in patients with the syndrome of inappropriate secretion of antidiuretic hormone.

These four tetracyclines are all natural products that have been isolated from *Streptomyces* spp. The more recent tetracyclines, such as methacycline, doxycycline, minocycline, lymecycline, meclocycline, and rolitetracycline are semisynthetic derivatives. *Methacycline*, like demeclocycline, has a longer half-life than tetracycline and has been given twice daily. *Doxycycline* and *minocycline* are both more active

in vitro than tetracycline against many species. More importantly, minocycline is active against some tetracycline-resistant bacteria, including strains of staphylococci. Both are well absorbed and, unlike the other tetracyclines, absorption is not significantly affected by the presence of food. They can be given in lower doses than the older members of the group and, having long half-lives, doxycycline is usually given once daily and minocycline twice daily. Also, they do not accumulate significantly in patients with renal impairment and can, with care, be given to such patients; however, usual doses of minocycline can lead to higher serum concentrations resulting in possible liver toxicity. Both doxycycline and minocycline are more lipid-soluble than the other tetracyclines and they penetrate well into tissues. The use of minocycline may, however, be limited by its vestibular adverse effects.

Tetracyclines are not generally the antibacterials of choice in Gram-positive or Gram-negative infections because of the emergence of resistant organisms and the discovery of drugs with narrower antimicrobial spectra. However, they have a place in the treatment of chlamydial infections, rickettsial infections such as typhus and the spotted fevers, mycoplasmal infections such as atypical pneumonia, pelvic inflammatory disease, Lyme disease, brucellosis, tularaemia, plague, cholera, periodontal disease, and acne. The tetracyclines have also been useful in the treatment of penicillin-allergic patients suffering from sexually transmitted diseases, actinomycosis, bronchitis, and leptospirosis. Minocycline may sometimes be used in multidrug regimens for leprosy. Doxycycline may be used for the treatment and prophylaxis of malaria; it is also used in the management of anthrax.

Described in this chapter are

- Chlortetracycline, p. 262.2
- Demeclocycline, p. 287.2
- Doxycycline, p. 290.1
- Lymecycline, p. 322.1
- Meclocycline, p. 323.2
- Methacycline, p. 324.3
- Minocycline, p. 326.3
- Oxytetracycline, p. 339.1
- Rolitetracycline, p. 358.1
- Tetracycline, p. 375.1

Miscellaneous Antibacterials

Spectinomycin is an aminocyclitol antibacterial with some similarities to streptomycin although it is not an aminoglycoside. Spectinomycin is active against many bacteria but its clinical use is restricted to the treatment of chancroid and gonorrhoea. Trospectomycin, a water-soluble derivative, has been investigated.

Mupirocin is an antibacterial produced by *Pseudomonas fluorescens* with activity against most strains of staphylococci and streptococci and also some Gram-negative bacteria. It is applied topically.

Fosfomycin is a derivative of phosphonic acid; it is active against Gram-positive and Gram-negative bacteria and is given orally or parenterally.

The fusidane antibacterial *fusidic acid* is derived from *Fusidium coccineum* and has a narrow spectrum of antibacterial activity, but it is very active against *Staphylococcus aureus* and has been used both topically and systemically in the treatment of staphylococcal infections. Resistance develops readily and it is often used with other antibacterials.

The polymyxins are basic antibacterials produced by the growth of different strains of *Bacillus polymyxa* (*B. aerosporus*). *Polymyxin B* and *colistin* have been used clinically, but their systemic use has been more or less abandoned because of their toxicity, notably to the kidneys and nervous system. They are not absorbed when taken orally and have therefore been given in gastrointestinal infections for their bactericidal activity against Gram-negative bacteria. They continue to be widely used as components of topical preparations.

Bacitracin, gramicidin, gramicidin S, and *tyrothricin* are polypeptide antibacterials also produced by certain strains of *Bacillus* spp. but they are active against Gram-positive bacteria. Like the polymyxins, they are toxic when used systemically and are therefore mainly used topically.

The halogenated hydroxyquinoline *clioquinol* has antibacterial, antifungal, and antiprotozoal activity. It was formerly used in gastrointestinal infections including amoebiasis but is of little value and can produce severe neurotoxicity. It is now mainly used locally for superficial infections of the skin and external ear. *Chlorquinaldol* and *halquinol* are used similarly.

Urinary antimicrobials such as *nitrofurantoin,* and also *methenamine* which has generally been given as the hippurate or mandelate, may be used in the treatment and prophylaxis of infections of the lower urinary tract. They are concentrated in the urine, but do not usually achieve antimicrobial concentrations in the blood.

The oxazolidinone *linezolid* has activity against Gram-positive organisms including vancomycin-resistant enterococci and meticillin-resistant *Staphylococcus aureus*. It is used in infections of the skin and respiratory tract due to these organisms.

The glycylcycline *tigecycline* has activity against Gram-positive bacteria, including meticillin-resistant *Staph. aureus,* and also against some Gram-negative and some anaerobic bacteria. It is used in the treatment of complicated skin and skin structure infections, complicated intra-abdominal infections, and community-acquired pneumonia.

The pleuromutilin antibacterial *retapamulin* is derived from the fungus *Clitopilus passeckerianus;* it has activity against *Staphylococcus aureus* and *Streptococcus pyogenes*. It is applied topically.

Described in this chapter are

- Acediasulfone, p. 216.1
- Arsanilic Acid, p. 222.2
- Avilamycin, p. 222.3
- Bacitracin, p. 227.3
- Bambermycin, p. 228.3
- Carbadox, p. 233.3
- Chlorquinaldol, p. 262.1
- Clioquinol, p. 275.1
- Clofoctol, p. 276.3
- Colistin, p. 277.3
- Daptomycin, p. 286.2
- Fosfomycin, p. 302.3
- Furaltadone, p. 303.3
- Furazidin, p. 303.3
- Fussafungine, p. 304.1
- Fusidic Acid, p. 304.1
- Gramicidin, p. 310.3
- Gramicidin S, p. 311.1
- Halquinol, p. 311.1
- Linezolid, p. 319.3
- Magainins, p. 322.3
- Mandelic Acid, p. 322.3
- Methenamine, p. 324.3
- Mupirocin, p. 329.2
- Nifuroxazide, p. 333.3
- Nifurpirinol, p. 333.3
- Nifurtoinol, p. 333.3
- Nifurzide, p. 334.1
- Nisin, p. 334.1
- Nitrofurantoin, p. 334.1
- Nitrofurazone, p. 335.1
- Nitroxoline, p. 335.2
- Novobiocin, p. 336.2
- Polymyxin B, p. 344.3
- Retapamulin, p. 350.1
- Spectinomycin, p. 360.1
- Taurolidine, p. 371.2
- Terizidone, p. 375.1
- Thenoic Acid, p. 378.3
- Thiostrepton, p. 380.1
- Tiamulin, p. 380.1
- Tigecycline, p. 381.2
- Tyrothricin, p. 386.1
- Valnemulin, p. 386.1
- Xibornol, p. 389.3

Choice of Antibacterial

Ideally, antibacterial treatment of infections should be chosen after the infecting organisms have been identified and the results of sensitivity tests are known. In practice, empirical treatment is often necessary initially, bearing in mind local patterns of infection and resistance. Other factors such as site of infection and tissue penetration are also important in deciding which antibacterial to give.

The prophylactic use of antibacterials is restricted mainly to patients undergoing some types of surgery. Other groups requiring infection prophylaxis include patients at special risk of developing endocarditis and those who have had rheumatic fever, who are splenectomised, or who are immunocompromised.

Abscess, abdominal

See under Abscess, Liver, p. 174.3, and under Peritonitis, p. 199.2.

Abscess, brain

Brain abscesses can result from otitis media, sinusitis, trauma, or dental sepsis, or they may be metastatic secondary to, for example, lung abscesses. Opportunistic infections in immunocompromised patients may present as brain abscesses.

Treatment of brain abscesses entails removal of pus or excision and use of high doses of antibacterials. Ideally the choice of antibacterial depends on the infecting organisms and penetration by the antibacterial into brain tissue and abscess pus. Until organisms can be cultured empirical treatment should be given.

There is very little good quality published information on the treatment of brain abscess. For many years, combined treatment with benzylpenicillin and chloramphenicol was the mainstay of empirical therapy, but a report by the British Society for Antimicrobial Chemotherapy,[1] based on published information and the authors' expertise, recommended the following regimens for first-line empirical treatment, according to the site of the abscess and origin of the infection:

- for frontal lobe abscesses originating from infection of the paranasal sinuses or teeth, a combination of metronidazole with one of cefuroxime, cefotaxime, or ceftriaxone
- for temporal lobe or cerebellar abscesses originating from infection of the middle ear or sphenoidal sinuses, ampicillin and metronidazole with either ceftazidime or gentamicin
- for abscesses associated with penetrating trauma, flucloxacillin, cefuroxime, cefotaxime, or ceftriaxone
- for metastatic abscesses, usually in the area supplied by the middle cerebral artery, one of cefuroxime, cefotaxime, or ceftriaxone, with or without metronidazole, or, if associated with endocarditis or cyanotic congenital heart disease, benzylpenicillin

Similar suggestions have been made by a more recent review,[2] which also suggested the use of oxacillin with metronidazole and a third-generation cephalosporin for empirical management of abscesses associated with penetrating trauma, and vancomycin plus a third-generation cephalosporin for abscess occurring postoperatively. Another review[3] suggested the latter combination for abscesses both after neurosurgery and trauma.

1. Infection in Neurosurgery Working Party of the British Society for Antimicrobial Chemotherapy. The rational use of antibiotics in the treatment of brain abscess. *Br J Neurosurg* 2000; 14: 525–30.
2. Lu C-H, *et al.* Strategies for the management of bacterial brain abscess. *J Clin Neurosci* 2006; 13: 979–85.
3. Hakan T. Management of bacterial brain abscesses. *Neurosurg Focus* 2008; 24: E4. Available at: http://thejns.org/doi/pdf/10.3171/FOC/2008/24/6/E4 (accessed 31/03/10)

Abscess, liver

Bacteria commonly responsible for pyogenic liver abscesses include Enterobacteriaceae, especially *Escherichia coli* and in some countries[1] *Klebsiella pneumoniae;* anaerobes, especially *Bacteroides fragilis;* and *Streptococcus milleri* (these can be microaerophilic). As elsewhere in the abdomen (see under Peritonitis, p. 199.2), infections are often mixed. Treatment involves percutaneous aspiration and drainage of pus and the use of high doses of antibacterials.[2,3] Broad-spectrum empirical therapy should be started immediately; more specific therapy may be possible when the results of cultures following diagnostic percutaneous aspiration of the abscess are known. Gentamicin with clindamycin has been commonly used[4,5] but other antibacterial combinations, involving cefoxitin, chloramphenicol, carboxypenicillins, third-generation cephalosporins, and metronidazole, might be appropriate.[5] A regimen of ampicillin, gentamicin, and metronidazole has become standard in some centres, but may be hazardous in patients with *Klebsiella*-related liver abscess, in whom a combination of an aminoglycoside with either an extended-spectrum beta-lactam such as piperacillin or a second- or third-generation cephalosporin, may be preferred.[1] Antibacterial therapy has been successful without surgical intervention, but may not be consistently so,[6] although this might be due to inadequate treatment against enteric anaerobes, especially *B. fragilis*.[5]

For the treatment of amoebic liver abscess, see under Amoebiasis in Antiprotozoals, p. 921.1.

1. Lederman ER, Crum NF. Pyogenic liver abscess with a focus on Klebsiella pneumoniae as a primary pathogen: an emerging disease with unique clinical characteristics. *Am J Gastroenterol* 2005; 100: 322–31.
2. Barakate MS, *et al.* Pyogenic liver abscess: a review of 10 years' experience in management. *Aust N Z J Surg* 1999; 69: 205–9.
3. Alvarez Pérez JA, *et al.* Clinical course, treatment, and multivariate analysis of risk factors for pyogenic liver abscess. *Am J Surg* 2001; 181: 177–86.
4. Herbert DA, *et al.* Pyogenic liver abscesses: successful non-surgical therapy. *Lancet* 1982; i: 134–6.
5. Herbert DA, *et al.* Medical management of pyogenic liver abscesses. *Lancet* 1985; i: 1384.
6. McCorkell SJ, Niles NL. Pyogenic liver abscesses: another look at medical management. *Lancet* 1985; i: 803–6.

Abscess, lung

Lung abscesses are often secondary to aspiration pneumonia and are discussed under Pneumonia, p. 202.1. The organisms involved are commonly anaerobic bacteria.

Actinomycosis

Actinomycosis is a rare, chronic, slow-growing, often polymicrobial infection caused mainly by Gram-positive anaerobic or microaerophilic bacteria of the genus *Actinomyces* (usually *A. israelii*) and sometimes by others such as *Propionibacterium* or *Bifidobacterium*. Such organisms are part of the normal flora of the oral cavity, gastrointestinal tract, female genital tract, or skin. They are of low pathogenicity and require a break in the mucosal barrier to cause infection; foreign bodies also appear to facilitate infection. Actinomycosis occurs worldwide and at any age but it is most commonly seen in men and those in the middle decades of life. Any site in the body can be involved; the most common are oral-cervicofacial and are usually associated with dental procedures or poor oral hygiene. Less commonly, thoracic, abdominal, or pelvic regions are involved (the latter usually associated with the use of intra-uterine contraceptive devices). Rarely, CNS, cutaneous, or disseminated infection may occur.

The infection is characterised by single or multiple indurations that spread regardless of tissue planes. Local swelling, inflammation, abscesses, woody fibrous tissue, and draining sinuses that exude characteristic yellow aggregates (sulfur granules) may develop. Diagnosis is difficult; the lesions may be mistaken for neoplasms.

Actinomycosis responds slowly to antibacterials, and long-term treatment is required to prevent recurrence.[1-3] The treatment of choice is high-dose intravenous benzylpenicillin for 2 to 6 weeks and then an oral penicillin (e.g. phenoxymethylpenicillin or amoxicillin) for 6 to 12 months,[1,2] although complicated cases may require up to 18 months of therapy.[2] Some patients may be successfully treated with less prolonged regimens of penicillin, especially if the disease burden is light;[1] uncomplicated oral-cervicofacial disease is particularly responsive to shorter treatment courses. Short-course regimes are generally not

advised for patients with large lesions and/or abdominal disease unless surgical debridement is performed.

Alternatives to penicillins include the tetracyclines, erythromycin, chloramphenicol, and clindamycin.[2,3] In one patient, actinomycosis resistant to conventional therapy responded to a prolonged course of ciprofloxacin;[4] in another, actinomycosis was eliminated with a 4-month course of levofloxacin.[5] There are also reports of success with imipenem, first generation cephalosporins, ceftriaxone, and piperacillin/tazobactam.[1,2,6] Actinomycosis is not susceptible to metronidazole, aminoglycosides, co-trimoxazole, penicillinase-resistant penicillins, or cefalexin.[2]

Most patients can be managed with medical therapy alone; however, drainage or aspiration of abscesses or excision of fistulas may be appropriate, and occasionally extensive surgery is indicated, especially if medical therapy fails or a critical location is involved.[2,3]

1. Sudhakar SS, Ross JJ. Short-term treatment of actinomycosis: two cases and a review. *Clin Infect Dis* 2004; **38**: 444–7.
2. Brook I. Actinomycosis: diagnosis and management. *South Med J* 2008; **101**: 1019–23.
3. Chaudhry SI, Greenspan JS. Actinomycosis in HIV infection: a review of a rare complication. *Int J STD AIDS* 2000; **11**: 349–55.
4. Macfarlane DJ, *et al.* Treatment of recalcitrant actinomycosis with ciprofloxacin. *J Infect* 1993; **27**: 177–80.
5. Ferreira D de FG, *et al.* Treatment of pulmonary actinomycosis with levofloxacin. *J Bras Pneumol* 2008; **34**: 243–8.
6. Yi F, *et al.* Actinomycotic infection of the abdominal wall mimicking a malignant neoplasm. *Surg Infect (Larchmt)* 2008; **9**: 85–9.

Anaerobic bacterial infections

Anaerobic bacteria (or anaerobes) are part of the normal microbial flora of the skin, mouth, gastrointestinal tract, and vagina. If their commensal relationship is disrupted by surgery, trauma, immunosuppression, poor blood supply, or tissue necrosis, some anaerobes can cause potentially serious infections. They often cause infections in the pleural spaces and lungs, upper respiratory tract, gastrointestinal tract, CNS, skin, and vagina; haematogenous spread can occur. Common anaerobic pathogens include *Bacteroides, Prevotella* (formerly non-fragilis *Bacteroides*), *Fusobacterium, Porphyromanas, Clostridium, Peptostreptococcus,* and *Actinomyces* spp. Apart from single species infections such as tetanus, gas gangrene, pseudomembranous colitis, and actinomycosis, most anaerobic infections are of mixed aetiology. Abscesses are often a feature. Infections include: brain abscess; acute necrotising gingivitis and other periodontal infections; chronic otitis media and chronic sinusitis; aspiration pneumonia and lung abscess; peritonitis and intra-abdominal abscess; bacterial vaginosis and pelvic inflammatory disease; cellulitis, ulcers, bites, and other wound infections.[1]

Management of anaerobic infections usually includes surgical procedures and antibacterial therapy. Sensitivity testing *in vitro* is often impractical and if done results may not be available for several days. Initial antibacterial treatment is therefore usually empirical,[1-5] should cover aerobes and anaerobes, and take into account local resistance rates and the site of infection. Antibacterials are usually given parenterally, in high doses, and for a prolonged duration (weeks to months).[3,5]

The antibacterials of choice are metronidazole, carbapenems, combinations of a beta lactam with a beta-lactamase inhibitor, and chloramphenicol as they have the highest activity (more than 95%) against obligate anaerobes. Tigecycline is also highly active and considered a promising new agent for anaerobic/mixed infections with multidrug-resistant bacteria. Cefoxitin and clindamycin are often effective, except for infections caused by *Bacteroides*. Penicillin alone is no longer recommended for mixed infection because of increasing resistance in Gram-negative anaerobes, but may still be used for gas gangrene and actinomycosis. Other antibacterials with low to moderate resistance rates include moxifloxacin and garenoxacin. Other drugs with potential for therapy may include oral nitazoxanide, ramoplanin, rifaximin, intravenous dalbavancin, and for topical use, retapamulin.[5]

Surveys of susceptibility patterns in clinical isolates of anaerobic bacteria have shown increasing resistance of the *B. fragilis* group (including *B. distasonis, B. fragilis, B. ovatus, B. thetaiotaomicron,* and *B. vulgatus*) to clindamycin, continuing penicillin resistance in non-fragilis *Bacteroides* spp. (now reclassified as *Prevotella* spp. and including the type species *P. melaninogenica*), and rare beta-lactamase-mediated resistance of *Fusobacterium* to penicillin.[5] A clinical isolate of *B. fragilis*, simultaneously resistant to metronidazole, amoxicillin with clavulanic acid, and imipenem, was reported in the UK;[6] treatment with clindamycin was successful on this occasion. Resistance of some *Clostridium* spp. to penicillin and clindamycin had declined, but no changes were noted for *Cl. perfringens*. The emergence of multidrug-resistant anaerobes has been noted.[5]

1. Styrt B, Gorbach SL. Recent developments in the understanding of the pathogenesis and treatment of anaerobic infections (first of two parts). *N Engl J Med* 1989; **321**: 240–6.
2. Styrt B, Gorbach SL. Recent developments in the understanding of the pathogenesis and treatment of anaerobic infections (second of two parts). *N Engl J Med* 1989; **321**: 298–302.
3. Finegold SM, Wexler HM. Present status of therapy for anaerobic infections. *Clin Infect Dis* 1996; **23** (suppl 1): S9–S14.
4. Brook I. Anaerobic infections. *Rev Med Microbiol* 1999; **10**: 137–53.
5. Boyanova L, *et al.* Antimicrobial resistance and the management of anaerobic infections. *Expert Rev Anti Infect Ther* 2007; **5**: 685–701.
6. Turner P, *et al.* Simultaneous resistance to metronidazole, co-amoxiclav, and imipenem in clinical isolate of Bacteroides fragilis. *Lancet* 1995; **345**: 1275–7.

Anthrax

Anthrax is caused by *Bacillus anthracis*, a spore-forming Gram-positive aerobe found in the soil. It most commonly infects herbivorous mammals. Humans can become infected by contact with infected animals or infected or contaminated animal products, or by inhalation of anthrax spores. There have also been some reports of anthrax being acquired through injecting or inhaling heroin contaminated with anthrax spores. Person-to-person transmission is highly unlikely, although secondary cases of cutaneous anthrax have occasionally been reported; airborne transmission from person-to-person does not occur. Although rare in western countries anthrax remains a problem in many areas, including Africa, Asia, some southern European countries, the Americas, and parts of Australia. It has also been used as a weapon for biological warfare.

In humans anthrax presents most often in the cutaneous form which is usually curable with antibacterial treatment. In other types the prognosis is poor without prompt treatment; a 33% case fatality rate has been reported for injection anthrax in the UK.

- In *cutaneous* anthrax a painless, pruritic papule, which enlarges to an ulcer may develop within hours, or up to 12 days, after contact. Later (2 to 6 days) a vesicle with a black eschar develops.
- The incubation period for *inhalation* anthrax is usually about 10 days. An initial non-specific flu-like illness may last from a few hours to days and is followed in some patients by a short period of recovery while others progress directly to respiratory failure.
- *Gastrointestinal* anthrax has an incubation period of up to 1 week (usually 2 to 5 days), with fever, abdominal pain, nausea, vomiting, gastric ulcers, haematemesis, and diarrhoea (usually bloody) progressing to hypotension, shock, and death in as little as 2 to 5 days after initial symptoms.
- *Injection* anthrax has an incubation period of 1 to 2 days or longer. Patients may show signs of severe sepsis, with or without evidence of soft tissue infection (such as necrotising fasciitis and cellulitis). Meningitis (especially haemorrhagic meningitis) and gastrointestinal symptoms may also occur.

The **treatment** of naturally occurring anthrax has traditionally been with benzylpenicillin with ciprofloxacin or doxycycline (or other tetracycline) as alternatives. Other drugs with *in vitro* activity are aminoglycosides, amoxicillin, chloramphenicol, clindamycin, imipenem, linezolid, the macrolides, meropenem, rifampicin, and vancomycin.[1-4]

There are currently no clinical study data on the optimal treatment for anthrax. For the treatment of naturally occurring anthrax in developing countries WHO considers that *B. anthracis* is probably still susceptible to benzylpenicillin and recommends it as the drug of choice.[5] In developed countries treatment recommendations and guidelines[1,2,4,6] are based largely on the experience gained during the 1979 incident in Sverdlovsk (accidental release of biological warfare agents), the 2001 attack in the USA (deliberate release), isolated case reports of naturally occurring disease, and *in vitro* data.

- TREATMENT IN DEVELOPING COUNTRIES.

  For mild uncomplicated cases of naturally occurring *cutaneous* anthrax, WHO recommends intramuscular procaine benzylpenicillin for 3 to 7 days; oral alternatives are phenoxymethylpenicillin or amoxicillin.[5] For patients with severe or potentially life-threatening anthrax with signs of systemic involvement treatment should start with intravenous benzylpenicillin and then be switched to intramuscular procaine benzylpenicillin after clinical improvement. Treatment is usually given for 10 to 14 days. The addition of a second drug is often recommended; benzylpenicillin may be given with clindamycin or clarithromycin in treating *inhalational* anthrax or with an aminoglycoside (such as streptomycin) in *gastrointestinal* anthrax. For anthrax *meningoencephalitis* benzylpenicillin (or a fluoroquinolone) should be given with an antibacterial that penetrates well to the CNS.[5] Those with penicillin allergy may be treated with ciprofloxacin or doxycycline; a fluoroquinolone plus rifampicin and vancomycin should be given if such patients have anthrax meningoencephalitis.[5]
- TREATMENT IN DEVELOPED COUNTRIES.

  Because of the risks of engineered drug-resistant strains of *B. anthracis*, inducible beta-lactamases, and *in vitro* resistance to ofloxacin, guidelines[1,2,4] for the treatment of anthrax (occurring after deliberate release) recommend the use of 2 or more antibacterials which should be started as soon as possible. Corticosteroids may be given as adjunctive therapy.

  For *cutaneous* anthrax, oral ciprofloxacin or oral doxycycline is generally recommended. A change to amoxicillin, particularly in pregnant women and children, may be considered if the organism is found to be susceptible or first-line drugs cannot be taken. Treatment for 7 to 10 days is usually recommended for cutaneous anthrax, but in the event of a deliberate release or if concurrent inhalation is suspected then treatment should be continued for 60 days. If there are signs of systemic involvement, extensive oedema, or lesions on the head or neck, intravenous, and a multidrug approach is recommended.[1,4]

  For the treatment of *inhalation* and *gastrointestinal* anthrax ciprofloxacin or doxycycline plus one or two additional antibacterials with *in vitro* activity are recommended until antimicrobial susceptibility is known. Treatment should be given for 60 days and should initially be given intravenously and then switched to oral therapy when clinically appropriate.[1,4] Raxibacumab is a monoclonal antibody that can be used with antibacterials in the treatment of inhalation anthrax. It neutralises the anthrax toxin that is mainly responsible for the high mortality rate.[7]

Anthrax can be **prevented** by controlling and eliminating infected animals and vaccinating livestock. Anthrax vaccines may be used for active immunisation in humans and are recommended for persons working with potentially infected animals or animal products (including laboratory workers).[8]

Postexposure prophylaxis should be used after inhalation exposure to anthrax spores. UK guidelines[4] suggest oral ciprofloxacin for 60 days, or initial treatment with oral ciprofloxacin for 5 days followed by oral doxycycline for 55 days; amoxicillin may be considered if the organism is found to be susceptible. The vaccine may also be given depending on individual risk from exposure. If the vaccine is used, antibacterial prophylaxis may be reduced to 4 weeks.[4] However, US guidelines[8] recommend both antibacterials and vaccination for all previously unvaccinated persons, consisting of a 60-day course of oral ciprofloxacin or doxycycline (or amoxicillin for pregnant women depending on susceptibility) and 3 doses of vaccine. Antibacterial prophylaxis should continue until 14 days after the third vaccine dose, and may need to be given for more than 60 days if vaccination has been delayed. A shorter 30-day course of antibacterial prophylaxis is recommended for partially or fully vaccinated workers if respiratory protection has been disrupted during occupational exposure.[8] Antibacterial prophylaxis alone may be considered for 7 to 14 days after naturally occurring gastrointestinal exposure, but initial observation only is recommended following cutaneous exposure.[8] Raxibacumab is also licensed for prevention of inhalation anthrax when alternatives cannot be used.

1. CDC. Update: investigation of bioterrorism-related anthrax and interim guidelines for exposure management and antimicrobial therapy, October 2001. *MMWR* 2001; **50**: 909–19. Correction. *ibid.*; 962. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5042a1.htm (accessed 22/05/07)
2. Inglesby TV, *et al.* Anthrax as a biological weapon, 2002: updated recommendations for management. *JAMA* 2002; **287**: 2236–52.
3. Baillie LWJ. Past, imminent and future human medical countermeasures for anthrax. *J Appl Microbiol* 2006; **101**: 594–606.
4. Health Protection Agency. *Anthrax: guidelines for action in the event of a deliberate release.* Version 6.2; issued 21st December, 2010. Available at: http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1194947401128 (accessed 02/02/11)
5. WHO. *Anthrax in humans and animals.* 4th ed. Geneva: WHO, 2008. Available at: http://www.who.int/csr/resources/publications/anthrax_webs.pdf (accessed 02/02/11)
6. Health Protection Scotland and NHS (National Services Scotland) *Interim Clinical Guidance for the Management of Suspected Anthrax in Drug Users.* Version 12.1. Available at: http://www.hps.scot.nhs.uk/anthrax/documents/clinical-guidance-for-use-of-anthrax-immune-globulin-v12-1-2010-03-19.pdf (accessed 30/01/11)
7. Migone T-S, *et al.* Raxibacumab for the treatment of inhalational anthrax. *N Engl J Med* 2009; **361**: 135–44.
8. CDC. Use of anthrax vaccine in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. *MMWR* 2010; **59** (RR-6): 1–30. Also available at: http://www.cdc.gov/mmwr/pdf/rr/rr5906.pdf (accessed 28/05/13)

Antibiotic-associated colitis

See under Gastro-enteritis p. 185.1.

Arthritis, bacterial

See under Bone and Joint Infections, p. 177.1.

Bacillary angiomatosis

See under Cat Scratch Disease, p. 178.3.

Bacterial vaginosis

Bacterial vaginosis (anaerobic vaginosis; non-specific vaginitis) results from a reduction of the normal vaginal bacteria (*Lactobacillus* spp.) and an overgrowth of anaerobic bacteria (including *Gardnerella vaginalis, Mycoplasma hominis,* or *Mobiluncus* or *Prevotella* spp.). It is a common and often distressing condition that is not thought to be sexually transmitted but is generally associated with sexual activity. Infections may be asymptomatic or result in a fishy-smelling vaginal discharge.

Various antibacterial regimens for the **treatment** of bacterial vaginosis are recommended in guidelines issued in the UK,[1] and in the USA[2] and also by WHO[3] but relapse is common after any regimen.

- **WHO:**
  - oral metronidazole 400 or 500 mg twice daily for 7 days

  alternatives are:
  - a single oral dose of metronidazole 2 g
  - intravaginal metronidazole 5 g of a 0.75% gel twice daily for 5 days
  - oral clindamycin 300 mg twice daily for 7 days
  - intravaginal clindamycin 5 g of a 2% cream at bedtime for 7 days
- **UK:**
  - oral metronidazole 400 mg twice daily for 5 to 7 days, *or*
  - a single oral 2-g dose of metronidazole, *or*
  - intravaginal metronidazole 0.75% gel once daily for 5 days, *or*
  - intravaginal clindamycin as a 2% cream once daily for 7 days

  alternatives are:
  - oral clindamycin 300 mg twice daily for 7 days
  - a single oral dose of tinidazole 2 g
- **USA:**
  - oral metronidazole 500 mg twice daily for 7 days, *or*
  - intravaginal metronidazole 5 g of a 0.75% gel once daily for 5 days, *or*
  - intravaginal clindamycin 5 g of a 2% cream at bedtime for 7 days

  alternatives are:
  - oral clindamycin 300 mg twice daily for 7 days
  - intravaginal clindamycin 100 mg at bedtime for 3 days
  - oral tinidazole 1 g daily for 5 days *or* 2 g daily for 2 days

A systematic review[4] of 24 clinical studies to assess the effects of antibacterials on bacterial vaginosis in non-pregnant women found clindamycin preparations (creams, ovules, and tablets), oral metronidazole, and oral or intravaginal tablets of lactobacillus probiotics to be effective. For further information on the use of probiotics in the treatment of bacterial vaginosis see Urological Infections, on p. 2597.2.

An association has been reported between bacterial vaginosis and adverse *pregnancy* outcomes, including miscarriage and premature births of low-weight infants, and some have advised treatment early in the second trimester of pregnancy.[5,6] A systematic review[7] of clinical studies has concluded that there is little evidence that screening and treatment of all pregnant women for bacterial vaginosis would prevent premature birth and its consequences, but there is some suggestion that treatment before 20 weeks of gestation may reduce the risk of preterm birth. Symptomatic pregnant women should be treated and the following regimens have been recommended:

- **WHO:**
  - oral metronidazole 200 or 250 mg three times daily for 7 days, after the first trimester, *or*
  - a single oral dose of metronidazole 2 g, if treatment is needed in the first trimester

  alternatives are:
  - oral clindamycin 300 mg twice daily for 7 days *or*
  - intravaginal metronidazole 5 g of a 0.75% gel twice daily for 7 days
- **USA:**
  - oral metronidazole 500 mg twice daily *or* 250 mg three times daily for 7 days *or*
  - oral clindamycin 300 mg twice daily for 7 days

Treatment of male sex partners does not prevent the recurrence of bacterial vaginosis.[1-3]

Patients co-infected with HIV should receive the same treatment as those who are HIV-negative.[2]

1. Clinical Effectiveness Group (British Association for Sexual Health and HIV). UK national guideline for the management of bacterial vaginosis 2012. Available at: http://www.bashh.org/documents/4413 (accessed 30/07/12)
2. CDC. Sexually transmitted diseases treatment guidelines, 2010. *MMWR* 2010; **59** (RR-12): 1–110. Also available at: http://www.cdc.gov/STD/treatment/2010/STD-Treatment-2010-RR5912.pdf (accessed 08/01/11) Correction. *ibid.* 2011; **60**: 18. [dose]
3. WHO. Guidelines for the management of sexually transmitted infections. Geneva: WHO, 2003. Also available at: http://whqlibdoc.who.int/publications/2003/9241546263.pdf (accessed 22/03/07)
4. Oduyebo OO, *et al.* The effects of antimicrobial therapy on bacterial vaginosis in non-pregnant women. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2009 (accessed 24/02/10).
5. Hay PE. Therapy of bacterial vaginosis. *J Antimicrob Chemother* 1998; **41**: 6–9.
6. Anonymous. Management of bacterial vaginosis. *Drug Ther Bull* 1998; **36**: 33–5.
7. McDonald HM, *et al.* Antibiotics for treating bacterial vaginosis in pregnancy. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 17/03/07).

Biliary-tract infections

Although the biliary-tract is normally free of bacteria, infections may follow partial or complete blockage of part of the biliary tree; the part blocked determines the clinical condition.

Acute cholecystitis results from blockage of the cystic duct, mostly caused by gallstones (acalculous cholecystitis refers to cholecystitis without gallstones). Bile stasis occurs after the blockage and leads to inflammation of the gallbladder and possibly secondary bacterial infection, which is mostly polymicrobial. Inadequate drainage increases the pressure within the bile duct, resulting in reflux of bacteria into the blood and lymph (bacteraemia). Complications can include gangrene, hepatic or intraperitoneal abscesses, peritonitis, and septicaemia. *Cholangitis* is caused by infection in an obstructed biliary system, usually the common bile duct. Suppurative cholangitis is associated with a higher mortality rate.

The organisms most commonly involved in both these conditions are *Escherichia coli* and *Klebsiella* spp.; *Enterococci* are less common. Anaerobes, mostly *Clostridium* and *Bacteroides* spp., are cultured in about 15% of cases, usually as part of a mixed infection and are more common in those with bile duct-to-bowel anastomosis or fistulas, the elderly, or seriously ill patients.[1-4]

In most cases of obstruction, definitive treatment depends on restoring drainage of bile by surgical or medical treatment of gallstones (p. 2639.1). Antibacterial therapy for cholecystitis and cholangitis is similar and aims to control bacteraemia; treatment may be complicated by the fact that biliary obstruction prevents adequate concentrations of many antibacterials being achieved in the bile. Choice of an antibacterial is determined by the severity of the disease, the suspected pathogen, antibacterial activity, and local antibacterial resistance patterns.[3-5]

Patients with mild illness may be treated with oral antibacterials; fluoroquinolones (levofloxacin and ciprofloxacin), first-generation cephalosporins (cefotiam, cefcapene, and cefazolin), or a broad-spectrum penicillin plus a beta-lactamase inhibitor (such as ampicillin with sulbactam) are options.[5] Broad-spectrum intravenous antibacterials that achieve high concentrations in both bile and blood are preferred for initial treatment in those with moderate to severe illness.[3-5] Antibacterials used for moderate illness and often, in combination, for severe infections, include the cephalosporins, fluoroquinolones, and ureidopenicillin (preferably mezlocillin and piperacillin).[1,3,4] Second-generation cephalosporins may be given for moderate infections, while third- and fourth-generation cephalosporins and aztreonam are given for more severe illness.[5] Metronidazole should be added if anaerobic infection is considered likely.[1,3,5] In penicillin-resistant cases (particularly for infections with *E. coli* or *Klebsiella* spp.) piperacillin with tazobactam may be considered. If patients have recently undergone nonsurgical biliary tract procedures or received a broad-spectrum antibacterial, it may be useful to add an aminoglycoside to cover *Pseudomonas* or *Enterobacter* spp.[1,3] In those with more severe illness, antibacterials with pseudomonal and enterococcal activity (such as imipenem, meropenem, or piperacillin with tazobactam)[4,5] and fluoroquinolones may be considered.[5] Antibacterial treatment is usually given for 5 to 14 days.[1,3,4]

Antibacterial prophylaxis is common in biliary surgery (see Surgical Infection, p. 211.1) to prevent acute cholangitis and wound infections. A single dose of an intravenous cephalosporin (cefazolin, cefoxitin, cefuroxime, or cefotaxime), piperacillin, or ciprofloxacin is often used for this purpose.[1,3]

Maintenance antibacterial therapy to reduce the number of episodes may have a role in those with recurrent cholangitis. Oral co-trimoxazole is the drug of choice, although there are also a few reports of oral ciprofloxacin being used;[1,3] a further alternative is amoxicillin (or ampicillin) plus a beta-lactamase inhibitor (clavulanic acid, sulbactam, or tazobactam).[1] An attempt is usually made after 3 to 4 months to stop this treatment.[1,3]

1. van den Hazel SJ, *et al.* Role of antibiotics in the treatment and prevention of acute and recurrent cholangitis. *Clin Infect Dis* 1994; **19**: 279–86.
2. Peña C, Gudiol F. Cholecystitis and cholangitis: spectrum of bacteria and role of antibiotics. *Dig Surg* 1996; **13**: 317–20.
3. Westphal J-F, Brogard J-M. Biliary tract infections: a guide to drug treatment. *Drugs* 1999; **57**: 81–91.
4. Jain MK, Jain R. Acute bacterial cholangitis. *Curr Treat Options Gastroenterol* 2006; **9**: 113–21.
5. Yoshida M, *et al.* Antimicrobial therapy for acute cholecystitis: Tokyo Guidelines. *J Hepatobiliary Pancreat Surg* 2007; **14**: 83–90.

Bites and stings

Dog, cat, or human bites are the most commonly encountered bite wounds. The resulting injury depends on the animal species and dentition, the ferocity of the attack, and the anatomical location of the bite. Dog bites most often cause crush injuries, lacerations, and abrasions, whereas the sharp pointed teeth of cats usually cause puncture wounds and lacerations. A major concern in all bite wounds is the risk of infection; it can be caused by nearly any group of pathogens (bacteria, viruses, rickettsia, spirochetes, or fungi). Patients presenting more than 8 hours after a bite injury often have infected wounds, with cat bites developing infection more rapidly than dog bites. Human bites have a higher complication and infection rate than animal bites.

Animal bite wound infections contain a mix of aerobes and anaerobes from both the skin of the patient and the mouth of the animal, although certain organisms are associated with particular animal species. Cat bites are most often associated with *Pasteurella multocida*; other organisms include *Porphyromonas* and *Moraxella* spp. *Bartonella henselae* can be transmitted via a scratch or bite of an infected cat or cat flea. See also under Cat Scratch Disease (p. 178.3). A common canine organism is *P. canis*. Other common organisms associated with cat and dog bites are *Streptococcus, Staphylococcus, Fusobacterium,* and *Bacteroides* spp.[1,2] A more unusual organism is *Capnocytophaga canimorsus* (formerly called dysgonic fermenter type 2 or DF-2) which has mostly been associated with dog bites.[3-5] It is an opportunistic pathogen especially hazardous to chronic alcohol users and immunocompromised patients, including splenectomised patients.[1,2] Infection with *C. canimorsus* after dog bites has led to fatal septicaemia, disseminated intravascular coagulation, meningitis, or endocarditis.[3]

Infected human bites are usually polymicrobial, however *Eikenella corrodens* has caused septic arthritis after a penetrating injury of the hand, and this may be complicated by infective endocarditis. Hepatitis B and C can be transmitted by human bites and HIV transmission has occasionally been reported.[2]

Management of cat and dog bites should include treatment of the wound to reduce the risk of acute infection. Prompt and thorough irrigation of the wound with tap water or normal saline aims to dislodge foreign matter and bacteria inoculated into the wound, and reduce the transmission of rabies virus. Established infection usually requires hospital admission for surgical debridement and drainage. A systematic review[6] concluded that there was insufficient evidence that prophylactic antibacterials given for dog bites were effective. There was evidence that antibacterials given after bites to the hand reduced infection and weak evidence to suggest that prophylactic antibacterials after human bites reduced infection. Prophylactic antibacterials are therefore not recommended for superficial and easily cleansed bite wounds;[1,5] prophylaxis should be reserved for the bites most likely to become infected (such as cat and human bites), where adequate debridement cannot be achieved, and in immunocompromised patients at high risk of infection.[5] If given, antibacterial prophylaxis should be given for 3 to 5 days;[2,5] it is initially empirical and should be directed toward the organisms that usually colonise the oral cavity of the animal until cultures results can direct treatment.[1]

Pasteurella spp. cause rapidly progressive skin and soft tissue infection and are generally resistant to dicloxacillin, flucloxacillin, first-generation cephalosporins, clindamycin, and erythromycin.[1,2] Benzylpenicillin is not effective against *S. aureus*, anaerobes, or *Eikenella*. Oral amoxicillin with clavulanic acid has excellent activity against *Pasteurella* spp., *Capnocytophaga* spp., anaerobes, and susceptible *S. aureus*, and is the drug of choice for prophylaxis.[1,2,5] Tetracycline or doxycycline with or without metronidazole is an alternative in penicillin-allergic patients.[1,2,5,7] Other alternatives include metronidazole with co-trimoxazole or a fluoroquinolone,[2] clindamycin with a fluoroquinolone, or clindamycin with co-trimoxazole (in children).[1] Parenteral ceftriaxone can be used in pregnancy;[1,5] cefuroxime and cefpodoxime are oral alternatives.[1] In areas where community-acquired MRSA incidence is high the choice of antibacterial may need to be modified. Doxycycline and co-trimoxazole are effective oral alternatives for coverage of MRSA; clindamycin may be a further alternative.[1] Antibacterials should be given parenterally when rapidly spreading cellulitis or signs of sepsis develop, or involvement of bone or joint is likely. Antibacterials for more severe established infections (as inpatient treatment) include combinations of a beta lactam and a beta-lactamase inhibitor (such as ampicillin with sulbactam, piperacillin with tazobactam, or ticarcillin with clavulanic acid). A carbapenem (such as ertapenem, meropenem, doripenem, or imipenem), ceftriaxone, aztreonam, or a fluoroquinolone with metronidazole are alternatives.[1] For very severe infections, empirical imipenem plus clindamycin has been given.[5] Treatment is usually given for 10 to 14 days for established cellulitis, 3 weeks for tenosynovitis, and 6 weeks for osteomyelitis.[5]

If necessary, prophylaxis or treatment for rabies (p. 2413.2) should be instituted. A combined tetanus and diphtheria vaccine (see p. 2383.1) should be given to patients whose primary tetanus immunisation is incomplete or unknown, or boosters are not up-to-date. For human

bites hepatitis B prophylaxis should be considered if the patient is not immune (see Hepatitis B Vaccine, p. 2389.3) and although there is limited evidence to support HIV postexposure prophylaxis it should be considered in high risk human bite injuries (see HIV Infection Prophylaxis, p. 961.1).[2]

Among the more unusual infections acquired from animals is seal finger, caused by an as yet unidentified organism and treated with tetracycline.[8] The Gram-negative bacilli *Spirillum minus* (or *minor*) and *Streptobacillus moniliformis* are both causes of rat-bite fever. In each case the treatment of choice is benzylpenicillin;[7] a tetracycline or streptomycin are alternatives.

Envenomation after bites and stings by snakes, scorpions, spiders, and some marine animals is usually treated symptomatically and with specific antivenoms and antisera (see Jellyfish Stings, p. 2397.1, Scorpion Stings, p. 2418.1, Snake Bites, p. 2419.2, Spider Bites, p. 2420.1, and Stone Fish Venom Antisera, p. 2420.2).

1. Oehler RL, *et al.* Bite-related and septic syndromes caused by cats and dogs. *Lancet Infect Dis* 2009; 9: 439–47.
2. Dendle C, Looke D. Management of mammalian bites. *Aust Fam Physician* 2009; 38: 868–74.
3. Pers C, *et al.* Capnocytophaga canimorsus septicemia in Denmark, 1982-1995; review of 39 cases. *Clin Infect Dis* 1996; 23: 71–5.
4. Le Moal G, *et al.* Meningitis due to Capnocytophaga canimorsus after receipt of a dog bite: case report and review of the literature. *Clin Infect Dis* 2003; 36: e42–e46.
5. Morgan M, Palmer J. Dog bites. *BMJ* 2007; 334: 413–7.
6. Medeiros I, Saconato H. Antibiotic prophylaxis for mammalian bites. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2001 (accessed 16/05/03).
7. Abramowicz M, ed. The choice of antibacterial drugs. In: *Handbook of antimicrobial therapy*. 19th ed. New Rochelle NY: The Medical Letter, 2011: 71.
8. Hartley JW, Pitcher D. Seal finger—tetracycline is first line. *J Infect* 2002; 45: 71–5.

Bone and joint infections

Infectious arthritis (septic or pyogenic arthritis) is an infection of the joints characterised by pain, fever, inflammation, and swelling. Bacteria are the most common cause of infectious arthritis, although fungi and viruses can also infect joints. In acute **bacterial arthritis**, joints are commonly infected from a contiguous source via the blood or from direct inoculation during a surgical procedure, injection, bite, or trauma. Infecting organisms include staphylococci, streptococci, enterococci, Enterobacteriaceae, *Pseudomonas aeruginosa*, and anaerobes, although the commonest is probably *Staphylococcus aureus*. In prosthetic joint infections coagulase-negative staphylococci are often implicated. *Haemophilus influenzae* is a common cause in young children, as is *Neisseria gonorrhoeae* in sexually active young adults. In addition to gonococcal arthritis, other specific types of bacterial arthritis include Lyme disease and meningococcal, salmonellal, and tuberculous arthritis (see under the appropriate disease for further details).

In **reactive arthritis** (aseptic arthritis) joint inflammation follows infection elsewhere in the body. It is generally secondary to sexually transmitted, especially chlamydial, infections, or to enteric infections with organisms such as *Salmonella, Shigella, Yersinia, Campylobacter,* and *Clostridium difficile*. The term Reiter's syndrome is usually reserved for reactive arthritis associated with extra-articular features such as urethritis and conjunctivitis.

Acute **osteomyelitis**, an infection of bone, is also characterised by pain, fever, and inflammation. Chronic infection can develop, with long periods of latency and recurrent relapse, and is associated with necrosis of the bone. Osteomyelitis is most often caused by spread from a contiguous source of infection such as a penetrating wound, soft tissue infection, or surgery, but can also be disseminated by the blood or secondary to vascular insufficiency such as diabetic foot infection. With the exception of *N. gonorrhoeae*, infecting organisms are similar to those in bacterial arthritis.

A systematic review and meta-analysis[1] of antibacterial **treatment** of bone and joint infections concluded that there was little high-quality evidence to support use of any one drug. In practice, treatment is usually started intravenously; if high bone concentrations can be achieved with an appropriate oral antibacterial, patients may be switched to oral therapy.

Treatment for *bacterial arthritis* is usually started intravenously, although it need not be given parenterally for the whole course.[2,3] Synovial penetration for most antibacterials is generally good, although peak concentrations tend to be lower and slower to achieve than those in plasma. Typically, the recommended duration of treatment is several weeks.[2,4,5] A shorter treatment course of about 10 days, with a higher dose of antibacterial, has been evaluated in children with bacterial arthritis.[6]

- Empirical treatment regimens for bacterial arthritis (as for osteomyelitis) usually include antibacterials with activity against staphylococci and streptococci. These include flucloxacillin, nafcillin, oxacillin, or cephalosporins.[4,5,7,8] Clindamycin is an alternative in patients who are penicillin-allergic.[4,5] Benzylpenicillin and ceftriaxone are also active against streptococci.[7] Alternatively, gentamicin can be added to an antistaphylococcal drug.[4,5] Vancomycin[4,5] or teicoplanin[5] are used if meticillin-resistant *Staph. aureus* is suspected; a second- or third-generation cephalosporin,[4] rifampicin, fusidic acid, or doxycycline[5] have also been added. In patients unable to take vancomycin, linezolid has been used as an alternative.[7] Coagulase-negative staphylococci are treated similarly.[7]
- Empirical antibacterial treatment for infections caused by Gram-negative bacteria include a third-generation cephalosporin or ciprofloxacin.[7] Ceftriaxone may be used for empirical treatment of bacterial arthritis where infection is thought to be caused by *N. gonorrhoeae*[4,7] or *N. meningitidis*.[4] Young children should be given a cephalosporin such as cefotaxime because of the likelihood of *H. influenzae* infection.[5]
- Infections caused by anaerobes can be treated with clindamycin; ampicillin-sulbactam or metronidazole are alternatives.[8]

In the treatment of *osteomyelitis* similar drugs are typically chosen to those listed above for treatment of bacterial arthritis. However, because penetration of antibacterials into bone may be variable and slow, particularly where there is necrosis or poor vascularisation, treatment, at least in adults, has often been more prolonged.[2,7,8] Treatment is generally given by the intravenous route but with some drugs, such as the quinolones or clindamycin, an early switch to oral therapy is possible.[7,8] Debridement of necrotic bone is important in the management of chronic osteomyelitis.[7,8] Children with osteomyelitis may respond more rapidly to treatment because of the greater vascularity of developing bone; shorter courses, and initial oral[2] or an early switch from intravenous to oral treatment[9] may be possible.

Antibacterials which have a good activity against surface-adhering and biofilm-producing bacteria are required for *prosthetic joint infection*; rifampicin is commonly used with a fluoroquinolone.[10] In one study[11] use of rifampicin with ciprofloxacin improved control of staphylococcal infections related to joint prostheses or fracture fixation devices in comparison with ciprofloxacin alone. Rifampicin has also been used with a penicillinase-resistant penicillin, vancomycin, or teicoplanin[10] for initial intravenous treatment of prosthetic joint infections; fusidic acid,[8,10] co-trimoxazole, or minocycline[10] have been added to rifampicin for continued oral treatment. As in osteomyelitis prolonged intravenous therapy may be needed;[2,8] debridement and removal of the prosthesis is important.[2,7] For reference to infection prophylaxis in orthopaedic patients, see under Surgical Infection, p. 211.1.

In *reactive arthritis* the role of antibacterials is less certain.[12] Results in arthritis associated with chlamydial infections have been more promising than in that triggered by enteric infections.[13] Long-term treatment with a tetracycline in addition to an NSAID has been reported to shorten the duration of reactive arthritis resulting from *Chlamydia trachomatis* infection.[14] For reference to the symptomatic treatment of reactive arthritis, see Spondyloarthropathies p. 14.3.

For mention of the use of tetracyclines, usually minocycline, in the treatment of *rheumatoid arthritis*, see under Musculoskeletal and Joint Disorders, p. 376.2.

1. Stengel D, *et al.* Systematic review and meta-analysis of antibiotic therapy for bone and joint infections. *Lancet Infect Dis* 2001; 1: 175–88. Correction. *ibid.* 2002; 2: 125.
2. Darley ESR, MacGowan AP. Antibiotic treatment of gram-positive bone and joint infections. *J Antimicrob Chemother* 2004; 53: 928–35.
3. Mathews CJ, *et al.* Bacterial septic arthritis in adults. *Lancet* 2010; 375: 846–55.
4. Coakley G, *et al.* British Society for Rheumatology Standards, Guidelines and Audit Working Group. BSR & BHPR, BOA, RCGP and BSAC guidelines for management of the hot swollen joint in adults. *Rheumatology (Oxford)* 2006; 45: 1039–41. Also available at: http://www.rheumatology.org.uk/includes/documents/cm_docs/2009/m/management_of_hot_swollen_joints_in_adults.pdf (accessed 26/02/10)
5. Anonymous. The management of septic arthritis. *Drug Ther Bull* 2003; 41: 65–8.
6. Peltola H, *et al.* Prospective, randomized trial of 10 days versus 30 days of antimicrobial treatment, including a short-term course of parenteral therapy, for childhood septic arthritis. *Clin Infect Dis* 2009; 48: 1201–10.
7. Abramowicz M, ed. The choice of antibacterial drugs. In: *Handbook of antimicrobial therapy*. 18th ed. New Rochelle NY: The Medical Letter; 2008: 39.
8. Lew DP, Waldvogel FA. Osteomyelitis. *Lancet* 2004; 364: 369–79.
9. Zaoutis T, *et al.* Prolonged intravenous therapy versus early transition to oral antimicrobial therapy for acute osteomyelitis in children. *Pediatrics* 2009; 123: 636–42.
10. Trampuz A, Zimmerli W. Antimicrobial agents in orthopaedic surgery: Prophylaxis and treatment. *Drugs* 2006; 66: 1089–1105.
11. Zimmerli W, *et al.* Role of rifampin for treatment of orthopedic implant-related staphylococcal infections: a randomized controlled trial. *JAMA* 1998; 279: 1537–41.
12. Toivanen A. Bacteria-triggered reactive arthritis: implications for antibacterial treatment. *Drugs* 2001; 61: 343–51.
13. Svenungsson B. Reactive arthritis. *BMJ* 1994; 308: 671–2.
14. Lauhio A. Reactive arthritis: consider combination treatment. *BMJ* 1994; 308: 1302–3.

Botulism

For a discussion of botulism and its management, see p. 2380.2.

Bronchitis

Bronchitis may be defined as inflammation of the bronchi and is associated with excessive sputum production and cough. It may be either acute or chronic and may be as a result of infection or may be triggered by irritants such as tobacco smoke, pollution, chemicals, or dust.

Acute bronchitis is a common, self-limiting, respiratory infection that manifests mainly as a cough with or without sputum production and lasts for up to 3 weeks; if the cough persists for more than 3 weeks other diagnoses should be considered. Respiratory viruses, such as those that cause colds and influenza, are the most usual cause of acute bronchitis; less than 10% of cases have a bacterial cause. Bacteria associated with acute bronchitis include *Mycoplasma pneumoniae, Bordetella pertussis,* and *Chlamydophila pneumoniae. Acute bronchiolitis* affects the small bronchi and bronchioles and in infants is usually caused by RSV (see Respiratory Syncytial Virus Infection, p. 963.3).

Chronic bronchitis is defined as cough and sputum production occurring on most days and lasting longer than 3 months in each of 2 consecutive years; other causes of cough should also have been excluded. Chronic bronchitis is often a feature of chronic obstructive airways disease (COPD—p. 1199.1). Patients with chronic bronchitis or COPD may suffer acute infective exacerbations characterised by increased dyspnoea, sputum production, and sputum purulence. These may be viral in origin, but bacteria are often present in purulent sputum, the commonest being *Streptococcus pneumoniae, Moraxella catarrhalis,* and *Haemophilus influenzae*.

Treatment. ACUTE BRONCHITIS.

Antibacterials are not recommended in most cases of acute bronchitis.[1,2] A systematic review[3] and meta-analysis[4] of clinical studies in patients with acute bronchitis suggested that although they may reduce the duration of symptoms, the benefit is modest. Similar findings were reported when amoxicillin was given for the treatment of bronchitis in a community with a high prevalence of HIV-infected patients.[5] However, patients with acute bronchitis suspected or confirmed to be caused by pertussis infection should be treated with a macrolide or co-trimoxazole.[2] For further information on the treatment of pertussis, see p. 200.3.

Beta agonist bronchodilators are sometimes used to relieve the cough even in people who do not have asthma. A systematic review[6] on the use of oral or inhaled beta agonists concluded that they should not be used for the treatment of uncomplicated acute bronchitis. However, in patients with airflow obstruction and wheezing at the onset of the illness some benefit was seen, but the evidence is not well supported. The American College of Chest Physicians (ACCP) suggests that in selected adult patients with wheezing and a cough, treatment with a beta agonist bronchodilator may be useful.[2] Inhaled antimuscarinic bronchodilators have not been studied for acute bronchitis and are therefore not recommended.[2] Antitussives containing codeine or dextromethorphan are occasionally useful and can be given for short-term symptomatic relief of coughing; however, expectorants and mucolytics are not recommended.[2]

ACUTE EXACERBATION OF CHRONIC BRONCHITIS (AECB).

Treatment of AECB includes bronchodilators, systemic corticosteroids, antibacterials, and oxygen as necessary. Treatment with antibacterials is discussed below, while treatment with other drugs is discussed under COPD (see p. 1199.1). The value of antibacterial treatment in AECB has been controversial and early studies were difficult to assess.[7-9] After a comparison of a broad-spectrum antibacterial (amoxicillin, co-trimoxazole, or doxycycline) with placebo,[10] it was considered that antibacterials were justified in patients with AECB characterised by increased dyspnoea, sputum production, and sputum purulence, a conclusion supported by a later systematic review.[11] An earlier meta-analysis of randomised studies also indicated a small improvement due to therapy in patients with AECB.[12] Amoxicillin, ampicillin, tetracyclines (such as doxycycline), broad-spectrum macrolides, second- or third-generation cephalosporins, or co-trimoxazole have traditionally been used for treatment of AECB,[13,14] but recent reports from the USA and Canada show reduced efficacy to penicillin, macrolides, and co-trimoxazole; however, antibacterial activity for the newer fluoroquinolones and combinations of a beta lactam and a beta-lactamase inhibitor have remained high.[13] Furthermore, a meta-analysis[14] to evaluate the comparative efficacy and safety of first-line antibacterials (considered to be amoxicillin, ampicillin, pivampicillin, co-trimoxazole, and doxycycline) and second-line antibacterials (considered to be amoxicillin with clavulanic acid, macrolides, second- or third-

generation cephalosporins, and fluoroquinolones) for the treatment of patients with AECB, reported that second-line antibacterials were more effective, but not less safe, compared with the first-line antibacterials.

Guidelines for the management of AECB were developed by the Canadian Chronic Bronchitis Working Group,[9] and the topic is also covered by general guidelines for the management of COPD available in many countries (see p. 1199.1), and internationally through the Global Initiative for Chronic Obstructive Lung Disease (GOLD).[15] These guidelines stratify patients according to risk to identify those needing antibacterial therapy or more aggressive treatment. Generally, treatment is determined according to the infecting pathogen, patterns of local bacterial resistance, and severity of symptoms. The oral route is preferred and treatment is usually given for 3 to 10 days.[15,16] Broadly, no antibacterial treatment is needed for mild exacerbations. If treatment is needed then ampicillin, amoxicillin, doxycycline, or co-trimoxazole may be considered. Alternatives include combinations of a beta lactam and a beta-lactamase inhibitor such as amoxicillin with clavulanic acid, a second- or third-generation cephalosporin, a second-generation macrolide, or a ketolide such as telithromycin. Patients needing hospitalisation with moderate to very severe COPD, but without risk of *Pseudomonas aeruginosa* should be treated with a fluoroquinolone or amoxicillin with clavulanic acid. Those at risk of *P. aeruginosa* should be treated with a fluoroquinolone.

Long-term prophylaxis in patients with frequent exacerbations of bronchitis is controversial. A systematic review[17] of the value of antibacterial prophylaxis in chronic bronchitis concluded that it did have a small but significant effect in reducing the number of days of illness, but that it had no place in routine therapy because of concerns over adverse effects and the development of resistance. Guidelines for COPD management do not advocate prophylactic use of antibacterials.

1. Wenzel RP, Fowler AA. Acute bronchitis. *N Engl J Med* 2006; 355: 2125–30.
2. Braman SS. Chronic cough due to acute bronchitis: ACCP evidence-based clinical practice guidelines. *Chest* 2006; 129 (1 suppl): 95S–103S.
3. Smith SM, *et al.* Antibiotics for acute bronchitis. Available in The Cochrane Database of Systematic Reviews: Issue 4. Chichester: John Wiley; 2004 (accessed 05/02/10).
4. Bent S, *et al.* Antibiotics in acute bronchitis: a meta-analysis. *Am J Med* 1999; 107: 62–7.
5. Nduba VN, *et al.* Placebo found equivalent to amoxicillin for treatment of acute bronchitis in Nairobi, Kenya: a triple blind, randomised, equivalence trial. *Thorax* 2008; 63: 999–1005.
6. Smucny J, *et al.* Beta-2-agonists for acute bronchitis. Available in The Cochrane Database of Systematic Reviews: Issue 4. Chichester: John Wiley; 2006 (accessed 26/02/10).
7. Anonymous. Antibiotics for exacerbations of chronic bronchitis? *Lancet* 1987; ii: 23–4.
8. Staley H, *et al.* Is an objective assessment of antibiotic therapy in exacerbations of chronic bronchitis possible? *J Antimicrob Chemother* 1993; 31: 193–7.
9. Balter MS, *et al.* Chronic Bronchitis Working Group. Canadian Thoracic Society. Canadian Infectious Disease Society. Canadian guidelines for the management of acute exacerbations of chronic bronchitis: executive summary. *Can Respir J* 2003; 10: 248–58.
10. Anthonisen NR, *et al.* Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987; 106: 196–204.
11. Ram FSF, *et al.* Antibiotics for exacerbations of chronic obstructive pulmonary disease. Available in The Cochrane Database of Systematic Reviews: Issue 2. Chichester: John Wiley; 2006 (accessed 26/04/10).
12. Saint S, *et al.* Antibiotics in chronic obstructive pulmonary disease exacerbations: a meta-analysis. *JAMA* 1995; 273: 957–60.
13. Balter M, Weiss K. Treating acute exacerbations of chronic bronchitis and community-acquired pneumonia: how effective are respiratory fluoroquinolones? *Can Fam Physician* 2006; 52: 1236–42.
14. Dimopoulos G, *et al.* Comparison of first-line with second-line antibiotics for acute exacerbations of chronic bronchitis: a metaanalysis of randomized controlled trials. *Chest* 2007; 132: 447–55.
15. Global initiative for chronic obstructive lung disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Updated 2009. Available at: http://www.goldcopd.com/download.asp?intId=554 (accessed 05/08/10)
16. Rodríguez-Roisín R. COPD exacerbations.5: management. *Thorax* 2006; 61: 535–44.
17. Staykova T, *et al.* Prophylactic antibiotic therapy for chronic bronchitis. Available in The Cochrane Database of Systematic Reviews: Issue 2. Chichester: John Wiley; 2001 (accessed 05/02/10).

Brucellosis

Brucellosis (also known as undulant or Mediterranean fever) is caused by *Brucella* spp., aerobic Gram-negative bacteria found mainly in livestock and domestic animals. Humans can become infected by direct contact with infected animals or animal material (such as the placenta), indirectly by consuming infected and unpasteurised milk products, or by inhalation of contaminated dust or droplets. Rarely, human infection has been reported from exposure to some live veterinary vaccines.[1,2] The principal *Brucella* spp. affecting humans are *B. melitensis*, from sheep, goats, camels, and sometimes cattle; *B. abortus*, from cattle, buffalo, camels, and yaks; *B. suis*, from pigs; and rarely *B. canis*, from dogs. Although rare or controlled in countries such as the UK brucellosis remains a problem in many areas, including eastern Europe, the Mediterranean region, South and Central America, Mexico, the Caribbean, the Indian subcontinent, parts of Africa and Asia, and the Middle East.

Symptoms usually develop 2 to 8 weeks after infection and resemble a flu-like illness with anorexia, fever, headache, lethargy, malaise, depression, myalgia and back pain, sweating, and weakness. Laboratory findings include anaemia, leucopenia, lymphocytosis, pancytopenia, and thrombocytopenia. Brucellosis may be acute, relapsing, or chronic (disease duration of more than 1 year) and can affect any part of the body, including joints (peripheral arthritis, sacroiliitis, and spondylitis), heart (endocarditis), liver (hepatitis), the CNS (meningitis, encephalitis, meningoencephalitis, meningovascular disease, brain abscesses, and demyelinating syndrome), and the reproductive system (epididymo-orchitis). Relapses occur in about 10% of patients, usually in the first year after infection, and typically cause milder symptoms.[3]

Treatment of brucellosis shortens the duration of illness, and reduces complications and the risk of relapse. Tetracyclines, although highly active against *Brucella* spp., are associated with high relapse rates when given as monotherapy and therefore combination therapy is now used. Common regimens are:

- doxycycline and rifampicin both orally for at least 6 weeks[4,5]
- doxycycline orally for 6 weeks with a parenteral aminoglycoside (streptomycin,[6,7] gentamicin,[5,8,9] or netilmicin[10]) for the first 1 to 2 weeks

Fewer relapses have been reported with doxycycline and streptomycin than with doxycycline and rifampicin, perhaps due to rifampicin reducing plasma concentrations of doxycycline.[11] Higher relapse rates have been reported with netilmicin than with gentamicin.[10] Studies[12,13] have shown that treatment with a fluoroquinolone plus either doxycycline or rifampicin is effective although fluoroquinolone monotherapy is not. A review of the literature on fluoroquinolone-based combination treatment did not support their use as first-line treatment,[13] but they can be considered as part of an alternative regimen for patients who have relapse or toxicity problems with the usual first-line antibacterials. Co-trimoxazole when used is usually given in triple-drug regimens.[3]

A systematic review and meta-analysis[14] of 30 randomised controlled studies on the treatment of brucellosis found that a triple drug regimen of doxycycline, gentamicin, and rifampicin was better than doxycycline plus an aminoglycoside. It also found that 6 weeks of treatment was associated with a lower rate of relapse than treatment regimens of 30 days or less.

Tetracyclines should be avoided in young *children* (usually specified as below 8 years of age in the US and below 12 years in the UK). The preferred regimens for these children appear to be co-trimoxazole with rifampicin both orally for at least 6 weeks or co-trimoxazole orally with parenteral gentamicin for the first 2 weeks.[5,6] Alternative regimens include rifampicin orally for at least 6 weeks with either gentamicin or netilmicin for the first 5 days.[6]

For the treatment of brucellosis during *pregnancy*, WHO recommends rifampicin monotherapy for 6 weeks as the drug of choice and that co-trimoxazole or tetracycline should only be given if rifampicin is unavailable; streptomycin is contra-indicated.[4] Co-trimoxazole with rifampicin for 4 weeks has also been tried.[6]

No one antibacterial combination has been found to be superior for the treatment of *spondylitis* although a 3-month course of doxycycline with ciprofloxacin has been proposed based on an evaluation of the literature.[13] In the treatment of *neurobrucellosis*, the length of therapy appears to be of critical importance; relapses may occur after treatment lasting only 2 to 3 weeks and it is recommended that doxycycline be given with 2 or more other drugs (rifampicin, an aminoglycoside, co-trimoxazole, or ceftriaxone) for several months depending on the response. Corticosteroids are often given but their efficacy is unproven. A similar treatment regimen is used in the management of paediatric neurobrucellosis and a 3-drug regimen (doxycycline, rifampicin, and an aminoglycoside) given for 3 months has been shown to be effective. In young children doxycycline should be replaced with co-trimoxazole.[16] Treatment of *endocarditis* in adults generally requires long-term triple or quadruple drug regimens (a tetracycline, an aminoglycoside, rifampicin, and/or co-trimoxazole) usually with surgical valve replacement.[17,18] Treatment should be continued for 3 months or longer and some recommend the addition of ceftriaxone and/or a fluoroquinolone to reduce the need for surgery. Cardiac complications in children are generally less severe than in adults and treatment with tetracycline for 3 weeks with streptomycin for 2 weeks has been found to be effective.[18]

Brucellosis can be **prevented** by controlling and eliminating infected animals, pasteurising milk products, and vaccinating cattle and other livestock. There is no human vaccine currently available for brucellosis, although many have been tested and some have been available periodically in various countries.[3]

1. Blasco JM, Díaz R. Brucella melitensis Rev-1 vaccine as a cause of human brucellosis. *Lancet* 1993; 342: 805.
2. Ashford DA, *et al.* Adverse events in humans associated with accidental exposure to the livestock brucellosis vaccine RB51. *Vaccine* 2004; 22: 3435–9.
3. Pappas G, *et al.* Brucellosis. *N Engl J Med* 2005; 352: 2325–36.
4. FAO/WHO. Joint FAO/WHO expert committee on brucellosis: sixth report. *WHO Tech Rep Ser 740* 1986. Also available at: http://libdoc.who.int/trs/WHO_TRS_740.pdf (accessed 21/05/07)
5. Health Protection Agency. Guidelines for action in the event of a deliberate release: brucellosis. Version 1.5, 18 June 2007. Available at: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1194947355003 (accessed 15/08/08)
6. Solera J, *et al.* Recognition and optimum treatment of brucellosis. *Drugs* 1997; 53: 245–56.
7. Solera J, *et al.* Doxycycline-rifampin versus doxycycline-streptomycin in treatment of human brucellosis due to Brucella melitensis. *Antimicrob Agents Chemother* 1995; 39: 2061–7.
8. Solera J, *et al.* Treatment of human brucellosis with doxycycline and gentamicin. *Antimicrob Agents Chemother* 1997; 41: 80–84.
9. Solera J, *et al.* A randomized, double-blind study to assess the optimal duration of doxycycline treatment for human brucellosis. *Clin Infect Dis* 2004; 39: 1776–82.
10. Solera J, *et al.* Treatment of human brucellosis with netilmicin and doxycycline. *Clin Infect Dis* 1996; 22: 441–5.
11. Colmenero JD, *et al.* Possible implications of doxycycline-rifampin interaction for treatment of brucellosis. *Antimicrob Agents Chemother* 1994; 38: 2798–2802.
12. Karabay O, *et al.* Ofloxacin plus rifampicin versus doxycycline plus rifampicin in the treatment of brucellosis: a randomized clinical trial [ISRCTN11871179]. *BMC Infect Dis* 2004; 4: 18. Available at: http://www.biomedcentral.com/1471-2334/4/18 (accessed 22/05/07)
13. Falagas ME, Bliziotis IA. Quinolones for treatment of human brucellosis: critical review of the evidence from microbiological and clinical studies. *Antimicrob Agents Chemother* 2006; 50: 22–33.
14. Skalsky K, *et al.* Treatment of human brucellosis: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2008; 336: 701–4.
15. Pappas G, *et al.* Treatment of brucella spondylitis: lessons from an impossible meta-analysis and initial report of efficacy of a fluoroquinolone-containing regimen. *Int J Antimicrob Agents* 2004; 24: 502–7.
16. Habeeb YKR, *et al.* Paediatric neurobrucellosis: case report and literature review. *J Infect* 1998; 37: 59–62.
17. Reguera JM, *et al.* Brucella endocarditis: clinical, diagnostic, and therapeutic approach. *Eur J Clin Microbiol Infect Dis* 2003; 22: 647–50.
18. Al Dahouk S, *et al.* Brucella endocarditis in prosthetic valves. *Can J Cardiol* 2006; 22: 971–4.

Campylobacter enteritis

See under Gastro-enteritis p. 186.1.

Cat scratch disease

Cat scratch disease usually occurs in humans after a cat scratch or bite. The condition is characterised by regional lymphadenopathy and is often self-limiting, but may be disseminated in immunocompromised patients. Disseminated disease typically involves the nervous system (including the retina), visceral organs, or bone.

In the 1980s a Gram-negative bacillus presumed to be responsible for cat scratch disease was isolated and subsequently named *Afipia felis*. However, it has since become apparent that *Bartonella henselae* (formerly *Rochalimaea henselae*) is the main cause of cat scratch disease.[1-3] There has been no specific antibacterial therapy and treatment with antibacterials is generally not recommended in patients with mild to moderate infection.[1,2] There are, however, reports of successful treatment with gentamicin, co-trimoxazole, and ciprofloxacin.[2] Azithromycin has also been found to be of benefit in adults[4] and a 5-day oral regimen is considered the treatment of choice in both adults and children with extensive lymphadenopathy. Oral doxycycline with oral rifampicin may be given as an alternative for these patients and this combination, given for 4 to 6 weeks, is the recommended treatment for complicated cat scratch disease.[1]

Bacillary angiomatosis, in which both *B. henselae* and *B. quintana* (the causative organism of trench fever) have been implicated, and **bacillary peliosis hepatis** (caused by *B. henselae*) occur mainly in immunocompromised patients, especially in those with HIV. Bacillary angiomatosis is generally characterised by cutaneous or subcutaneous vascular lesions. Symptoms of bacillary peliosis, where lesions affect the liver, are non-specific, with or without cutaneous involvement.[1,3] Disseminated disease in immunocompromised patients has responded to treatment with doxycycline, erythromycin or azithromycin.[2] Oral erythromycin for 3 months is the drug of choice for bacillary angiomatosis; it should be given intravenously in severe disease. Oral or intravenous doxycycline may be given as an alternative. Immunocompromised patients with acute, life-threatening infection should be treated with rifampicin plus erythromycin or rifampicin plus doxycycline; the latter choice is preferred in CNS disease.[1,3] Care is required in patients with AIDS since the lesions of bacillary angiomatosis closely resemble those of Kaposi's sarcoma, and if the diagnosis is missed, life-saving antibacterial therapy may not be given.[5]

1. Rolain JM, *et al.* Recommendations for treatment of human infections caused by Bartonella species. *Antimicrob Agents Chemother* 2004; 48: 1921–33.
2. Florin TA, *et al.* Beyond cat scratch disease: widening spectrum of Bartonella henselae infection. *Pediatrics* 2008; 121: e1413–25.
3. English R. Cat-scratch disease. *Pediatr Rev* 2006; 27: 123–8.
4. Bass JW, *et al.* Prospective randomized double blind placebo-controlled evaluation of azithromycin for treatment of cat-scratch disease. *Pediatr Infect Dis J* 1998; 17: 447–52.

5. Taylor AG, *et al.* Cat-scratch, Kaposi's sarcoma, and bacillary angiomatosis. *Lancet* 1993; **342**: 686.

Cellulitis

See under Skin Infections, p. 209.1.

Cervicitis

Gonorrhoea in women occurs mainly as cervicitis, but mucopurulent cervicitis is frequently caused by sexually transmitted *Chlamydia trachomatis*. The two infections often occur together and should be treated concurrently. Guidelines for treatment are given under Gonorrhoea, p. 206.2, and Chlamydial Infections, p. 179.1.

Chancroid

See under Sexually Transmitted Diseases, p. 206.2

Chlamydial infections

The chlamydia organism belongs to the family Chlamydiaceae. Species that are pathogenic in man are *Chlamydophila pneumoniae*, *Chlamydophila psittaci*, and *Chlamydia trachomatis*; they are generally sensitive to tetracyclines or erythromycin.

C. pneumoniae (formerly classified as a TWAR strain of *C. psittaci*) is a respiratory pathogen. It was first described as a cause of community-acquired pneumonia (see Pneumonia, p. 202.1), but has since been associated with other clinical presentations including pharyngitis (see p. 200.3) and has been implicated in the pathogenesis of ischaemic heart disease (see Atherosclerosis, p. 1250.2).

C. psittaci is transmitted to man from birds and causes psittacosis, which also affects the lungs (see Psittacosis, p. 204.1).

C. trachomatis causes a wide range of diseases. Many are sexually transmitted and the spectrum is similar to that with *Neisseria gonorrhoeae* (see Gonorrhoea, p. 206.2); infections with the two organisms often occur together. In women *C. trachomatis* may cause endometritis, pelvic inflammatory disease, ectopic pregnancy, and infertility. In the USA[1,2] routine screening for *C. trachomatis* infection is recommended in all sexually active women aged 25 years or younger, whether or not they are pregnant, and in women aged over 25 years if they are considered to be at increased risk of infection.

Guidelines produced by WHO,[3] by expert groups in the UK,[4,5] and by the CDC in the USA[2] for the **treatment** of uncomplicated anogenital infection with *C. trachomatis* are as follows:

- **WHO:**
  - oral doxycycline 100 mg twice daily for 7 days, *or*
  - a single oral dose of azithromycin 1 g

  alternatives, given for 7 days, are:
  - oral amoxicillin 500 mg three times daily
  - oral erythromycin 500 mg four times daily
  - oral ofloxacin 300 mg twice daily
  - oral tetracycline 500 mg four times daily
- **UK:**
  - first-line therapy is the same as WHO

  alternatives are:
  - oral erythromycin 500 mg twice daily for 10 to 14 days
  - oral ofloxacin 200 mg twice daily *or* 400 mg once daily for 7 days
- **USA:**
  - first-line therapy is the same as WHO

  alternatives, given for 7 days, are:
  - oral erythromycin 500 mg four times daily
  - oral erythromycin ethylsuccinate 800 mg four times daily
  - oral ofloxacin 300 mg twice daily
  - oral levofloxacin 500 mg once daily

Pregnant women infected with *C. trachomatis* may be at risk of premature rupture of membranes and preterm labour (see Premature Labour, p. 203.3). They may also infect their offspring to cause ophthalmia neonatorum (see Neonatal Conjunctivitis, p. 195.2) or pneumonia (p. 202.1). Infected pregnant women should be treated and the following regimens have been recommended:

- **WHO:** treatment for 7 days with:
  - oral erythromycin 500 mg four times daily *or*
  - oral amoxicillin 500 mg three times daily
- **UK:**
  - as for WHO, *or*
  - oral erythromycin 500 mg twice daily for 14 days, *or*
  - a single oral dose of azithromycin 1 g
- **USA:**
  - a single oral dose of azithromycin 1 g *or*
  - oral amoxicillin 500 mg three times daily for 7 days

  alternatives are:
  - erythromycin-containing regimens

Sexual partners of those infected with *C. trachomatis* should be tested and treated.[2-4]

For further reference to sexually transmitted *C. trachomatis* infections, see under Epididymitis (p. 183.2), Pelvic Inflammatory Disease (p. 198.3), and Urethritis (p. 214.3)

Specific serotypes of *C. trachomatis* are responsible for another sexually transmitted disease, lymphogranuloma venereum (p. 207.2).

Reactive arthritis (see Bone and Joint Infections, p. 175.1) may be secondary to chlamydial infections.

Other *C. trachomatis* infections that are not sexually transmitted include trachoma and inclusion conjunctivitis in adults (see Trachoma, p. 212.1).

1. US Preventive Services Task Force. Screening for chlamydial infection (June 2007). Available at: http://www.ahcpr.gov/clinic/uspstf/uspschlm.htm (accessed 03/08/07)
2. CDC. Sexually transmitted diseases treatment guidelines, 2010. *MMWR* 2010; **59** (RR-12): 1–110. Also available at: http://www.cdc.gov/STD/treatment/2010/STD-Treatment-2010-RR5912.pdf (accessed 08/01/11) Correction. *Ibid.* 2011; **60**: 18. [dose]
3. WHO. Guidelines for the management of sexually transmitted infections. Geneva: WHO, 2003. Also available at: http://whqlibdoc.who.int/publications/2003/9241546263.pdf (accessed 22/03/07)
4. Clinical Effectiveness Group (British Association for Sexual Health and HIV). 2006 UK national guideline for the management of genital tract infection with Chlamydia trachomatis. Available at: http://www.bashh.org/documents/61/61.pdf (accessed 18/08/08)
5. Scottish Intercollegiate Guidelines Network. Management of genital *Chlamydia trachomatis* infection (issued March 2009). Available at: http://www.sign.ac.uk/pdf/sign109.pdf (accessed 25/02/10)

Cholera and other vibrio infections

See under Gastro-enteritis p. 186.2.

Cystic fibrosis

Cystic fibrosis is a genetic disorder associated with the production of abnormally viscous mucus. The underlying defect is mutation in the gene that codes for cystic fibrosis transmembrane conductance regulator (CFTR), a protein that functions as a chloride channel. Mutations result in defective ion transport with reduced chloride ion secretion and accelerated sodium ion absorption, and related changes in the composition and properties of mucin secreted. Now that patients with cystic fibrosis usually survive into adulthood, it is increasingly seen to be a multisystem disease. However, the main clinical manifestations are still pulmonary disease, with recurrent bacterial infections and the production of copious viscous sputum, and malabsorption due to pancreatic insufficiency. Other complications include male infertility and hepatobiliary disease. There is increased salt loss in sweat.

Pulmonary disease is the main cause of mortality. Cystic fibrosis is an underlying cause of bronchiectasis (chronic dilatation of the bronchi) as a result of excessive secretion of mucus and recurrent infections. Cough and excessive production of sputum are characteristic of cystic fibrosis and the lungs are generally colonised with bacterial pathogens, especially mucoid strains of *Pseudomonas aeruginosa*. Pseudomonal pulmonary infection is the main cause of morbidity and mortality in cystic fibrosis. Monitoring of bacterial pathogens in the sputum, including their sensitivity, is necessary for rational treatment. Apart from *Ps. aeruginosa*, *Staphylococcus aureus* is often present and may be the main pathogen in infants. *Burkholderia cepacia* complex (*Pseudomonas cepacia*) has been recognised as a cause of serious lung infection in cystic fibrosis and is readily transmitted by social contact. In a proportion who acquire it, *B. cepacia* has been associated with rapid deterioration and death. Other bacteria isolated include *Haemophilus influenzae* and atypical *Mycobacteria* spp.

Various diagnostic methods are available[1-3] and clinical diagnosis of cystic fibrosis may be confirmed by establishing that chloride concentrations in sweat are raised. This may be done by using the pilocarpine sweat test (see Pilocarpine, p. 2011.1). Identification of gene mutation is possible and may be used for further confirmation of the diagnosis and identification of carrier status. In some areas neonatal screening programs to measure immunoreactive trypsinogen concentrations (a marker associated with pancreatic injury) have been instituted, to allow for early intervention.[2,3]

The reduced morbidity and improved survival in patients with cystic fibrosis are largely due to the management of pulmonary disease with antibacterials and physiotherapy and to nutritional management. Several reviews have discussed both established and experimental therapy.[1-5] Despite the successes, the evidence base for some procedures is scanty,[2] and there may be variations in management between centres. However, the cornerstones of current management are:[1-3]

- mechanical airway clearance, with the use of adjuncts such as dornase alfa and hypertonic saline
- prevention or eradication of pulmonary infections in early disease
- suppression of bacterial load through antibacterial treatment of chronic infection in more advanced disease
- use of ibuprofen or azithromycin to control lung inflammation
- aggressive antibacterial treatment of pulmonary exacerbations
- nutritional support to ensure an adequate intake of calories and salt, with supplementation of pancreatic enzymes and the fat-soluble vitamins A, D, E, and K
- maintaining regular physical activity

Guidelines for the management of infants with cystic fibrosis have been developed by the Cystic Fibrosis Foundation in the USA.[6]

Airway clearance by manual chest percussion and mechanical techniques including chest-wall or airway oscillation helps to loosen secretions and aid their removal.[7] Dornase alfa[8] is given by aerosol inhalation and reduces the viscosity of the sputum by breaking down the large quantities of DNA released by degenerating inflammatory cells. The use of dornase alfa has been associated with some improvement in lung function and it might be a useful adjunct to bronchial drainage, although it is unclear whether it prevents the development of progressive lung damage. However, a randomised, multicentre, placebo-controlled study in children showed that dornase alfa maintained lung function and reduced the risk of exacerbations over a 96-week period.[9] US guidelines therefore also recommend the long-term use of dornase alfa to improve lung function and reduce exacerbations.[10] Nebulised or oral mucolytics, such as acetylcysteine, carbocysteine, ambroxol, glutathione, and mesna are generally not considered to be effective in cystic fibrosis.[11] Inhalation of hypertonic saline has, however, been shown to be of benefit[12] (see p. 1798.1) and has become part of management in many centres.[1-3] Inhaled mannitol may be added to standard therapy to improve mucus clearance.[13] The time required for such therapies and their associated monitoring may prove challenging to patients and their families.[1]

In young patients with early disease, **prevention or eradication of infection** for as long as possible is a reasonable aim, in order to maintain good lung function.[2] Staphylococcal infections commonly develop during the first decade of life, and while some clinicians start antistaphylococcal antibacterials on diagnosis of cystic fibrosis, others wait until the first clinical infection occurs. Once started, antistaphylococcal therapy is continued indefinitely in some centres, while others only treat when symptomatic exacerbations or positive sputum cultures occur. Systematic reviews confirmed that antistaphylococcal treatment is effective and also concluded that prophylaxis is likely to be beneficial in young children with cystic fibrosis.[14,15] In the UK, flucloxacillin or co-amoxiclav are commonly given.[2] It is unclear whether intermittent or continuous therapy produces the best clinical outcome. Other potential disadvantages to prophylaxis are the possible early acquisition of *Ps. aeruginosa* infection[16] (this seems to be a risk mainly if broad spectrum cephalosporins are given) and an increased incidence of drug-resistant staphylococci with continuous therapy.[17] In view of this risk of earlier or more frequent *Ps. aeruginosa* infection, guidelines developed in the USA, by the Cystic Fibrosis Foundation, do not support the prophylactic use of oral antistaphylococcal antibacterials.[10]

Management of **chronic infection** is aimed at control of bacterial load,[2] (since permanent eradication is impossible), improving lung function, and reducing exacerbations.[10] Selection of an antibacterial must be individualised, and will depend on the infecting organisms,[2] and local prescribing policies and availability. Long-term intermittent treatment with inhaled antibacterials, particularly tobramycin, is favoured;[1-3,10] other nebulised antibacterials that may be of benefit include aztreonam and colistin.[1,18] A systematic review confirmed that inhaled antipseudomonal antibacterials improved lung function and reduced the frequency of exacerbations.[19] Although there is some evidence of an increase in resistance with such treatment,[19] it is claimed to be less frequent than feared.[1] However, US guidelines concluded that there was insufficient evidence to recommend for or against the long-term use of nebulised antibacterials other than tobramycin, including colistin, gentamicin, or ceftazidime.[10] Oral antipseudomonal therapy has not been conclusively shown to be of benefit in chronic infection,[20] and is generally avoided because of fears of resistance.[1]

The macrolide azithromycin is, however, used orally in chronic infection, but may be acting as an immunomodulator to **reduce inflammation** rather than specifically as an antibacterial.[1-3,10,21] A systematic review[22] on the use of macrolides in cystic fibrosis found evidence of a small but significant improvement in respiratory function at 6 months with azithromycin compared with placebo; the role of other macrolides was unclear. A small anti-inflammatory benefit has also been reported from treatment with high-dose oral ibuprofen,[23] and this is used in some centres, particularly in the USA to slow the loss of lung function.[2,10] However, there are some concerns about the potential for adverse effects; it has been recommended that if used, such therapy be stopped in patients who require intravenous aminoglycosides, and should be avoided in those with gastrointestinal risk factors.[23] Systematic reviews[24,25] and the US guide-

lines[10] concluded there was insufficient evidence to support a role for either inhaled or oral corticosteroid therapy, except in the management of patients who develop allergic bronchopulmonary aspergillosis.[2] However, a retrospective analysis of observational data collected for 2978 children, 6 to 17 years of age, who were given inhaled corticosteroid therapy reported a slower decline in lung function as determined by the FEV_1.[26]

Aggressive management of exacerbations with appropriate antibacterials is crucial.[1,2,27,28] Treatment should be based on recent culture results, but there appears to be no additional value in combination antibacterial sensitivity testing.[29] In patients with *Ps. aeruginosa* infection a combination of intravenous antibacterials, typically an aminoglycoside such as tobramycin and a beta-lactam with antipseudomonal activity such as ceftazidime, is favoured.[3,27,28,30,31] Once-daily dosing with the aminoglycoside is as effective as giving it in divided doses, and may be associated with less nephrotoxicity in children.[32] High doses are necessary because of the poor penetration of these antipseudomonal antibacterials into the site of infection and their increased renal clearance in patients with cystic fibrosis.[33,34] Treatment is generally given for 2 to 3 weeks although there is no good evidence to support a particular length of therapy.[31,35] Intermittent elective intravenous therapy has become more practical with the development of regimens that enable patients to be treated at home.[30,36] US guidelines[31] recommend that airway clearance should be increased as part of the treatment of an acute exacerbation and chronic maintenance therapies be continued; there is no clear evidence for or against continued use of inhaled antibacterials in patients given the same antibacterial intravenously.

Infection with *B. cepacia* complex is difficult to treat because most antipseudomonal antibacterials are ineffective. Co-trimoxazole has been suggested[37] and can be given orally;[28] meropenem and ceftazidime have some *in-vitro* activity, and temocillin has been tried.[28] Other problems may include meticillin-resistant *Staph. aureus* infections; intravenous teicoplanin has been used, as have oral doxycycline or linezolid where sensitivity patterns permit.[28] The possibility of fungal or viral infections should also be considered.[28]

Nutritional management of cystic fibrosis should ensure adequate calorie intake from a balanced diet in order to counteract malabsorption due to pancreatic insufficiency and the increased metabolic requirements of patients with cystic fibrosis.[38,39] Supplements of the fat-soluble vitamins A, D, and E, and sometimes vitamin K, may be necessary. Investigation of bone mineral density[40] and direct assessment of vitamin status[41] suggest that current supplements may be inadequate. Pancreatic enzymes, as pancreatin or pancrelipase, are taken before or with each meal or snack.[42]

Many **other interventions** have been tried.[43,44]

Bronchodilators including both beta agonists and antimuscarinics may be useful in selected patients although there are few meaningful results from clinical studies.[45] A therapeutic trial is often justified in individual patients since it is difficult to predict which patients will respond.[43] While use by nebuliser is regarded as most effective, inhalers may be more practical where compatibility with other nebulised drugs could be a problem.[44] $Alpha_1$-proteinase inhibitor, the main inhibitor of neutrophil elastase in the lung has also been investigated[46] as has pentoxifylline,[47] a drug with anticytokine activity. Although cysteinyl leukotrienes have been found in increased concentrations in airway secretions of patients with cystic fibrosis and thought to contribute to lung disease, there is insufficient evidence to recommend the routine use of leukotriene inhibitors and antagonists (such as montelukast) to improve lung function and reduce exacerbations.[10]

Treatment aimed at modifying the pulmonary disease process rather than treating the disease symptoms has also included ion transport therapy. This involves the use of drugs that either inhibit sodium ion absorption across airway epithelia (for example the sodium channel blocker amiloride) or induce chloride ion secretion. However, nebulised amiloride was not found to be a useful adjunct in patients on optimal treatment.[48] The use of oral ivacaftor, a CFTR potentiator that increases chloride ion transport, has been shown to improve lung function in patients with a G551D mutation in the CFTR gene.[49]

In patients with severe lung disease, oxygen therapy may give some relief of symptoms but its effect on mortality and morbidity is uncertain.[50] At present the only available treatment for patients with end stage pulmonary disease is lung transplantation. Although individuals with cystic fibrosis do as well as those referred for transplantation with other lung diseases, the 5-year survival rate after the procedure is reported to be only 50%.[1]

Somatic **gene therapy** represents the nearest approach to a cure for cystic fibrosis.[51] It aims to introduce the normal CFTR gene sequence into cells of affected tissue. Most effort has been directed at gene delivery to the lungs using adenovirus vectors or liposomes, but results have been variable.[52-55] Difficulties encountered include inefficient gene transfer, immunity to viral vectors, and a systemic inflammatory reaction provoked by plasmid DNA. For a discussion of the general principles of gene therapy, see p. 2511.2.

1. Boyle MP. Adult cystic fibrosis. *JAMA* 2007; **298**: 1787–93.
2. Davies JC, *et al.* Cystic fibrosis. *BMJ* 2007; **335**: 1255–9.
3. O'Sullivan BP, Freedman SD. Cystic fibrosis. *Lancet* 2009; **373**: 1891–904.
4. Doull IJM. Recent advances in cystic fibrosis. *Arch Dis Child* 2001; **85**: 62–6.
5. Tonelli MR, Aitken ML. New and emerging therapies for pulmonary complications of cystic fibrosis. *Drugs* 2001; **61**: 1379–85.
6. Borowitz D, *et al.* Cystic Fibrosis Foundation evidence-based guidelines for management of infants with cystic fibrosis. *J Pediatr* 2009; **155** (6 suppl): S73–S93.
7. Flume PA, *et al.* Clinical Practice Guidelines for Pulmonary Therapies Committee. Cystic fibrosis pulmonary guidelines: airway clearance therapies. *Respir Care* 2009; **54**: 522–37. Also available at: http://www.rcjournal.com/contents/04.09/04.09.0522.pdf (accessed 28/04/10)
8. Jones AP, Wallis C. Dornase alfa for cystic fibrosis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2010 (accessed 25/08/10).
9. Quan JM, *et al.* A two-year randomized, placebo-controlled trial of dornase alfa in young patients with cystic fibrosis with mild lung function abnormalities. *J Pediatr* 2001; **139**: 813–20.
10. Flume PA, *et al.* Cystic Fibrosis Foundation, Pulmonary Therapies Committee. Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. *Am J Respir Crit Care Med* 2007; **176**: 957–69. Also available at: http://ajrccm.atsjournals.org/cgi/reprint/176/10/957.pdf (accessed 28/04/10)
11. Nash EF, *et al.* Nebulized and oral thiol derivatives for pulmonary disease in cystic fibrosis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009 (accessed 02/03/10).
12. Wark P, McDonald VM. Nebulised hypertonic saline for cystic fibrosis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 02/03/10).
13. Burness CB, Keating GM. Mannitol dry powder for inhalation: in patients with cystic fibrosis. *Drugs* 2012; **72**: 1411–21.
14. McCaffery K, *et al.* Systematic review of antistaphylococcal antibiotic therapy in cystic fibrosis. *Thorax* 1999; **54**: 380–3.
15. Smyth A, Walters S. Prophylactic antibiotics for cystic fibrosis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 16/05/05).
16. Stutman HR, *et al.* Antibiotic prophylaxis in infants and young children with cystic fibrosis: a randomized controlled trial. *J Pediatr* 2002; **140**: 299–305.
17. Elborn JS. Treatment of Staphylococcus aureus in cystic fibrosis. *Thorax* 1999; **54**: 377–8.
18. Beringer P. The clinical use of colistin in patients with cystic fibrosis. *Curr Opin Pulm Med* 2001; **7**: 434–40.
19. Ryan G, *et al.* Nebulised anti-pseudomonal antibiotics for cystic fibrosis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 25/06/08).
20. Remmington T, *et al.* Oral anti-pseudomonal antibiotics for cystic fibrosis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 25/06/08).
21. Giamarellos-Bourboulis EJ. Macrolides beyond the conventional antimicrobials: a class of potent immunomodulators. *Int J Antimicrob Agents* 2008; **31**: 12–20.
22. Southern KW, *et al.* Macrolide antibiotics for cystic fibrosis. Available in the Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 02/03/07).
23. Lands LC, Stanojevic S. Oral non-steroidal anti-inflammatory drug therapy for cystic fibrosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 25/06/08).
24. Cheng K, *et al.* Oral steroids for cystic fibrosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 1999 (accessed 16/05/05).
25. Balfour-Lynn IM, Welch K. Inhaled corticosteroids for cystic fibrosis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009 (accessed 25/02/10).
26. Ren CL, *et al.* Relationship between inhaled corticosteroid therapy and rate of lung function decline in children with cystic fibrosis. *J Pediatr* 2008; **153**: 746–51.
27. Ferkol T, *et al.* Cystic fibrosis pulmonary exacerbations. *J Pediatr* 2006; **148**: 259–64.
28. Smyth A, Elborn JS. Exacerbations in cystic fibrosis: 3. Management. *Thorax* 2008; **63**: 180–4.
29. Aaron SD, *et al.* Combination antibiotic susceptibility testing to treat exacerbations of cystic fibrosis associated with multiresistant bacteria: a randomised, double-blind, controlled clinical trial. *Lancet* 2005; **366**: 463–71.
30. Banerjee D, Stableforth D. The treatment of respiratory Pseudomonas infection in cystic fibrosis: what drug and which way? *Drugs* 2000; **60**: 1053–64.
31. Flume PA, *et al.* Clinical Practice Guidelines for Pulmonary Therapies Committee. Cystic fibrosis pulmonary guidelines: treatment of pulmonary exacerbations. *Am J Respir Crit Care Med* 2009; **180**: 802–8.
32. Smyth AR, Bhatt J. Once-daily versus multiple-daily dosing with intravenous aminoglycosides for cystic fibrosis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 25/02/10).
33. Rey E, *et al.* Drug disposition in cystic fibrosis. *Clin Pharmacokinet* 1998; **35**: 313–29.
34. Touw DJ, *et al.* Pharmacokinetic optimisation of antibacterial treatment in patients with cystic fibrosis: current practice and suggestions for future directions. *Clin Pharmacokinet* 1998; **35**: 437–59.
35. Fernandes B, *et al.* Duration of intravenous antibiotic therapy in people with cystic fibrosis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 25/06/08).
36. Wolter JM, *et al.* Home intravenous therapy in cystic fibrosis: a prospective randomized trial examining clinical, quality of life and cost aspects. *Eur Respir J* 1997; **10**: 896–900.
37. Abramowicz M, ed. The choice of antibacterial drugs. In: *Handbook of antimicrobial therapy*. 19th ed. New Rochelle NY: The Medical Letter, 2011: 68.
38. Bowler IM, *et al.* Resting energy expenditure and substrate oxidation rates in cystic fibrosis. *Arch Dis Child* 1993; **68**: 754–9.
39. Green MR, *et al.* Nutritional management of the infant with cystic fibrosis. *Arch Dis Child* 1995; **72**: 452–6.
40. Haworth CS, *et al.* Low bone mineral density in adults with cystic fibrosis. *Thorax* 1999; **54**: 961–7.
41. Feranchak AP, *et al.* Prospective, long-term study of fat-soluble vitamin status in children with cystic fibrosis identified by newborn screen. *J Pediatr* 1999; **135**: 601–10.
42. Stallings VA, *et al.* Clinical Practice Guidelines on Growth and Nutrition Subcommittee. Ad Hoc Working Group. Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review. *J Am Diet Assoc* 2008; **108**: 832–9.
43. Conway SP, Watson A. Nebulised bronchodilators, corticosteroids, and rhDNase in adult patients with cystic fibrosis. *Thorax* 1997; **52** (suppl 2): S64–8.
44. Spencer DA. Nebulised bronchodilators, antibiotics and rhDNase for children with cystic fibrosis. *Thorax* 1997; **52** (suppl 2): S89–S91.
45. Halfhide C, *et al.* Inhaled bronchodilators for cystic fibrosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 25/06/08).
46. McElvaney NG, *et al.* Aerosol α-1-antitrypsin treatment for cystic fibrosis. *Lancet* 1991; **337**: 392–4.
47. Aronoff SC, *et al.* Effects of pentoxifylline on sputum neutrophil elastase and pulmonary function in patients with cystic fibrosis: preliminary observations. *J Pediatr* 1994; **125**: 992–7.
48. Burrows E, *et al.* Sodium channel blockers for cystic fibrosis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 25/06/08).
49. Accurso FJ, *et al.* Effect of VX-770 in persons with cystic fibrosis and the G551D-CFTR mutation. *N Engl J Med* 2010; **363**: 1991–2003.
50. Elphick HE, Mallory G. Oxygen therapy for cystic fibrosis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009 (accessed 25/02/10).
51. Jaffé A, *et al.* Prospects for gene therapy in cystic fibrosis. *Arch Dis Child* 1999; **80**: 286–9.
52. Colledge WH, Evans MJ. Cystic fibrosis gene therapy. *Br Med Bull* 1995; **51**: 82–90.
53. Coutelle C. Gene therapy approaches for cystic fibrosis. *Biologicals* 1995; **23**: 21–5.
54. Southern KW. Gene therapy for cystic fibrosis: current issues. *Br J Hosp Med* 1996; **55**: 495–9.
55. Plotte TR, Laube BL. Gene therapy in cystic fibrosis. *Chest* 2001; **120**: 124S–131S.

Diarrhoea, infective

See Gastro-enteritis, p. 184.2.

Diphtheria

Diphtheria is an acute infection with the Gram-positive aerobe *Corynebacterium diphtheriae*, some strains of which produce an exotoxin. It occurs worldwide and is endemic to many countries. The efficacy of immunisation (see Diphtheria Vaccines, p. 2382.3) has rendered the disease rare in most developed countries, but infection is still common in parts of the world with low rates of immunisation. Although the risk to travellers is said to be low, diphtheria should be considered in patients returning from endemic areas with a sore throat; most cases occur in those who are unvaccinated or inadequately immunised.

Diphtheria has an incubation period of about 1 to 5 days;[1-3] onset of symptoms is gradual. These range from a moderately sore throat, low-grade fever, and swollen glands, to more serious manifestations caused by the exotoxin from toxigenic strains. The exotoxin causes local destruction of mucous membranes and epithelium, leading to the formation of a characteristic adherent pseudomembrane that coats the tonsillopharyngeal region and may obstruct the upper airways. Swelling of the neck occurs in severe cases. Toxin can be absorbed systemically, resulting in damage to cardiac, renal, hepatic, and neural tissue.[2,3] Respiratory diphtheria has a mortality rate of 5 to 10% even when treated. Cutaneous diphtheria, characterised by chronically infected skin lesions, is usually caused by non-toxigenic strains and has fewer complications.

Diphtheria is highly contagious and patients should be isolated.[1] Treatment of respiratory infection is mainly with antitoxin (see p. 2382.2).[1,4] Parenteral benzylpenicillin or erythromycin are also given to eliminate *C. diphtheriae*, thereby terminating toxin production and preventing the spread of infection to contacts.[1,4] Penicillin or erythromycin may be given orally once the patient is able to swallow comfortably. Antibacterials should be given for a total of 14 days; those who continue to harbour the bacteria should be treated for a further 10 days. Infection with diphtheria does not always confer immunity, therefore those recovering from the disease should also receive active immunisation.[3] Cutaneous infection is treated similarly, although antitoxin is of benefit only if very large ulcers are present. Close contacts of primary cases of diphtheria, and those in the community identified as asymptomatic carriers, may be given a 7-day prophylactic course of erythromycin orally or a single intramuscular dose of benzylpenicillin,[1] in addition to boosters or primary immunisation with diphtheria vaccine. Cultures should be taken 24 and 48 hours after stopping therapy to confirm eradication.[1] Epidemics are most effectively controlled by mass immunisation of the entire population.[2,3]

1. Bonnet JM, Begg NT. Control of diphtheria: guidance for consultants in communicable disease control. *Commun Dis Public Health* 1999; **2**: 242–9.
2. Vitek CR. Diphtheria. *Curr Top Microbiol Immunol* 2006; **304**: 71–94.
3. WHO. Diptheria vaccine. *Wkly Epidem Rec* 2006; **81**: 24–32.
4. Abramowicz M, ed. The choice of antibacterial drugs. In: *Handbook of antimicrobial therapy*. 19th ed. New Rochelle NY: The Medical Letter,2011: 62.

Ear infections

See Otitis Externa, p. 197.1, and Otitis Media, p. 197.2.

Ehrlichiosis

Ehrlichioses are a group of diseases produced by infection with rickettsia-like bacteria of the family Anaplasmataceae, a family that contains the genera *Anaplasma, Ehrlichia, Neorickettsia,* and *Wolbachia.* At one time such organisms were considered to be only animal pathogens but it is now recognised that humans may also become infected.[1-8] One of the earliest human forms of ehrlichiosis identified was Sennetsu fever, a disease found in Japan and Malaysia, and which is caused by *N. sennetsu* (*E. sennetsu*). Subsequently *Anaplasma phagocytophilum* (*E. phagocytophila*), *E. chaffeensis, E. ewingii,* and possibly *E. canis* have emerged as tick-borne human pathogens.

E. chaffeensis mainly infects mononuclear cells and in humans the resulting disease is commonly called human monocytic (or monocytotropic) ehrlichiosis (HME) whereas *A. phagocytophilum* mainly infects granulocytes and in humans produces human granulocytic (or granulocytotropic) ehrlichiosis (HGE), now also known as human granulocytic anaplasmosis (HGA). *E. ewingii* and *E. canis* mainly infect granulocytes and mononuclear cells respectively.

Some patients with HGA may also be co-infected with *Borrelia burgdorferi,* the cause of Lyme disease, and/or *Babesia microti,* the cause of babesiosis, as they are all transmitted by tick bites from the same *Ixodes* spp. For details on the treatment of patients with HGA co-infected with Lyme disease, see p. 192.1.

Human ehrlichiosis is characterised by fever, headache, myalgia, and malaise. Laboratory findings include leucopenia, thrombocytopenia, and elevated liver enzymes.[1,2] Symptoms more commonly seen in patients with HME are gastrointestinal disturbances, cough, confusion, and skin rash. HME is a relatively severe infection and patients may require hospitalisation for complications such as acute respiratory distress, coagulopathy, hepatitis, hepatic failure, meningoencephalitis, acute renal failure, and shock. Fulminant infections may give rise to other opportunistic infections, particularly in immunocompromised patients. Fatalities have been reported in 2 to 3% of patients with HME. Clinical symptoms of infections with *E. ewingii* or *A. phagocytophilum* are generally similar to those of *E. chaffeensis*[3,4] although usually less severe. Cough, confusion, and skin rash have not been seen with infections caused by *E. ewingii* and most cases have been diagnosed in immunocompromised patients; no deaths have been reported. HGA is generally a mild, self-limiting disease, but may be severe in about 5 to 7% of patients and reported fatalities are less than 1%. Most severe cases have been diagnosed in immunocompromised patients. Skin rash, gastrointestinal and respiratory disturbances, and CNS involvement are less frequent with HGA.[1]

Prompt **treatment** is recommended[9] due to the potential for serious complications. Treatment for all infections is with a tetracycline, preferably doxycycline, given for 7 to 10 days or for at least 3 days after the patient has become afebrile. Chloramphenicol has been used as an alternative for HME, although its efficacy is controversial and it should not be considered as a first-line treatment.[1,5] It is also not effective against *A. phagocytophilum in vitro.* Despite the known adverse effects of doxycycline in children, the American Academy of Pediatrics[10] and the Infectious Diseases Society of America (IDSA)[11] state that a shortened course may be given to those who are less than 8 years of age who are severely ill and not co-infected with Lyme disease; the dose is 4 mg/kg daily in two divided doses (to a maximum of 100 mg/dose) and should be given for at least 3 days after the patient has become afebrile. Successful treatment of HGA with rifampicin has been reported in pregnancy (gestational age of 10 to 36 weeks)[12] and in 2 children with non-life-threatening infection.[13] The IDSA[11] recommends that patients with mild disease who cannot be given a tetracycline may be given rifampicin 300 mg twice daily for 7 to 10 days; children may be given 10 mg/kg twice daily. Antibacterial susceptibility testing has suggested that rifamycins and fluoroquinolones are promising alternatives in the treatment of HGA.[14]

1. Paddock CD, Childs JE. Ehrlichia chaffeensis: a prototypical emerging pathogen. *Clin Microbiol Rev* 2003; 16: 37–64.
2. Dumler JS, *et al.* Human granulocytic anaplasmosis and Anaplasma phagocytophilum. *Emerg Infect Dis* 2005; 11: 1828–34.
3. Blanco JR, Oteo JA. Human granulocytic ehrlichiosis in Europe. *Clin Microbiol Infect* 2002; 8: 763–72.
4. Buller RS, *et al.* Ehrlichia ewingii, a newly recognized agent of human ehrlichiosis. *N Engl J Med* 1999; 341: 148–55.
5. Schaffner W, Standaert SM. Ehrlichiosis—in pursuit of an emerging infection. *N Engl J Med* 1996; 334: 262–3.
6. Dumler JS, *et al.* Ehrlichioses in humans: epidemiology, clinical presentation, diagnosis, and treatment. *Clin Infect Dis* 2007; 45 (suppl 1): S45–S51.
7. Bakken JS, Dumler S. Human granulocytic anaplasmosis. *Infect Dis Clin North Am* 2008; 22: 433–48.
8. Thomas RJ, *et al.* Current management of human granulocytic anaplasmosis, human monocytic ehrlichiosis and Ehrlichia ewingii ehrlichiosis. *Expert Rev Anti Infect Ther* 2009; 7: 709–22.
9. Hamburg BJ, *et al.* The importance of early treatment with doxycycline in human ehrlichiosis. *Medicine (Baltimore)* 2008; 87: 53–60.
10. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases,* 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.
11. Wormser GP, *et al.* The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2006; 43: 1089–1134. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/508667 (accessed 18/08/08)
12. Dhand A, *et al.* Human granulocytic anaplasmosis during pregnancy: case series and literature review. *Clin Infect Dis* 2007; 45: 589–93.
13. Krause PJ, *et al.* Successful treatment of human granulocytic ehrlichiosis in children using rifampin. Abstract: *Pediatrics* 2003; 112: 667. Full version: http://www.pediatrics.org/cgi/content/full/112/3/e252 (accessed 09/10/06)
14. Klein MB, *et al.* Antibiotic susceptibility of the newly cultivated agent of human granulocytic ehrlichiosis: promising activity of quinolones and rifamycins. *Antimicrob Agents Chemother* 1997; 41: 76–9.

Endocarditis

Infective endocarditis[1-3] is an infection of the endocardium after invasion of the bloodstream by bacteria or fungi, and particularly affects the heart valves. Infection has traditionally been classified as acute or subacute; however, changes in the clinical spectrum of infection have meant that some now prefer to classify it into the categories:[1,4]

- native-valve endocarditis (often associated with congenital or chronic rheumatic heart disease, and classically due to streptococci although cases due to staphylococcal infection are increasingly frequent)
- prosthetic valve endocarditis (which may occur early, within 60 days of surgery, which is often due to staphylococci, or late, in which case it is often due to streptococci or more exotic organisms such as the HACEK group)
- endocarditis in intravenous drug users (usually associated with infection by skin pathogens, especially *Staphylococcus aureus*)
- nosocomial endocarditis (related to catheter implantation or other invasive medical or surgical procedures; it is usually due to staphylococci or enterococci and has a high mortality rate). An increasing incidence is also seen in patients undergoing haemodialysis

Treatment of infective endocarditis is essential, as infection can result in heart failure, embolisation and infarction of major organs, and death. Diagnosis is often difficult as many of the symptoms (which include fever, malaise, headache, petechiae, and splinter haemorrhages under the nails) are non-specific. A set of diagnostic criteria known as the Duke criteria have been developed, and some modifications subsequently proposed.[4,5] The Duke criteria identify endocarditis mainly on the basis of microbiological data (blood culture of the infecting organism) and anatomical lesions of the valves (identified by echocardiography or the development of new valvular regurgitation); minor criteria such as development of fever, or presence of predisposing conditions such as heart defects or intravenous drug use, are also considered.[4,5]

Virtually any organism can cause endocarditis but streptococci, enterococci, and staphylococci continue to be major culprits.

- Among the commonest causes are the alpha-haemolytic *streptococci* originating mainly from the mouth and throat; they have been called viridans streptococci or even '*Streptococcus viridans*' (although this is not a true species) and include *Str. mitis, Str. mutans, Str. oralis, Str. salivarius,* and *Str. sanguis.* Other streptococci originate in the gut and include *Str. bovis.*
- Also increasingly common is endocarditis due to *staphylococci* such as *Staphylococcus aureus,* a common cause in intravenous drug abusers, but endocarditis may also be caused by coagulase-negative *staphylococci,* particularly *Staph. lugdunensis.* Prosthetic valve infection is often caused by *Staph. epidermidis* or other staphylococci.
- *Enterococci* (faecal streptococci) originate in the gut and include *Enterococcus faecalis* and, to a lesser extent, *E. faecium.* Endocarditis due to any of these bacteria is commonly subacute or insidious.

Less common causes of endocarditis include:[3,4,6]

- Gram-negative bacteria such as the Enterobacteriaceae and
- *Pseudomonas* spp.
- the HACEK group of slow-growing organisms (*Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella*)
- the rickettsia *Coxiella burnetii* (the cause of Q fever, p. 204.1)
- *Bartonella* spp. (also formerly classified as rickettsia)
- fungi such as *Candida* and *Aspergillus* (see p. 565.3).

Guidelines for the treatment and prophylaxis of endocarditis have been issued by bodies in many countries. Although some common principles can be identified, recommendations must be localised because of differences in patterns of infection and drug resistance, variations in the availability of antibacterials and local policies for their use, and differences in medical practice. Countries also vary in the degree to which such guidelines are accepted in practice.

Endocarditis treatment.

Treatment of endocarditis relies on prompt identification of the infecting organisms and their sensitivity to antibacterials. Three sets of blood cultures, each from a separate venepuncture, should be taken before antimicrobial treatment is started; MICs for the causative organism should be measured. As already mentioned, guidelines vary,[7-10] but in general:

- a microbicidal antibacterial, or combination of antibacterials, should be used for treatment; many regimens are based on a beta-lactam or glycopeptide plus an aminoglycoside
- treatment should be given at high doses, and by the intravenous route
- except in the most sensitive infections, treatment should be given for at least 4 weeks (or at least 6 weeks if the patient has prosthetic valves or other prosthetic material implanted in the heart)
- ideally, it is preferable to wait for the results of blood culture before starting therapy; however, empirical treatment is given to patients presenting with acute or severe disease
- associated complications such as heart failure should be managed appropriately; management may include referral for early surgical intervention

If *empirical treatment* is to be given until the laboratory results are known, then it is most likely to be with gentamicin plus benzylpenicillin, ampicillin, or amoxicillin.[8] An isoxazolyl penicillin (cloxacillin, dicloxacillin, flucloxacillin, or oxacillin) may be added,[7] or used instead in more severe or acute presentations;[8] ampicillin with sulbactam or amoxicillin with clavulanic acid have also been recommended.[9] Vancomycin with[9] or without ciprofloxacin[7,8] is likely to be the antibacterial of choice in penicillin-allergic patients requiring empirical treatment. Vancomycin may be used empirically with an aminoglycoside and rifampicin in patients with prosthetic valves[8,9] or where penicillin resistance is suspected.[8]

Once the causative organism and its antibacterial susceptibility have been identified, appropriate *pathogen-directed* therapy may be begun.

- **Streptococcal endocarditis.** Streptococci vary in their susceptibility to penicillin, and guidelines generally divide regimens according to whether the organism is of low, intermediate, or high penicillin resistance, although at what MIC these categories are defined varies between guidelines.

  For uncomplicated cases of infection with the most *penicillin sensitive streptococci,* benzylpenicillin may be used, with or without gentamicin[7-10] or netilmicin.[9] Typically, if used alone in native-valve infection it would be given for 4 weeks, whereas the combination regimen is given only for 2 weeks.[7-10] Indicative doses would be 1.2 to 2.4 g of benzylpenicillin every 4 or 6 hours, and gentamicin 1 mg/kg every 8 hours or as a single daily dose of 3 mg/kg. Ceftriaxone[8-10] or vancomycin[7-10] may be considered as an alternative, although these are more often given to treat less sensitive strains, or in patients unable to tolerate penicillin.

  For *streptococci less sensitive to penicillin* benzylpenicillin may be given as above but for 4 to 6 weeks,[7-9] usually with gentamicin for at least the first 2 weeks. Alternatively, 4 weeks of treatment with ceftriaxone or vancomycin may be considered.[8-10] Typical doses are 2 g daily of ceftriaxone as a single injection, or 30 mg/kg of vancomycin daily (up to a usual maximum of 2 g daily), in 2 divided doses.

  For *penicillin resistant streptococci* treatment is similar to that for enterococcal endocarditis.[7-9] A combination of vancomycin and gentamicin may be given for 4 to 6 weeks. Streptomycin is a possible alternative to gentamicin for *gentamicin resistant* isolates.[8]

  For *streptococci in penicillin-allergic patients,* vancomycin for 4 to 6 weeks may be given;[9,10] UK guidelines advise 4 weeks of treatment combined with gentamicin for the first 2 weeks.[8] Teicoplanin, typically in doses of 6 to 10 mg/kg daily (higher loading doses should be given initially to establish a suitable trough concentration) is a possible alternative to vancomycin.[8]

  For patients with *prosthetic valve endocarditis,* a regimen similar to that for less sensitive streptococci (above) has been suggested, given for at least 6 weeks.[8-10]
- **Staphylococcal endocarditis.** The treatment of staphylococcal endocarditis is based on the use of an isoxazolyl penicillin or a glycopeptide. In contrast to streptococcal or enterococcal endocarditis, the benefits of adding an aminoglycoside are uncertain, and guidelines differ in whether they recommend this. Combination therapy is recommended where prosthetic valves or other intracardiac prostheses are present.

  For *meticillin sensitive staphylococci,* typically an isoxazolyl penicillin (such as flucloxacillin) is given in a dose of

2 g every 4 to 6 hours for at least 4 weeks.[7-10] Some guidelines continue to recommend addition of gentamicin for the first 3 to 5 days of therapy.[9,10] Patients with right-sided endocarditis due to intravenous drug abuse may respond to shorter courses of 2 weeks of combination therapy with an isoxazolyl penicillin plus gentamicin.[8,10]

For *staphylococci resistant to meticillin/oxacillin*, vancomycin may be given alone for 6 weeks,[7,10] or with rifampicin or perhaps gentamicin or sodium fusidate (depending on sensitivity) for at least 4 weeks.[8,9] Such combinations may also be appropriate in patients with *penicillin allergy*. Teicoplanin should not be used as the reported incidence of treatment failure is unacceptably high.[8]

For *staphylococcal endocarditis in the presence of intracardiac prostheses* either an isoxazolyl penicillin or vancomycin may be used with rifampicin or gentamicin or both; an indicative regimen might be intravenous doses of 2 g of the penicillin every 4 to 6 hours, or 1 g of vancomycin every 12 hours, plus rifampicin 300 mg orally every 8 hours, both given for at least 6 weeks, plus gentamicin 1 mg/kg intravenously every 8 hours (or as a single daily dose of 3 mg/kg) for the first 2 weeks.[8-10] Gentamicin may be given for the entire period of treatment if the infection is due to more recalcitrant strains of meticillin-resistant *Staph. aureus* or coagulase-negative staphylococci.[8]

- **Enterococcal endocarditis.** Treatment of enterococcal endocarditis is based on combinations of an aminoglycoside with another antibacterial, usually a beta lactam or a glycopeptide, depending on the sensitivity of the isolated organism.

  For *gentamicin sensitive, penicillin sensitive enterococci*: intravenous bolus injections of ampicillin or amoxicillin 2 g (or benzylpenicillin 2.4 g) every 4 hours and gentamicin 1 mg/kg every 8 or 12 hours (or as a single daily dose of 3 mg/kg), both given for at least 4 weeks.[7,8,10]

  If the patient is *allergic to penicillin*, or the isolate is *penicillin resistant but gentamicin sensitive*, then a combination of vancomycin or teicoplanin with gentamicin may be given for at least 4 weeks.[7-10]

  For *enterococci with high level gentamicin resistance*, a penicillin as above may be used with streptomycin 7.5 mg/kg twice daily (intramuscularly or intravenously) for at least 4 weeks.[8,10] If there is also *penicillin resistance*, or the patient is *penicillin allergic*, streptomycin as above may be given with vancomycin or teicoplanin.[8] If streptomycin cannot be used then more prolonged treatment courses should be given for at least 8 weeks.[8,9] Endocarditis due to *multiply resistant enterococci* not susceptible to penicillin, gentamicin, or vancomycin, is still infrequent and there seem to be no established regimens; options may include the use of linezolid, daptomycin, tigecycline, or quinupristin/dalfopristin where available.[7-10] A combination of ampicillin with ceftriaxone[9,10] or imipenem,[10] given for at least 8 weeks, has been suggested for multiply resistant *E. faecalis* infection.
- **HACEK endocarditis.** The HACEK organisms are slow and difficult to culture and treatment must often, therefore, be empirical. Traditionally, treatment for this group of organisms was based on ampicillin and gentamicin. However, because of the emergence of beta-lactamase producing strains, empirical treatment is now based on beta-lactamase-stable cephalosporins.

  Preferred treatment for native-valve endocarditis due to HACEK organisms is therefore with intramuscular or intravenous ceftriaxone (usually in a dose of 2 g once daily) for 4 weeks,[7-10] although cefotaxime[7] or other third-generation cephalosporin[9,10] may be used instead. UK guidelines recommend addition of gentamicin for the first 2 weeks of therapy.[8] Alternatively, if the isolate is penicillin sensitive, ampicillin plus 2 to 4 weeks of gentamicin,[8,9] or ampicillin-sulbactam[10] have been suggested. Some guidelines consider that a fluoroquinolone such as ciprofloxacin for 4 weeks, orally or intravenously, may also be effective.[9,10]
- **Endocarditis due to other organisms.** Treatment of endocarditis due to other organisms depends greatly on the organism and its susceptibility; early surgery is often required. For endocarditis due to *Pseudomonas* spp. a combination of an antipseudomonal beta lactam with tobramycin has been suggested.[9] Endocarditis associated with the intracellular pathogen *Coxiella burnetii* requires very prolonged oral therapy (see Q-fever, p. 204.1) with doxycycline,[8,9] in combination with hydroxychloroquine[9] or a fluoroquinolone (such as ciprofloxacin or ofloxacin).[8,9] Regimens suggested for *Bartonella* endocarditis have included a penicillin (or ampicillin with sulbactam) or ceftriaxone in combination with gentamicin or netilmicin, or doxycycline plus gentamicin.[8-10] For other potential causes of culture-negative endocarditis, empirical treatment with a penicillin or vancomycin plus gentamicin, sometimes in combination with a third antibacterial such as rifampicin or ciprofloxacin, has been suggested.[10]

Endocarditis prophylaxis.

Because of the potentially severe consequences of endocarditis, antibacterial prophylaxis was widely practised in patients considered to be at increased risk when they were exposed to procedures likely to produce bacteraemia. Much of the evidence to support the practice was circumstantial and the benefits and risks were therefore hard to calculate. Revision of this practice in recent years has resulted in a major shift of emphasis away from giving antibacterial prophylaxis to all at-risk patients, to recommending prophylaxis for high-risk patients only. Guidelines[9,11-15] have been periodically issued to guide the selection of patients considered to be at high risk for endocarditis, the high-risk procedures requiring prophylaxis, and the antibacterial to be used; recommendations may vary considerably between countries.

Patients generally considered to be at risk of developing endocarditis include those with:

- acquired valvular heart disease, including valve disease in patients who have received a cardiac transplant
- some types of congenital heart disease
- hypertrophic cardiomyopathy
- prosthetic valves or pulmonary shunts
- a history of endocarditis

Procedures that were thought likely to produce bacteraemia and therefore to require prophylactic treatment included any dental intervention likely to cause bleeding, other oral or upper-respiratory tract operations such as tonsillectomy, certain gastrointestinal procedures such as sclerotherapy for oesophageal varices or biliary-tract surgery, and some urinary-tract surgery. Whether prophylaxis is truly needed before dental procedures is a subject of controversy. A systematic review[16] concluded there was no evidence that antibacterial prophylaxis was effective or ineffective against bacterial endocarditis in people at risk undergoing an invasive dental procedure. US guidelines[12,14] recommend antibacterial prophylaxis only for dental procedures that involve manipulation of gingival tissues or periapical region of teeth, or perforation of oral mucosa in patients considered to be at the highest risk of developing adverse outcomes from endocarditis (such as those with a history of infective endocarditis, cardiac valve replacement surgery, or some patients with congenital heart disease). US guidelines also recommend antibacterial prophylaxis for high-risk patients for procedures on infected skin, skin structures, or musculoskeletal tissue, but do not recommend standard prophylaxis for respiratory, genito-urinary or gastrointestinal tract procedures.[14] Similar recommendations were made in the UK by the British Society for Antimicrobial Chemotherapy (BSAC) in 2006[11] for high-risk patients undergoing invasive dental procedures, but the BSAC was more cautious in modifying the guidance for respiratory, gastrointestinal, and genito-urinary procedures. Subsequent guidelines issued by NICE[13] and adopted by the *BNF* essentially abolished the requirement for standard antibacterial prophylaxis in any procedure. In 2009 the Task Force on Infective Endocarditis of the European Society of Cardiology[9] also reduced the number of indications for prophylaxis. Their guideline for antibacterial prophylaxis before dental procedures is similar to that for the US and UK (BSAC) and standard prophylaxis is also not generally recommended for respiratory, genito-urinary, or gastrointestinal tract procedures. Most guidelines still recommend appropriate antibacterial prophylaxis for high-risk patients undergoing invasive respiratory, gastrointestinal, or genito-urinary procedures to treat an established infection or where pre-existing infection is suspected.[9,12-14]

Antibacterial prophylaxis is aimed mainly at viridans streptococci and HACEK organisms before dental, oral, respiratory, and oesophageal procedures, and at enterococci, *Strep. bovis*, and the Enterobacteriaceae before gastrointestinal and genito-urinary procedures. Drugs should be given in a regimen that assures adequate blood concentrations throughout the procedure. They are generally given as a single dose before the procedure; the oral route is used if possible.

- A penicillin such as amoxicillin is the basis for prophylactic therapy, typically in a single dose of 2 to 3 g orally or 1 to 2 g intravenously or intramuscularly.[9,11,14,15] For *dental* procedures it may be replaced, in patients allergic to penicillin or who have received more than a single dose in the previous month, by clindamycin 600 mg orally or 300 to 600 mg intravenously, or by azithromycin or clarithromycin 500 mg orally. Doses should be given 30 to 60 minutes before the procedure.[9,11,14]
- For *gastrointestinal* or *genito-urinary* procedures the penicillin is usually combined with a single dose of gentamicin 1.5 or 2 mg/kg intravenously or intramuscularly before the procedure; a second dose of amoxicillin (typically half the initial dose) may be given after 6 hours. In patients allergic to penicillin, or who have received more than a single dose of penicillin in the previous month, amoxicillin may be substituted with an infusion of 1 g of vancomycin over 1 to 2 hours before the procedure,[13] or injection of 400 mg of teicoplanin immediately beforehand.[7,9,11]
- For *nasal packing and intubation* flucloxacillin 1 g intravenously is given; in penicillin allergic patients clindamycin 600 mg intravenously may be used.[11]
- For *infected skin, skin structure, or musculoskeletal tissue* procedures a penicillin such as amoxicillin is usually given in a single oral or intravenous dose of 2 g, or a cephalosporin such as cefalexin is given in a single oral dose of 2 g. Vancomycin or clindamycin may be given to patients allergic to penicillin or who are known or suspected of having an infection caused by a meticillin-resistant strain of staphylococcus.[12,14]

1. Moreillon P, Que Y-A. Infective endocarditis. *Lancet* 2004; 363: 139–49.
2. Beynon RP, *et al.* Infective endocarditis. *BMJ* 2006; 333: 334–9.
3. Prendergast BD. The changing face of infective endocarditis. *Heart* 2006; 92: 879–85.
4. Hill EE, *et al.* Evolving trends in infective endocarditis. *Clin Microbiol Infect* 2006; 12: 5–12.
5. Li JS, *et al.* Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis* 2000; 30: 633–8.
6. Brouqui P, Raoult D. Endocarditis due to rare and fastidious bacteria. *Clin Microbiol Rev* 2001; 14: 177–207.
7. Antibiotic Expert Group. Therapeutic Guidelines: Antibiotic (version 13) Melbourne: Therapeutic Guidelines Ltd.; 2006.
8. Elliott TSJ, *et al.* Guidelines for the antibiotic treatment of endocarditis in adults: report of the Working Party of the British Society for Antimicrobial Chemotherapy. *J Antimicrob Chemother* 2004; 54: 971–81. Also available at: http://jac.oxfordjournals.org/cgi/reprint/54/6/971.pdf (accessed 16/03/06)
9. Habib G, *et al.* Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). *Eur Heart J* 2009; 30: 2369–413. Full version: http://eurheartj.oxfordjournals.org/content/30/19/2369.full.pdf+html (accessed 21/04/10)
10. Baddour LM, *et al.* American Heart Association. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association (endorsed by the Infectious Diseases Society of America). Executive summary. *Circulation* 2005; 111: 3167–84. Correction. *ibid.*; 112: 2373. Full version: http://circ.ahajournals.org/cgi/reprint/111/23/e394.pdf (accessed 07/03/06)
11. Gould FK, *et al.* Guidelines for the prevention of endocarditis: report of the Working Party of the British Society for Antimicrobial Chemotherapy. *J Antimicrob Chemother* 2006; 57: 1035–42. Also available at: http://jac.oxfordjournals.org/cgi/reprint/dkl121v1.pdf (accessed 06/07/06)
12. Wilson W, *et al.* Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation* 2007; 116: 1736–54. Also available at: http://circ.ahajournals.org/cgi/reprint/116/15/1736.pdf (accessed 24/08/10)
13. NICE. Prophylaxis against infective endocarditis: antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures (issued March 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/CG64NICEguidance.pdf (accessed 16/06/08)
14. Nishimura RA, *et al.* ACC/AHA 2008 guideline update on valvular heart disease: focused update on infective endocarditis: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation* 2008; 118: 887–96. Also available at: http://circ.ahajournals.org/cgi/reprint/118/8/887.pdf (accessed 05/05/10)
15. Infective Endocarditis Prophylaxis Expert Group. Prevention of endocarditis. 2008 update from Therapeutic guidelines: antibiotic (version 13) and Therapeutic guidelines: oral and dental (version 1). Melbourne: Therapeutic Guidelines Ltd.; 2008.
16. Oliver R, *et al.* Antibiotics for the prophylaxis of bacterial endocarditis in dentistry. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 20/04/10).

Endometritis

Endometritis (or endomyometritis) is an infection of the endometrium and can be divided into obstetric and non-obstetric, acute and chronic endometritis. It is thought to result from an ascending infection from the lower genital tract. Spread occurs from there to the tubes and ovaries. In non-obstetric patients it may be a part of pelvic inflammatory disease (p. 198.3) or due to invasive gynaecologic procedures, while in obstetric patients it may be a postoperative complication of caesarean section. Symptoms include uterine tenderness, abdominal or pelvic pain, dyspareunia, dysuria, fever, malaise, and abnormal vaginal bleeding or discharge (including foul-smelling lochia in obstetric patients).

Endometritis is a polymicrobial disease usually involving 2 to 3 organisms some of which are found in the normal vaginal flora. Common causative organisms include Gram-positive cocci (such as *Staphylococcus* spp. and *Streptococcus* spp.), Gram-negative bacteria (such as *Escherichia coli, Klebsiella* spp., *Proteus* spp., *Enterobacter* spp., *Gardnerella vaginalis, Neisseria* spp.), anaerobes (such as *Bacteroides* spp. *Peptostreptococcus* spp.), and other organisms such as *Mycoplasma* spp., *Ureaplasma* spp., and *Mycobacterium tuberculosis*.

Women undergoing caesarean section are reported to have a 5 to 20-fold greater chance of infection than women who give birth vaginally and the incidence of endometritis for caesarean deliveries ranges from 20 to 85%. Antibacterial **prophylaxis** may be given at caesarean section to prevent postpartum endometritis as well as wound and urinary-tract infections. A systematic literature review[1] has shown prophylaxis to be beneficial after both elective and non-elective caesarean section; endometritis was reduced by two-thirds to three-quarters irrespective of whether the antibacterials were given before or after clamping of the umbilical cord. Traditionally prophylactic antibacterials for caesarean delivery have been given at cord clamping, but a meta-analysis provided evidence that prophylaxis given before skin incision significantly decreased the incidence of postpartum endometritis and other infectious morbidities, without affecting neonatal outcomes.[2]

Many different drug regimens have been reported to be effective in reducing postoperative infection but it is not clear if there is a drug of choice. Furthermore, differences in how prophylactic antibacterials have been given have been noted. A systematic review[3] to evaluate prophylactic antibacterial regimens used for caesarean section found that ampicillin and first-generation cephalosporins were appropriate. Extended-spectrum penicillins, second- or third-generation cephalosporins, and combination regimens were not more effective; there was also no evidence to suggest that a multiple-dose regimen was more effective than a single-dose regimen. Clindamycin was considererred to be an appropriate alternative for penicillin-allergic women.

Patients with endometritis should be **treated** with broad-spectrum antibacterials. For postpartum endometritis (also known as puerperal fever), intravenous gentamicin and clindamycin are appropriate.[4] A second- or third-generation cephalosporin plus metronidazole; or amoxicillin (or ampicillin) with gentamicin and metronidazole are alternatives; co-formulated ampicillin with sulbactam can be used as monotherapy. Doxycycline should be used if *Chlamydia* is suspected to be the causative organism. In most cases improvement is usually seen within 48 to 72 hours. Parenteral therapy is continued until the patient has been afebrile for longer than 24 hours; oral therapy is not necessary after successful intravenous therapy.[4]

1. Smaill FM, Gyte GML. Antibiotic prophylaxis versus no prophylaxis for preventing infection after cesarean section. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 21/04/10).
2. Costantine MM, *et al.* Timing of perioperative antibiotics for cesarean delivery: a metaanalysis. *Am J Obstet Gynecol* 2008; **199**: 301.e1–6.
3. Hopkins L, Smaill FM. Antibiotic prophylaxis regimens and drugs for cesarean section. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1999 (accessed 21/04/10).
4. French LM, Smaill FM. Antibiotic regimens for endometritis after delivery. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 18/08/05).

Enterococcal infections

Although enterococci are part of the normal intestinal flora they may also be responsible for serious infections. The genus *Enterococcus* includes at least 12 species with *Enterococcus faecalis* (formerly *Streptococcus faecalis*) and *E. faecium* being responsible for the majority of human infections. Infections commonly caused by enterococci include urinary-tract infections, endocarditis, bacteraemia, catheter-related infections, surgical wound infections, and intra-abdominal and pelvic infections; less commonly enterococci may infect the bone, joints, and the meninges.

Despite not being particularly pathogenic in humans, infections due to enterococci are of increasing concern because of drug resistance[1-7] The most significant types of resistance in the enterococci are:

- high-level resistance to the aminoglycosides
- ampicillin resistance caused by beta-lactamase production
- glycopeptide resistance including vancomycin resistance
- multidrug resistance to ampicillin, aminoglycosides (high-level resistance), and glycopeptides

Enterococci have both intrinsic resistance and the ability to acquire new mechanisms of resistance to antibacterials; although some species (such as *E. faecium*) are more intrinsically resistant than others.[3,6] Enterococci are intrinsically resistant to beta lactams (particularly cephalosporins and penicillinase-resistant penicillins), low concentrations of aminoglycosides, clindamycin, co-trimoxazole, and fluoroquinolones.[1,3] They also have acquired resistance to high concentrations of beta lactams and aminoglycosides, the glycopeptides (vancomycin and teicoplanin), chloramphenicol, erythromycin, fluoroquinolones, fusidic acid, nitrofurantoin, rifampicin, and tetracyclines.[3] At least 6 types of acquired vancomycin resistance have been described[6] (see also p. 389.1); those causing concern are VanA enterococci as they show high-level resistance to vancomycin and cross-resistance to teicoplanin and VanB organisms, which are resistant to a range of vancomycin concentrations but retain susceptibility to teicoplanin.[3,5,6] The epidemiology of vancomycin-resistant enterococci (VRE)[3-5] and resultant antibacterial prescribing practices differ between North America and Europe;[3] the USA has *much higher rates of VRE than anywhere in Europe.*[3,5-7]

Unusual patterns of susceptibility and drug and multidrug resistance make treatment of an infection difficult. Antibacterials must be chosen according to local patterns of resistance and antibacterial sensitivity tests.[2,3] In general, uncomplicated enterococcal infections, such as urinary-tract infections, tend to be treated with ampicillin, benzylpenicillin, or vancomycin.[1,3] For more serious enterococcal infections, including bacteraemia, meningitis, and endocarditis, an aminoglycoside (such as gentamicin or streptomycin) is added unless there is high-level resistance.[3] For penicillin-allergic patients or in treatment of ampicillin-resistant strains of bacteria vancomycin is given with an aminoglycoside.[1,3,5,6]

Benzylpenicillin and ampicillin are an option for patients infected with VRE isolates that still retain susceptibility.[2] However, most are resistant to benzylpenicillin and ampicillin and the choice of antibacterial is therefore limited to those introduced more recently into clinical practice such as quinupristin/dalfopristin or linezolid. Both these drugs have activity against vancomycin-resistant *E. faecium* infections and linezolid also has activity against non-*E. faecium* species, but most *E. faecalis* and non-*E. faecium* isolates are intrinsically resistant to quinupristin/dalfopristin.[1-3,6] Acquired resistance has been reported to quinupristin/dalfopristin[1] and linezolid-resistant enterococci have emerged[2,8,9] and spread nosocomially.[2] Daptomycin and tigecycline have *in-vitro* activity against VRE but clinical data on the treatment of VRE infections are lacking;[2] resistance to daptomycin has been reported.[10-12] The second generation glycopeptides, oritavancin and telavancin, are also often bactericidal against enterococci and although resistance to these newer drugs is rare, it has been documented.[6] Many VRE isolates are susceptible to nitrofurantoin, which has been used to treat lower urinary-tract infection but is not suitable for treating other VRE infections.[1,2] Dalbavancin is active against glycopeptide-resistant enterococci with the VanB phenotype, but has little activity against the more common VanA phenotype.[2] Chloramphenicol may be effective against VRE (see Enterococcal Infections, p. 260.1). Ramoplanin, ketolides,[3] and the mannopeptimycins (a new class of glycopeptides)[2] are being studied as further treatment options. In general, there are no effective antibacterials available to eradicate VRE in those colonised with the organism.[1,2]

A few cases of horizontal transfer of the vanA gene from vancomycin-resistant *E. faecalis* to MRSA, creating MRSA with high-level resistance to vancomycin, have been documented in hospitalised patients mainly in the USA.[4,7] The lack of effective antibacterials has placed emphasis on measures to prevent the spread of vancomycin-resistant enterococci;[13] without extensive control measures, large-scale emergence of vancomycin-resistant *S. aureus* (VRSA) may occur.[4]

1. Murray BE. Vancomycin-resistant enterococcal infections. *N Engl J Med* 2000; **342**: 710–21.
2. Zirakzadeh A, Patel R. Vancomycin-resistant enterococci: colonization, infection, detection, and treatment. *Mayo Clin Proc* 2006; **81**: 529–36.
3. Gold HS. Vancomycin-resistant enterococci: mechanisms and clinical observations. *Clin Infect Dis* 2001; **33**: 210–9.
4. Willems RJ, *et al.* Global spread of vancomycin-resistant Enterococcus faecium from distinct nosocomial genetic complex. *Emerg Infect Dis* 2005; **11**: 821–8.
5. Sood S, *et al.* Enterococcal infections and antimicrobial resistance. *Indian J Med Res* 2008; **128**: 111–21.
6. Woodford N, Livermore DM. Infections caused by Gram-positive bacteria: a review of the global challenge. *J Infect* 2009; **59** (suppl 1): S4–S16.
7. Leclercq R. Epidemiological and resistance issues in multidrug-resistant staphylococci and enterococci. *Clin Microbiol Infect* 2009; **15**: 224–31.
8. Auckland C, *et al.* Linezolid-resistant enterococci: report of the first isolates in the United Kingdom. *J Antimicrob Chemother* 2002; **50**: 743–6.
9. Kainer MA, *et al.* Response to emerging infection leading to outbreak of linezolid-resistant enterococci. *Emerg Infect Dis* 2007; **13**: 1024–30.
10. Long JK, *et al.* Daptomycin-resistant Enterococcus faecium in a patient with acute myeloid leukemia. *Mayo Clin Proc* 2005; **80**: 1215–6.
11. Hayden MK, *et al.* Development of Daptomycin resistance in vivo in methicillin-resistant Staphylococcus aureus. *J Clin Microbiol* 2005; **43**: 5285–7.
12. Munoz-Price LS, *et al.* Emergence of resistance to daptomycin during treatment of vancomycin-resistant Enterococcus faecalis infection. *Clin Infect Dis* 2005; **41**: 565–6.
13. Siegel JD, *et al.* Healthcare Infection Control Practices Advisory Committee (HICPAC). Management of multidrug-resistant organisms in healthcare settings, 2006. Available at: http://www.cdc.gov/ncidod/dhqp/pdf/ar/MDROGuideline2006.pdf (accessed 05/08/08)

Epididymitis

Epididymitis is often associated with urethritis, and in young men (less than 35 years) occurs most commonly as a complication of sexually transmitted infection with *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, but may occur in homosexual males as a result of infection with enteric organisms, particularly *Escherichia coli*.

In men over 35 years and in children, epididymitis is not usually sexually transmitted but generally results from bacteriuria secondary to urinary-tract infection with *Pseudomonas aeruginosa* and other Gram-negative bacilli, urinary-tract instrumentation or surgery, systemic disease, or immunosuppression.

Guidelines produced by WHO,[1] by an expert group in the UK,[2] and by the CDC in the USA[3] for the **treatment** of epididymitis are as follows, although recommendations may need to be localised because of differences in patterns of infection and drug resistance:

- **WHO:**
  for chlamydial epididymitis:
  - oral doxycycline 100 mg twice daily for 7 days, *or*
  - a single dose of oral azithromycin 1 g

  alternatives, given for 7 days, are:
  - oral amoxicillin 500 mg three times daily
  - oral erythromycin 500 mg four times daily
  - oral ofloxacin 300 mg twice daily
  - oral tetracycline 500 mg four times daily

  Unless it can be excluded, patients should also be treated concurrently for gonorrhoea (p. 206.2).
- **UK:**
  for disease most probably due to any sexually-transmitted pathogen:
  - a single intramuscular dose of ceftriaxone 500 mg, *plus* oral doxycycline 100 mg twice daily for 10 to 14 days

  for probable chlamydial infections or infections with other non-gonococcal organisms:
  - oral doxycycline 100 mg twice daily for 10 to 14 days, *or*
  - oral ofloxacin 200 mg twice daily for 14 days

  for infections most probably due to enteric organisms:
  - oral ofloxacin 200 mg twice daily for 14 days, *or*
  - oral ciprofloxacin 500 mg twice daily for 10 days

  in patients allergic to cephalosporins and/or tetracyclines infections from all causes may be treated with:
  - oral ofloxacin 200 mg twice daily for 14 days
- **USA:** empirical treatment recommended:
  recommended initial treatment:
  - a single intramuscular dose of ceftriaxone 250 mg *plus* oral doxycycline 100 mg twice daily for 10 days

  additional therapy if likely cause of infection is possibly an enteric organism:
  - oral ofloxacin 300 mg twice daily for 10 days, *or*
  - oral levofloxacin 500 mg once daily for 10 days

Sexual contacts should also be treated if epididymitis is caused by a sexually transmitted pathogen.[2,3]

Patients co-infected with HIV should receive the same treatment as those who are HIV-negative.[3]

1. WHO. Guidelines for the management of sexually transmitted infections. Geneva: WHO, 2003. Also available at: http://whqlibdoc.who.int/publications/2003/9241546263.pdf (accessed 22/03/07)
2. Clinical Effectiveness Group (British Association for Sexual Health and HIV). 2010 United Kingdom national guideline for the management of epididymo-orchitis. Available at: http://www.bashh.org/documents/3546 (accessed 30/07/12)
3. CDC. Sexually transmitted diseases treatment guidelines, 2010. *MMWR* 2010; **59** (RR-12): 1–110. Also available at: http://www.cdc.gov/STD/treatment/2010/STD-Treatment-2010-RR5912.pdf (accessed 08/01/11) —Correction. *ibid.* 2011; **60**: 18. [dose]

Epiglottitis

Epiglottitis (or supraglottitis) is an inflammation of the epiglottis and adjacent structures that may occur at any age. It is a potentially life-threatening condition in which previously healthy persons may develop sudden upper airway obstruction within hours. Symptoms include severe sore throat, fever, dysphagia, drooling, distress, and inspiratory stridor. It is often due to bacteraemic infection with *Haemophilus influenzae* type b (see p. 188.2); other bacteria implicated include *H. parainfluenzae, Streptococcus pneumoniae, Pasteurella multocida, Staphylococcus aureus,* beta-haemolytic streptococci, *Branhamella catarrhalis,* and *Klebsiella pneumoniae.* Epiglottitis may also be caused by viruses, fungi, and mechanical injury. Traditionally epiglottitis has occurred mainly in young children, and although the incidence has decreased in this age group since the introduction of a vaccine,[1] cases due to *H. influenzae* still occur in young unvaccinated children, particularly in resource-poor countries. Acute epiglottitis is being increasingly seen in adults.[1-4]

Treatment and prophylaxis is similar to that for Haemophilus influenzae meningitis (see under Meningitis, p. 193.1). Immediate management includes the maintenance of an adequate airway and the intravenous use of antibacterials active against *H. influenzae* type b and other likely causative organisms. Chloramphenicol has been the drug of choice, but second- or third-generation cephalosporins such as cefuroxime, cefotaxime, and ceftriaxone with or without metronidazole are increasingly used.[1,2,4-7] Other intravenous antibacterials that have been used include amoxicillin with clavulanic acid, ampicillin with sulbactam, aminoglycosides, and erythromycin;[2,4,6] oral amoxicillin with clavulanic acid has been given as maintenance therapy.[4] Corticosteroids have been given to reduce mucosal oedema, although there are no data to prove any benefit.[6,7] Prophylaxis with rifampicin may be given to index cases and contacts (see Meningitis Prophylaxis under Rifampicin, p. 353.2).

1. Frantz TD, *et al.* Acute epiglottitis in adults: analysis of 129 cases. *JAMA* 1994; **272**: 1358–60.

2. Pino Rivero V, *et al.* Epiglotitis aguda en adultos: nuestra experiencia clínica en 30 casos. *Acta Otorrinolaringol Esp* 2007; **58**: 263–5.
3. Ames WA, *et al.* Adult epiglottitis: an under-recognized, life-threatening condition. *Br J Anaesth* 2000; **85**: 795–7.
4. Ng HL, *et al.* Acute epiglottitis in adults: a retrospective review of 106 patients in Hong Kong. *Emerg Med J* 2008; **25**: 253–5.
5. Sawyer SM, *et al.* Successful treatment of epiglottitis with two doses of ceftriaxone. *Arch Dis Child* 1994; **70**: 129–32.
6. Alcaide ML, Bisno AL. Pharyngitis and epiglottitis. *Infect Dis Clin North Am* 2007; **21**: 449–69. Correction. *Ibid.*; 847–8.
7. Sobol SE, Zapata S. Epiglottitis and croup. *Otolaryngol Clin North Am* 2008; **41**: 551–66.

Escherichia coli enteritis

See p. 186.3.

Eye infections

Conjunctivitis is a common superficial eye disorder and may be caused by infection with bacteria, viruses, or, less often, fungi. Acute bacterial conjunctivitis is often caused by staphylococci or streptococci in adults, and *Haemophilus influenzae* and *Moraxella catarrhalis* (*Branhamella catarrhalis*) in children. Other causes of bacterial conjunctivitis include gonococci (see Gonorrhoea, p. 206.2) and *Chlamydia trachomatis* (see Trachoma, p. 212.1). Neonatal chlamydial and gonococcal conjunctivitis are discussed under Neonatal Conjunctivitis, p. 195.2. Uncomplicated bacterial conjunctivitis may be self-limiting but empirical treatment with topical antibacterials is often given. In the UK, topical chloramphenicol remains the treatment of choice despite concerns over the potential risk of aplastic anaemia (see Ocular Use under Precautions of Chloramphenicol, p. 260.3). Alternatives include gentamicin, tobramycin, erythromycin (especially when infection with Gram-positive organisms is suspected), fluoroquinolones including ciprofloxacin and ofloxacin, framycetin, fusidic acid (especially for staphylococcal infections), and polymyxin B in combination with bacitracin, trimethoprim, or neomycin.

Blepharitis is an infection of the lid margins. It usually presents as a chronic condition and may require prolonged treatment, typically involving local hygiene to remove encrustations and topical application of a broad-spectrum antibacterial ointment.

Keratitis may be caused by infection of the cornea by bacteria, fungi, viruses, or protozoa, usually after trauma to the surface of the eye, including that due to contact lens wear (see Contact Lens Care, p. 1731.2). Common bacterial pathogens include staphylococci, streptococci, *Pseudomonas* spp., and Enterobacteriaceae. Bacterial keratitis is potentially sight-threatening and requires prompt aggressive treatment with broad-spectrum antibacterials. It is customary to obtain material for sensitivity testing, but increasingly, empirical treatment is then begun without delay. Frequent or continuous topical application of drops or the use of local drug delivery devices have been used to ensure prolonged elevated drug concentrations. Subconjunctival or systemic therapy may occasionally be necessary. Topical treatment with cefazolin and either gentamicin or tobramycin has traditionally been used when *Pseudomonas* is not suspected. More recently, fluoroquinolones or ceftazidime have been used, and semisynthetic penicillins or vancomycin are other alternatives. For the treatment of Acanthamoeba keratitis, see p. 921.2.

Endophthalmitis is a devastating ocular disease resulting from infection of the ocular cavity, usually after penetrating trauma or surgery. Depending on the route of infection, causative organisms often include staphylococci, streptococci, *H. influenzae*, *Bacillus cereus*, and *Propionibacterium acnes*. Fungal infections occur less commonly. Bacterial endophthalmitis requires immediate aggressive treatment with antibacterials, usually given intravitreally. The value of concurrent parenteral antibacterials is unclear. The choice of antibacterial for intravitreal use depends on the most likely pathogen. Third-generation cephalosporins or vancomycin are used, but aminoglycosides may produce retinal toxicity. Clindamycin may be effective if *B. cereus* is suspected. Adjunctive treatment includes vitrectomy, surgical removal of infected lens structures, and corticosteroids to control inflammatory and immune responses.

For a discussion of fungal infections of the eye, see p. 565.3; for cytomegalovirus retinitis and ocular herpes simplex infections, see under Cytomegalovirus Infections, p. 956.2, and Herpes Simplex Infections, p. 957.2, respectively.

Some general references are given below.

1. Baum J. Infections of the eye. *Clin Infect Dis* 1995; **21**: 479–88.
2. Leeming JP. Treatment of ocular infections with topical antibacterials. *Clin Pharmacokinet* 1999; **37**: 351–60.
3. Robert P-Y, Adenis J-P. Comparative review of topical ophthalmic antibacterial preparations. *Drugs* 2001; **61**: 175–85.
4. Sheikh A, Hurwitz B. Antibiotics versus placebo for acute bacterial conjunctivitis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 12/06/08).
5. Suwan-apichon O, *et al.* Topical corticosteroids as adjunctive therapy for bacterial keratitis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 13/06/08).

Gas gangrene

Gas gangrene (or clostridial myonecrosis) is a life-threatening bacterial infection caused by exotoxin-producing *Clostridium* spp., which invade muscle tissue and cause tissue necrosis, gas production, and systemic toxicity. They are anaerobic, Gram-positive bacteria normally found in soil and the gastrointestinal tract of humans and animals. Infection usually results from deep trauma or surgery, and more than 80% of cases are caused by *C. perfringens*. Spontaneous or nontraumatic gas gangrene is rare and is almost exclusively caused by *C. septicum*. The typical incubation period is usually less than 24 hours but may range from 6 hours to 6 weeks. However, once symptoms start clinical deterioration occurs within hours and is characterised by rapidly increasing pain, fever, and muscle swelling. Systemic toxicity may cause altered mental status, and the progression to septicaemia, shock, and death can be rapid. *C. perfringens* alpha toxin has a negative inotropic effect on cardiac myocytes causing severe, refractory hypotension, while the release of theta toxin leads to shock through peripheral vasodilatation; renal shutdown due to myonecrosis may occur. Mortality from traumatic gas gangrene is about 25% and for spontaneous gas gangrene ranges from 67 to 100%.

Mortality can be improved by rapid diagnosis and early treatment, which involves aggressive surgical exploration and debridement, and intravenous antibacterial therapy. Amputation may be needed in 15 to 20% of patients. Benzylpenicillin is the drug of choice; adding clindamycin is considered beneficial. However, it may be difficult to distinguish gas gangrene from other soft tissue infections and so empirical antibacterial treatment usually covers Gram-positive, Gram-negative, and anaerobic bacteria. Regimens that have been used include:

- a penicillin plus gentamicin and metronidazole
- a second-generation cephalosporin (such as cefuroxime) plus metronidazole
- clindamycin plus a fluoroquinolone in penicillin-allergic patients
- vancomycin or linezolid should be considered in those at risk for MRSA

Other antibacterials used have included combinations of a beta lactam and beta-lactamase inhibitor (such as ticarcillin with clavulanate, ampicillin with sulbactam, or piperacillin with tazobactam), third-generation cephalosporin, chloramphenicol, and tetracycline. Hyperbaric oxygen is used as an adjunct to surgical debridement although its efficacy has not been established. Gas-gangrene antitoxins are now rarely used.

References.

1. Wang C, *et al.* Hyperbaric oxygen for treating wounds: a systematic review of the literature. *Arch Surg* 2003; **138**: 272–9.
2. Rekha A, Gopalan TR. Civilian gas gangrene: a clinical challenge. *Int J Low Extrem Wounds* 2007; **6**: 98–101.
3. Dylewski J, *et al.* A case of Clostridium septicum spontaneous gas gangrene. *CJEM* 2007; **9**: 133–5.

Gastro-enteritis

Diarrhoea is a symptom of simple gastro-enteritis and of most intestinal infections. It is a major problem in developing countries, but is common worldwide. Although viruses are often responsible, the severest forms of infectious diarrhoea are generally those due to bacteria. Common bacterial pathogens include *Campylobacter jejuni*, *Escherichia coli*, *Salmonella enteritidis*, *Shigella* spp., *Vibrio cholerae*, and *Yersinia enterocolitica*. Intestinal protozoa also cause diarrhoea and are important in AIDS-associated diarrhoea. For discussions of viral and protozoal gastro-enteritis and their treatment, see p. 953.3 and p. 923.2, respectively. Many of these organisms are easily transmitted through food or water, or from person to person, and some may be particularly severe in immunocompromised persons or those with structural abnormalities of the gastrointestinal tract.

Treatment of acute diarrhoea of any aetiology includes fluid replacement, antidiarrhoeal drugs, probiotics, vitamin and mineral supplementation, and antibacterials. Treatment with antibacterials is discussed below, while the classification of diarrhoea and other treatments are discussed under Diarrhoea (see p. 1808.2). WHO[1] recommends that diarrhoea be managed with oral rehydration therapy and continued feeding and that antibacterials should not be routinely given as it is often difficult to distinguish whether the diarrhoea is caused by an organism responsive to antibacterials. Furthermore drug sensitivity of the causative organism is not always known and use of antibacterials could promote the development of resistant bacteria.[1] However, diagnostic capacities are more widely available in the developed world and some clinicians consider such an approach to be unnecessarily conservative in adults with severe acute diarrhoea in developed countries[2] in whom empirical treatment with fluoroquinolones can relieve symptoms and shorten the illness without significant adverse effects. In the USA, empirical therapy is considered for any patients with moderate to severe, febrile, community-acquired diarrhoea, especially if invasive disease is suspected; stool samples should be obtained for identification of the causative organism.[3,4] Empirical therapy may also be given to those with severe nosocomial diarrhoea while waiting for results of assay for *C. difficile* toxin (see also Antibiotic-associated Colitis, p. 185.1), and for moderate to severe travellers' diarrhoea (below).[4]

In **infants and children** oral rehydration therapy is universally recognised as appropriate initial treatment of acute diarrhoea,[5] but it has been underutilised in both developed and developing countries.[6] and a preference for the use of intravenous rehydration therapy with Ringer's lactate solution or normal saline was noted in the USA.[7] Nutritional support and management of secondary complications, including systemic infections, is also particularly important in this age group. Antibacterials have little place in management in most cases[1,5] WHO[1] has stipulated that antibacterials should only be used in children with bloody diarrhoea that is probably caused by *Shigella* (see p. 188.1), suspected cholera with severe dehydration (see p. 186.2), or diarrhoea associated with serious non-intestinal infections (such as pneumonia or urinary-tract infection).[1] Treatment of protozoal infections such as giardiasis and amoebiasis is rarely indicated.[1]

Persistent or prolonged diarrhoea may not have an infective cause and antibacterial treatment should not be started unless a pathogen can be identified. **Tropical sprue** is a syndrome characterised by acute or chronic diarrhoea, weight loss, and malabsorption of nutrients. It occurs in residents of or visitors to the tropical and subtropical regions. The exact pathogenetic sequence is unknown but it is thought that bacterial overgrowth, disturbed gut motility, and hormonal and histopathologic abnormalities contribute to its development in susceptible persons.[8] Treatment with tetracycline and folate is effective in some patients, although relapses after treatment are common.[8]

HIV-associated diarrhoea. Diarrhoea is common in HIV infection and AIDS (p. 959.2) and causative organisms may be bacterial, protozoal, or viral. The most common bacterial cause is the *Mycobacterium avium* complex (see Nontuberculous Mycobacterial Infections, p. 196.1); others include *Campylobacter*, *Salmonella*, and *Shigella* spp. Supportive care and appropriate conventional antibacterial therapy may be adequate, as described under the specific infections, below.

'Food poisoning' is the term used when a preformed toxin in food is ingested, resulting in an intoxication rather than an enteric infection. It is generally a self-limiting form of gastro-enteritis and most people recover from a case of food poisoning within 1 to 2 days,[9] although serious outbreaks of foodborne illness have been associated with bacteria such as *Salmonella enteritidis*. *Staphylococcus aureus* can produce a heat-stable toxin that causes vomiting within 2 to 7 hours of eating improperly cooked or stored food containing it, while *Clostridium perfringens* toxin causes watery diarrhoea without vomiting within 8 to 14 hours after eating contaminated meat, vegetables, or poultry. *Bacillus cereus* may cause vomiting or diarrhoea, depending on the toxin produced, after eating contaminated fried rice, vegetable sprouts, or other food items.[9]

Travellers' diarrhoea.[10-14] is acquired by ingesting contaminated water or foodstuffs. Although it occurs worldwide, the highest rates (20 to 60%) are in travellers from developed, high-income countries visiting developing, low-income regions.[13,14] Travellers diarrhoea is most commonly caused by bacterial enteric pathogens, of which the commonest bacterial pathogen is enterotoxigenic *E. coli*, although enteroadherent *E. coli* is also sometimes involved. Other bacteria include *Campylobacter jejuni*, and *Salmonella* and *Shigella* spp., *Vibrio cholerae*, and non-cholera vibrios such as *V. parahaemolyticus* are rare in travellers. Viruses and the protozoa *Giardia intestinalis*, *Entamoeba histolytica*, and *Cryptosporidium* may also be responsible. Recommendations for the management of travellers' diarrhoea are published by national and international bodies including WHO,[15] the DOH in the UK,[16] and the CDC in the USA.[17] Clinical features depend on the pathogen responsible and treatment varies according to severity and duration of diarrhoea. Onset of diarrhoea is generally delayed with *Giardia* and *Entamoeba* because of the incubation period.

Diarrhoea is often mild and self-limiting and increased fluid intake (in adults) or oral rehydration therapy (for infants, young children, the elderly, or those with cholera-like diarrhoea) is usually all that will be required. Symptomatic treatment with antimotility drugs such as loperamide may be of benefit in mild to moderate diarrhoea. However, antimotility drugs may worsen diarrhoeal illness caused by invasive bacterial pathogens and should be used with caution in those with high fevers, chills, or bloody diarrhoea.[10] Bismuth salicylate may be used to reduce the frequency of diarrhoea. Information on the value of probiotics in the treatment of travellers' diarrhoea is insufficient.[13]

Studies have shown that antibacterials are effective and a single dose (or for up to 3 days of treatment) of an appropriate antibacterial will improve symptoms within 20 to 36 hours and shorten the duration of diarrhoea by 1 to 2 days.[13] Fluoroquinolones are effective in most areas of the world, except where potentially resistant *Campylobacter* is common (as in South and South East Asia). Azithromycin may be given as an alternative in these areas; it can also be used in the treatment of pregnant women and young children with travellers' diarrhoea. Co-trimoxazole was the drug of choice for many years but widespread bacterial resistance has now limited its usefulness.[10,12] It may still be used in those who fail to respond to a fluoroquinolone and antiprotozoal drugs (such as metronidazole) in areas where cyclosporiasis is suspected.[10] Rifaximin has been found to be effective treatment of mainly *E coli* associated travellers diarrhoea in Mexico and Jamaica, but is less effective and not recommended against invasive agents, such as *Campylobacter* and *Shigella*.[13,18] A systematic review and meta-analysis[19] found that combination treatment with an antibacterial and loperamide, given early in the course of the illness was superior to treatment with either agent alone; combination therapy could be considered for people who need prompt resolution of symptoms.[13] When the infecting bacteria are known, specific therapy may be necessary, as described for *Campylobacter* spp. (p. 186.1), cholera and other vibrio infections (p. 186.2), *Escherichia coli* (p. 186.3), *Salmonella* spp. (p. 187.2), *Shigella* spp. (p. 188.1), and *Yersinia* infections (p. 188.2).

The risk of developing travellers' diarrhoea can be reduced by avoiding possibly contaminated foods as embodied in the advice to *'cook it, boil it, peel it, or forget it'*. Prophylactic drug regimens have been suggested, including various antibacterials, in addition to bismuth salicylate and probiotics. However, routine antimicrobial prophylaxis is not generally recommended because of the danger of drug reactions, superinfections, and increasing bacterial resistance;[10,11,13] it should be reserved for those at special risk.[10,11,20] Many authorities prefer early treatment, including self-medication (with an antibacterial), with clear instructions on when medical help should be sought. If prophylaxis is given it should be started at the start of the at-risk period, and continued for 2 days after the risk stops; prophylaxis should be limited to 3 weeks.[10] A fluoroquinolone is the drug of choice when travelling to most areas of the world; azithromycin can be considered an alternative and rifaximin may be considered for regions where *E coli* predominates, such as Latin America and Africa. Sulfonamides, co-trimoxazole, and tetracyclines should not be used because of widespread resistance.[10,13]

1. WHO. *The treatment of diarrhoea: a manual for physicians and other senior health workers*. 4th ed. Geneva: WHO, 2005. Available at: http://whqlibdoc.who.int/publications/2005/9241593180.pdf (accessed 13/04/10)
2. Gorbach SL. Treating diarrhoea. *BMJ* 1997; 314: 1776–7.
3. Guerrant RL, *et al.* Infectious Diseases Society of America. Practice guidelines for the management of infectious diarrhea. *Clin Infect Dis* 2001; 32: 331–50. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/318514 (accessed 18/08/08)
4. Thielman NM, Guerrant RL. Clinical practice. Acute infectious diarrhea. *N Engl J Med* 2004; 350: 38–47.
5. Koletzko S, Osterrieder S. Acute infectious diarrhea in children. *Dtsch Arztebl Int* 2009; 106: 539–47.
6. The United Nations Childrens Fund (UNICEF)/WHO. Diarrhoea: why children are still dying and what can be done. Geneva: WHO, 2009. Available at: http://whqlibdoc.who.int/publications/2009/9789241598415_eng.pdf (accessed 13/04/10)
7. Hartling L, *et al.* Oral versus intravenous rehydration for treating dehydration due to gastroenteritis in children. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 29/04/10).
8. Nath SK. Tropical sprue. *Curr Gastroenterol Rep* 2005; 7: 343–9.
9. DuPont HL. Clinical practice. Bacterial diarrhea. *N Engl J Med* 2009; 361: 1560–9.
10. Al-Abri SS, *et al.* Traveller's diarrhoea. *Lancet Infect Dis* 2005; 5: 349–60.
11. DuPont HL. Travellers' diarrhoea: contemporary approaches to therapy and prevention. *Drugs* 2006; 66: 303–14.
12. DuPont HL. Therapy for and prevention of traveler's diarrhea. *Clin Infect Dis* 2007; 45 (suppl 1): S78–S84.
13. Hill DR, Ryan ET. Management of travellers' diarrhoea. *BMJ* 2008; 337: a1746. Full version: http://www.bmj.com/cgi/section_pdf/337/oct06_2/a1746.pdf (accessed 29/04/10)
14. Baldi F, *et al.* Focus on acute diarrhoeal disease. *World J Gastroenterol* 2009; 15: 3341–8.
15. WHO. *International travel and health*. 2010 ed. Available at: http://www.who.int/ith/ITH2010chapter3.pdf (accessed 12/04/10)
16. DoH. *Health information for overseas travel*. 2001 ed. Available at: http://www.archive.official-documents.co.uk/document/doh/hinfo/travel19.htm (accessed 12/04/10)
17. CDC. Travelers Diarrhea. In: *The Yellow Book: CDC Health Information for International Travel; 2010*. Available at: http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/travelers-diarrhea.aspx (accessed 12/4/10)
18. Sanders JW, *et al.* Azithromycin and loperamide are comparable to levofloxacin and loperamide for the treatment of traveler's diarrhea in United States military personnel in Turkey. *Clin Infect Dis* 2007; 45: 294–301.
19. Riddle MS, *et al.* Effect of adjunctive loperamide in combination with antibiotics on treatment outcomes in traveler's diarrhea: a systematic review and meta-analysis. *Clin Infect Dis* 2008; 47: 1007–14.
20. Rendl-Wagner P, Kollaritsch H. Drug prophylaxis for travelers' diarrhea. *Clin Infect Dis* 2002; 34: 628–33.

Antibiotic-associated colitis. *Clostridium difficile* is an anaerobic Gram-positive organism; 2 toxins (A and B) formed by the organism are responsible for an infectious colitis that affects about 20% of hospitalised patients taking antibacterials. Synonymous terms used to refer to the spectrum of disease due to *C. difficile* are:

- antibiotic-associated colitis (AAC)
- *C. difficile*-associated diarrhoea (CDAD)
- *C. difficile* colitis, and
- pseudomembranous colitis (which specifically describes the formation of a membranous exudate in the colon and occurs in about 50% of cases of AAC)

The term antibiotic-associated diarrhoea is usually used for milder disease that is not caused by *C. difficile* or its toxins.

Exposure to antibacterials is the most significant risk factor for development of disease. Antibacterial use alters the normal bowel flora, predisposing to the overgrowth of *C. difficile* and the production of its toxins. The incidence of AAC varies considerably but is increasing worldwide due to broad-spectrum antibacterial use.[1,2] AAC has been associated with the use of most antibacterials, but particularly with clindamycin, lincomycin, ampicillin, amoxicillin, and cephalosporins (especially second and third generation); and, less frequently, with fluoroquinolones, tetracycline, carbapenems, trimethoprim, the macrolides (erythromycin, clarithromycin, azithromycin), and other penicillins. Antibacterials occasionally reported to cause the disease include aminoglycosides, co-trimoxazole, and chloramphenicol. The perception that fluoroquinolones are low risk for AAC has been challenged[3] and studies[4-6] have shown a significant association between ciprofloxacin usage and AAC, with the risk increasing with longer courses of therapy.[6] It has also been suggested that the newer fluoroquinolones (such as moxifloxacin and gatifloxacin) may have different effects on intestinal flora and therefore be more likely to cause AAC; preliminary data from 3 studies appear to support this hypothesis.[2] Antibacterials usually used to treat AAC such as vancomycin and metronidazole have also been shown to cause disease. The role of acid suppression in AAC is unclear.[7]

Symptoms usually develop 5 to 10 days after starting antibacterial therapy, but may develop after a single day of use or can occur up to 10 weeks after stopping treatment. Colonisation generally occurs after ingestion of the acid-resistant spores that are common contaminants from patients who harbour *C. difficile*. Hospitalised patients and residents of long-term care facilities are at higher risk of colonisation with *C. difficile* although colonisation can occur in the outpatient setting. The clinical presentation of AAC can range from mild self-limited diarrhoea to severe colitis with pseudomembrane formation complicated by development of toxic megacolon or colonic perforation. The usual presentation is cramping and abdominal pain with profuse, mucoid, greenish, malodorous watery stools.

Diarrhoea resolved within 48 to 72 hours in 20 to 25% of patients after stopping the offending drug,[1] and giving fluid and electrolyte replacement. If it is not possible to stop antibacterial treatment, a drug less likely to promote AAC may be given.[1,3] In the past early specific antibacterial therapy was only given to patients with severe illness characterised by high fever, marked abdominal pain, and marked leucocytosis and to elderly, toxic, or debilitated patients, or those unresponsive to supportive therapy.[8] However, with the increased incidence of fulminant AAC and the rapid clinical deterioration of some patients, delaying specific AAC antibacterial therapy is no longer advised.[1,3] Antibacterials are probably unnecessary in mild disease[9] and chemoprophylaxis for asymptomatic carriers is not recommended.[3,7] Antidiarrhoeal and antimotility drugs should be avoided since they may aggravate the condition and may occasionally increase the possibility of toxic megacolon.[1] A literature review,[10] however, concluded that antimotility drugs, used with an active antibacterial, may provide safe and effective symptomatic relief and assist in reducing the passage of infectious stools in the hospital environment.

The choice of initial antibacterial therapy depends on the severity of disease and different regimens are used to treat first or second episodes of AAC, recurrent episodes, and very severe or fulminant disease.[1] Vancomycin or metronidazole are widely used when antibacterial treatment is necessary.[1,3,7,8] Metronidazole can be given orally or intravenously as appropriate. Vancomycin is given orally or via a retention enema; it should not be given intravenously since it does not give rise to adequate concentrations of the drug in the bowel lumen.[1] Metronidazole tends to be the drug of first choice and vancomycin is reserved for those who do not respond to, or who cannot tolerate, metronidazole, for those who are severely immunocompromised, and for those with severe illness.[1,7,8] This view is also endorsed by expert bodies in the USA whose aim is to provide guidelines for preventing the spread of vancomycin resistance.[11] Oral fidaxomicin has also been shown to be effective and is a potential treatment alternative.[12,13] The severity of the diarrhoea often decreases within 48 to 72 hours, but may not stop for a week or more. Treatment is usually continued for 10 to 14 days.[1] Other drugs that have been investigated in the treatment of AAC include teicoplanin,[14-16] fusidic acid,[16,17] and bacitracin,[18] although experience with their use remains limited. A systematic review[9] found that metronidazole, bacitracin, rifaximin, nitazoxanide, or fusidic acid seemed to be as effective as vancomycin in terms of symptomatic cure, and teicoplanin might be slightly more effective. Bacitracin and fusidic acid seemed to be less effective than vancomycin in terms of bacteriological cure and resolution.[9] Ramoplanin has also been investigated.[1,3]

The anion-exchange resins colestyramine and colestipol hydrochloride have been shown to bind the *Cl. difficile toxin in vitro*, and colestyramine has been used to treat pseudomembranous colitis[19] and recurrent AAC.[1] The use of vancomycin together with colestyramine has been suggested,[20] but the value of the combination is uncertain. Colestyramine binds to vancomycin, resulting in a reduction of biologic activity in stool and in general, the use of colestyramine and colestipol is not recommended.[1,21] An experimental toxin-binding polymer, tolevamer (or GT 160-2461) has also been investigated.[1,3]

It is thought that patients who develop recurrent AAC are unable to mount a protective immune response to *C. difficile* and its toxins;[3,7,21] normal immunoglobulin products that contain IgG have been shown to neutralise the toxins A and B,[3] and may benefit patients with severe and/or relapsing AAC when no other therapeutic options are available.[1,21] Oral immunoglobulin A, used with vancomycin, was effective in controlling severe diarrhoea in a child who had not responded to other therapies.[22] Normal immunoglobulin given intravenously was also effective when added to vancomycin and metronidazole therapy in 2 elderly patients unresponsive to antibacterials alone.[23] Vaccines against *C. difficile* have also been investigated.[1] A single infusion of 2 monoclonal antibodies against *C. difficile* toxins A and B was reported to significantly reduce the recurrence of infection when given with either metronidazole or vancomycin therapy.[24]

Treatment and prevention strategies aimed at colonising the gut with non-pathogenic organisms have included use of lactic-acid-producing organisms (probiotics) such as *Lactobacillus*,[8,25] and the yeasts *Saccharomyces boulardii*,[8] and *S. cerevisiae*.[26] A systematic review[27] of studies that used probiotics as adjunctive therapy to antibacterials (vancomycin or metronidazole) for treatment of an initial episode of *C. difficile* colitis or recurrent infection in adults found there was insufficient evidence to recommend adjunctive probiotics. However, another systematic review[28] on the use of probiotics in children reported that they may be effective for preventing AAC. Data on regimens containing *Lactobacillus* organisms or *S. boulardii* for the treatment of recurrent AAC are poor and conflicting.[1,3] Some experts, however, consider probiotics to be a safe and reasonable option for prevention of initial infections and possibly for treatment of recurrent infections.[7]

For patients with severe or fulminant infection who have a functioning gastrointestinal tract, oral vancomycin is the preferred therapy.[1] However, treatment of patients with a compromised gastrointestinal tract is difficult because reliable concentrations of orally administered drug at the site of infection cannot be assured.[1] Vancomycin given via a nasogastric tube or by retention enema plus intravenous metronidazole have been tried.[1,3,7] Intravenous tigecycline has been successfully used in 4 patients with severe refractory AAC.[29]

About 15 to 30% of patients develop a second episode of AAC after successful treatment of the first episode; treatment with the same drug used to treat the first episode is recommended.[1,3,7,21] Higher recurrence rates of up to 65% occur in patients who have had 2 or more previous episodes.[3,7] Vancomycin is usually preferred for the treatment of recurrent infection[1,3,7,21] because long or repeated courses of metronidazole have the potential to cause peripheral neuropathy.[1,7,21] Management strategies used have included tapered or pulsed dosed vancomycin followed by course of rifaximin,[1,7,21] nitazoxanide,[7] or rifampicin.[21] If episodes of recurrent AAC continue, other treatment options such as alternative antibacterials (nitazoxanide or rifaximin), probiotics, immunological therapy, faecal reconstitution (stool transplantation), and toxin-binding products may be tried.[7,21]

1. Gerding DN, *et al.* Treatment of Clostridium difficile infection. *Clin Infect Dis* 2008; 46 (suppl 1): S32–42.
2. Blondeau JM. What have we learned about antimicrobial use and the risks for *Clostridium difficile*-associated diarrhoea? *J Antimicrob Chemother* 2009; 63: 238–42.
3. Williams OM, Spencer RC. The management of *Clostridium difficile* infection. *Br Med Bull* 2009; 91: 87–110.
4. McCusker ME, *et al.* Fluoroquinolone use and *Clostridium difficile*-associated diarrhea. *Emerg Infect Dis* 2003; 9: 730–3.
5. Loo VG, *et al.* A predominantly clonal multi-institutional outbreak of *Clostridium difficile*-associated diarrhea with high morbidity and mortality. *N Engl J Med* 2005; 353: 2442–9.
6. Pépin J, *et al.* Emergence of fluoroquinolones as the predominant risk factor for *Clostridium difficile*-associated diarrhea: a cohort study during an epidemic in Quebec. *Clin Infect Dis* 2005; 41: 1254–60.
7. Leffler DA, Lamont JT. Treatment of *Clostridium difficile*-associated disease. *Gastroenterology* 2009; 136: 1899–912.

8. Malnick SDH, Zimhony O. Treatment of Clostridium difficile-associated diarrhea. *Ann Pharmacother* 2002; 36: 1767–75.
9. Nelson R. Antibiotic treatment for Clostridium difficile-associated diarrhea in adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 05/08/08).
10. Koo HL, *et al.* Antimotility agents for the treatment of *Clostridium difficile* diarrhea and colitis. *Clin Infect Dis* 2009; 48: 598–605.
11. Hospital Infection Control Practices Advisory Committee (HICPAC). Recommendations for preventing the spread of vancomycin resistance. *MMWR* 1995; 44(RR-12): 1–13. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr4412.pdf (accessed 18/05/04)
12. Louie TJ, *et al.* Fidaxomicin versus vancomycin for *Clostridium difficile* infection. *N Engl J Med* 2011; 364: 422–31.
13. Mullane KM, *et al.* Efficacy of fidaxomicin versus vancomycin as therapy for *Clostridium difficile* infection in individuals taking concomitant antibiotics for other concurrent infections. *Clin Infect Dis* 2011; 53: 440–7.
14. de Lalla F, *et al.* Treatment of Clostridium difficile-associated disease with teicoplanin. *Antimicrob Agents Chemother* 1989; 33: 1125–7.
15. de Lalla F, *et al.* Prospective study of oral teicoplanin versus oral vancomycin for therapy of pseudomembranous colitis and Clostridium difficile-associated diarrhea. *Antimicrob Agents Chemother* 1992; 36: 2192–6.
16. Wenisch C, *et al.* Comparison of vancomycin, teicoplanin, metronidazole, and fusidic acid for the treatment of Clostridium difficile-associated diarrhea. *Clin Infect Dis* 1996; 22: 813–18.
17. Cronberg S, *et al.* Fusidic acid for the treatment of antibiotic-associated colitis induced by Clostridium difficile. *Infection* 1984; 12: 276–9.
18. Dudley MN, *et al.* Oral bacitracin vs vancomycin therapy for Clostridium difficile-induced diarrhea: a randomized double-blind trial. *Arch Intern Med* 1986; 146: 1101–4.
19. Pruksananonda P, Powell KR. Multiple relapses of Clostridium difficile-associated diarrhea responding to an extended course of cholestyramine. *Pediatr Infect Dis J* 1989; 8: 175–8.
20. Shwed JA, Rodvold KA. Anion-exchange resins and oral vancomycin in pseudomembranous colitis. *DICP Ann Pharmacother* 1989; 23: 70–1.
21. Johnson S. Recurrent *Clostridium difficile* infection: a review of risk factors, treatments, and outcomes. *J Infect* 2009; 58: 403–10.
22. Tjellström B, *et al.* Oral immunoglobulin A supplement in treatment of Clostridium difficile enteritis. *Lancet* 1993; 341: 701–2.
23. Salcedo J, *et al.* Intravenous immunoglobulin therapy for severe Clostridium difficile colitis. *Gut* 1997; 41: 366–70.
24. Lowy I, *et al.* Treatment with monoclonal antibodies against *Clostridium difficile* toxins. *N Engl J Med* 2010; 362: 197–205.
25. Vanderhoof JA, *et al.* Lactobacillus GG in the prevention of antibiotic-associated diarrhea in children. *J Pediatr* 1999; 135: 564–8.
26. Schellenberg D, *et al.* Treatment of Clostridium difficile diarrhoea with brewer's yeast. *Lancet* 1994; 343: 171–2.
27. Pillai A, Nelson R. Probiotics for treatment of *Clostridium difficile*-associated colitis in adults. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 03/05/10).
28. Johnston BC, *et al.* Probiotics for the prevention of pediatric antibiotic-associated diarrhea. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 03/05/10).
29. Herpers BL, *et al.* Intravenous tigecycline as adjunctive or alternative therapy for severe refractory *Clostridium difficile* infection. *Clin Infect Dis* 2009; 48: 1732–5.

Campylobacter enteritis. *Campylobacter* spp.[1-4] are the most common cause of bacterial gastroenteritis in both developed and developing countries. In developing countries, disease occurs mainly in young children, while in developed countries the highest rates are seen among children less than 5 years of age and young adults, particularly men from 20 to 29 years of age. It is also a common cause of diarrhoea in travellers to developing countries. Although about 16 species of *Campylobacter* have been identified, more than 90% of cases are caused by *C. jejuni* and most of the other infections are caused by *C. coli*.[5,6] Campylobacter enteritis is a zoonosis and the main route of transmission is thought to be foodborne, via undercooked meats and meat products. Other routes of transmission include raw or contaminated milk, contaminated water, contact with pets and farm animals, and from doorstep deliveries of foil-topped bottled milk that have been pecked by birds.

Symptoms usually occur 2 to 5 days after exposure, but can range from 1 to 11 days. Some patients may be asymptomatic while others may have diarrhoea (sometimes bloody), abdominal pain, fever, headache, nausea, and vomiting. Illness usually lasts for 2 to 6 days but may last up to several weeks. Significant post-infection complications may include irritable bowel syndrome (15%), reactive arthritis (1%), Guillain-Barré syndrome (0.1%), and toxic megacolon. Fatalities due to dehydration are rare and usually occur in the very young or elderly patients, or in those already suffering from another serious disease such as AIDS.

Infection is usually self-limiting and in most cases fluid and electrolyte replacement is generally sufficient (see Diarrhoea, p. 1808.2).[1,2] Antibacterials are generally not required but can be considered for patients with severe or prolonged symptoms or who are immunocompromised.[2,3] Those that have been used include erythromycin, azithromycin, tetracycline, and ciprofloxacin. However, due to widespread use of these antibacterials in veterinary practice and as additives to animal feeds (particularly poultry), selection for resistant *Campylobacter* spp. has occurred[4,6] and increasing numbers of ciprofloxacin-resistant cases are being reported worldwide.[2,6-8] Resistance rates in the USA and Canada are reported to be about 19 to 47%, while 17 to 99% of *Campylobacter* isolates in Europe are resistant to fluoroquinolones.[8] This has prompted the withdrawal of fluoroquinolones from use in commercial poultry farming in the USA.[9] Rates of macrolide resistance have stayed stable and low in many countries, but an increase has been reported in human strains in some countries,[5,6] particularly in the developing countries.[5] The prevalence of erythromycin resistance in *C. jejuni* has remained low (below 12% of isolates) but a higher frequency of resistance (up to 70%) is reported in *C. coli*. Globally, multiple antibacterial resistance (resistance to three or more different classes of antibacterial) is emerging in *Campylobacter* clinical isolates.[6]

Erythromycin is considered to be the drug of choice for treatment of *Campylobacter* infections; the newer macrolides, azithromycin and clarithromycin are alternatives.[2,10] *Campylobacter* species also are generally susceptible to aminoglycosides, chloramphenicol, clindamycin, nitrofurans, and imipenem,[2,6] but high rates of resistance make tetracycline, amoxicillin, ampicillin, metronidazole, or cephalosporins a poor choice.[2]

1. Skirrow MB. Foodborne illness: Campylobacter. *Lancet* 1990; 336: 921–3.
2. Allos BM. Campylobacter jejuni infections: update on emerging issues and trends. *Clin Infect Dis* 2001; 32: 1201–6.
3. Galanis E. Campylobacter and bacterial gastroenteritis. *CMAJ* 2007; 177: 570–1.
4. Senok AC, Botta GA. Campylobacter enteritis in the Arabian Gulf. *J Infect Dev Ctries* 2009; 3: 74–82.
5. Gibreel A, Taylor DE. Macrolide resistance in Campylobacter jejuni and Campylobacter coli. *J Antimicrob Chemother* 2006; 58: 243–55.
6. Quinn T, *et al.* Antibiotic-resistant Campylobacter: could efflux pump inhibitors control infection? *J Antimicrob Chemother* 2007; 59: 1230–6.
7. Campylobacter Sentinel Surveillance Scheme Collaborators. Ciprofloxacin resistance in Campylobacter jejuni: case-case analysis as a tool for elucidating risks at home and abroad. *J Antimicrob Chemother* 2002; 50: 561–8.
8. Luangtongkum T, *et al.* Antibiotic resistance in Campylobacter: emergence, transmission and persistence. *Future Microbiol* 2009; 4: 189–200.
9. Nelson JM, *et al.* Fluoroquinolone-resistant Campylobacter species and the withdrawal of fluoroquinolones from use in poultry: a public health success story. *Clin Infect Dis* 2007; 44: 977–80.
10. Abramowicz M, ed. The choice of antibacterial drugs. In: *Handbook of antimicrobial therapy*. 19th ed. New York: The Medical Letter, 2011: 62.

Cholera and other vibrio infections. Cholera[1] results from infection with the enterotoxin-producing Gram-negative bacillus *Vibrio cholerae*, which causes acute secretory diarrhoea. Outbreaks are associated with two serogroups of *V. cholerae*, O1 and O139. Serogroup O1 can then be divided into two biotypes (classical and El Tor) and each of these has three serotypes (Inaba, Ogawa, and Hikojima). Other strains of *V. cholerae* can cause mild diarrhoea but such infections do not develop into epidemics. Cholera is considered to be endemic in many countries and the pathogen causing it cannot currently be eliminated from the environment.

Transmission occurs mainly through ingestion of contaminated water and food, but may also be spread through direct faecal-oral contamination. Severe disease is characterised by a sudden onset of acute watery diarrhoea that can lead to death within hours in previously healthy adults, due to severe dehydration. If untreated, as many as 50% of patients may die, but with proper treatment, the fatality rate is about 1%. Individuals with lower immunity, such as malnourished children or people infected with HIV, are at increased risk of death. The incubation period is usually 24 to 72 hours, but can range from 2 hours to 5 days. This short incubation period enhances the potentially explosive pattern of outbreaks, as the number of cases can rise very quickly. About 75% of people will not develop any symptoms. However, the pathogens stay in the faeces for 7 to 14 days and are shed back into the environment, potentially infecting others. Among people developing symptoms, 80% of episodes are of mild to moderate severity and the remaining cases may develop severe watery diarrhoea with signs of dehydration.

A guideline for the prevention and control of cholera outbreaks has been developed by WHO.[2] Individuals can reduce the risk of contracting cholera by good personal hygiene, avoiding possibly contaminated foodstuffs, and by boiling or otherwise disinfecting drinking water. Methods of preventing or containing cholera epidemics include ensuring a safe water supply, providing good sanitation, and promoting safe handling and preparation of foods. Routine treatment of a community with mass chemoprophylaxis, parenteral vaccination, and travel and trade restrictions are not effective. Oral cholera vaccines containing either live attenuated or inactivated strains are available in some countries. Mass vaccination campaigns using the oral killed whole-cell *V. cholerae* O1 with purified recombinant B-subunit of cholera toxoid (WC/rBS) vaccine have been conducted in emergency settings to protect at-risk populations from potential cholera outbreaks.[3] Use of oral cholera vaccines in such settings should not replace control measures such as improved water supplies, adequate sanitation, and health education.[2,3] Vaccination is not recommended once a cholera outbreak has started, because of its 2-dose regimen and the time required to reach protective efficacy.[2] Oral cholera vaccines are suitable for use by travellers. For further information on Cholera Vaccines see, p. 2381.1.

Most cases of vibrio gastro-enteritis are mild to moderate and generally require no therapy other than fluid and electrolyte replacement with an appropriate oral rehydration solution (see Diarrhoea, p. 1808.2). Patients with severe gastro-enteritis, dehydration, and shock should receive vigorous fluid replacement, preferably with intravenous isotonic solutions such as Ringer's lactate.[1,2,4] Supplementary zinc has been shown to be effective in reducing duration of diarrhoea and successive diarrhoeal episodes in children up to 5 years of age.[2,5,6] Antibacterials can be given in severe cholera to decrease the duration and volume of diarrhoea, reduce the volume of rehydration fluids needed, and shorten the duration of vibrio excretion.[1] WHO recommends a single dose of doxycycline (300 mg) for adults or a 3-day (12-dose) course of tetracycline or a 3-day (6-dose) course of co-trimoxazole for adults and children; furazolidone or erythromycin are considered suitable alternatives.[4] Recommendations from the USA for adults specify a tetracycline as the first choice with co-trimoxazole, azithromycin, or a fluoroquinolone such as ciprofloxacin as alternatives.[7] In the UK, tetracyclines or ciprofloxacin are usually used. One study has suggested that single-dose ciprofloxacin might be preferred to doxycycline, particularly in areas of tetracycline resistance,[8] and in Bangladesh, ampicillin has been found to be as effective as either erythromycin or tetracycline[9] and may be a useful alternative in children. Studies[10-12] in Bangladesh and India found single-dose azithromycin to be effective in children and adults. In children a single dose of ciprofloxacin was also reported to be effective in terms of clinical cure, but was less effective than a 3-day (12-dose) course of erythromycin in eradicating *V. cholerae* from stool.[13]

Widespread antibacterial resistance in *V. cholerae* was very uncommon before 1977, but reports of resistance to some antibacterials (including tetracycline, ampicillin, kanamycin, streptomycin, sulphonamides, trimethoprim, and gentamicin) have appeared from several cholera-endemic countries.[1] Fluoroquinolone-resistant strains have also been reported from India[1] and a multidrug resistant strain of *V. cholerae* O1 (resistant to co-trimoxazole, tetracycline, furazolidone, and erythromycin) has been reported from Bangladesh.[14] *V. cholerae* O139 strains are also resistant to co-trimoxazole, chloramphenicol, and low levels of streptomycin.[1] *V. cholerae* O1 and O139 show spatial and temporal fluctuations, with periods of resistance fluctuating with periods of sensitivity.[1]

Marine or halophilic *Vibrio* spp. known to cause gastroenteritis include *V. parahaemolyticus* which is responsible for food poisoning from raw or undercooked seafood, especially in Japan.[15,16] Another halophilic sp., *V. vulnificus*, is increasingly associated with wound infection and septicaemia.[15] On the basis of *in-vitro* sensitivity testing[17] and anecdotal clinical experience, empirical therapy with aminoglycosides, ceftazidime, imipenem, or ciprofloxacin should all be effective.[18]

1. Sack DA, *et al.* Cholera. *Lancet* 2004; 363: 223–33.
2. WHO. Prevention and control of cholera outbreaks: WHO policy and recommendations (issued 25th November 2008). Available at: http://www.who.int/cholera/technical/WHOPolicyNovember2008.pdf (accessed 07/04/10)
3. WHO. Cholera: global surveillance summary, 2008. *Wkly Epidem Rec* 2009; 84: 309–24. Also available at: http://www.who.int/wer/2006/wer8131.pdf (accessed 07/04/10)
4. WHO. *The treatment of diarrhoea: a manual for physicians and other senior health workers*. 4th ed. Geneva: WHO,2005. Available at: http://whqlibdoc.who.int/publications/2005/9241593180.pdf (accessed 07/04/10)
5. Roy SK, *et al.* Zinc supplementation in children with cholera in Bangladesh: randomised controlled trial. *BMJ* 2008; 336: 266–8.
6. Larson CP, *et al.* Zinc treatment to under-five children: applications to improve child survival and reduce burden of disease. *J Health Popul Nutr* 2008; 26: 356–65.
7. Abramowicz M, ed. The choice of antibacterial drugs. In: *Handbook of antimicrobial therapy*. 19th ed. New Rochelle NY: The Medical Letter, 2011: 71.
8. Khan WA, *et al.* Randomised controlled comparison of single-dose ciprofloxacin and doxycycline for cholera caused by Vibrio cholerae O1 or O139. *Lancet* 1996; 348: 296–300.
9. Roy SK, *et al.* A randomized clinical trial to compare the efficacy of erythromycin, ampicillin and tetracycline for the treatment of cholera in children. *Trans R Soc Trop Med Hyg* 1998; 92: 460–2.
10. Khan WA, *et al.* Comparison of single-dose azithromycin and 12-dose, 3-day erythromycin for childhood cholera: a randomised, double-blind trial. *Lancet* 2002; 360: 1722–7.
11. Bhattacharya MK, *et al.* Azithromycin in the treatment of cholera in children. *Acta Paediatr* 2003; 92: 676–8.
12. Saha D, *et al.* Single-dose azithromycin for the treatment of cholera in adults. *N Engl J Med* 2006; 354: 2452–62.
13. Saha D, *et al.* Single-dose ciprofloxacin versus 12-dose erythromycin for childhood cholera: a randomised controlled trial. *Lancet* 2005; 366: 1085–93.
14. Anonymous. Emergence of a unique, multi-drug resistant strain of Vibrio cholerae 01 in Bangladesh. *Health and Science Bulletin* 2005; 3: ICDDR,B. Available at: http://centre.icddrb.org/images/hsb32_Engemergence.pdf (accessed 07/04/10)
15. Anonymous. Shuck your oysters with care. *Lancet* 1990; 336: 215–16.
16. Doyle MP. Foodborne illness: pathogenic Escherichia coli, Yersinia enterocolitica, and Vibrio parahaemolyticus. *Lancet* 1990; 336: 1111–15.
17. French GL, *et al.* Antimicrobial susceptibilities of halophilic vibrios. *J Antimicrob Chemother* 1989; 24: 183–94.
18. French GL. Antibiotics for marine vibrios. *Lancet* 1990; 336: 568–9.

Escherichia coli enteritis. *Escherichia coli* is a normal intestinal commensal and member of the anaerobic Gram-negative family of bacteria the Enterobacteriaceae. However, some strains have acquired genes that enable them

to cause intestinal infection. When ingested, the following strains can cause diarrhoea:

- enteropathogenic *E. coli* (EPEC): may cause hospital nursery outbreak but is most often found in developing countries and mainly causes watery diarrhoea in infants and children
- enteroinvasive *E. coli* (EIEC): produces an invasive type of diarrhoea resembling that of *Shigella* dysentery
- enterotoxigenic *E. coli* (ETEC): is an important cause of travellers' diarrhoea and diarrhoea in infants and children (see Gastro-enteritis, p. 182.2). It is widespread in areas with poor sanitation and is a common contaminant of food and water sources. The incubation period is 1 to 3 days; the infection is usually self-limiting and lasts for less than 5 days
- enterohaemorrhagic *E. coli* (EHEC); also known as Shiga-toxin producing *E. coli* or STEC: is associated with haemorrhagic colitis, haemolytic-uraemic syndrome, and thrombotic thrombocytopenic purpura. Most outbreaks have been linked to O157:H7 strains; the incubation period is 1 to 5 days and the illness usually lasts for 4 to 10 days. Children and the elderly are at greater risk of severe disease,[1] but the illness is usually self-limiting.[2] Cases have generally been linked with the consumption of foods derived from cattle, especially undercooked beef and unpasteurised milk, although there have been outbreaks associated with the consumption of fresh vegetables and unpasteurised juices, probably as a result of faecal contamination. Person-to-person spread is also common, and direct spread from infected animals may occur. *E. coli* O157 has also been reported as a cause of epidemic haemorrhagic colitis in Africa, where it may be difficult to distinguish from shigellosis[3,4]
- enteroadherent *E. coli* (EAEC): is a cause of chronic diarrhoea in young children

As with any form of diarrhoea (p. 1808.2), fluid and electrolyte replacement is key to treatment. The use of antibacterials is controversial. Those with mild symptoms or who are improving do not need antibacterial treatment. Treatment is advised for those with prolonged symptoms, those who relapse, or those considered to be high-risk; antibacterials may also be used for outbreaks of EPEC diarrhoea in nurseries.[5] Severe EIEC infection with evidence of systemic involvement can be treated with antibacterials recommended for shigellosis (see p. 188.1).[5,6] Treatment of EHEC is generally supportive, including correcting and maintaining the fluid and electrolyte balance.[2] There is uncertainty as to whether antibacterials influence the course of enterohaemorrhagic *E. coli* infection and the development of haemolytic-uraemic syndrome[7] or thrombotic thrombocytopenic purpura;[1,2,8] the non-antibacterial treatment of these two latter complications is discussed in Plasma, under Thrombotic Microangiopathies, p. 1159.1. In the absence of conclusive evidence, most experts do not recommend the use of empirical antibacterial treatment.[5,6] Oral preparations of Vero cytotoxin-binding resins are under investigation.

1. Mead PS, Griffin PM. Escherichia coli O157:H7. *Lancet* 1998; 352: 1207–12.
2. Subcommittee of the PHLS Advisory Committee on Gastrointestinal Infections. Guidelines for the control of infection with Vero cytotoxin producing Escherichia coli (VTEC). *Commun Dis Public Health* 2000; 3: 14–23. Also available at: http://www.hpa.org.uk/cdph/issues/CDPHvol3/No1/vtec.pdf (accessed 18/08/08)
3. Isaäcson M, *et al.* Haemorrhagic colitis epidemic in Africa. *Lancet* 1993; 341: 961.
4. Paquet C, *et al.* Aetiology of haemorrhagic colitis epidemic in Africa. *Lancet* 1993; 342: 175.
5. Casburn-Jones AC, Farthing MJ. Management of infectious diarrhoea. *Gut* 2004; 53: 296–305.
6. DuPont HL. Clinical practice. Bacterial diarrhea. *N Engl J Med* 2009; 361: 1560–9.
7. Safdar N, *et al.* Risk of hemolytic uremic syndrome after antibiotic treatment of Escherichia coli O157:H7 enteritis: a meta-analysis. *JAMA* 2002; 288: 996–1001.
8. Farthing M, *et al.* The management of infective gastroenteritis in adults: a consensus statement by an expert panel convened by the British Society for the Study of Infection. *J Infect* 1996; 33: 143–52.

Necrotising enterocolitis. Necrotising enterocolitis is characterised by diffuse or focal necrosis of the ileum or colon (or both) and is one of the most common gastrointestinal emergencies in newborn infants. It mainly affects those born before 36 weeks' gestational age, with the majority of cases occurring in very low birth-weight infants (less than 1500 g). Although the pathogenesis of necrotising enterocolitis is poorly understood, there is evidence to suggest that multiple, interacting mechanisms are involved, including immaturity of the gastrointestinal tract, intestinal ischaemia, reperfusion injury with activation of proinflammatory cellular cascades, enteral feeding, and the presence of pathogenic bacterial flora in the intestine. Bacteria implicated in the disease include *Pseudomonas, Escherichia coli, Klebsiella, Salmonella* spp., and *Clostridium* spp.

Onset of illness is usually 3 to 10 days (but may range from 1 to 90 days) after birth. Necrotising enterocolitis may present as a benign illness with mild inflammation of the intestinal wall and mainly gastrointestinal symptoms, or as a catastrophic illness characterised by full-thickness intestinal necrosis with perforation, respiratory and cardiovascular collapse, metabolic acidosis, disseminated intravascular coagulopathy, grossly bloody stools, multi-system organ failure, and in some cases death. Early signs are non-specific and sepsis rather than necrotising enterocolitis may initially be suspected.

The severity of the disease is usually staged according to modified Bell's criteria and recommendations for **management** of necrotising enterocolitis are based on these criteria.[1-3] Depending on the stage of disease, necrotising enterocolitis can be treated medically and/or surgically.[1] When necrotising enterocolitis is suspected treatment involves stopping oral feeds (bowel rest), starting total parenteral nutrition, and giving parenteral antibacterials to limit bacterial invasion and translocation.[3] Antibacterials should cover aerobic and anaerobic enteric bacteria. Ampicillin (or similar penicillin derivatives) or vancomycin may be used for Gram-positive aerobic cover and an aminoglycoside (such as gentamicin) or a third-generation cephalosporin (such as cefotaxime) may be used against Gram-negative aerobes. Metronidazole or clindamycin are given for anaerobic cover.[3] If the diagnosis of necrotising enterocolitis (Bells stage II or above) is confirmed then antibacterials are continued for 7 to 14 days.[2,3]

A systematic review has concluded that *prophylactic* oral antibacterials might well reduce the incidence of necrotising enterocolitis in low birth-weight or preterm infants in a high-risk environment,[4] but there are concerns about adverse outcomes, and prophylactic use (particularly of vancomycin) is not generally recommended because of the risk of inducing resistance. It has been suggested[5] that oral immunoglobulins may prevent necrotising enterocolitis in low-birth-weight infants; however, a systematic review[6] concluded that the available evidence did not support this claim. There is, however, good evidence that supplementation with enteral probiotics reduces the risk of severe necrotising enterocolitis and death in premature infants born weighing less than 1500 g,[7,8] but there were insufficient data to determine their value in infants weighing less than 1000 g at birth.[7] Supplementation with arginine has also been investigated,[9] but there is insufficient evidence to determine its value.

Necrotising enteritis in older children and adults, known as **pigbel**, has been attributed to toxins produced by *Clostridium perfringens*. Both sporadic and epidemic forms are mainly seen in the highlands of Papua New Guinea, but sporadic cases have been reported elsewhere. Treatment is supportive with surgical intervention where necessary. A vaccine is available for prophylaxis.

1. Hall N, Pierro A. Necrotizing enterocolitis. *Hosp Med* 2004; 65: 220–5.
2. Lin PW, Stoll BJ. Necrotising enterocolitis. *Lancet* 2006; 368: 1271–83.
3. Thompson AM, Bizzarro MJ. Necrotizing enterocolitis in newborns: pathogenesis, prevention and management. *Drugs* 2008; 68: 1227–38.
4. Bury RG, Tudehope D. Enteral antibiotics for preventing necrotizing enterocolitis in low birthweight or preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2001 (accessed 16/05/05).
5. Elbl MM, *et al.* Prevention of necrotizing enterocolitis in low-birth-weight infants by IgA-IgG feeding. *N Engl J Med* 1988; 319: 1–7.
6. Foster J, Cole M. Oral immunoglobulin for preventing necrotizing enterocolitis in preterm and low birth-weight neonates. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 16/05/05).
7. Alfaleh K, Bassler D. Probiotics for prevention of necrotizing enterocolitis in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 22/04/10).
8. Deshpande G, *et al.* Updated meta-analysis of probiotics for preventing necrotizing enterocolitis in preterm neonates. *Pediatrics* 2010; 125: 921–30.
9. Shah P, Shah V. Arginine supplementation for prevention of necrotising enterocolitis in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 05/08/08).

Salmonella enteritis. *Salmonella* spp. are Gram-negative bacteria belonging to the Enterobacteriaceae family. They can be divided into:

- those causing enteric fever, namely *S. typhi* and *S. paratyphi*, where infection is systemic although affecting the gastrointestinal tract (see under Typhoid and Paratyphoid Fever, p. 214.1)
- non-typhoid *Salmonella* (NTS), including *S. enteritidis* and *S. typhimurium*, which cause acute gastro-enteritis invasive infections with bacteraemia, and localised infections, which are discussed here

NTS infection is usually transmitted through ingestion of contaminated food of animal origin, especially, beef, poultry and eggs, and dairy products. Animal-to-human transmissions can occur particularly after handling amphibians and reptiles, and outbreaks of hospital-acquired NTS have also been reported. NTS occurs worldwide; in developed countries it is usually a mild, self-limiting diarrhoeal disease that resolves in a few days without active treatment. In less developed areas NTS may cause serious invasive disease. Epidemiological data from some countries in sub-Saharan Africa indicate that it is one of the most common causes of bacteraemia in adults and children. Invasive disease is more common and symptoms most severe in the elderly, infants, people with chronic conditions such as diabetes, or those who are immunocompromised.

Gastroenteritis caused by *Salmonella* spp. is often clinically similar to that caused by other bacterial pathogens. Many patients are asymptomatic or have a mild disease. Symptoms usually begin 24 to 48 hours (range 8 to 72 hours) after infection, with fever, headache, abdominal cramps, and diarrhoea. These symptoms and possibly also nausea, loss of appetite, and vomiting, usually last for 3 to 7 days. Less than 5% of cases are complicated by *Salmonella* bacteraemia; complications of this can include endocarditis, meningitis, mycotic aneurysms, septic arthritis, and osteomyelitis.

Uncomplicated NTS enteritis is usually **managed** by fluid and electrolyte replacement (see Diarrhoea, p. 1808.2).[1,2] Antidiarrhoeal drugs are generally not recommended as they may prolong bacterial excretion.[1,2] Antibacterials have a limited role and are not usually recommended for uncomplicated cases.[1] A meta-analysis[3] of antimicrobial therapy for *Salmonella* enteritis found that antibacterial therapy produced no clinical benefit in uncomplicated disease and that it may prolong *Salmonella* detection in stools. Antibacterials may be given to those patients with severe gastroenteritis, those who are at a high risk for invasive disease, or those with proven bacteraemia.[1,2]

Drug resistance has limited the usefulness of traditional first-line empirical antibacterial agents such as benzylpenicillin, ampicillin, co-trimoxazole, chloramphenicol, tetracyclines, sulphonamides, streptomycin, and gentamicin.[2,4-6] Multiresistant R-type strains of *S. typhimurium*, including DT 104, have further limited the treatment options.[7-11] Empirical treatment with oral ciprofloxacin, oral azithromycin, or intravenous ceftriaxone is recommended although there is also increasing resistance to these antibacterials (especially ciprofloxacin).[1,4] Nalidixic acid resistance has been reported and has been shown to predict lack of response to fluoroquinolones.[2] Resistance to cephalosporins has also been recognised.[4,12-13] For patients with a recent travel history, azithromycin may therefore be the preferred first line option.[1] Carbapenems such as imipenem, meropenem, and ertapenem may be useful for multidrug resistant infections.[4]

Treatment is usually given for 3 to 7 days[1,2,4] and is often extended to 14 days in immunocompromised patients.[2] In HIV-infected adults, the CDC recommends ciprofloxacin for 7 to 14 days in those with a CD4+ T lymphocyte count of 200 cells/microlitre or more with mild gastroenteritis (with or without bacteraemia); 2 to 6 weeks treatment is recommended for those with a CD4+ T lymphocyte count of less than 200 cells/microlitre.[14] Relapses in infection have been well-documented in HIV-infected patients and recurrent *Salmonella* might require chronic suppressive therapy.[14]

Empirical treatment for patients with bacteraemia should be with both a fluoroquinolone and a third-generation cephalosporin to account for multidrug resistant organisms.[2] Monotherapy should be given once sensitivities are known;[2] third-generation cephalosporins may be used and ceftriaxone is considered appropriate for treatment of meningitis.[5,6] Bacteraemia usually needs a 7- to 14-day course of antibacterial treatment[2,6] and longer courses may be needed in those with immunosuppression.[6] Those with meningitis may need 4 weeks of treatment[6] and 6 weeks of treatment has been suggested for those with endovascular infections.[2]

Chronic carriage can be treated with amoxicillin (1 g three times daily for 3 months), co-trimoxazole (960 mg twice daily for 3 months), or ciprofloxacin (750 mg twice daily for 1 month).[2]

1. Darby J, Sheorey H. Searching for Salmonella. *Aust Fam Physician* 2008; 37: 806–10.
2. Crum-Cianflone NF. Salmonellosis and the gastrointestinal tract: more than just peanut butter. *Curr Gastroenterol Rep* 2008; 10: 424–31.
3. Sirinavin S, Garner P. Antibiotics for treating salmonella gut infections. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 1999 (accessed 16/05/05).
4. Parry CM, Threlfall EJ. Antimicrobial resistance in typhoidal and nontyphoidal salmonellae. *Curr Opin Infect Dis* 2008; 21: 531–8.
5. Morpeth SC, *et al.* Invasive non-typhi *Salmonella* disease in Africa. *Clin Infect Dis* 2009; 49: 606–11.
6. Chimalizeni Y, *et al.* The epidemiology and management of non typhoidal salmonella infections. *Adv Exp Med Biol* 2010; 659: 33–46.
7. Threlfall EJ, *et al.* Increasing spectrum of resistance in multiresistant Salmonella typhimurium. *Lancet* 1996; 347: 1053–4.
8. Anonymous. Multidrug-resistant Salmonella serotype typhimurium—United States, 1996. *JAMA* 1996; 277: 1513.
9. Anonymous. Emergence of multidrug-resistant salmonella. *WHO Drug Inf* 1997; 11: 21.
10. Threlfall EJ, *et al.* Multiresistant *Salmonella typhimurium* DT 104 and salmonella bacteraemia. *Lancet* 1998; 352: 287–8.
11. Fey PD, *et al.* Ceftriaxone-resistant salmonella infection acquired by a child from cattle. *N Engl J Med* 2000; 342: 1242–9.
12. Tzouvelekis LS, *et al.* Emergence of resistance to third-generation cephalosporins amongst Salmonella typhimurium isolates in Greece: report of the first three cases. *J Antimicrob Chemother* 1998; 42: 273–5.
13. Dunne EF, *et al.* Emergence of domestically acquired ceftriaxone-resistant *Salmonella* infections associated with AmpC β-lactamase. *JAMA* 2000; 284: 3151–6.

14. CDC. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR* 2009; 58 (RR-4): 1–207. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5804.pdf (accessed 25/04/10)

Shigellosis. Shigellosis (bacillary dysentery) is an enteric infection caused by *Shigella dysenteriae, S. flexneri, S. boydii,* or *S. sonnei* (also called groups A, B, C, and D respectively), Gram-negative bacteria belonging to the Enterobacteriaceae family. It is endemic in most of the developing world and is the most important cause of bloody diarrhoea worldwide, resulting in at least 80 million cases and an estimated 700 000 deaths each year, mainly among children under 5 years of age.[1] *S. sonnei* and *S. boydii* usually cause relatively mild disease, whereas a specific serotype of *S. dysenteriae,* Sd1 or Shiga bacillus, is the organism responsible for shigella epidemics and causes the most severe, prolonged, and potentially fatal disease. The distribution of different species varies geographically.

Shigella are spread through the fecal-oral route, and disease is commonest where there is overcrowding and poor hygiene and sanitation. Onset typically occurs 12 to 96 hours after exposure, and the illness may range from mild, self-limiting, watery diarrhoea to severe colitis and dysentery with blood and mucous in the stools. Severity depends both on the infecting organism and patient-specific factors including age and degree of malnutrition.

As with any form of diarrhoea (p. 1808.2), rehydration is the key to treatment.[2] Although most milder infections, particularly those due to *S. sonnei,* will resolve without treatment within 4 to 7 days, all cases of bloody diarrhoea should be treated promptly with an antibacterial that is effective against *Shigella.* The aim of antibacterial therapy is to speed recovery, reduce the seriousness of the disease, and decrease the length of time that patients are infective. The choice of antibacterial has changed over time as resistance to various antibacterials developed; different patterns of resistance have been reported around the world. As widespread resistance has developed to traditional first-line drugs including ampicillin, co-trimoxazole, and nalidixic acid, WHO[1] considers ciprofloxacin to be the drug of choice for empirical treatment in patients of all age groups; in adolescents and children, for whom quinolones are not routinely recommended (see Precautions, under Ciprofloxacin, p. 266.1), the benefit is thought to outweigh the risk. Fluoroquinolone resistance has been reported in some parts of the world (particularly the Indian subcontinent),[2-5] and where local strains of *Shigella* are known to be resistant, second-line antibacterials recommended by WHO include oral pivmecillinam, and parenteral ceftriaxone. Azithromycin is also recommended for second-line use in adults by WHO, and as an alternative for children by the American Academy of Pediatrics,[6] although there have been concerns regarding rapid development of resistance; *Shigella* spp. resistant to azithromycin have already been reported in Europe[7] and resistance to azithromycin and ceftriaxone in the Indian subcontinent.[8] A systematic review[9] of 16 studies (1748 subjects) to evaluate the safety and efficacy of antibacterials in the treatment of *Shigella* dysentery found limited evidence that most of the commonly used antibacterials (ampicillin, co-trimoxazole, nalidixic acid, fluoroquinolones, pivmecillinam, ceftriaxone, and azithromycin) reduced diarrhoea and the duration of fever compared with no antibacterial treatment, but insufficient evidence to recommend any specific antibacterial. To accommodate temporal and geographical shifts and antibacterial resistance in *Shigella* strains around the world, it recommended that empirical therapy should be guided by local or regional antibacterial sensitivity patterns.[9] Effective antibacterial treatment should lead to symptomatic improvement within the first 48 hours; where this does not occur, the possibility of antibacterial resistance should be considered.[1]

Vitamin A may be a useful adjunct to treatment, especially in children in developing countries who are at risk for malnutrition (see Diarrhoea, under Vitamin A, p. 2100.1).[6] Supplemental zinc, which may reduce the incidence and severity of diarrhoea both in the acute period and in the next 2 to 3 months, is also recommended for children up to 5 years of age (see Diarrhoea, under Zinc Sulfate, p. 2127.2).[1]

Oral shigella vaccines are being studied for prophylaxis.

1. WHO. *Guidelines for the control of shigellosis, including epidemics due to shigella dysenteriae type 1.* Geneva: WHO,2005. Available at http://whqlibdoc.who.int/publications/2005/9241592330.pdf (accessed 02/09/09)
2. Niyogi SK. Shigellosis. *J Microbiol* 2005; 43: 133–43.
3. Mensa L, *et al.* Quinolone resistance among Shigella spp. isolated from travellers returning from India. *Clin Microbiol Infect* 2008; 14: 279–81.
4. Sarkar K, *et al.* Shigella dysenteriae type 1 with reduced susceptibility to fluoroquinolones. *Lancet* 2003; 361: 785.
5. Sur D, *et al.* Multidrug-resistant Shigella dysenteriae type 1: forerunners of a new epidemic strain in eastern India? *Emerg Infect Dis* 2003; 9: 404–5.
6. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases,* 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.
7. Boumghar-Bourtchai L, *et al.* Macrolide-resistant Shigella sonnei. *Emerg Infect Dis* 2008; 14: 1297–9.
8. Rahman M, *et al.* Increasing spectrum in antimicrobial resistance of Shigella isolates in Bangladesh: resistance to azithromycin and ceftriaxone and decreased susceptibility to ciprofloxacin. *J Health Popul Nutr* 2007; 25: 158–67.
9. David KV, *et al.* Antibiotic therapy for Shigella dysentery. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 27/04/10).

Yersinia enteritis. *Yersinia enterocolitica* is a Gram-negative bacterium of the Enterobacteriaceae family and the species most commonly responsible for yersiniosis. *Y. enterocolitica* has been isolated in patients worldwide, but the infection appears to occur mainly in cooler climates and in some of these countries it rivals *Salmonella* and *Campylobacter* and exceeds *Shigella* as a cause of acute bacterial gastro-enteritis. Pigs are a major reservoir for *Y. enterocolitica* strains that infect humans and infection is usually transmitted by eating contaminated food, especially raw or undercooked pork products, or drinking contaminated unpasteurised milk or untreated water; transmission through blood transfusion is rare.

Infection with *Y. enterocolitica* occurs most often in young children. Symptoms usually develop 3 to 7 days after exposure and vary depending on the age of the person infected. Common symptoms in children include diarrhoea (which is often bloody), fever and abdominal pain, which last for up to three weeks or longer. Older children and adults can present with right-sided abdominal pain and fever that may be confused with appendicitis. In some patients, complications such as reactive polyarthropathy, erythema nodosum, and life-threatening bacteraemia may develop. Increased susceptibility to *Yersinia* infection has occurred in patients with iron overload treated with desferrioxamine (see p. 1547.2).

As with any form of diarrhoea (p. 1808.2), rehydration is the key to **treatment** and most forms of mild uncomplicated enteritis do not require antibacterials. However, systemic infection and bacteraemia require antibacterial treatment.[1] Reports of antibacterial susceptibility from different parts of the world indicate that *Y. enterocolitica* is susceptible to many antimicrobial agents.[1] Drugs with good intracellular activity such as trimethoprim, co-trimoxazole, tetracycline, chloramphenicol, or fluoroquinolones may be preferred.[2] Doxycycline or co-trimoxazole have been recommended[3] for complicated gastrointestinal and focal extra-intestinal infections or doxycycline and an aminoglycoside empirically in bacteraemia. Co-trimoxazole as first choice or alternatively a fluoroquinolone, an aminoglycoside, or cefotaxime have also been recommended.[4] A study[1] undertaken in a paediatric hospital in the USA to determine the antibacterial susceptibility pattern of *Y. enterocolitica* reported that susceptibility patterns of the organism had not changed over the 12-year study period. The most active agents *in vitro* were cefotaxime, ceftriaxone, cefepime, co-trimoxazole, gentamicin, tobramycin, imipenem, and ciprofloxacin; all were also considered to be clinically appropriate. Systemic cefotaxime and ceftriaxone were effective for treating bacteraemia. The majority of isolates were resistant to ampicillin and first-generation cephalosporins. Similar susceptibility patterns were reported in a study conducted in China.[5] A patient with chronic *Yersinia* infection who responded well to tetracycline or co-trimoxazole, but relapsed on withdrawal, was treated successfully with ciprofloxacin.[6]

1. Abdel-Haq NM, *et al.* Antibiotic susceptibilities of Yersinia enterocolitica recovered from children over a 12-year period. *Int J Antimicrob Agents* 2006; 27: 449–52.
2. Hoogkamp-Korstanje JAA. Antibiotics in *Yersinia enterocolitica* infections. *J Antimicrob Chemother* 1987; 20: 123–31.
3. Cover TL, Aber RC. *Yersinia enterocolitica. N Engl J Med* 1989; 321: 16–24.
4. Abramowicz M, ed. The choice of antibacterial drugs. In: *Handbook of antimicrobial therapy.* 19th ed. New Rochelle NY: The Medical Letter, 2011: 67.
5. Zheng H, *et al. Yersinia enterocolitica* infection in diarrheal patients. *Eur J Clin Microbiol Infect Dis* 2008; 27: 741–52.
6. Read RC, Barry RE. Relapsing yersinia infection. *BMJ* 1990; 300: 1694.

Gonorrhoea

See under Sexually Transmitted Diseases, p. 206.2.

Granuloma inguinale

See under Sexually Transmitted Diseases, p. 207.1.

Haemophilus influenzae infections

Haemophilus influenzae is a Gram-negative bacterium that colonises the upper respiratory tract in the majority of healthy people. Most are carriers of non-encapsulated (or nontypeable) strains, but a small proportion carry *H. influenzae* type b (Hib), the most virulent of the 6 encapsulated strains. Transmission is by close contact with an infected person or by inhalation of respiratory tract droplets. In most developed countries there has been a decrease in the rate of nasopharyngeal colonisation by Hib and in the incidence of Hib infection since the introduction and widespread use of Hib conjugate vaccine. However, Hib infection still occurs in unimmunised children or those who have not completed the childhood immunisation schedule; Hib infections are uncommon in children more than 6 years old. Hib strains cause systemic disease, the most serious being meningitis which mainly affects children less than 2 years old. Other invasive conditions include bacteraemia, cellulitis, epiglottitis, septic arthritis, and pneumonia and empyema. In developing countries pneumonia is responsible for more deaths than meningitis. Non-encapsulated strains invade the mucosal surface causing infections such as otitis media, sinusitis, and conjunctivitis and infect patients with chronic bronchitis. These strains are a common cause of community-acquired pneumonia in adults, especially those with chronic obstructive airways disease or AIDS.

Choice of treatment. For further details of these infections and their management, see under the specific disease side-headings. Ampicillin and chloramphenicol have been the antibacterials of choice against *H. influenzae,* but increasing resistance, especially to ampicillin, should be borne in mind; there have been several reports of multiresistant strains.[1-4] Parenteral cephalosporins such as ceftriaxone or cefotaxime have been found to be effective[5] and are currently preferred for serious *H. influenzae* type b infections.[6] There have been treatment failures in *H. influenzae* meningitis with cefuroxime and there is argument over its efficacy.[5] Meropenem is a further alternative.[6]

For upper respiratory infections and bronchitis caused by nontypable strains oral antibacterials may be used. About 20 to 35% of these strains are resistant to ampicillin and some experts suggest co-trimoxazole (or trimethoprim in the UK) as the preferred antibacterial; ampicillin, amoxicillin (with or without clavulanic acid), oral second- or third-generation cephalosporins, a tetracycline, a fluoroquinolone, or the macrolides azithromycin or clarithromycin are suggested alternatives.[6]

Prophylaxis. Immunisation is the most effective way of preventing Hib in infants and children and vaccination is included in the infant immunisation schedules in some developing and most developed countries including the UK and USA. However, there are no vaccines available for the prevention of disease caused by nontypable *H. influenzae.* For further information on haemophilus influenzae vaccines see p. 2387.2.

Young children who develop invasive Hib disease have a low but significant risk of a second episode of Hib infection and are also more likely to become asymptomatic carriers and transmit the organism to others. Household contacts of index cases, especially young children and those with underlying medical problems such as immunosuppression and asplenia, are also at increased risk of developing invasive Hib disease. Recommendations for the prevention of secondary Hib disease have been made[7,8] and usually include chemoprophylaxis with rifampicin (or alternatively ceftriaxone) for the index case and for close contacts of the index case. For further information on chemoprophylaxis see Meningitis Prophylaxis, under Uses and Administration of Rifampicin, p. 353.2.

1. Sturm AW, *et al.* Outbreak of multiresistant non-encapsulated Haemophilus influenzae infections in a pulmonary rehabilitation centre. *Lancet* 1990; 335: 214–16.
2. Brightman CAJ, *et al.* Family outbreak of chloramphenicol-ampicillin resistant Haemophilus influenzae type b disease. *Lancet* 1990; 335: 351–2.
3. Barclay K, *et al.* Multiresistant Haemophilus influenzae. *Lancet* 1990; 335: 549.
4. Scott GM, *et al.* Outbreaks of multiresistant Haemophilus influenzae infection. *Lancet* 1990; 335: 925.
5. Powell M. Chemotherapy for infections caused by Haemophilus influenzae: current problems and future prospects. *J Antimicrob Chemother* 1991; 27: 3–7.
6. Abramowicz M, ed. The choice of antibacterial drugs. In: *Handbook of antimicrobial therapy.* 19th ed. New Rochelle NY: The Medical Letter, 2011: 69.
7. DoH, Public Health England. Revised recommendations for the prevention of secondary Haemophilus influenzae type b (Hib) disease (updated 1 July, 2013). Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/231009/Revised_recommendations_for_the_preventions_of_secondary_Haemophilus_influenzae_type_b_disease.pdf (accessed 11/09/13)
8. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases,* 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Helicobacter pylori infections

Antibacterial therapy is used to eradicate *Helicobacter pylori* infection in peptic ulcer disease (p. 1816.2) and MALT lymphoma of the stomach (p. 698.1). The role of *H. pylori* and the value of its eradication in dyspepsia (p. 1809.3) and gastro-oesophageal reflux disease (p. 1810.2) is less clear.

Infections in immunocompromised patients

Patients with a defective immune system are at increased risk of infection. Primary immune deficiency is rare, whereas secondary deficiency is more common: immunosuppressive therapy, cancer and its treatment, HIV infection, or splenectomy may cause neutropenia and

impaired humoral and cellular immunity in varying degrees. The risk and severity of infections depends upon the duration of compromised immunity, the degree to which immune function is compromised, whether cellular or humoral functions are affected, and upon breaches in physical barriers, for example due to severe mucositis or prolonged vascular access. Thus patients with profound neutropenia or a history of splenectomy are prone to rapidly progressive and potentially life-threatening infections; those with neutropenia induced by cytotoxic chemotherapy or by preparation for transplantation are particularly vulnerable to acute infections whereas those in whom immunosuppression results from viral infections or congenital defects are at lower risk of acute infections.[1] Patients in whom neutropenia persists for more than 10 days are not only at risk of opportunistic bacterial infections but also susceptible to viral, fungal, and parasitic infections.

Infectious diseases are a major cause of morbidity and mortality in patients with AIDS (see HIV-associated Infections and Complications, p. 960.3). Some are due to common pathogens, but others are opportunistic and are caused by normally avirulent commensals. Children with HIV infection appear to be at special risk of serious bacterial infections with common encapsulated bacteria. For further reference to some bacterial infections associated with AIDS, see Gastro-enteritis (p. 182.2), Nontuberculous Mycobacterial Infections (p. 196.1), and Tuberculosis (p. 212.2). Detailed guidelines for the prevention and treatment of opportunistic infections (including some bacterial infections) among HIV-infected adults, adolescents, and children have been developed in the USA.[2,3] Fungal, protozoal, and viral infections which can affect immunocompromised patients are discussed in the relevant chapters under Infections in Immunocompromised Patients, p. 566.2, p. 923.3, and p. 962.2, respectively.

Reports from Europe and the USA show that over the past few decades there has been a shift in the occurrence of bacteraemia in febrile neutropenic patients from Gram-negative organisms to Gram-positive organisms.[4] Factor influencing this change include changes in clinical practice such as the use of central venous catheters, changes in antibacterial use, and antibacterial resistance; when antibacterial prophylaxis is given, local resistance patterns have been shown to affect the aetiology of infections.[4]

TREATMENT. Onset of fever in neutropenic patients is indicative of potentially serious infection that may progress to septicaemia and death. The severity of infections depends on many factors (see above) and it is therefore difficult to produce a standard drug regimen; in addition, the choice of empirical therapy must be adapted according to prevailing local antibacterial susceptibility patterns. Guidelines have been produced in many countries, of which those issued by the Infectious Diseases Society of America[5] for both the initial and subsequent management of febrile neutropenic patients are fairly typical:

- empirical antibacterial therapy should be given promptly to all neutropenic patients at the onset of fever; afebrile neutropenic patients who show signs and symptoms compatible with infections should also receive empirical antibacterial treatment
- consideration should be given to whether the patient requires vancomycin therapy. If so, treatment should begin with vancomycin plus cefepime, ceftazidime, or a carbapenem, with or without an aminoglycoside.
- if vancomycin is not indicated, intravenous monotherapy should be given with
  - either a cephalosporin (cefepime, although concerns have been raised about its safety,[6] or ceftazidime) or a carbapenem (imipenem-cilastatin or meropenem) for uncomplicated cases
  - in more complicated cases, or where resistance is a problem, combined treatment should be given with an aminoglycoside and one of cefepime, ceftazidime, a carbapenem, or an antipseudomonal penicillin such as ticarcillin with clavulanic acid or piperacillin with tazobactam.
- low-risk patients may be treated empirically either orally with ciprofloxacin and amoxicillin with clavulanic acid, or intravenously as for uncomplicated cases above. Initial treatment with oral antibacterials alone is, however, not recommended for children[5]

The initial regimen usually needs to be given for 3 to 5 days in order to determine its efficacy. In *patients in whom fever resolves* and in whom a causative organism is identified, antibacterial treatment should be modified for the specific organisms and broad-spectrum antibacterials continued for at least 7 days or until culture results are negative and the patient has clinically recovered.[5] In afebrile patients in whom no causative organism is found but who were considered at high risk at the onset of treatment, the same antibacterials should be continued intravenously; those considered at low risk initially may be switched to oral therapy with ciprofloxacin plus either amoxicillin-clavulanic acid (adults) or cefixime (children).[5]

Patients in whom fever persists throughout the first 3 to 5 days but for whom no aetiology is determined may have a non-bacterial infection, a bacterial infection that is refractory to treatment, the emergence of a second infection, or drug fever.[5] Such patients should be reassessed and then one of three options followed. If the patient's condition is clinically stable, the same antibacterial treatment may be continued; if there is still no change in the patient's condition, consideration should be given to stopping vancomycin if it has been given. Alternatively, if there is evidence of progressive disease or drug toxicity, the antibacterials given may be changed; if vancomycin has not been given, it may be added to the regimen. The third option is to add an antifungal drug (amphotericin B) with or without a change to the antibacterial regimen if the patient is febrile through days 5 to 7 and resolution of neutropenia is not imminent.[5]

The optimum *duration of therapy* is governed by the clinical situation. The most important determinant of successfully stopping antibacterials is the neutrophil count:[5]

- if no infection is identified after day 3, the neutrophil count exceeds 500 cells/mm^3 for 2 consecutive days, and the patient has been afebrile for at least 48 hours, then antibacterial treatment may be stopped
- if neutropenia persists in the absence of fever, it is reasonable to stop antibacterial treatment after 5 to 7 days in patients who were initially considered at low risk and who are clinically well, though such patients should be closely monitored and intravenous antibacterials reinstigated immediately on recurrence of fever or evidence of infection.[5] In afebrile patients with profound neutropenia (less than 100 cells/mm^3), or in those with mucositis or other risk factors, continuous antibacterial treatment should be considered throughout the entire neutropenic period
- in patients with persistent fever and prolonged neutropenia in whom haematological recovery cannot be anticipated, consideration may be given to stopping antibacterials after 2 weeks if no infection has been identified and careful observation is possible.[5]
- clinically well patients with persistent fever may have their antibacterials stopped after 4 to 5 days if the neutrophil count remains at least 500 cells/mm^3 throughout this period and there is no sign of infection and no response to therapy; such patients should be closely monitored for subsequent infections which are usually easily treatable, and empirical amphotericin B should be considered despite cessation of antibacterials if fever persists for 5 to 7 days after the start of initial therapy[5]
- patients who remain febrile after recovery from neutropenia and despite broad-spectrum antibacterials should be reassessed for undiagnosed infection which may be fungal, mycobacterial, or viral

The routine use of colony-stimulating factors as an adjunct to antibacterial treatment is not generally recommended[5] but may be indicated in febrile neutropenic patients at high risk of serious infections or infection-related complications; examples include some patients with malignant neoplasms[7,8] and those with persistent severe neutropenia and infections that are not responsive to antibacterials alone.[5] A systematic review[9] of the use of colony-stimulating factors in patients with febrile neutropenia due to cancer chemotherapy concluded that their use did not affect overall mortality but did reduce time spent in hospital and the neutrophil recovery time.

PROPHYLAXIS. Most infections in immunocompromised patients are caused by organisms from their own alimentary tract and in cancer patients, for example, may follow chemotherapy-induced mucosal damage to the tract. Several prophylactic strategies have been used to try to reduce the risk of infection during severe neutropenia, such as isolation of the patient, granulocyte transfusion, active or passive immunisation, acceleration of granulocyte recovery, and antibacterial prophylaxis. Possible antibacterial prophylactic regimens have included selective decontamination of the alimentary tract using oral nonabsorbable antibacterials (see also under Intensive Care, p. 189.3) or treatment with absorbable antibacterials (most commonly a fluoroquinolone or co-trimoxazole). A systematic review of 101 randomised, controlled, studies in 12 599 afebrile neutropenic patients (mostly with leukaemia) found that antibacterial prophylaxis significantly decreased the risk of death from all causes by 34% when compared with no intervention; the most significant reduction in mortality was associated with the use of fluoroquinolones.[10]

Although antibacterial prophylaxis is also effective in afebrile patients likely to be neutropenic, the efficacy of empirical treatment means that prophylaxis is less widely used[11] and the Infectious Diseases Society of America[5] discourages routine use; reasons include toxicity of the antibacterial, potential fungal overgrowth, and problems of bacterial resistance.

Immunocompromised patients may benefit from appropriate immunisation against common infections, although precautions relating to the use of live vaccines in such patients should be observed (p. 2375.2).

The duration and severity of neutropenia can be reduced by the use granulocyte or granulocyte-macrophage colony-stimulating factors, and this may be a useful adjunct in infection control in selected patients.[7] Bone marrow protective agents such as amifostine are also being studied.

1. Pizzo PA. Fever in immunocompromised patients. *N Engl J Med* 1999; 341: 893–900.
2. CDC. Guidelines for the prevention and treatment of Opportunistic infections among HIV-exposed and HIV-infected children: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. *MMWR* 2009; 58 (RR-11): 1–166. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5811.pdf (accessed 10/05/10)
3. CDC. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR* 2009; 58: (RR-4): 1–207. Also available at http://www.cdc.gov/mmwr/pdf/rr/rr5804.pdf (accessed 10/05/10)
4. Ramphal R. Changes in the etiology of bacteremia in febrile neutropenic patients and the susceptibilities of the currently isolated pathogens. *Clin Infect Dis* 2004; 39 (suppl 1): S25–S31.
5. Hughes WT, *et al.* Infectious Diseases Society of America. 2002 Guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis* 2002; 34: 730–51. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/339215 (accessed 18/08/08)
6. Paul M, *et al.* Empirical antibiotic monotherapy for febrile neutropenia: systematic review and meta-analysis of randomized controlled trials. *J Antimicrob Chemother* 2006; 57: 176–89.
7. Smith TJ, *et al.* American Society of Clinical Oncology. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol* 2006; 24: 3187–3205. Also available at: http://www.jco.org/cgi/reprint/JCO.2006.06.4451v2.pdf (accessed 18/08/08)
8. Aapro MS, *et al.* European Organisation for Research and Treatment of Cancer (EORTC) Granulocyte Colony-Stimulating Factor (G-CSF) Guidelines Working Party. EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphomas and solid tumours. *Eur J Cancer* 2006; 42: 2433–53.
9. Clark OAC, *et al.* Colony stimulating factors for chemotherapy induced febrile neutropenia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 16/05/05).
10. Gafter-Gvili A, *et al.* Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 10/05/10).
11. Kerr KG. The prophylaxis of bacterial infections in neutropenic patients. *J Antimicrob Chemother* 1999; 44: 587–91.

Intensive care

Like immunocompromised patients (p. 186.3), those in intensive care units (ICUs) are often very susceptible to endogenous infections, especially respiratory and urinary-tract infections, arising from gastrointestinal colonisation by aerobic Gram-negative bacilli acquired in hospital. The incidence of pneumonia in ICU patients ranges from 7 to more than 40%,[1] and mortality from ventilator-associated pneumonia may exceed 30 to 50%.[2,3] For further information on ventilator-associated pneumonia see under Pneumonia, p. 202.1.

Selective decontamination regimens aim to reduce this risk by eliminating potentially pathogenic organisms from the throat and intestines while preserving the indigenous, mostly anaerobic, flora.[4]

- selective decontamination of the digestive tract (SDD), uses non-absorbable antibacterials given orally and through a nasogastric tube; in some studies systemic antibacterials (usually cephalosporins) were added in the first 4 days of the ICU stay to prevent early infections
- selective oropharyngeal decontamination, (SOD) uses topical oral application of antibacterials or antiseptics, such as chlorhexidine gluconate or povidone-iodine

In an initial report[5] in 1984 SDD reduced the incidence of nosocomial infection from 81 to 16% in a group of multiple trauma patients. Since then further studies have been done to evaluate the efficacy of SDD in ICU patients. While results showed that SDD reduced infection-related morbidity, its effect on mortality was not clear. Furthermore other outcomes, such as beneficial effects on duration of ventilation, ICU or hospital stay, and cost-efficacy were also uncertain.[6] Selection of antibacterial resistance is considered a serious adverse effect[6] and the preventive effects of SDD have been considerably lower in ICUs with high endemic levels of antibacterial drug resistance.[7] SOD may therefore be an attractive option because the antiseptics and antibacterials used have a low potential for induction and selection of antibacterial resistance.[8] A systematic review and meta-analysis[3] of 11 randomised controlled studies (up until May 2006) suggested that in mechanically ventilated patients, antiseptic SOD prophylaxis reduced the incidence of ventilator-associated pneumonia; but no firm conclusions could be made on the effect of antibacterial SOD. Neither of the two oral decontamination regimens appeared to affect mortality, duration of mechanical ventilation, or stay in the ICU. A later meta-analysis[1] of 36 randomised controlled studies (published up until March 2009 and involving 6914 patients) assessed the effect of prophylactic antibacterial regimens for the

prevention of respiratory-tract infections and overall mortality in adults receiving intensive care. It found that a combination of topical and systemic prophylactic antibacterials reduced respiratory-tract infections and overall mortality; treatment based on topical prophylaxis alone reduced respiratory infections but not mortality. A large, multicentre study[9] conducted in 13 ICUs using cluster randomisation showed that the use of either SOD or SDD was associated with improved mortality in critically ill adults.

The risk of antibacterial resistance was evaluated in only one study[1,10] This prospective, randomised, controlled study of 934 patients admitted to a surgical and medical ICU compared a SDD regimen with a control group receiving standard treatment.[10] Colonisation with Gram-negative bacteria resistant to ceftazidime, ciprofloxacin, imipenem, colistin, or tobramycin occurred in 16% of SDD patients and in 26% of those in the control group. No patient in either group was colonised with MRSA, while 1% of all patients were colonised with vancomycin-resistant enterococcus.

Although SDD reduces hospital-acquired pneumonia, US guidelines discourage routine antibacterial prophylaxis,[7,11] especially in hospital settings where there are high levels of antibacterial resistance,[7] and particularly in relation to prevention of nosocomial pneumonia.[11] CDC guidelines do, however, recommend topical oral chlorhexidine gluconate 0.12% during the perioperative period only for adults undergoing cardiac surgery.[7]

Another potential source of infection in intensive care is from the use of **intravascular catheters**. Catheter-related bloodstream infections occur in 3 to 10% of patients with inserted catheters[12,13] and are a leading cause of nosocomial bloodstream infection in ICUs.[13] Most serious catheter-related infections are associated with central venous catheters.[14] Conditions that compromise host defences (including severe burns and malnutrition), severe sepsis, or severe and sustained multiple organ dysfunctions are associated with a higher risk of catheter-related bloodstream infections.[15] Colonisation of the catheter tip due to migration of skin organisms from the insertion site into the cutaneous catheter tract is the most common route of infection for short-term central venous catheters.[13,15] For long-term catheters (those staying in place more than 15 days), colonisation is mainly due to manipulation of the venous line with migration of organisms along the internal lumen of the catheter.[13,15] The ability of organisms to adhere to host proteins such as fibronectin that commonly build up on catheter tips, makes colonisation easier.[13,15] The organisms implicated most often are coagulase-negative staphylococci;[13,14] other organisms commonly involved include *Staphylococcus aureus, Candida* spp., *Enterococci*, and Gram-negative bacilli.[13]

Guidelines for the **prevention** of infection associated with both peripheral intravascular and central venous catheterisation have been developed.[14,16-18] Prevention and control of infection involves several interventions, which should be used in combination.[13-15,19] Intervention measures include:

- barrier precautions at the time of catheter insertion
- disinfection of the skin at the insertion site with chlorhexidine or alternatively povidone-iodine
- the use of catheters impregnated with antibacterial (usually rifampicin or minocycline) or antiseptic agents (commonly chlorhexidine or silver sulfadiazine)
- use of good aseptic technique and hand hygiene (see p. 1733.1) when accessing or maintaining the catheter system

Antibacterial prophylaxis has not been shown to reduce the rate of infection when given during catheter insertion,[13,15] but when antibacterials were given with a central venous catheter in place, risks for catheter colonisation and bloodstream infections were significantly reduced.[13] However, the use of prophylactic antibacterials is discouraged because of concern over the emergence of resistant organisms.[18,19] Antibacterial ointments (such as bacitracin, mupirocin, neomycin, and polymyxin B) or antiseptic ointments applied to catheter-insertion sites increase the rate of catheter colonisation by fungi, promote the emergence of antibacterial-resistant bacteria, and have not been shown to decrease the rate of infections.[13] Studies suggest that anticoagulants such as heparin and low-molecular-weight heparins are able to decrease fibrin sheath and thrombus formation around the catheter and in so doing reduce catheter-related infections.[15,20] Routine replacement of short-term catheters as a means to reduce infection rates is not recommended.[13,18]

Guidelines for the diagnosis and **management** of intravascular catheter-related infections have been developed by experts in the USA.[21] Antibacterials for catheter-related infections are often given empirically and the choice of drug should take into account local antibacterial susceptibility data and the severity of disease, and should usually cover coagulase-negative staphylococci. Empirical therapy with vancomycin is generally recommended where there is a high prevalence of MRSA. Daptomycin may be given as an alternative if isolates have vancomycin MIC values greater than 2 micrograms/mL. Linezolid is not recommended for empirical therapy.[21] For empirical treatment of infection thought to be caused by Gram-negative bacilli, a fourth-generation cephalosporin, carbapenem, or combinations of a beta lactam and beta-lactamase inhibitor, with or without an aminoglycoside is recommended; combination antibacterial treatment should be given when multidrug-resistant Gram-negative bacilli (such as *Pseudomonas aeruginosa*) are suspected in neutropenic or severely ill patients with sepsis, or in those known to be colonised with such pathogens.[21]

Antibacterial treatment can be stopped after 10 to 14 days if a response is seen within 2 to 3 days. A longer treatment duration of 4 to 6 weeks is recommended for patients with persistent fungaemia or bacteraemia after catheter removal, for patients who are found to have infective endocarditis or suppurative thrombophlebitis, and for paediatric patients with osteomyelitis; 6 to 8 weeks of treatment are recommended for adults with osteomyelitis.[21]

1. Liberati A, *et al.* Antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving intensive care. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 04/05/10).
2. Kollef MH. The prevention of ventilator-associated pneumonia. *N Engl J Med* 1999; **340**: 627–34. Correction. *ibid.*; **341**: 294.
3. Chan EY, *et al.* Oral decontamination for prevention of pneumonia in mechanically ventilated adults: systematic review and meta-analysis. *BMJ* 2007; **334**: 889.
4. Krueger WA, Unertl KE. Selective decontamination of the digestive tract. *Curr Opin Crit Care* 2002; **8**: 139–44.
5. Stoutenbeek CP, *et al.* The effect of selective decontamination of the digestive tract on colonisation and infection rate in multiple trauma patients. *Intensive Care Med* 1984; **10**: 185–92.
6. Bonten MJM, *et al.* Selective decontamination of the digestive tract: all questions answered? *Crit Care* 2003; **7**: 203–5.
7. American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005; **171**: 388–416. Also available at: http://www.thoracic.org/sections/publications/statements/pages/mtpi/guide1-29.html (accessed 25/05/06)
8. Koeman M, *et al.* Oral decontamination with chlorhexidine reduces the incidence of ventilator-associated pneumonia. *Am J Respir Crit Care Med* 2006; **173**: 1348–55.
9. de Smet AMGA, *et al.* Decontamination of the digestive tract and oropharynx in ICU patients. *N Engl J Med* 2009; **360**: 20–31.
10. de Jonge E, *et al.* Effects of selective decontamination of digestive tract on mortality and acquisition of resistant bacteria in intensive care: a randomised controlled trial. *Lancet* 2003; **362**: 1011–6.
11. CDC. Guidelines for preventing health-care–associated pneumonia, 2003: recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee. *MMWR* 2004; **53** (RR-3): 1–36. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5303.pdf (accessed 07/05/10)
12. Bhutta A, *et al.* Reduction of bloodstream infections associated with catheters in paediatric intensive care unit: stepwise approach. *BMJ* 2007; **334**: 362–5.
13. Frasca D, *et al.* Prevention of central venous catheter-related infection in the intensive care unit. *Crit Care* 2010; **14**: 212.
14. O'Grady NP, *et al.* Guidelines for the prevention of intravascular catheter-related infections. *MMWR* 2002; **51**(RR-10): 1–29. Correction. *ibid.*; **51**: 711. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5110.pdf (accessed 12/07/04)
15. Timsit JF. Diagnosis and prevention of catheter-related infections. *Curr Opin Crit Care* 2007; **13**: 563–71.
16. DoH. Guidelines for preventing infections associated with the insertion and maintenance of central venous catheters. *J Hosp Infect* 2001; **47** (suppl): S47–S67. Also available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4005817?IdcService=GET_FILE&dID=140806&Rendition=Web (accessed 07/05/10)
17. NICE. Infection control: prevention of healthcare-associated infections in primary and community care (June 2003). Section 5: central venous catheterisation. Available at: http://www.nice.org.uk/nicemedia/pdf/Infection_control_fullguideline.pdf (accessed 07/05/10)
18. Bishop L, *et al.* Guidelines on the insertion and management of central venous access devices in adults. *Int J Lab Hematol* 2007; **29**: 261–78.
19. McGee DC, Gould MK. Preventing complications of central venous catheterization. *N Engl J Med* 2003; **348**: 1123–33.
20. Abdelkefi A, *et al.* Randomized trial of prevention of catheter-related bloodstream infection by continuous infusion of low-dose unfractionated heparin in patients with hematologic and oncologic disease. *J Clin Oncol* 2005; **23**: 7864–70.
21. Mermel LA, *et al.* Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009; **49**: 1–45. Correction. *ibid.* 2010; **50** 457.

Legionnaires' disease

Legionella pneumophila is an aerobic, Gram-negative bacterium that was first identified in 1977 as the result of an outbreak of severe pneumonia at a convention of the American Legion. Legionnaires' disease is the pneumonic form of the infection and is a relatively common cause of community acquired pneumonia (see p. 202.1); non-pneumonic infection (called Pontiac fever) is a milder, usually self-limiting, flu-like illness. Legionellosis has been suggested as a broad term to cover pneumonic and non-pneumonic clinical syndromes caused by any *Legionella* spp., which may include *L. bozemanii, L. micdadei* (Pittsburgh pneumonia agent), and *L. wadsworthii*. These bacteria are found worldwide in the environment and particularly in warm water and warm damp places. Infection is usually transmitted by aerosolisation or aspiration. Serious outbreaks have been associated with infected air-conditioning systems or water supplies. Older adults, smokers, and immunocompromised people are particularly susceptible to Legionnaires' disease. Symptoms usually begin 2 to 14 days after being exposed to the bacteria and are similar to other forms of pneumonia. The severity of disease ranges from a mild cough to a rapidly progressive pneumonia with respiratory failure, shock, and multi-organ failure.

The mortality rate from Legionnaires' disease is dependent on the severity of the disease, the appropriateness of initial antibacterial treatment, the setting where infection was acquired, and host factors. In untreated immunocompromised patients the mortality rate may be 40 to 80%; if treated appropriately this decreases to 5 to 30%. For immunocompetent patients the mortality rate is about 10 to 15%. The usual **treatment** for mild to moderate *Legionella* infections is with an oral macrolide, with erythromycin now increasingly replaced by azithromycin;[1,2] clarithromycin, roxithromycin, or telithromycin may be further acceptable alternative macrolides.[1,2] Oral fluoroquinolones (such as ciprofloxacin, levofloxacin, or moxifloxacin) are also increasingly recommended as alternatives to the macrolides.[1-3] Doxycycline or co-trimoxazole are further alternatives.[1,2,4] For severe infections or in immunocompromised patients parenteral therapy (if available) with azithromycin, clarithromycin, or a fluoroquinolone is recommended.[1,2] Combination intravenous treatment with erythromycin and rifampicin has also been used for severe infections.[2] Rifampicin has also been given with fluoroquinolones or doxycycline, especially in severe or deteriorating illness or in immunocompromised patients, although this may be of little further benefit.[2] Generally about 7 to 10 days of treatment should be given to those with mild to moderate infections, while those with more severe infections, multisystem disease, or who are immunocompromised should be treated for up to 21 days.[1,2] However, patients treated with oral azithromycin may only need 3 to 5 days treatment due to its long half-life and tissue retention.[1,2]

1. Roig J, Rello J. Legionnaires' disease: a rational approach to therapy. *J Antimicrob Chemother* 2003; **51**: 1119–29.
2. Amsden GW. Treatment of Legionnaires' disease. *Drugs* 2005; **65**: 605–14.
3. Diederen BMW. Legionella spp. and Legionnaires' disease. *J Infect* 2008; **56**: 1–12.
4. Abramowicz M, ed. The choice of antibacterial drugs. In: *Handbook of antimicrobial therapy*. 19th ed. New Rochelle NY: The Medical Letter, 2011: 70.

Leprosy

Leprosy (Hansen's disease) is a chronic disease caused by the bacillus, *Mycobacterium leprae;* it has a prolonged incubation period (years) and slow onset of symptoms. Disease results from bacillary infiltration of the peripheral nervous system, skin, eyes, respiratory mucosa, bones, and testes. It is not highly infectious and transmission requires both prolonged close contact with an infected patient and an inherent immunological susceptibility to the disease in the exposed person. Clinical leprosy may be regarded as a consequence of deficient cell-mediated immunity in susceptible individuals; most individuals are naturally immune, and symptoms are suppressed. The clinical manifestations depend on the bacillary load and the host's immune response to the mycobacterium. Patients with leprosy may be classified as having:

- **Multibacillary** (or lepromatous) leprosy, which occurs when cellular immunity is largely deficient, and includes the sub-groups lepromatous (LL), borderline lepromatous (BL), and midborderline leprosy (BB), as well as any other types giving a positive skin smear for acid-fast bacilli. Generally the lepromin test (p. 2543.3) is negative.
- **Paucibacillary** (or tuberculoid) leprosy, which results when cellular immunity is only partially deficient, and includes the sub-groups borderline tuberculoid (BT), tuberculoid (TT), and indeterminate leprosy (I) when the skin smear is negative. Generally the lepromin test is positive.

For the purpose of treatment, WHO classifies patients with more than 5 skin lesions as having multibacillary leprosy, and those with 1 to 5 skin lesions as having paucibacillary leprosy. The use of this clinical classification avoids the necessity to provide facilities for bacteriological examination of skin smears.

Changes in the hosts immune response to the mycobacteria may result in **lepra reactions** and unless treated these may lead to severe nerve and tissue damage.[1] Most reactions belong to one of two main types:

- **Type 1** lepra reactions, or reversal reactions, are caused by spontaneous increases in T-cell reactivity to mycobacterial antigens (type IV hypersensitivity) and occur in patients with borderline forms of leprosy. These reactions are characterised by erythema and oedema of the skin and tenderness of peripheral nerves. Prompt treatment with corticosteroids is necessary to prevent permanent nerve damage.[2-5] Treatment is usually continued for 3 to 6 months. Adding azathioprine may

permit the use of lower cumulative doses of corticosteroid.[6] Methotrexate was found to be effective in treating a patient intolerant to corticosteroids,[7] while ciclosporin is considered to be effective for chronic neuritis.[2,8] Prophylactic use of low-dose corticosteroids during the first 4 months of standard multidrug treatment for leprosy has also been investigated, and found to decrease the number of reactional episodes by 75%; but the protective effect was lost by the end of 12 months.[9]

- Type 2 lepra reactions, also known as erythema nodosum leprosum (ENL), represent a systemic inflammatory response (type III hypersensitivity) to dead bacteria and are accompanied by high levels of circulating tumour necrosis factor alpha (TNF α). This reaction occurs only in patients with borderline lepromatous or lepromatous leprosy. Mild type 2 reactions may be treated with anti-inflammatories but moderate or severe reactions should be treated with corticosteroids or thalidomide (in males and post menopausal women).[2-4] The incidence and severity of ENL has decreased since the inclusion of clofazimine in multidrug regimens, probably owing to the drug's anti-inflammatory action.[2] Clofazimine does not act as rapidly as either corticosteroids or thalidomide, nor is it as effective.[2] However, clofazimine may be used with a corticosteroid in patients with severe ENL who are not responding adequately to treatment with corticosteroids alone or when the risk of toxicity with corticosteroids is high; it may be given alone when corticosteroids are contra-indicated.[10] Other TNF α inhibiting drugs that have been tried include pentoxifylline[5,11] and infliximab.[12] Chloroquine has also been used with limited effect.[1] Antileprotic drug therapy is generally continued during lepra reactions.

Although measures to manage the consequences of nerve damage and lepra reactions are an important part of the management of leprosy, curative antibacterial therapy is the mainstay of **treatment**. Dapsone monotherapy, long the basis of this, has been replaced since the 1980s with multidrug oral regimens designed to overcome the development of resistance. Dapsone, rifampicin, and clofazimine form the elements of the standard combinations.[5,13] Newer alternatives include clarithromycin, minocycline, and fluoroquinolones such as ofloxacin, moxifloxacin, and pefloxacin. These may be used as second-line therapy for patients unable to tolerate dapsone or clofazimine. Ethionamide or protionamide have been used in light-skinned patients to avoid clofazimine's tendency to pigment the skin, but are no longer recommended because of their risk of hepatotoxicity.

The most widely used multidrug regimens are those recommended by WHO[10] and in these the choice of drugs and length of treatment are based on the clinical classification outlined above.

- MULTIBACILLARY LEPROSY

The standard regimen recommended by WHO for multibacillary leprosy is rifampicin 600 mg and clofazimine 300 mg both given once a month, with clofazimine 50 mg and dapsone 100 mg both daily. Treatment is continued for 12 months.[4,10]

A 2-year treatment duration was chosen originally because it is highly effective in the majority of cases and avoids the need to assess response with skin smears. However, such a long treatment duration is an obstacle to implementing treatment programmes in areas where healthcare is inaccessible or the infrastructure is poor. Ongoing clinical studies and experience with patients defaulting from treatment have encouraged WHO to now recommend that treatment for 12 months is adequate.[4] Early hopes that reducing duration of treatment to as little as one month would be possible have not been supported by a study using daily rifampicin and ofloxacin.[14]

In patients for whom rifampicin is unsuitable because of resistance or intolerance, WHO recommends[10] daily treatment with clofazimine 50 mg, ofloxacin 400 mg, and minocycline 100 mg for the first 6 months; treatment is then continued for at least a further 18 months with clofazimine plus either minocycline or ofloxacin.

If the toxic effects of dapsone are severe, it should be stopped and treatment continued with rifampicin and clofazimine in the standard dosage for 12 months.[10]

Rifampicin 600 mg, ofloxacin 400 mg, and minocycline 100 mg (ROM) given once a month for 24 months was found to be as effective as the WHO standard regimen given for 24 months[15] and has been suggested as an alternative regimen, particularly for those who cannot take clofazimine.[3,10]

- PAUCIBACILLARY LEPROSY

The WHO recommended regimen[4,10] for paucibacillary leprosy is rifampicin 600 mg monthly and dapsone 100 mg daily. Treatment is continued for 6 months. If there are severe toxic effects with dapsone it should be substituted with clofazimine 300 mg monthly and 50 mg daily for 6 months.[10]

On the basis of a clinical study[16] showing that a single dose each of rifampicin 600 mg, ofloxacin 400 mg, and minocycline 100 mg given together is only slightly less effective than standard multidrug treatment, WHO has suggested that this is a suitable alternative for patients with single-lesion paucibacillary leprosy.[3] However, reservations have been expressed about the study, including concerns regarding the short follow-up[17] and poor microbiological rationale.[18]

- RELAPSE

Relapse after a recommended course of multidrug therapy for multibacillary or paucibacillary leprosy can occur and WHO recommends re-treatment with the initial regimen.[3,4] Although the relapse rate after standard multidrug therapy for multibacillary leprosy is generally low,[3,19] there is insufficient information on the long-term efficacy of shorter treatment courses.[14]

- PREGNANCY

Standard multidrug therapy is safe during pregnancy.[4,5] Leprosy patients who are pregnant or breast feeding may experience clinical deterioration and, in general, antileprotic therapy is continued in such patients.

- PROPHYLAXIS

Leprosy is spread from person to person through respiratory droplets, so household contacts may become infected. A systematic review and meta-analysis[20] has concluded that prophylaxis, usually with dapsone, in some household contacts may prevent disease in this high-risk group. A large randomised placebo-controlled study[21] found that a single dose of rifampicin given to contacts of new patients with leprosy significantly reduced the incidence of developing leprosy in the first 2 years but no difference was noted beyond 2 years. WHO[3] suggests that contacts of newly diagnosed cases should be examined for evidence of leprosy and then advised how to watch for early signs of the disease; prophylaxis with rifampicin or other antileprotics is not recommended in leprosy control programmes. BCG vaccine appears to be protective. Vaccines specifically against leprosy are under investigation.

- ELIMINATION

The multidrug therapy regimens recommended by WHO have been widely implemented in recent years raising the possibility of eliminating leprosy as a public health problem: that is, reducing the prevalence to less than 1 case per 10 000 population in endemic areas. Considerable progress towards this target has been made, and it was announced in 2001 that the global level of leprosy had decreased by over 90%. Full control of leprosy, however, has still not been attained in several countries and continued efforts are necessary. WHO has since developed a global strategy for the further reduction of the leprosy burden and sustained leprosy control.[22]

1. Walker SL, Lockwood DNJ. The clinical and immunological features of leprosy. *Br Med Bull* 2006; 77–78: 103–21.
2. Britton WJ, Lockwood DNJ. Leprosy reactions: current and future approaches to management. *Baillieres Clin Infect Dis* 1997; 4: 1–23.
3. WHO. WHO expert committee on leprosy. *WHO Tech Rep Ser 874* 1998. Also available at: http://libdoc.who.int/trs/WHO_TRS_874.pdf (accessed 13/07/07)
4. WHO. *Guide to eliminate leprosy as a public health problem*. 1st ed. Geneva: WHO,2000. Also available at: http://www.who.int/lep/resources/Guide_Int_E.pdf (accessed 28/06/07)
5. Britton WJ, Lockwood DNJ. Leprosy. *Lancet* 2004; 363: 1209–19.
6. Marlowe SNS, *et al*. Clinical outcomes in a randomized controlled study comparing azathioprine and prednisolone versus prednisolone alone in the treatment of severe leprosy type 1 reactions in Nepal. *Trans R Soc Trop Med Hyg* 2004; 98: 602–9.
7. Biosca G, *et al*. Methotrexate treatment for type 1 (reversal) leprosy reactions. *Clin Infect Dis* 2007; 45: e7–e9.
8. De Sena CBC, *et al*. Cyclosporine A treatment of leprosy patients with chronic neuritis is associated with pain control and reduction in antibodies against nerve growth factor. *Lepr Rev* 2006; 77: 121–9.
9. Smith WCS, *et al*. Steroid prophylaxis for prevention of nerve function impairment in leprosy: randomised placebo controlled trial (TRIPOD 1). *BMJ* 2004; 328: 1459–62.
10. WHO. *The final push strategy to eliminate leprosy as a public health problem: questions and answers*. 2nd ed. Geneva: WHO, 2003. Available at: http://www.who.int/lep/resources/Final_Push_%20QA.pdf (accessed 20/12/10)
11. Moreira AL, *et al*. Comparison of pentoxifylline, thalidomide and prednisone in the treatment of ENL. *Int J Lepr Other Mycobact Dis* 1998; 66: 61–5.
12. Faber WR, *et al*. Treatment of recurrent erythema nodosum leprosum with infliximab. *N Engl J Med* 2006; 355: 739.
13. Sansarricq H, ed. *Multidrug therapy against leprosy: development and implementation over the past 25 years*. Geneva: WHO,2004. Available at: http://www.who.int/lep/resources/MDT_Full.pdf (accessed 28/06/07)
14. Ji B, *et al*. High relapse rate among lepromatous leprosy patients treated with rifampin plus ofloxacin daily for 4 weeks. *Antimicrob Agents Chemother* 1997; 41: 1953–6.
15. Villahermosa LG, *et al*. Parallel assessment of 24 monthly doses of rifampin, ofloxacin, and minocycline versus two years of World Health Organization multi-drug therapy for multi-bacillary leprosy. *Am J Trop Med Hyg* 2004; 70: 197–200.
16. Single-lesion Multicentre Trial Group. Efficacy of single-dose multidrug therapy for the treatment of single-lesion paucibacillary leprosy. *Lepr Rev* 1997; 68: 341–9.
17. Lockwood DNJ. Rifampicin/minocycline and ofloxacin (ROM) for single lesions—what is the evidence? *Lepr Rev*. 1997; 68: 299–300.
18. Katoch VM. Is there a microbiological rationale for single-dose treatment of leprosy? *Lepr Rev* 1998; 69: 2–5.
19. WHO Leprosy Unit. Risk of relapse in leprosy. *Indian J Lepr* 1995; 67: 13–26.
20. Smith CM, Smith WCS. Chemoprophylaxis is effective in the prevention of leprosy in endemic countries: a systematic review and meta-analysis. *J Infect* 2000; 41: 137–42.
21. Moet FJ, *et al*. COLEP Study Group. Effectiveness of single dose rifampicin in preventing leprosy in close contacts of patients with newly diagnosed leprosy: cluster randomised controlled trial. *BMJ* 2008; 336: 761–4.
22. WHO. *Global strategy for further reducing the leprosy burden and sustaining leprosy control activities (plan period: 2006—2010)*. Geneva: WHO, 2005. Available at: http://www.who.int/lep/resources/GlobalStrategy.pdf (accessed 13/12/06)

Leptospirosis

Leptospirosis is a zoonotic infection caused by serovars of spirochaetes from the genus *Leptospira*, such as *Leptospira interrogans*. These are carried by wild, domestic, and farm animals, and can be spread to humans by contact with urine, blood, or tissue of infected animals or a contaminated environment. Leptospirosis is more common in tropical and subtropical areas, where the climate and greater contact with infected environments increase the likelihood of infection. Occupational groups most at risk include farmers and agricultural workers, although there have been outbreaks among participants in water-sports. The organisms enter the body through broken skin or intact mucous membranes, can infect any internal organ, and cause damage to the walls of small blood vessels. Many infected people remain asymptomatic and most patients with symptoms have a relatively mild course of infection with an acute flu-like illness characterised by fever, myalgia, headache, and conjunctival suffusion. A small proportion, however, develop severe leptospirosis (Weil's disease), with haemorrhagic complications, jaundice, and renal impairment.

The routine use of antibacterials to treat leptospirosis is controversial as most cases are self-limiting,[1] and there is insufficient evidence to provide clear guidelines for treatment. However, treatment is usually recommended as soon as the diagnosis of leptospirosis is suspected,[1,2] and preferably within 5 days of the onset of symptoms.[2] Intravenous benzylpenicillin is recommended for severe leptospirosis.[2] Intravenous ceftriaxone,[3] cefotaxime, or doxycycline[4] are alternatives. Aminoglycosides such as streptomycin are used in some countries.[5] Oral antibacterials such as amoxicillin, ampicillin, doxycycline, or erythromycin may be used in milder infections.[2] Jarisch-Herxheimer reactions may occur after penicillin treatment (see Adverse Effects, under Benzylpenicillin p. 231.2).[1] Preliminary data have suggested that azithromycin may be effective in mild to moderate leptospirosis; fluoroquinolones and carbapenems have also shown activity *in vitro*.[5]

The incidence of leptospirosis in US soldiers in Panama was reduced when they were given prophylaxis with weekly oral doxycycline throughout the period of exposure.[6] Prophylaxis has been suggested for travellers at increased risk of infection, beginning 1 to 2 days before and continuing throughout the period of exposure.[7] Leptospirosis vaccines are available in some countries (see p. 2397.3).

1. Bharti AR, *et al*. Peru-United States Leptospirosis Consortium. Leptospirosis: a zoonotic disease of global importance. *Lancet Infect Dis* 2003; 3: 757–71.
2. WHO, International Leptospirosis Society. *Human leptospirosis: guidance for diagnosis, surveillance and control*. Geneva: WHO, 2003. Available at: http://www.who.int/csr/don/en/WHO_CDS_CSR_EPH_2002.23.pdf (accessed 15/12/08)
3. Panaphut T, *et al*. Ceftriaxone compared with sodium penicillin G for treatment of severe leptospirosis. *Clin Infect Dis* 2003; 36: 1507–13.
4. Suputtamongkol Y, *et al*. An open, randomized, controlled trial of penicillin, doxycycline, and cefotaxime for patients with severe leptospirosis. *Clin Infect Dis* 2004; 39: 1417–24.
5. Griffith ME, *et al*. Antimicrobial therapy of leptospirosis. *Curr Opin Infect Dis* 2006; 19: 533–7.
6. Takafuji ET, *et al*. An efficacy trial of doxycycline chemoprophylaxis against leptospirosis. *N Engl J Med* 1984; 310: 497–500.
7. Abramowicz M, ed. The choice of antibacterial drugs. In: *Handbook of antimicrobial therapy*. 19th ed. New Rochelle NY: The Medical Letter, 2011: 357.

Listeriosis

Listeriosis is an infection caused by *Listeria monocytogenes*, an anaerobic, food-borne, Gram-positive bacterium that occurs ubiquitously and is found in soil, water, and vegetation. It is able to grow in a wide range of temperatures, including those found under refrigeration.

Although exposure to *L. monocytogenes* is inevitable, infection is relatively rare in humans.[1-3] When it occurs, it follows ingestion of food contaminated with a high concentration of the bacteria; foods at high risk of contamination include processed and unprocessed dairy products (especially those made with unpasteurised milk), cold meats, pâté, raw vegetables, and salads. The incubation period may range from 1 or 2 days up to 3 months. Those who are immunocompetent may have a self-limiting gastroenteritis after consumption,[1,2] and a mild cutaneous infection has occurred in those who have directly handled infected products or animals.[1,2] Occasionally invasive disease (listeriosis) occurs, especially in the immunocom-

promised, the young and elderly, and in pregnant women and their fetuses and neonates. Listerial meningitis and bacteraemia are the most common presentations; the latter may lead to endocarditis.[1,3] *L. monocytogenes* may also cause meningoencephalitis, focal CNS infection, and infection of visceral organs, the eye, bones, and joints, and pleural, peritoneal, and pericardial spaces.[1,2] Listeriosis is fatal in up to a third of cases.[1,2,4]

Listerial infection is especially dangerous to the fetus and neonate. Pregnant women are prone to developing listerial bacteraemia (although CNS involvement is rare). The bacteria cross the placenta and infect the fetus; fetal distress, spontaneous abortion, still-birth, or premature delivery may then occur. Maternal deaths are rare but the fetal mortality rate is up to 50%. Infection may also occur during delivery, and perinatal sepsis or meningitis are common. Late-onset illness may develop up to a month after delivery.[1,2]

The treatment of choice is intravenous ampicillin at high doses,[1-4] although penicillin is also active. An aminoglycoside, usually gentamicin, is often added for synergy.[1-5] Those with a penicillin allergy may be given co-trimoxazole,[1,3-5] vancomycin,[1,3] teicoplanin,[1] or erythromycin.[5] Reports of the successful use of other antibacterials include listerial meningitis treated with levofloxacin and meropenem;[6] endocarditis in a patient intolerant of standard therapy treated with oral linezolid;[3] listerial meningitis and brain abscesses refractory to standard therapy treated with intravenous linezolid and meropenem;[4] and rhombencephalitis successfully treated with linezolid.[7] Rifampicin has also been used but resistance has been reported with monotherapy.[5] Cephalosporins,[1,5] fosfomycin,[5] and nalidixic acid[5] are ineffective. Some fluoroquinolones (such as ciprofloxacin) show decreased susceptibility, however, the newer fluoroquinolones such as levofloxacin and moxifloxacin have strong bactericidal activity against *L. monocytogenes*.[5] Therapy should continue for 2 weeks in those with bacteraemia, 3 weeks in meningitis, 4 to 6 weeks in endocarditis, and 6 to 8 weeks in brain abscess or encephalitis.

1. Swaminathan B, Gerner-Smidt P. The epidemiology of human listeriosis. *Microbes Infect* 2007; **9**: 1236–43.
2. Ramaswamy V, *et al.* *Listeria*—review of epidemiology and pathogenesis. *J Microbiol Immunol Infect* 2007; **40**: 4–13.
3. Muñoz P, *et al.* First report of *Listeria monocytogenes* endocarditis treated with linezolid. *Int J Antimicrob Agents* 2006; **28**: 480–1.
4. Manfredi R, *et al.* *Listeria monocytogenes* meningitis and multiple brain abscesses in an immunocompetent host. Favorable response to combination linezolid-meropenem treatment. *J Chemother* 2006; **18**: 331–3.
5. Allerberger F, Wagner M. Listeriosis: a resurgent foodborne infection. *Clin Microbiol Infect* 2010; **16**: 16–23.
6. Viale P, *et al.* Major role of levofloxacin in the treatment of a case of *Listeria monocytogenes* meningitis. *Diagn Microbiol Infect Dis* 2007; **58**: 137–9.
7. Morosi S, *et al.* A case of rhombencephalitis caused by Listeria monocytogenes successfully treated with linezolid. *J Infect* 2006; **52**: e73–e75.

Lyme disease

Lyme disease is a seasonal infectious disease caused by the spirochaete *Borrelia burgdorferi* and transmitted mainly by *Ixodes* ticks. *I. scapularis*, one of the species of ticks that may cause Lyme disease, may also be infected with, and transmit, *Anaplasma phagocytophilum* and/or *Babesia microti* and therefore the bite from this tick may lead to Lyme disease, human granulocytic anaplasmosis (see Ehrlichiosis, p. 179.1), or babesiosis (p. 922.2) as a single infection or as a co-infection.[1] Lyme disease was first recognised in the 1970s in Lyme, Connecticut, but when the spirochaete responsible was later identified, it was found to occur worldwide with regional variations. Lyme disease is a multisystem disease characterised by inflammatory reactions that mainly affects the skin, nervous system, heart, and joints, and can be divided into 3 stages. In the early stage a characteristic skin lesion (erythema migrans) occurs at the site of the tick bite and may be accompanied by flu-like or meningitis-like symptoms. This may be followed weeks or months later by signs of disseminated infection, including neurological and cardiac abnormalities, and even years later by chronic arthritis and the late skin manifestation acrodermatitis chronica atrophicans, both signs of persistent infection.

Appropriate **treatment** should prove curative, especially in the early stages. Recommendations for treatment[1-4] give oral tetracyclines (doxycycline or tetracycline) and the beta-lactam antibacterials (amoxicillin, phenoxymethylpenicillin, or cefuroxime) as the antibacterials of choice for *early* Lyme disease in the absence of neurological symptoms or advanced AV block. Treatment is usually for 14 days (range 10 to 21 days for doxycycline and 14 to 21 days for amoxicillin or cefuroxime). The macrolides (azithromycin, clarithromycin, erythromycin, and roxithromycin) are less effective and should only be used in patients allergic to, or who cannot be given, first-line drugs.[2,3] Young children (usually specified as below 8 years of age in the US and below 12 years in the UK) may be given amoxicillin or cefuroxime.[1,3] Pregnant women should avoid tetracyclines but may be given any of the other oral regimens.[1,3]

Adults and children presenting with *neurological symptoms*, either early or late, should be treated with intravenous ceftriaxone, cefotaxime, or benzylpenicillin for 14 to 28 days. Patients allergic to cephalosporins or penicillins may be given oral doxycycline 200 to 400 mg daily in 2 divided doses.[1,3] Early Lyme disease with *cardiac* complications may be treated with either an oral or intravenous antibacterial for 14 to 21 days. Lyme *arthritis* can generally be effectively treated with one of the oral regimens given for 28 days. Patients with ongoing or recurrent joint pain after the initial treatment course may be re-treated with either another 4-week course of oral antibacterials or with intravenous ceftriaxone for 2 to 4 weeks. *Acrodermatitis chronica atrophicans* may be treated with an oral antibacterial for 21 days.[3]

A small percentage of patients continue to have non-specific symptoms after appropriate treatment of Lyme disease; there is some controversy over whether prolonged treatment is effective in these patients and studies have suggested otherwise.[5-8] The use of antibacterials in patients with chronic (more than 6 months) subjective symptoms after recommended treatment is hotly debated[9,10] but the Infectious Diseases Society of America (IDSA) does not support such therapy.[3]

Adults and older children *co-infected* with *A. phagocytophilum* should be treated with doxycycline for 10 days. In the US, recommended treatment for severely ill children less than 8 years of age is doxycycline for 4 to 5 days followed by amoxicillin or cefuroxime to complete a 14-day course. Patients with mild illness and who cannot be given a tetracycline may be given rifampicin 300 mg twice daily for 7 to 10 days plus amoxicillin or cefuroxime.[3]

Preventive measures against Lyme disease include the use of tick repellents, physical protection,[3,11,12] and prompt removal of attached ticks.[3] Most guidelines[3,11] do not support the use of empirical antibacterial therapy or serologic testing after tick bites as generally the risk of infection is low,[13] particularly if the tick is removed promptly. The risk of infection may, however, be greater if the tick has fed to repletion.[14] A study[15] has shown that empirical treatment with a single dose of doxycycline given within 72 hours of a tick bite may be warranted in endemic areas where the probability of infection is high. Although routine antibacterial prophylaxis is not recommended by the IDSA,[3] they recommend that a single dose of doxycycline may be given provided that the tick has been attached for 36 hours or more, prophylaxis can be started within 72 hours of the time of tick removal, and the tick species can be identified as *I. scapularis*. Lyme disease vaccines are available in some countries.

1. Steere AC. Lyme disease. *N Engl J Med* 2001; **345**: 115–25.
2. Loewen PS, *et al.* Systematic review of the treatment of early Lyme disease. *Drugs* 1999; **57**: 157–73.
3. Wormser GP, *et al.* The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2006; **43**: 1089–1134. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/508667 (accessed 18/08/08)
4. Wormser GP. Early Lyme disease. *N Engl J Med* 2006; **354**: 2794–2801.
5. Klempner MS, *et al.* Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. *N Engl J Med* 2001; **345**: 85–92.
6. Kaplan RF, *et al.* Cognitive function in post-treatment Lyme disease: do additional antibiotics help? *Neurology* 2003; **60**: 1916–22.
7. Krupp LB, *et al.* Study and treatment of post Lyme disease (STOP-LD): a randomized double masked clinical trial. *Neurology* 2003; **60**: 1923–30.
8. Baker PJ. Perspectives on "chronic Lyme disease". *Am J Med* 2008; **121**: 562–4.
9. Auwaerter PG. Point: antibiotic therapy is not the answer for patients with persisting symptoms attributable to lyme disease. *Clin Infect Dis* 2007; **45**: 143–8.
10. Stricker RB. Counterpoint: long-term antibiotic therapy improves persistent symptoms associated with lyme disease. *Clin Infect Dis* 2007; **45**: 149–57.
11. American Academy of Pediatrics Committee on Infectious Diseases. Prevention of Lyme disease. *Pediatrics* 2000; **105**: 142–7.[Retired October 2003] Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics;105/1/142 (accessed 01/09/10)
12. Hayes EB, Piesman J. How can we prevent Lyme disease? *N Engl J Med* 2003; **348**: 2424–30.
13. Shapiro ED, *et al.* A controlled trial of antimicrobial prophylaxis for Lyme disease after deer-tick bites. *N Engl J Med* 1992; **327**: 1769–73.
14. Matuschka F-R, Spielman A. Risk of infection from and treatment of tick bite. *Lancet* 1993; **342**: 529–30.
15. Nadelman RB, *et al.* Prophylaxis with single-dose doxycycline for the prevention of Lyme disease after an Ixodes scapularis tick bite. *N Engl J Med* 2001; **345**: 79–84.

Lymphogranuloma venereum

See under Sexually Transmitted Diseases, p. 207.2.

Melioidosis

Melioidosis (or Whitmore's disease)[1-3] is caused by the Gram-negative aerobic bacterium *Burkholderia pseudomallei* (*Pseudomonas pseudomallei*), and *naturally occurring infection* is common in tropical and sub-tropical regions where it is found in soil, mud, and water; it is endemic in south-east Asia and northern Australia.[1] Its true incidence and distribution may, however, be much wider than originally thought. *B. pseudomallei* has some features that makes it a candidate for *deliberate release* as a bioweapon.

Naturally acquired infection usually occurs by inoculation, or sometimes by inhalation or aspiration. Most cases occur in people with some underlying medical condition such as diabetes, chronic kidney or liver disease, or those who are immunocompromised (but HIV infection does not appear to be a major risk factor); person-to-person spread is extremely rare. The incubation period ranges from 1 to 21 days and is thought to depend on the size and route of the inoculum; latent intervals as long as 62 years have been reported. The expected incubation period after deliberate release of aerosol-based biological weapons is 10 to 14 days. Diagnosis is difficult because of the broad range of clinical manifestations. Melioidosis ranges from localised infection to acute pneumonia and fulminant septic infection; any organ or part of the body can become chronically infected. However, most cases present as a febrile illness with severe pneumonia and sepsis. Patients may become overwhelmed by the infection and die from septic shock within 48 hours of developing symptoms. Untreated, the mortality rate for melioidosis with septicaemia approaches 100%, but with optimal treatment this can be reduced: in Thailand melioidosis is associated with a case fatality rate of about 50%,[1,2] while in Australia, the rate is about 20%.[2] The prognosis of melioidosis is much better in children than in adults, and relapse is rare.[1]

Melioidosis is difficult to treat, and response to **treatment** is often slow despite high-dose parenteral antibacterials being given. *B. pseudomallei* is also intrinsically resistant to many antibacterials including some third-generation cephalosporins, penicillins, rifamycins, and aminoglycosides; it shows relative resistance to fluoroquinolones and macrolides.[2] Treatment was based on anecdotal regimens until, in a study from Thailand,[4] intravenous ceftazidime halved the mortality of severe melioidosis when compared with conventional parenteral treatment with high doses of chloramphenicol intravenously, doxycycline, and co-trimoxazole. As a result ceftazidime came to be considered the treatment of choice for the intensive phase of treatment.[1,2,5] Alternatives include the carbapenems such as imipenem and meropenem,[1,2,5] Cefoperazone with sulbactam and amoxicillin with clavulanic acid have also proved effective and the latter may be given as empirical treatment for septicaemia in areas where melioidosis is endemical.[1,2] Resistance to ceftazidime and amoxicillin-clavulanic acid has been reported,[6] emphasising the importance of careful monitoring for the emergence of resistance during treatment. Ceftazidime plus co-trimoxazole, both given intravenously, has been advocated by some for severe melioidosis, especially in patients with septicaemia.[7] High dose parenteral antibacterial treatment should be given for at least 10 to 14 days for systemic infections followed by eradication-phase (or maintenance treatment) with oral antibacterials. Prolonged intensive-phase parenteral therapy is generally used for deep-seated infections such as osteomyelitis, multiple undrained abscesses, or CNS infection. Granulocyte colony-stimulating factor (G-CSF) has been added to intensive phase therapy (usually meropenem) to decrease early mortality in patients presenting with severe sepsis.[2,3] Introduction of G-CSF therapy at one hospital in Australia was reported to decrease the mortality rate from 95 to 10%.[8] However, a study in Thailand, reported no significant effect on mortality when G-CSF was given to patients with severe sepsis.[9]

Oral treatment should only be started when there is clear evidence of clinical improvement.[1] In Thailand, a conventional treatment regimen of chloramphenicol given for the first 8 weeks of oral treatment, with doxycycline and co-trimoxazole given for 20 weeks, has been associated with relapse rates of about 10%;[1,2] this rate increased to nearly 30% if antibacterial treatment was taken for 8 weeks or less.[1] Lower relapse rates have been reported in Australia where co-trimoxazole monotherapy is given for 3 to 6 months.[2] A regimen of co-trimoxazole with doxycycline was found to be equivalent to the conventional regimen, as defined by culture-confirmed recurrence,[10] and treatment for at least 12 to 20 weeks is recommended by some experts.[3] In children and pregnant women high doses of amoxicillin with clavulanic acid may be given.[1,2,11] Some patients with mild infections, including skin and soft-tissue lesions and parotid abscesses, have been successfully treated with the oral regimens alone.[12]

Although there is no evidence of the protective efficacy of postexposure antibacterial **prophylaxis** in preventing melioidosis, on the basis of *animal* experiments doxycycline or co-trimoxazole may be given orally for 7 days to those known to have been exposed to heavy contamination.[13]

1. White NJ. Melioidosis. *Lancet* 2003; **361**: 1715–22.
2. Cheng AC, Currie BJ. Melioidosis: epidemiology, pathophysiology, and management. *Clin Microbiol Rev* 2005; **18**: 383–416.
3. Peacock SJ. Melioidosis. *Curr Opin Infect Dis* 2006; **19**: 421–8.
4. White NJ, *et al.* Halving of mortality of severe melioidosis by ceftazidime. *Lancet* 1989; **ii**: 697–701.

5. Samuel M, Ti TY. Interventions for treating melioidosis. Available in The Cochrane Database of Systematic Reviews: Issue 4. Chichester: John Wiley; 2002 (accessed 16/05/05).
6. Dance DAB, *et al.* Development of resistance to ceftazidime and co-amoxiclav in Pseudomonas pseudomallei. *J Antimicrob Chemother* 1991; **28**: 321–4.
7. Sookpranee M, *et al.* Multicenter prospective randomized trial comparing ceftazidime plus co-trimoxazole with chloramphenicol plus doxycycline and co-trimoxazole for treatment of severe melioidosis. *Antimicrob Agents Chemother* 1992; **36**: 158–62.
8. Cheng AC, *et al.* Adjunctive granulocyte colony-stimulating factor for treatment of septic shock due to melioidosis. *Clin Infect Dis* 2004; **38**: 32–7.
9. Cheng AC, *et al.* A randomized controlled trial of granulocyte colony-stimulating factor for the treatment of severe sepsis due to melioidosis in Thailand. *Clin Infect Dis* 2007; **45**: 308–14.
10. Chaowagul W, *et al.* Open-label randomized trial of oral trimethoprim-sulfamethoxazole, doxycycline, and chloramphenicol compared with trimethoprim-sulfamethoxazole and doxycycline for maintenance therapy of melioidosis. *Antimicrob Agents Chemother* 2005; **49**: 4020–5.
11. Rajchanuvong A, *et al.* A prospective comparison of co-amoxiclav and the combination of chloramphenicol, doxycycline, and co-trimoxazole for the oral maintenance treatment of melioidosis. *Trans R Soc Trop Med Hyg* 1995; **89**: 546–9.
12. Gibney KB, *et al.* Cutaneous melioidosis in the tropical top end of Australia: a prospective study and review of the literature. *Clin Infect Dis* 2008; **47**: 603–9.
13. Health Protection Agency. Glanders and melioidosis: guidelines for action in the event of a deliberate release (issued October 2008). Available at: http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1194947412449 (accessed 22/03/10)

Meningitis

Meningitis[1–4] refers to infection of the subarachnoid space and meninges, which may be caused by viruses, bacteria, protozoa, or fungi. The symptoms and signs of meningitis result from the host inflammatory response to infection. Whereas viruses cause the majority of generally mild cases of infectious meningitis, bacterial meningitis is usually a more serious condition. Meningitis may occasionally be a manifestation of non-infectious (auto-immune or neoplastic) disease. This section discusses bacterial meningitis and its management. For reference to fungal meningitis, see p. 566.3.

The bacteria most often found in adult or childhood meningitis (from 3 months of age) are *Neisseria meningitidis* (meningococci) and *Streptococcus pneumoniae* (pneumococci). *N. meningitidis* A, C, and W135 are the main subtypes involved in epidemics in the African meningitis belt, whereas B and C subtypes are responsible for outbreaks in Europe and North America. *Haemophilus influenzae* meningitis was a common cause of meningitis in infants and young children before the availability of *H. influenzae* type b vaccine, and this pathogen is still found in non-vaccinated young children, particularly in resource-poor countries. In neonates, infants, pregnant women, immunocompromised patients, and the elderly, *Listeria monocytogenes* and Gram-negative bacilli may also be encountered, and *Str. agalactiae* may cause meningitis in neonates and infants. Meningitis after head trauma, neurosurgery, or in the presence of CSF shunts is not infrequently caused by staphylococci (both *Staphylococcus aureus* and coagulase-negative staphylococci) or Gram-negative bacilli.

The bacteria are transmitted from person to person through droplets of respiratory or throat secretions. Infection is spread by prolonged close contact (such as kissing, sneezing and coughing, living in close quarters or dormitories, and sharing eating or drinking utensils). The average incubation period is 4 days, ranging between 2 and 10 days. The clinical presentation of acute bacterial meningitis is largely dependent on the patient's age. The classic manifestations of meningitis in older children and adults, including fever, headache, neck stiffness, photophobia, confusion, and vomiting, are rarely present in infants. In general, the younger the patient, the more subtle and atypical are the signs and symptoms. Fatality rates can be as low as 2% in infants and children, and as high as 20 to 30% in neonates and adults depending on the causative bacteria and patient's age. Brain damage, transient or permanent deafness, or learning disability may occur in up to one-third of survivors. A less common but more severe (often fatal) form of meningococcal disease is meningococcal septicaemia which is characterised by a widespread haemorrhagic rash, acute adrenal insufficiency, and rapid circulatory collapse. (For further information see Meningococcal Infections, p. 194.1.)

Choice of treatment. Bacterial meningitis is a medical emergency and almost universally requires hospitalisation. Death may occur in a matter of hours if left untreated. If a patient with suspected bacterial meningitis cannot be transferred to hospital urgently, UK guidelines[5] advise that treatment with parenteral benzylpenicillin should be started before transfer. Alternative antibacterials include a third generation cephalosporin or chloramphenicol.[6] Patients with suspected or confirmed bacterial meningitis should have blood and/or CSF samples taken for culture and receive *empirical* therapy until the causative organism has been identified and susceptibility patterns have become available.[7–9] Empiric antibacterials are given intravenously in relatively high doses, and treatment should be targeted at specific organisms as soon as the results of blood and/or CSF cultures are known. The choice of empirical therapy depends on the bacterial pathogens (and their antibacterial susceptibility patterns) that are most likely to have caused meningitis and varies with age and the presence of predisposing factors such as trauma or neurosurgery. Guidelines have been published for the UK[7,8,10,11] and the USA,[9] and country specific guidelines should be consulted where available.

- In most countries, a third generation cephalosporin (high-dose ceftriaxone or cefotaxime) is recommended as empirical treatment for bacterial meningitis in adults and children. These drugs are active against *N. meningitidis*, most *Str. pneumoniae* strains, and *H. influenzae*, and penetrate CSF well.
- Where ceftriaxone or cefotaxime are not available or are unaffordable, a combination of ampicillin and chloramphenicol or chloramphenicol alone may be used as an alternative.[12] For those patients allergic to both penicillins and cephalosporins, a combination of vancomycin and chloramphenicol may be given.[7]
- In patients over 55 years ampicillin should be added to cover *Listeria*.[8]
- Empirical treatment in neonates may also include ampicillin to cover *Listeria*, and an aminoglycoside to cover Gram-negative organisms.[9,13]
- In the USA and other areas where penicillin and cephalosporin-resistant pneumococci or meticillin-resistant staphylococci are encountered, vancomycin (with or without rifampicin) should be given with a third-generation cephalosporin to children or adults with bacterial meningitis.[4,7–10]
- Vancomycin together with ceftazidime (or/cefepime or meropenem) should be given to patients with meningitis complicating neurosurgery, head trauma, or CSF shunts. Because of concern of suboptimal CSF penetration, vancomycin should not be used alone in patients with meningitis due to resistant pneumococci or staphylococci, especially when dexamethasone is given as well.

The duration of antibacterial treatment depends on the organism isolated. For *Str. pneumoniae* 10 to 14 days of treatment is recommended and for *H. influenzae* 7 to 14 days. For *N. meningitidis* 7 days, treatment is sufficient. In *L. monocytogenes* and group B streptococcal meningitis, antibacterials should be given for a minimum of 14 to 21 days while Gram-negative bacilli should be treated for a minimum of 3 weeks.[9,14] For discussion on a shorter duration of treatment see Meningitis, under Uses and Administration of Ceftriaxone, p. 256.1.

Chloramphenicol is effective for the treatment of epidemic meningococcal meningitis and ceftriaxone or chloramphenicol are the drugs of choice for patients over 2 years of age in areas with limited health facilities.[1,15] An intramuscular dose of ceftriaxone (100 mg/kg to a maximum of 4 g) was found to be as effective as an intramuscular dose of oily chloramphenicol (100 mg/kg to a maximum of 3 g) for the treatment of meningococcal meningitis during epidemics in resource-poor settings.[16] For children under 3 months, intravenous ampicillin plus cefotaxime or gentamicin are recommended to cover probable bacteria for this age group, while for children aged between 3 months and 5 years, intravenous ceftriaxone is recommended. Those older than 5 years of age may be given intravenous ceftriaxone or ampicillin.[15]

Prophylaxis. Immunisation is the most effective way of preventing bacterial meningitis in children and since the introduction of effective conjugate vaccines against the common meningeal pathogens the epidemiology of bacterial meningitis has changed. In the developed world where these vaccines are routinely given as part of childhood immunisation programmes bacterial meningitis has become a disease of adults rather than of infants and children.[3] Vaccination is recommended for travellers to areas affected by meningococcal outbreaks and is compulsory for pilgrims going to Saudi Arabia. Several vaccines are available to prevent bacterial meningitis. Unconjugated polysaccharide vaccines against *N. meningitidis* subtypes A, C, Y, and/ or W135, in various combinations, have been available for many years and are recommended for children older than 2 years who are at high risk of infection, such as those with asplenia and with terminal complement deficiencies, and students living in dormitories. A newer conjugated tetravalent ACWY meningococcal vaccine protects against A, C, W135 and Y meningococcal subtypes and is now a visa requirement for pilgrims to Saudi Arabia. A monovalent conjugate vaccine against *N. meningitidis* subtype C has recently been licensed in developed countries for use in children and adolescents. This conjugate vaccine produces better protection than unconjugated polysaccharide vaccine, in children under 2 years of age.[1,5] It has been more difficult to develop vaccines against the group B subtype, however, several avenues of research have resulted in the production of an effective vaccine against this subtype. For further information on meningococcal vaccines see, p. 2401.3. The newer conjugate *Haemophilus* vaccines (see p. 2387.2) are similarly more immunogenic than the polysaccharide vaccine, and universal immunisation of infants with these conjugate vaccines has been associated with more than 99% reduction in invasive *H. influenzae* type b diseases in developed countries.[2] In 2000, a conjugate vaccine, directed against the seven most prevalent invasive pneumococcal strains in the USA, was approved for routine childhood immunisation and since 2009 a 13-valent conjugate vaccine has been available in several countries. Three doses of the 7-valent vaccine, given at 2, 4, and 6 months of age, were associated with a reduction of more than 90% in invasive pneumococcal infections, including sepsis and meningitis.[2] For further information on pneumococcal vaccines see, p. 2410.1.

- Close contacts of patients infected with meningococcus A, Y, or W135 should be offered tetravalent meningococcal vaccine; children < 1 year of age should receive 2 doses 1 month apart.[5]
- Those exposed to serogroup C infection who are unimmunised or incompletely immunised should be vaccinated with a meningococcal C vaccine. Those who completed a course more than one year before should be offered a booster.[5]
- All unimmunised index cases under the age of 25 years should also be offered a meningococcal C vaccine. Cases of confirmed serogroup C disease who have previously been immunised with meningococcal C or tetravalent vaccines should be offered a meningococcal C vaccine before discharge from hospital.[5]

Antibacterial treatment does not eliminate nasopharyngeal carriage of *N. meningitidis* and **chemoprophylaxis** should be given to close contacts of the index case (irrespective of vaccination status) to reduce the risk of invasive disease.[5] A systematic review[17] found that ceftriaxone, ciprofloxacin, and rifampicin were all effective at eradicating carriage for up to 2 weeks although resistance to rifampicin may occur after prophylactic treatment; penicillin was less effective.

- A single oral dose of ciprofloxacin or, alternatively, oral rifampicin twice daily for 2 days should be given to close contacts as soon as possible (preferably within 24 hours) after diagnosis of the index case. For pregnant women, a single oral dose of either ciprofloxacin or azithromycin, or a single parenteral dose of ceftriaxone can be used.[5]
- If further cases occur within a group of close contacts within 4 weeks of receiving prophylaxis, then repeat prophylaxis should be with an alternative recommended antibacterial.[5]
- Index cases (except those whose disease was treated with ceftriaxone) should be given antibacterial prophylaxis before discharge from hospital.[5] Chemoprophylaxis is also recommended for healthcare workers whose mouth or nose is directly exposed to large particle droplets or secretions from the respiratory tract of a probable or confirmed index case of meningococcal disease during acute illness and until 24 hours of systemic antibacterial treatment has been completed.[5]

Similarly, treatment of *H. influenzae* meningitis does not eliminate nasopharyngeal carriage of the organism and rifampicin should be given to index cases for 4 days before discharge from hospital. Anyone who has been in direct or prolonged close contact with the infected persons should also be given rifampicin for 4 days. Unvaccinated children should be immunised.

Chemoprophylaxis is not normally indicated for close contacts of pneumococcal and other types of bacterial meningitis.[7,14]

The WHO recommendation for outbreak control is mass vaccination of persons residing in districts in the epidemic phase as well as surrounding districts in an alert phase. It is estimated that a mass immunisation campaign, promptly implemented, can avoid 70% of cases.[1]

Adjunctive treatment. Mortality and morbidity, including deafness in children, remain high in meningitis despite effective antibacterial therapy. Endotoxins and other microbial products, released from bacteria after antibacterial treatment, are able to elicit a severe inflammatory response, suggesting that anti-inflammatory drugs may be of benefit. A systematic review[18] of adjunctive corticosteroid therapy concluded that corticosteroids reduce mortality, neurological sequelae, and especially the risk of severe hearing loss in both children and adults. This systematic review concludes that corticosteroids should be given before, or with the first dose of antibacterial in adults; the same recommendations apply to children living in high-income countries. However, results from a study in sub-Saharan Africa[19] did not support the routine use of adjunctive corticosteroids in the treatment of adults with bacterial meningitis in resource-poor countries where *Strep. pneumoniae* is the main pathogen and where a large number of patients are also likely to have advanced HIV disease. Another study[20] of dexamethasone in Vietnamese patients over 14 years of age with suspected bacterial meningitis reported that dexamethasone did not improve survival in all patients; significant benefit was only seen in patients with proven bacterial meningitis, including those given prior

treatment with antibacterials. This finding was thought to be due to patients with tuberculosis meningitis in the treatment group. The results of a later systematic review and meta-analysis,[21] which included these 2 studies, suggested that in patient populations similar to those seen in high-income countries and in populations with a low prevalence of HIV, adjunctive treatment with corticosteroids improved survival and neurologic recovery in adults and adolescents. For information on the use of corticosteroids in tuberculous meningitis see Tuberculosis, under Uses of Corticosteroids, p. 1614.3.

Careful management of fluid and electrolyte balance may be important in the treatment of meningitis and fluid restriction to prevent cerebral oedema has been widely advocated and used in children.[22,23] This practice was based on reports of hyponatraemia which were attributed to inappropriately increased concentrations of antidiuretic hormone. However, subsequent studies have suggested that the raised concentration of antidiuretic hormone may be an appropriate host response to hypovolaemia, and that more liberal use of parenteral fluids may be beneficial.[2] A systematic review[22] concluded that there is some evidence to support the use of intravenous fluids, in preference to restricted fluid intake, particularly in the first 48 hours in settings with high mortality rates. However, where children present early and mortality rates are lower, there is probably little benefit and insufficient evidence to guide practice; it has been suggested that fluids should not be restricted in children.[14] The British Infection Society working party[7,8] recommends that adult patients with meningitis should not be fluid restricted in an attempt to reduce cerebral oedema.

1. WHO. Meningococcal meningitis. *Fact sheet No. 141* November 2012. Available at: http://www.who.int/mediacentre/factsheets/fs141/en (accessed 04/04/13)
2. Sáez-Llorens X, McCracken GH. Bacterial meningitis in children. *Lancet* 2003; 361: 2139–48.
3. Nudelman Y, Tunkel AR. Bacterial meningitis: epidemiology, pathogenesis and management update. *Drugs* 2009; 69: 2577–96.
4. van de Beek D, *et al.* Advances in treatment of bacterial meningitis. *Lancet* 2012; 380: 1693–702.
5. Health Protection Agency. Guidance for public health management of meningococcal disease in the UK (updated March 2012). Available at: http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1194947389261 (accessed 04/04/13)
6. Sudarsanam T, *et al.* Pre-admission antibiotics for suspected cases of meningococcal disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 29/07/08).
7. Begg N, *et al.* British Infection Society Working Party. Consensus statement on diagnosis, investigation, treatment and prevention of acute bacterial meningitis in immunocompetent adults. *J Infect* 1999; 39: 1–15.
8. British Infection Society. Early management of suspected bacterial meningitis and meningococcal septicaemia in immunocompetent adults—second edition (12/04). Available at: http://www.britishinfectionsociety.org/drupal/sites/default/files/MeningitisAlgorithm03.pdf (accessed 04/04/13)
9. Tunkel AR, *et al.* Infectious Diseases Society of America. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis* 2004; 39: 1267–84. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/425368 (accessed 18/08/08)
10. Heyderman RS; British Infection Society. Early management of suspected bacterial meningitis and meningococcal septicaemia in immunocompetent adults—second edition. *J Infect* 2005; 50: 373–4.
11. NICE. Bacterial meningitis and meningococcal septicaemia: management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care (issued June 2010, revised September 2010). Available at: http://www.nice.org.uk/nicemedia/live/13027/49339/49339.pdf (accessed 16/05/11)
12. Prasad K, *et al.* Third generation cephalosporins versus conventional antibiotics for treating acute bacterial meningitis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 20/06/08).
13. Heath PT, *et al.* Neonatal meningitis. *Arch Dis Child Fetal Neonatal Ed* 2003; 88: F173–F178.
14. El Bashir H, *et al.* Diagnosis and treatment of bacterial meningitis. *Arch Dis Child* 2003; 88: 615–20.
15. Médecins Sans Frontières. *Clinical guidelines: diagnosis and treatment manual for curative programmes in hospitals and dispensaries: guidance for prescribing— 2010 edition.* Paris: MSF, 2010.
16. Nathan N, *et al.* Ceftriaxone as effective as long-acting chloramphenicol in short-course treatment of meningococcal meningitis during epidemics: a randomised non-inferiority study. *Lancet* 2005; 366: 308–13.
17. Zalmanovici Trestioreanu A, *et al.* Antibiotics for preventing meningococcal infections. Available in The Cochrane Database of Systematic Reviews; Issue 8. Chichester: John Wiley; 2011 (accessed 08/03/12).
18. Brouwer MC, *et al.* Corticosteroids for acute bacterial meningitis. Available in The Cochrane Database of Systematic Reviews; Issue 9. Chichester: John Wiley; 2010 (accessed 04/04/13).
19. Scarborough M, *et al.* Corticosteroids for bacterial meningitis in adults in sub-Saharan Africa. *N Engl J Med* 2007; 357: 2441–50.
20. Nguyen TEM, *et al.* Dexamethasone in Vietnamese adolescents and adults with bacterial meningitis. *N Engl J Med* 2007; 357: 2431–40.
21. Assiri AM, *et al.* Corticosteroid administration and outcome of adolescents and adults with acute bacterial meningitis: a meta-analysis. *Mayo Clin Proc* 2009; 84: 403–9.
22. Maconochie IK, *et al.* Fluid therapy for acute bacterial meningitis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 24/03/10).
23. Yogev R, Guzman-Cottrill J. Bacterial meningitis in children: critical review of current concepts. *Drugs* 2005; 65: 1097–112.

Meningococcal infections

Meningococcal disease[1-3] refers to systemic infection with *Neisseria meningitidis* and may present clinically either as meningitis or septicaemia, or both. Less common forms of metastatic meningococcal infection include polyarthritis, pericarditis, pneumonitis, and genito-urinary-tract infections. *N. meningitidis* is a Gram-negative bacterium, occurring worldwide, and is classified into several serotypes. Serotypes A, C, and W135 are responsible for epidemic meningitis in sub-Saharan Africa, while serotypes B and C are the cause of outbreaks in Europe and North America. The number of cases of meningococcal disease due to serotype C has decreased significantly after the introduction of vaccination in developed countries.

Infections are more common in young children under 5 years of age and in adolescents. *N. meningitidis* only infects humans and about 10 to 25% of the population may be carriers of the organism. The bacteria are carried in the pharynx and may sometimes penetrate the mucosa and spread through the bloodstream causing systemic disease that may rapidly progress to shock and death. Patients with meningococcal disease and asymptomatic nasopharyngeal carriers may spread meningococcal infection via respiratory droplets or throat secretions. Close and prolonged contact such as kissing, sneezing and coughing, living in close quarters, and sharing eating or drinking utensils are established risk factors.[1,2,4] Symptoms and signs during the early stage of meningococcal disease are non-specific and include fever, vomiting, malaise, and lethargy. Most patients with meningococcal septicaemia develop a vasculitic rash (petechiae or purpura) which is often scant or absent in patients with meningitis. Purpuric rash, drowsiness or impaired consciousness, and shock are late presentations and associated with high mortality rates, which may be up to 50% in severe forms. Meningococcal meningitis usually presents with headache, neck stiffness, photophobia, and drowsiness. Mortality from meningococcal meningitis is less than in septicaemia and may be below 5% with prompt treatment.[1,2,5]

Guidelines for prevention and control of meningococcal disease have been developed for the UK[6-8] and the USA.[9,10]

Choice of treatment. Mortality is reduced by early recognition of the disease and prompt treatment with antibacterials. In the UK, rapid admission to hospital is considered the highest priority in suspected meningococcal disease; benzylpenicillin should be given parenterally, preferably intravenously, as soon as possible (either before or after transfer).[1,5-8] Alternative antibacterials include a third-generation cephalosporin or chloramphenicol.[5] Both initial empirical and later treatment may be with benzylpenicillin, ampicillin, chloramphenicol, or third-generation cephalosporins such as cefotaxime or ceftriaxone.[4,5,7,11,12] However, there are concerns about calcium chelation when ceftriaxone is given with parenteral calcium-containing products and therefore some experts advise cefotaxime as the drug of choice.[7,13] In infants less than 3 months of age ampicillin (or amoxicillin) should be added to provide cover against listerial infection.[7] Oily chloramphenicol or ceftriaxone are used during epidemics in Africa and in areas with limited health facilities.[4] Uncomplicated meningococcal disease usually requires 7 days of antibacterial treatment. For further details of the treatment of meningococcal meningitis, including the treatment of close contacts, see Meningitis, p. 191.1. Immunisation is the most effective way of preventing meningococcal meningitis and several vaccines are available (see Meningococcal Vaccines, p. 2401.3).

1. Welch SB, Nadel S. Treatment of meningococcal infection. *Arch Dis Child* 2003; 88: 608–14.
2. Singh J, Arrieta AC. Management of meningococcemia. *Indian J Pediatr* 2004; 71: 909–13.
3. Stephens DS, *et al.* Epidemic meningitis, meningococcaemia, and Neisseria meningitidis. *Lancet* 2007; 369: 2196–2210.
4. WHO. Meningococcal meningitis. *Fact sheet No. 141* 2010. Available at: http://www.who.int/mediacentre/factsheets/fs141/en (accessed 24/03/10)
5. Meningitis Research Foundation. Meningococcal meningitis and septicaemia: guidance notes, diagnosis and treatment in general practice—2008 edition. Available at: http://www.meningitis.org/assets/x/50631 (accessed 24/03/10)
6. Health Protection Agency. Guidance for public health management of meningococcal disease in the UK (updated March 2012). Available at: http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1194947389261 (accessed 04/04/13)
7. Scottish Intercollegiate Guidelines Network. Management of invasive meningococcal disease in children and young people: a national clinical guideline (issued May 2008). Available at: http://www.sign.ac.uk/pdf/sign102.pdf (accessed 24/03/10)
8. NICE. Bacterial meningitis and meningococcal septicaemia: management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care (issued June 2010, revised September 2010). Available at: http://www.nice.org.uk/nicemedia/live/13027/49339/49339.pdf (accessed 17/05/11)
9. CDC. Recommendations of the Advisory Committee on Immunization Practices (ACIP): prevention and control of meningococcal disease. *MMWR* 2013; 62(RR-2): 1–22. Also available at: http://www.cdc.gov/mmwr/pdf/rr/rr6202.pdf (accessed 04/04/13)
10. American Academy of Pediatrics Committee on Infectious Diseases. Prevention and control of meningococcal disease: recommendations for use of meningococcal vaccines in pediatric patients. *Pediatrics* 2005; 116: 496–505. Full version: http://pediatrics.aappublications.org/cgi/reprint/116/2/496.pdf (accessed 20/03/06)
11. Meningitis Research Foundation. Management of meningococcal disease in children and young people—seventh edition 10/10. Available at: http://www.meningitis.org/assets/x/50150 (accessed 04/04/13)
12. British Infection Society. Early management of suspected bacterial meningitis and meningococcal septicaemia in immunocompetent adults—second edition (12/04). Available at: http://www.britishinfectionsociety.org/drupal/sites/default/files/MeningitisAlgorithm03.pdf (accessed 01/05/13)
13. Cathie K, *et al.* Drug use in acute meningococcal disease. *Arch Dis Child Educ Pract Ed* 2008; 93: 151–8.

Mouth infections

Infections of the mouth include those of dental origin such as dental caries, abscesses, gingivitis, and periodontal infections, and those without a dental origin. Infections arising in the nasal cavity, middle ear, oropharynx, and paranasal sinuses can also affect the oral cavity. Emphasis has shifted from treatment to prevention of oral diseases.[1] This discussion deals mainly with infections of dental origin.

The organisms most often found in oral infections are viridans streptococci, a variety of anaerobes, and facultative streptococci.

Dental caries[2] is a chronic disease caused by the erosion of tooth enamel due to acid produced by bacteria (usually *Streptococcus mutans*) in plaque. This process is affected by salivary flow and composition, exposure to fluoride, dietary sugar content, and preventative measures such as tooth brushing and flossing. Fluoride in various forms is used in dental caries prophylaxis, where it may promote remineralisation or reduce acid production by plaque bacteria.[1,2] For further information on the use of fluoride for dental caries prophylaxis see under Uses and Administration of Sodium Fluoride, p. 2089.2. Sugar-free chewing gum can also help prevent caries by stimulating the production of saliva.[3,4] For further references see Dental Caries under Xylitol, p. 2220.3. Dental caries vaccines have been investigated.

The term **periodontal disease**[5] refers to conditions affecting the supporting structures around the teeth (periodontium), including the gingiva, peridontal ligament, cementum, and alveolar bone. Pathogenic bacteria in the plaque, genetic factors, tobacco and alcohol use, diabetes, immunosuppression, and the use of some drugs can contribute to such disease. **Gingivitis** (or gum disease) is an inflammation of the gums surrounding the teeth in response to bacterial biofilm or plaque that accumulates between the gingiva and the teeth; irritation from plaque causes pockets to develop where the gingiva separates from the tooth. Gingivitis may or may not develop into periodontitis, but periodontitis is always preceded by gingivitis. **Periodontitis** is an infection of the periodontium causing inflammation of the periodontal ligament, gingiva, cementum, and alveolar bone. With ongoing inflammation the periodontal connective tissue breaks down and destruction of the local alveolar bone occurs. Periodontal infections are usually mixed infections[6,7] and are associated with an increase in the number of Gram-negative and anaerobic bacteria.[5,6]

Most gingivitis and periodontitis can be prevented and treated by adequate oral hygiene and plaque removal using mechanical means such as toothbrushing. Mechanical removal of calculus is necessary where the build up is significant. Antiseptics may also help to reduce plaque accumulation and several, but most notably chlorhexidine, have been used.[6,8] Oral antibacterials may be used as an adjunct to scaling, root planing, or drainage in patients with refractory disease, who are immunocompromised, or have signs of systemic illness.[5,7] Antibacterials commonly used include tetracyclines, metronidazole, amoxicillin (with or without clavulanic acid), ciprofloxacin, and clindamycin.[6] Combination therapy with metronidazole and either amoxicillin or ciprofloxacin, or amoxicillin with clavulanic acid followed by doxycycline has also been used.[6] Dentoalveolar abscesses originating from the periodontal tissue (usually caused by anaerobic bacteria) may be treated with metronidazole; clindamycin is an alternative.[7] Those originating from periapical tissues (usually caused by mixed infections) can be treated with amoxicillin, metronidazole, or clindamycin.[7] Antibacterial treatment may be stopped once the systemic signs of the infection have resolved (usually after 2 to 3 days of treatment).[7] In the UK, the *BNF* advises against the routine use of clindamycin in oral infections, but notes that it can be used for the treatment of dentoalveolar abscess that has not responded to penicillin or metronidazole.

Prevotella intermedia, fusiform bacteria, and spirochaetes have also been linked with **acute necrotising ulcerative gingivitis** (ANUG; also called Vincent's infection or trench mouth). ANUG may result in accelerated destruction of affected tissues, as well as local or systemic spread of infection. Treatment involves debridement and an oral penicillin with metronidazole; clindamycin monotherapy is an alternative. Antibacterials and antiseptics delivered locally to the periodontal pocket may be of value.[6]

1. WHO. Recent advances in oral health: report of a WHO expert committee. *WHO Tech Rep Ser 826* 1992. Available at: http://libdoc.who.int/trs/WHO_TRS_826.pdf (accessed 18/08/08)
2. Selwitz RH, *et al.* Dental caries. *Lancet* 2007; 369: 51–9.
3. Edgar WM. Sugar substitutes, chewing gum and dental caries—a review. *Br Dent J* 1998; 184: 29–32.

4. Van Loveren C. Sugar alcohols: what is the evidence for caries-preventive and caries-therapeutic effects? *Caries Res* 2004; **38**: 286–93.
5. Pihlstrom BL, *et al.* Periodontal diseases. *Lancet* 2005; **366**: 1809–20.
6. Greenwell H, Bissada NF. Emerging concepts in periodontal therapy. *Drugs* 2002; **62**: 2581–7.
7. Ellison SJ. The role of phenoxymethylpenicillin, amoxicillin, metronidazole and clindamycin in the management of acute dentoalveolar abscesses–a review. *Br Dent J* 2009; **206**: 357–62.
8. Eley BM. Antibacterial agents in the control of supragingival plaque—a review. *Br Dent J* 1999; **186**: 286–96.

Mycetoma

Mycetoma[1,2] is a localised infection found worldwide, but most commonly in the tropics and subtropics. Infection mainly results from trauma to the skin, and may spread locally through the lymphatic system to surrounding tissues, progressively destroying connective tissue (fascia) and bone. It is characterised by painless soft-tissue swelling, draining sinus tracts, and discharge of grains composed of large aggregates of filaments (fungal or actinomycete). The foot is most often affected (70 to 80% of cases), less often hand (12%), legs, and knee joints. The term Madura foot is used for mycetoma affecting the foot. Mycetomas may be caused by various organisms; those caused by fungi such as *Madurella mycetomatis* are called eumycetomas and are discussed on p. 567.1. Those caused by the filamentous bacteria, actinomycetes, are called **actinomycetomas**: *Nocardia brasiliensis* is the commonest actinomycete responsible; others include *Actinomadura madurae, A. pelletieri,* and *Streptomyces somaliensis*. For details of systemic infections caused by *Nocardia* spp., see under Nocardiosis, p. 195.3.

Combined drug treatment is preferred for actinomycetomas so as to avoid resistance and eradicate residual infection; cures are usually achieved after treatment for 4 to 24 months.[1,2] The most common regimen is streptomycin and dapsone; co-trimoxazole may replace dapsone in patients who have not responded to initial treatment after a few months and in those who cannot tolerate dapsone. Successful treatment has been reported with amikacin, either as monotherapy or with co-trimoxazole.[1] Rifampicin, sulfonamides, or pyrimethamine with sulfadoxine, have been tried in resistant infections and are considered suitable for second-line therapy;[1] amoxicillin with clavulanic acid has also been used successfully.[3] A two-step regimen[4] has also been used: intensive therapy with benzylpenicillin, gentamicin, and co-trimoxazole for 5 to 7 weeks is followed by maintenance therapy with amoxicillin and co-trimoxazole for 2 to 5 months after clinical remission. More recently, a modified two-step regimen[5] has been tried, omitting benzylpenicillin and giving gentamicin and co-trimoxazole for 4 weeks followed by maintenance therapy with doxycycline and co-trimoxazole for 5 to 6 months after remission.

Surgery is indicated for patients with infections resistant to drug therapy, deep or extensive infections, or infections with bone involvement that will not respond to long-term conventional therapy; amputation may be required in some cases.[1,2]

1. Fahal AH. Mycetoma: a thorn in the flesh. *Trans R Soc Trop Med Hyg* 2004; **98**: 3–11.
2. Lichon V, Khachemoune A. Mycetoma: a review. *Am J Clin Dermatol* 2006; **7**: 315–21.
3. Bonifaz A, *et al.* Treatment of actinomycetoma due to Nocardia spp. with amoxicillin-clavulanate. *Br J Dermatol* 2007; **156**: 308–11.
4. Ramam M, *et al.* A two-step schedule for the treatment of actinomycotic mycetomas. *Acta Derm Venereol* 2000; **80**: 378–80.
5. Ramam M, *et al.* A modified two-step treatment for actinomycetoma. *Indian J Dermatol Venereol Leprol* 2007; **73**: 235–9.

Necrotising enterocolitis

See p. 185.1.

Necrotising fasciitis

Necrotising fasciitis[1–5] is an uncommon but severe soft-tissue infection resulting in necrosis of the subcutaneous tissue and adjacent fascia, together with severe systemic illness, and is associated with high morbidity and mortality rates. Type I infections are caused by a mixture of aerobic and anaerobic organisms, whereas type II are monomicrobial infections due to group A streptococci or staphylococci and may be associated with a toxic shock syndrome (p. 211.3). Some definitions recognise type III infections due to *Vibrio vulnificus*, mainly occurring in patients with liver disease and often rapidly progressive and fatal. Necrotising fasciitis can affect any part of the body but is most common on the extremities, the perineum, and the trunk. (The term Fournier's gangrene has been used to describe rapidly progressive necrotising fasciitis of the perineum and genitals.) Necrotising fasciitis usually follows trauma, and most patients have pre-existing conditions that predispose to infection, such as diabetes mellitus, chronic renal failure, peripheral vascular disease, or parenteral drug abuse.

Complete debridement of the infected tissue is considered essential for treatment; repeated debridements are necessary until infection is controlled. Intravenous antibacterial therapy is given as an adjunct and should be continued until no further debridements are needed.[1–5] Antibacterial treatment regimens should cover Gram-positive, Gram-negative, and anaerobic organisms. The possibility of infection with group A *Streptococcus* or *Clostridium* species should also be considered. Possible treatment regimens for *mixed infections* include monotherapy with ertapenem, imipenem, meropenem, piperacillin-tazobactam, or tigecycline.[4] Multidrug regimens for mixed infections include:

- benzylpenicillin and clindamycin plus a fluoroquinolone or an aminoglycoside[4]
- benzylpenicillin and gentamicin plus metronidazole or clindamycin[1]
- ampicillin-sulbactam and clindamycin plus ciprofloxacin[2]
- patients known to be hypersensitive to penicillins may be given clindamycin or metronidazole with an aminoglycoside or fluoroquinolone[2]

If group A *Streptococcus* or *Clostridium* is the likely cause, a combination of clindamycin and benzylpenicillin should be used.[2]

Until *meticillin-resistant staphylococcal infection* has been ruled out, treatment regimens should also include vancomycin, daptomycin, linezolid, or quinupristin/dalfopristin.[4,5]

Hyperbaric oxygen therapy has also been beneficial although prospective controlled studies are lacking.[1,3–6] Intravenous normal immunoglobulins have also been tried in patients with staphylococcal or streptococcal necrotising fasciitis but further study is considered warranted.[2–5]

1. Hasham S, *et al.* Necrotising fasciitis. *BMJ* 2005; **330**: 830–3. Correction. *ibid.*; 1143.
2. Stevens DL, *et al.* Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. *Clin Infect Dis* 2005; **41**: 1373–1406. Corrections. *ibid.*; 1830 and *ibid.* 2006; **42**: 1219. [dose error] Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/497143 (accessed 15/12/08)
3. Kihiczak GG, *et al.* Necrotizing fasciitis: a deadly infection. *J Eur Acad Dermatol Venereol* 2006; **20**: 365–9.
4. Anaya DA, Dellinger EP. Necrotizing soft-tissue infection: diagnosis and management. *Clin Infect Dis* 2007; **44**: 705–10.
5. Sarani B, *et al.* Necrotizing fasciitis: current concepts and review of the literature. *J Am Coll Surg* 2009; **208**: 279–88.
6. Jallali N, *et al.* Hyperbaric oxygen as adjuvant therapy in the management of necrotizing fasciitis. *Am J Surg* 2005; **189**: 462–6.

Neonatal conjunctivitis

Conjunctivitis of the newborn, also known as ophthalmia neonatorum, is defined as any conjunctivitis with discharge occurring during the first 28 days of life.[1] That due to *Neisseria gonorrhoeae* is the most serious; it usually appears by the third day after birth and can rapidly result in blindness; systemic infections, especially severe septicaemia, may occur. *Chlamydia trachomatis* is another major cause of neonatal conjunctivitis (inclusion conjunctivitis); it characteristically occurs 5 to 14 days after birth and is less threatening to sight than gonococcal infection, but may also infect the nasopharynx and can cause pneumonia. Chlamydial conjunctivitis is more common than gonococcal conjunctivitis in developed countries. Both organisms are sexually transmitted and the infants of mothers with such genital-tract infections are infected during their passage through the birth canal. Other less serious bacterial causes of neonatal conjunctivitis include *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus* spp., and *Pseudomonas* spp.; they are often hospital-acquired.[1]

The management of gonococcal and chlamydial neonatal conjunctivitis varies from country to country depending on the prevalence of gonorrhoea and *C. trachomatis* infection and on bacterial resistance.

- PROPHYLAXIS

  The ideal method of prophylaxis is to treat the infected mother during pregnancy, but this is not always possible. Where the risk of *gonococcal infection* is high, ocular prophylaxis at birth is particularly important because of the rapid onset of conjunctivitis and its potential seriousness and is preferable to early diagnosis and treatment of the neonate.[2] Cleansing of the neonate's eyes immediately after birth followed by the topical application of either tetracycline 1% eye ointment,[3] erythromycin 0.5% eye ointment,[4] or silver nitrate 1% eye drops is advised[5] and is sometimes required by law.[4] Silver nitrate[1] is active against all strains of *N. gonorrhoeae* regardless of their susceptibility to antibacterials; it is inexpensive and widely available, but may cause chemical conjunctivitis and has been ineffective in preventing chlamydial conjunctivitis (see below). Tetracycline has been reported to be as effective as silver nitrate in protecting against gonococcal conjunctivitis caused by multiresistant strains[5] and WHO now lists both drugs as the drugs of choice.[3]

  The value of prophylaxis against *chlamydial neonatal conjunctivitis* is less certain. Tetracycline ointment has been reported to be less effective in preventing chlamydial infection than gonococcal infection[5] and erythromycin ointment has also been unreliable.[6] Silver nitrate is generally considered ineffective,[1] despite an unexpected reduction in the incidence of chlamydial conjunctivitis in one study.[5] The CDC[4] does not recommend prophylactic antibacterial treatment for infants born to mothers with untreated chlamydial infection. Screening and treatment of pregnant women for *C. trachomatis* infection may be a more effective method of control than ocular prophylaxis.[5,7] This approach also tackles the more serious problem of pneumonia.[8]

  Neonatal conjunctivitis continues to cause blindness, especially in developing countries. Povidone-iodine is less expensive and perhaps more readily available in such countries than silver nitrate or erythromycin. In a study in Kenya involving more than 3000 infants[9] a 2.5% ophthalmic solution of povidone-iodine appeared to be a more effective prophylactic than either a 1% ophthalmic solution of silver nitrate or erythromycin 0.5% eye ointment. In particular, there were fewer cases of chlamydial conjunctivitis with povidone-iodine.

- TREATMENT

  All cases of neonatal conjunctivitis should be treated for both *N. gonorrhoeae* and *C. trachomatis* because of the possibility of mixed infection.[3] *Gonococcal neonatal conjunctivitis* must be treated systemically. WHO[3] recommends ceftriaxone 50 mg/kg by intramuscular injection as a single dose (to a maximum of 125 mg) or, if ceftriaxone is not available, spectinomycin 25 mg/kg (to a maximum of 75 mg) or kanamycin 25 mg/kg (to a maximum of 75 mg) by intramuscular injection as a single dose.

  In the USA, CDC[4] recommends a single intravenous or intramuscular injection of ceftriaxone 25 to 50 mg/kg (up to 125 mg) when there is no evidence of disseminated infection.

  See also under Gonorrhoea (p. 206.2) for the treatment of infants exposed to gonorrhoea at birth or with established gonococcal infection at any site.

  For *nongonococcal neonatal conjunctivitis* WHO[3] and CDC[4] recommend erythromycin 50 mg/kg daily in 4 divided doses orally for 14 days; WHO[3] recommend co-trimoxazole 240 mg twice daily for 14 days as an alternative. There is no indication that topical therapy is of additional benefit.[3,4]

1. WHO. *Conjunctivitis of the newborn: prevention and treatment at the primary health care level.* Geneva: WHO, 1986.
2. Laga M, *et al.* Epidemiology and control of gonococcal ophthalmia neonatorum. *Bull WHO* 1989; **67**: 471–8.
3. WHO. Guidelines for the management of sexually transmitted infections. Geneva: WHO, 2003. Also available at: http://whqlibdoc.who.int/publications/2003/9241546263.pdf (accessed 22/06/04)
4. CDC. Sexually transmitted diseases treatment guidelines, 2010. *MMWR* 2010; **59** (RR-12): 1–110. Also available at: http://www.cdc.gov/STD/treatment/2010/STD-Treatment-2010-RR5912.pdf (accessed 08/01/11) Correction. *ibid.* 2011; **60**: 18. [dose]
5. Laga M, *et al.* Prophylaxis of gonococcal and chlamydial ophthalmia neonatorum: a comparison of silver nitrate and tetracycline. *N Engl J Med* 1988; **318**: 653–7.
6. Black-Payne C, *et al.* Failure of erythromycin ointment for post natal ocular prophylaxis of chlamydial conjunctivitis. *Pediatr Infect Dis J* 1989; **8**: 491–5.
7. Hammerschlag MR, *et al.* Efficacy of neonatal ocular prophylaxis for the prevention of chlamydial and gonococcal conjunctivitis. *N Engl J Med* 1989; **320**: 769–72.
8. Schachter J. Why we need a program for the control of Chlamydia trachomatis. *N Engl J Med* 1989; **320**: 802–4.
9. Isenberg SJ, *et al.* A controlled trial of povidone-iodine as prophylaxis against ophthalmia neonatorum. *N Engl J Med* 1995; **332**: 562–6.

Nocardiosis

Nocardia spp. are Gram-positive aerobic branching bacteria that cause systemic or localised infection. The principal pathogenic species in man is *N. asteroides*; others include *N. brasiliensis, N. pseudobrasiliensis,* and *N. caviae*. Localised chronic infection or actinomycetoma is described under Mycetoma (above). Systemic nocardiosis is mainly a lung infection and often involves abscess formation; it occurs especially in immunocompromised patients and may be disseminated with abscesses in the brain and subcutaneous tissues.

The treatment of choice has been a sulfonamide such as sulfadiazine or co-trimoxazole,[1–5] although a study *in vitro* indicated that the fixed ratio of trimethoprim:sulfamethoxazole in co-trimoxazole might contain too little trimethoprim for optimal activity.[6] Sulfafurazole[7] has been used successfully. There have been reports of the effective treatment of nocardiosis with amikacin,[8,9] linezolid,[10,11] minocycline,[12,13] or ciprofloxacin with doxycycline.[14] Imipenem may also be used,[15] and is most active when combined with amikacin; the combination is considered by some to be the best choice for initial therapy when parenteral antibacterials are required.[16,17] Other suggested alternatives include meropenem,[15,16] cefuroxime,[16] cefotaxime,[16] and ceftriaxone;[15,16] due to their relatively low toxicity and excellent CSF penetration, these antibacterials may be particularly useful in cerebral nocardiosis.[16]

Treatment of nocardiosis needs to be prolonged and may continue for at least 6 to 12 months, depending on the site of infection and the immune status of the patient.[3,16]

1. Abdi EA; *et al.* Nocardia infection in splenectomized patients: case reports and a review of the literature. *Postgrad Med J* 1987; 63: 455–8.
2. Smego RA, *et al.* Treatment of systemic nocardiosis. *Lancet* 1987; i: 456.
3. Pillice GA. Treatment of nocardiosis. *Lancet* 1987; i: 1261–2.
4. Varghese GK, *et al.* Nocardia brasiliensis meningitis. *Postgrad Med J* 1992; 68: 986.
5. Agterof MJ, *et al.* Nocardiosis: a case series and a mini review of clinical and microbiological features. *Neth J Med* 2007; 65: 199–202.
6. Bennett JE, Jennings AE. Factors influencing susceptibility of Nocardia species to trimethoprim-sulfamethoxazole. *Antimicrob Agents Chemother* 1978; 13: 624–7.
7. Poland GA, *et al.* Nocardia asteroides pericarditis: report of a case and review of the literature. *Mayo Clin Proc* 1990; 65: 819–24.
8. Goldstein FW, *et al.* Amikacin-containing regimens for treatment of nocardiosis in immunocompromized patients. *Eur J Clin Microbiol* 1987; 6: 198–200.
9. Meier B, *et al.* Successful treatment of a pancreatic Nocardia asteroides abscess with amikacin and surgical drainage. *Antimicrob Agents Chemother* 1986; 29: 150–1.
10. Moylett EH, *et al.* Clinical experience with linezolid for the treatment of Nocardia infection. *Clin Infect Dis* 2003; 36: 313–18.
11. Jodlowski TZ, *et al.* Linezolid for the treatment of Nocardia spp. infections. *Ann Pharmacother* 2007; 41: 1694–9.
12. Petersen EA, *et al.* Minocycline treatment of pulmonary nocardiosis. *JAMA* 1983; 250: 930–2.
13. Naka W, *et al.* Unusually located lymphocutaneous nocardiosis caused by Nocardia brasiliensis. *Br J Dermatol* 1995; 132: 609–13.
14. Bath PMW, *et al.* Treatment of multiple subcutaneous Nocardia asteroides abscesses with ciprofloxacin and doxycycline. *Postgrad Med J* 1989; 65: 190–1.
15. Abramowicz M, ed. The choice of antibacterial drugs. In: *Handbook of antimicrobial therapy*. 19th ed. New Rochelle NY: The Medical Letter, 2011: 73.
16. Corti ME, Villafañe Fioti MF. Nocardiosis: a review. *Int J Infect Dis* 2003; 7: 243–50.
17. Ameen M, *et al.* Efficacy of imipenem therapy for Nocardia actinomycetomas refractory to sulfonamides. *J Am Acad Dermatol* 2010; 62: 239–46.

Nontuberculous mycobacterial infections

Environmental mycobacteria are widespread, and many species other than those responsible for leprosy (p. 188.3) and tuberculosis (p. 212.2) are facultative parasites capable of producing disease in man. These organisms, which have been referred to as atypical, nontuberculous (NTM), tuberculoid, opportunistic, or MOTT (mycobacteria other than tuberculous), are rarely, if ever, transmitted from person to person but are acquired from the environment. Symptomatic infections are usually associated with focal or generalised defects in the host's immune system. The diseases produced include localised skin and soft tissue lesions, pulmonary infections, lymphadenitis, and disseminated infections.

Cutaneous disease may follow traumatic inoculation with *Mycobacterium marinum* ('swimming pool' or 'fish-tank' granuloma), *M. ulcerans* (Buruli ulcer), *M. chelonae* (*M. chelonei*), *M. abscessus* (formerly *M. chelonae* subspecies), or *M. fortuitum*. Ulcerated lesions due to *M. haemophilum* have been described mainly in immunocompromised patients.

Pulmonary disease may be clinically indistinguishable from pulmonary tuberculosis, and has most frequently been attributed to the *M. avium* complex (MAC), which includes *M. avium* and *M. avium-intracellulare*, or to *M. kansasii*, and to a lesser extent *M. xenopi*; less common causes include *M. abscessus*, *M. asiaticum*, *M. celatum*, *M. chelonae*, *M. fortuitum*, *M. malmoense*, *M. scrofulaceum*, *M. simiae*, and *M. szulgai*.

Lymphadenitis, which is usually self-limiting and occurs particularly in children under 5 years of age, may be caused by many species but the great majority of cases are due to *M. avium* complex, *M. genavense*, *M. malmoense*, and *M. scrofulaceum* (sometimes collectively known as the MAIS complex).

Dissemination of opportunistic mycobacterial infections may occur rapidly in immunocompromised patients. The majority of cases have been attributed to the *M. avium* complex; other species implicated include *M. abscessus*, *M. celatum*, *M. chelonae*, *M. genavense*, *M. haemophilum*, *M. kansasii*, *M. malmoense*, *M. scrofulaceum*, and *M. simiae*.

The treatment depends on the site and nature of the infection and whether immunodeficiency is present. Both HIV-negative and HIV-positive patients may be affected and the possibility of drug interactions should be borne in mind in patients receiving antiretroviral therapy.

- MYCOBACTERIUM AVIUM COMPLEX (MAC).

  US guidelines[1,2] produced by the CDC, National Institutes of Health, HIV Medicine Association, and Infectious Diseases Society of America recommend that the **treatment of HIV-positive patients** with MAC should consist of at least 2 antimycobacterial drugs. Clarithromycin is the preferred first drug (with azithromycin as an alternative) and is given with ethambutol. Use of a third, and possibly, fourth, drug should be considered in patients with advanced immunosuppression (CD4+ T lymphocyte count less than 50 cells/microlitre), high mycobacterial loads, or if the patient is not taking effective HAART. Rifabutin is often used as the third drug, while a fluoroquinolone (ciprofloxacin, levofloxacin, or moxifloxacin) or aminoglycoside (amikacin or streptomycin) can be considered when a fourth drug is needed or rifabutin cannot be used. In ***disseminated*** disease, patients who are not taking HAART should generally delay starting antiretroviral treatment until after at least 2 weeks of treatment for MAC has been completed, in order to reduce the risk of significant drug interactions or complications due to immune reconstitution syndrome. Those already on HAART should continue this treatment if possible.

  Earlier UK guidelines from the British Thoracic Society (1999, not subsequently updated)[3] for treatment of HIV-positive patients with MAC broadly concur with the US recommendations. Rifampicin or rifabutin, ethambutol, and clarithromycin or azithromycin were recommended. A fluoroquinolone such as ciprofloxacin, or even amikacin, might be added for patients who were intolerant of first-line drugs or who failed to respond. UK guidelines recommended lifelong treatment; the US considers that treatment may be stopped in selected patients (see Chemoprophylaxis, below). In ***disseminated*** disease, the same treatment should be given and continued indefinitely.

  A prospective, randomised study[4] undertaken to compare 3 regimens (clarithromycin and ethambutol, clarithromycin and rifabutin, and all 3 drugs) for the treatment of disseminated MAC in patients with AIDS found that all regimens appeared to provide effective treatment and the differences were not statistically significant. However, patients taking the 3-drug regimen had greater overall clinical efficacy, a lower relapse rate, and a lower risk of death.

  The 1999 British Thoracic Society guidelines[3] state that treatment for **HIV-negative patients** with MAC pulmonary disease should consist of rifampicin and ethambutol for 24 months, with or without isoniazid. In extrapulmonary disease affecting lymph nodes, surgical excision of the nodes should be undertaken; chemotherapy with rifampicin, ethambutol, and clarithromycin for up to 2 years should be considered if disease recurred or where excision was incomplete or impossible. In sites other than lymph nodes, chemotherapy should be given for 18 to 24 months. US guidelines[5] from the American Thoracic Society and the Infectious Diseases Society of America suggest that for mild nodular or bronchiectatic pulmonary disease, an intermittent regimen of clarithromycin (or azithromycin), rifampicin, and ethambutol three times weekly is usually sufficient; therapy should be continued until sputum cultures have been negative for 12 months. For severe pulmonary disease or in previously treated patients, a daily regimen should be used; addition of intermittent amikacin or streptomycin for the first few months of therapy can also be considered.

  Prophylactic treatment is used to reduce the incidence of disseminated MAC disease in patients with HIV infection. There appears to be a tendency to delay starting prophylaxis until later in the disease process; US guidelines[2,5] recommend starting prophylaxis in adults and adolescents at a CD4+ T lymphocyte count of less than 50 cells/microlitre with either azithromycin or clarithromycin. If these drugs cannot be tolerated then rifabutin may be given as an alternative. Combination therapy with one of the macrolides and rifabutin is not recommended. US guidelines state that prophylaxis need not be lifelong in patients responding to HAART; specifically, primary prophylaxis may be stopped in adults and adolescents whose CD4+ T lymphocyte count has increased to more than 100 cells/microlitre for 3 months or more, but should be restarted if the CD4+ count falls to below 50 to 100 cells/microlitre again. Observational data from a large cohort of patients in the USA found no evidence of increased risk of MAC in patients who had stopped primary prophylaxis in accordance with these guidelines.[6]

  US guidelines[2,5] also state that it may be possible to stop secondary prophylaxis (chronic maintenance therapy) in HIV-infected adults and adolescents who have completed at least 12 months of treatment for MAC, who remain asymptomatic with respect to MAC, and who have a sustained response to HAART (CD4+ T lymphocyte count greater than 100 cells/microlitre for more than 6 months). Secondary prophylaxis should be restarted if CD4+ T lymphocyte count falls below 100 cells/microlitre. In children, CD4+ T lymphocyte count thresholds for starting, stopping, or resuming prophylaxis vary depending on the age of the child.[1]

  In the UK, however, the earlier British Thoracic Society guidelines noted there was no general agreement about when prophylaxis should be used. If prophylaxis were to be given to patients with a CD4+ T lymphocyte count below 50 cells/microlitre the first drug of choice would be azithromycin; clarithromycin was an alternative and azithromycin with rifabutin would be a third choice.[3] These guidelines, partly based on studies which predate the wide use of HAART, recommended that prophylaxis be continued indefinitely.[3]

- MYCOBACTERIUM KANSASII INFECTION.

  UK guidelines stated that infections with *M. kansasii* might be treated with rifampicin (or rifabutin) and ethambutol.[3] Pulmonary disease in HIV-negative patients was usually treated for 9 months whereas HIV-positive patients should receive therapy for 2 years or until the sputum has been negative for 12 months. For disseminated infection in HIV-positive patients, clarithromycin should be added and possibly also isoniazid. The place of macrolides and fluoroquinolones in pulmonary or disseminated *M. kansasii* infection remained to be established. In extrapulmonary disease in HIV-negative patients, chemotherapy with rifampicin and ethambutol might be used before excision of an infected lymph node. In other extrapulmonary disease the guidelines stated that the data were insufficient to make recommendations, but considered that rifampicin and ethambutol for 9 months appeared sensible, with the addition of protionamide and streptomycin and/or a macrolide if the condition is not responding.[3] US guidelines[5] suggest the use of rifampicin, ethambutol, and isoniazid for *M. kansasii* pulmonary infection; treatment should be continued until sputum cultures have been negative for 12 months. For disseminated disease in immunocompromised patients, indefinite treatment may be required until sufficient recovery of immune status occurs.

- OTHER OPPORTUNISTIC MYCOBACTERIA.

  In *M. malmoense* and *M. xenopi* **pulmonary** disease, UK guidelines have recommended that rifampicin and ethambutol should be given for 2 years in HIV-negative patients. Extrapulmonary *M. malmoense* infections should be treated in the same manner as extrapulmonary MAC or *M. kansasii* infections. *M. malmoense* infection rarely occurs in AIDS patients, but if necessary, treatment with rifampicin, ethambutol, and clarithromycin, and possibly isoniazid should be used. For *M. xenopi* in HIV-positive patients the guidelines stated that there was no evidence on which to base recommendations; treatment as for pulmonary or disseminated MAC infection was suggested.[3]

  For pulmonary disease due to rapidly growing bacteria (*M. abscessus*, *M. chelonae*, *M. fortuitum*, and *M. gordonae*) and other species (*M. genavense*, *M. haemophilum*, *M. simiae*, *M. szulgai*, and *M. ulcerans*) surgery should be used if possible. Drug therapy should probably include rifampicin, ethambutol, and clarithromycin. Amikacin, cefoxitin, imipenem, quinolones, and sulfonamides might have a place in treatment. For extrapulmonary disease due to these organisms, there had been several anecdotal reports outlining treatment but there was no evidence from controlled clinical studies.[3] Successful treatment of *M. simiae* infection in patients with AIDS was reported with clarithromycin, ethambutol, and ciprofloxacin.[7] Surgical treatment and intensive antibacterial regimens have been used for *M. scrofulaceum* infections.[8] Symptomatic improvement was achieved in an AIDS patient with *M. celatum* infection with a regimen of isoniazid, rifampicin, and ethambutol.[9]

  For **cutaneous** infections due to *M. marinum* (swimming-pool granuloma or fish-tank granuloma) many antibacterial regimens have been used,[10] including rifampicin with ethambutol[11] or isoniazid, rifabutin with ciprofloxacin,[12] minocycline with co-trimoxazole,[13] clarithromycin with rifabutin[14] or ciprofloxacin[12] or ethambutol.[12] Monotherapy with clarithromycin, minocycline, doxycycline, or co-trimoxazole have each been tried, mainly in small series of patients. US guidelines[5] suggest that for treatment of *M. marinum* infection, the use of 2 active antimycobacterials until 1 to 2 months after symptoms of infection have resolved may be a reasonable approach.

  Buruli ulcer, due to *M. ulcerans*, is difficult to treat and usually requires surgery; responses to antimycobacterial monotherapies have been generally disappointing. However, recent evidence suggests that combination antibacterial therapy may reduce the healing time and recurrence rates of ulcers, and minimise or avoid the need for surgery.[15] Treatment of nodules and plaques of early Buruli ulcers with rifampicin and streptomycin for up to 12 weeks, showed inhibition of growth 4 weeks after starting treatment.[16] Furthermore, no lesions enlarged during the treatment period. WHO therefore recommends the use of rifampicin and streptomycin or amikacin for 8 weeks.[17] Consensus recommendations issued by practitioners in Victoria, Australia[18] consider surgery to be the best treatment for Buruli ulcer, with antibacterial therapy being indicated for more extensive disease. Use of antibacterials may also possibly allow more conservative resection and reduce the risk of relapse. The recommended oral regimens were: at least 3 months of rifampicin given with clarithromycin, ciprofloxacin, or moxifloxacin. For more severe or extensive

disease patients may also require intravenous amikacin for 4 to 8 weeks in addition to oral therapy. Reports of other therapies include a beneficial response with topical nitrogen oxides in a small pilot study of 37 patients with Buruli ulcer,[19] and healing after local application of phenytoin.[20]

Cutaneous disease due to *M. haemophilum* infection has been treated with an initial treatment course of rifabutin, ciprofloxacin, and clarithromycin, followed by clarithromycin for 2 years.[21] *M. chelonae* was successfully treated with clarithromycin and linezolid for one month, followed by a further 5 months of treatment with clarithromycin.[22]

1. CDC. Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. *MMWR* 2009; **58** (RR-11): 1–166. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5811.pdf (accessed 05/02/10)
2. CDC. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR* 2009; **58**: (RR-4): 1–207. Also available at: http://www.cdc.gov/mmwr/pdf/rr/rr5804.pdf (accessed 05/02/10)
3. Subcommittee of the Joint Tuberculosis Committee of the British Thoracic Society. Management of opportunist mycobacterial infections: Joint Tuberculosis Committee guidelines 1999. *Thorax* 2000; **55**: 210–18. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Opportunist%20Mycobacteria/Guidelines/OppMyco.pdf (accessed 18/08/08)
4. Benson CA, *et al.* A prospective, randomized trial examining the efficacy and safety of clarithromycin in combination with ethambutol, rifabutin, or both for the treatment of disseminated Mycobacterium avium complex disease in persons with acquired immunodeficiency syndrome. *Clin Infect Dis* 2003; **37**: 1234–43.
5. American Thoracic Society. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med* 2007; **175**: 367–416. Correction. *ibid.*: 744–5. [dose] Also available at: http://ajrccm.atsjournals.org/cgi/reprint/175/4/367 (accessed 05/02/10)
6. Brooks JT, *et al.* Discontinuation of primary prophylaxis against Mycobacterium avium complex infection in HIV-infected persons receiving antiretroviral therapy: observations from a large national cohort in the United States, 1992—2002. *Clin Infect Dis* 2005; **41**: 549–53.
7. Barzilai A, *et al.* Successful treatment of disseminated Mycobacterium simiae infection in AIDS patients. *Scand J Infect Dis* 1998; **30**: 143–6.
8. Bailey WC. Treatment of atypical mycobacterial disease. *Chest* 1983; **84**: 625–8.
9. Piersimoni C, *et al.* Disseminated infection due to Mycobacterium celatum in patient with AIDS. *Lancet* 1994; **344**: 332.
10. Aubry A, *et al.* Sixty-three cases of Mycobacterium marinum infection: clinical features, treatment, and antibiotic susceptibility of causative isolates. *Arch Intern Med* 2002; **162**: 1746–52.
11. Donta ST, *et al.* Therapy of Mycobacterium marinum infections: use of tetracyclines vs rifampin. *Arch Intern Med* 1986; **146**: 902–4.
12. Laing RBS, *et al.* Antimicrobial treatment of fish tank granuloma. *J Hand Surg (Br)* 1997; **22B**: 135–7.
13. Gray SF, *et al.* Fish tank granuloma. *BMJ* 1990; **300**: 1069–70.
14. Laing RBS, *et al.* New antimicrobials against Mycobacterium marinum infection. *Br J Dermatol* 1994; **131**: 914.
15. Sizaire V, *et al.* Mycobacterium ulcerans infection: control, diagnosis, and treatment. *Lancet Infect Dis* 2006; **6**: 288–96.
16. Etuaful S, *et al.* Efficacy of the combination rifampin-streptomycin in preventing growth of Mycobacterium ulcerans in early lesions of Buruli ulcer in humans. *Antimicrob Agents Chemother* 2005; **49**: 3182–6.
17. WHO. *Provisional guidance on the role of specific antibiotics in the management of Mycobacterium ulcerans disease (Buruli ulcer).* Geneva: WHO, 2004. Available at: http://whqlibdoc.who.int/hq/2004/WHO_CDS_CPE_GBUI_2004.10.pdf (accessed 13/12/06)
18. Johnson PD, *et al.* Consensus recommendations for the diagnosis, treatment and control of Mycobacterium ulcerans infection (Bairnsdale or Buruli ulcer) in Victoria, Australia. *Med J Aust* 2007; **186**: 64–8.
19. Phillips R, *et al.* Pilot randomized double-blind trial of treatment of Mycobacterium ulcerans disease (Buruli ulcer) with topical nitrogen oxides. *Antimicrob Agents Chemother* 2004; **48**: 2866–70.
20. Adjei O, *et al.* Phenytoin in the treatment of Buruli ulcer. *Trans R Soc Trop Med Hyg* 1998; **92**: 108–9.
21. Elsayed S, Read R. Mycobacterium haemophilum osteomyelitis: case report and review of the literature. *BMC Infect Dis* 2006; **6**: 70. Available at: http://www.biomedcentral.com/content/pdf/1471-2334-6-70.pdf (accessed 13/12/06)
22. Kyle SD, Porter WM. Mycobacterium chelonae infection successfully treated with oral clarithromycin and linezolid. *Br J Dermatol* 2004; **151**: 1101.

Obstetric disorders

See under: Endometritis (the prophylaxis and treatment of postpartum endometritis), p. 180.3; Premature Labour, p. 203.3; and Urinary-Tract Infections in Pregnancy, p. 215.3. See also Neonatal Conjunctivitis, p. 193.2, and Perinatal Streptococcal Infections, p. 199.2.

Osteomyelitis

See under Bone and Joint Infections, p. 175.1.

Otitis externa

Otitis externa is a general term used to describe inflammation of the skin of the external auditory canal that may be due to infection with bacteria, viruses, or fungi or secondary to skin disorders such as eczema. Otitis externa is associated with high humidity, warmer temperatures, swimming, local trauma, or obstruction of the ear canal. Subtypes include acute localised otitis externa, acute diffuse otitis externa (swimmer's ear), chronic otitis externa, and necrotising (malignant) otitis externa. Acute diffuse disease is characterised by erythema, itching, pain, purulent discharge, oedema, fullness, and deafness. If left untreated or if treated inadequately it may progress to chronic otitis externa. Chronic otitis externa may also result from allergic contact dermatitis or other underlying skin conditions, such as eczema. Malignant otitis externa is rare and occurs mainly in immunocompromised persons and in diabetics and can be life-threatening if temporal bone infections occur.

The treatment of both acute and chronic otitis externa includes thorough cleansing and the use of appropriate acidifying and/or antibacterial ear drops, with or without a corticosteroid, even though some have doubted the value of topical antibacterials. A systematic review[1] that examined the effects of ear cleaning, topical treatments (generally acetic acid, antibacterials, corticosteroids, or combinations of these), and oral antibacterials on the resolution of acute uncomplicated otitis externa found that topical therapy was effective, but there was little evidence that one treatment was better than another in short-term management. Ear drops containing aminoglycosides, such as gentamicin, neomycin, or framycetin, or polymyxins should not be used when the ear drum is perforated because of the risk of ototoxicity.

The management of the various subtypes of otitis externa has been described.[2-5]

Acute localised otitis externa is an infection of the hair follicle (furunculosis), commonly due to *Staphylococcus aureus*. It may cause severe pain, which may be treated with an analgesic such as paracetamol or ibuprofen. If the furuncle is not pointing (ready to rupture spontaneously), local heat application and systemic treatment with a penicillinase-resistant penicillin such as flucloxacillin or a first-generation cephalosporin such as cefalexin may be used.[2] Others have suggested application of topical antibacterials using wicks which are left in the ear canal for 3 to 5 days.[4] Pointed furuncles require incision and drainage followed by a course of topical and/or oral antibacterials.[2,4]

In *acute diffuse otitis externa*, *Staphylococcus aureus*, *S. epidermidis*, and *Pseudomonas* spp. are often present. Treatment includes thorough cleansing of the ear canal and instillation of ear drops including acidifying agents (2% acetic acid) and antibacterials such as aminoglycosides, fluoroquinolones (ciprofloxacin and ofloxacin), chloramphenicol, or polymyxin B, with or without corticosteroids such as dexamethasone.[2,4] Antifungals may sometimes be required. A wick may be used if instillation proves difficult.[2] Systemic antibacterials may be necessary in severe cases of otitis externa.[2,4]

Chronic otitis externa is treated similarly, although the topical antibacterials and corticosteroids used should not be the same as those used previously for the treatment of acute disease.[2]

Necrotising (malignant) otitis externa, due to fulminating infection, especially with *Pseudomonas*, is uncommon but can occur in susceptible patients. Topical antibacterials are not effective and systemic treatment with antipseudomonal drugs such as gentamicin, ceftazidime, a carbapenem, or a fluoroquinolone is needed for about 4 to 8 weeks.[2,4] However, resistance to ciprofloxacin has been reported.[6] Combination treatment with an aminoglycoside and another antipseudomonal drug or a penicillin (such as azlocillin, piperacillin, or ticarcillin) may also be used.[2,4]

1. Kaushik V, *et al.* Interventions for acute otitis externa. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 17/03/10).
2. Brook I. Treatment of otitis externa in children. *Paediatr Drugs* 1999; **1**: 283–9.
3. Hughes E, Lee JH. Otitis externa. *Pediatr Rev* 2001; **22**: 191–7.
4. Ong YK, Chee G. Infections of the external ear. *Ann Acad Med Singapore* 2005; **34**: 330–34.
5. Osguthorpe JD, Nielsen DR. Otitis externa: review and clinical update. *Am Fam Physician* 2006; **74**: 1510–16.
6. Cooper MA, *et al.* Ciprofloxacin resistance developing during treatment of malignant otitis externa. *J Antimicrob Chemother* 1993; **32**: 163–4.

Otitis media

Otitis media is a general term used to describe inflammation of the middle ear that usually results from dysfunction of the Eustachian tube after a viral infection of the nasopharynx. It is one of the most frequent childhood illnesses seen in general practice. Subtypes of otitis media may be classified as follows:

- *acute otitis media (AOM)* is seen especially in young children and is often due to bacterial and/or viral infection and is sometimes associated with upper respiratory-tract infection. It is characterised by rapid onset, ear discomfort, and pain. Common bacterial pathogens include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* (*Branhamella catarrhalis*)
- *recurrent acute otitis media* refers to frequent episodes of AOM (3 or more episodes within 6 months or 4 episodes within 12 months) and may be due to relapse or re-infection
- *otitis media with effusion (OME) or serous otitis media*, commonly known as 'glue ear', is defined as the accumulation of fluid in the middle ear without local or systemic illness. It may be associated with recurrent upper respiratory-tract infection and is characterised by deafness although some episodes may be asymptomatic
- *chronic suppurative otitis media (CSOM)* is often preceded by one or more episodes of AOM and is associated with perforation of the ear drum, and continued infection and inflammation in the middle ear causing persistent or recurrent discharge and deafness. The condition has been divided into inactive or active. Inactive disease (tubotympanic disease) is typically characterised by perforation of the ear drum, deafness, and a profuse mucoid discharge associated with upper respiratory-tract infection. In active disease (attico-antral disease) there may be cholesteatoma with bone involvement. The commonest infecting organisms are *Pseudomonas aeruginosa* and anaerobes. Other common infecting aerobic organisms are diphtheroids, *Staphylococcus aureus*, and *Klebsiella*.[1]

TREATMENT

Treatment of *acute otitis media* aims to relieve symptoms, avoid complications, and prevent relapse, recurrence, and progression to the chronic state. Sometimes an analgesic such as paracetamol may be all that is required as long as frequent inspection is possible. However, it is common practice to prescribe a systemic antibacterial as well as an analgesic,[2] although the need for routine antibacterial treatment is questionable.[3-5] Systemic antibacterial treatment aims to speed resolution and prevent complications. However, meta-analyses and reviews have shown only modest benefits from routine use of antibacterials[6-8] and experience from studies where antibacterials were not given routinely for AOM has suggested that there is no consequent increase in complications.[4,8,9] Another meta-analysis[10] to estimate the natural history of AOM found that about 60% of children not initially treated with an antibacterial showed symptomatic improvement within 24 hours, and that symptoms resolved within 3 days in about 80% of these children. Suppurative complications occurred in about 0.12% of children not immediately treated with antibacterials and in 0.24% of those given immediate treatment. A systematic review[9] reported that clinical signs and symptoms resolved within 4 to 7 days in 78% of children not initially treated with an antibacterial. However, some clinicians have argued that although the benefit is modest, it is significant and therefore the routine use of antibacterials is clinically justifiable.[6] A later systematic review[11] concluded that antibacterials do provide a small benefit in very young children and a further meta-analysis[12] reported that most benefit was seen in children under 2 years of age with bilateral AOM, and in children with both AOM and discharge. Another suggested approach has been to delay the start of antibacterials for 72 hours and to then only give them if the patient remains unwell.[8,13,14] No one antibacterial has been found to be superior to another in the treatment of AOM.[9] Adjunctive treatment with topical and systemic decongestants and antihistamines has not been found to be beneficial[15] and there is insufficient information to conclude whether there is any benefit from the use of topical analgesics (including corticosteroids, local anaesthetics, and NSAIDs).[16]

The American Academy of Pediatrics has produced guidelines[17] for the diagnosis and management of uncomplicated AOM in children from 2 months to 12 years of age. They suggest that in a select group of children an observation period may be recommended depending on the patient's age, the diagnostic certainty, and the severity of illness. These children should be given symptomatic treatment and observed for 48 to 72 hours; if the illness worsens during the observation period or there is no improvement then systemic antibacterials should be considered. Pain management is important, and appropriate analgesics should be offered. If antibacterial treatment is given high-dose amoxicillin (80 to 90 mg/kg daily) is recommended for most children. In children with severe illness or those not responding to amoxicillin and thought to be infected with *H. influenzae* or *M. catarrhalis* high-dose amoxicillin with clavulanic acid should be given. Alternatives in penicillin-allergic children include cephalosporins, azithromycin, or clarithromycin. Similar recommendations have been made for the treatment of AOM in the UK.[18]

Duration of therapy for AOM has varied from 5 to 10 or more days. A systematic review[19] of published clinical studies suggests that a 5-day treatment course may be given to children with uncomplicated AOM. The American Academy of Pediatrics recommends treatment with antibacterials for 10 days in younger children (up to 6 years of age) and for children with severe disease; those aged 6 years or older with mild to moderate disease may be given treatment for 5 to 7 days.[17]

Penicillin-resistant strains of *Str. pneumoniae* have been reported in children with otitis media and are reported to be increasingly prevalent.[20] About one-quarter of *Str.*

pneumoniae isolates, one third of *H. influenzae* isolates, and nearly all *M. catarrhalis* isolates are resistant to penicillin and amoxicillin.[2] However, resistance rates vary between countries[21], and many penicillin-resistant strains remain sensitive *in vivo* to high-dose amoxicillin.[20,22,23]

Optimal treatment of *otitis media with effusion* is controversial and the majority of cases will resolve spontaneously within 3 months. Guidelines have been developed in the USA[24] for the diagnosis and management of uncomplicated disease in children from 2 months to 12 years of age. They suggest careful assessment and observation for at least 3 months before considering surgery. Those at increased risk of developmental difficulties such as children with cleft palate or Down's syndrome should be referred to a specialist. Similar recommendations have been made for the treatment of OME in the UK.[25] Antihistamines, decongestants, and mucolytics are ineffective.[24-26] Oral or topical intranasal corticosteroids alone or with an antibacterial have only short-term benefit[27] and their use is not recommended as routine treatment.[24,25] A meta-analysis[28] on the use of antibacterials for the treatment of OME failed to find any benefit and their use cannot be justified.[24,25]

Treatment of *chronic suppurative otitis media* aims to stop the discharge, eradicate the infection, heal the ear drum, and to prevent serious complications. Treatment options for uncomplicated cases include aural toilet (thorough cleansing and mopping of the ear), systemic antibacterials, and topical treatments with either an antiseptic or antibacterial, sometimes also with a corticosteroid. Surgery may be needed if complications develop.[1,29] There is controversy over the use of ear drops containing aminoglycosides or polymyxins in the presence of a perforated ear drum, as they are potentially ototoxic. However, it is considered that deafness is more likely to result from untreated disease than from a short course of these ear drops. A systematic review[29] found that treatment with topical fluoroquinolone ear drops was more effective at drying the ear than no drug treatment or topical antiseptics; effects of topical non-fluoroquinolone antibacterials when compared with no drug treatment or topical antiseptics were less clear. Another systematic review[30] found that ear drops containing fluoroquinolones were also more effective than systemic antibacterials at drying the ear. Effects of topical non-fluoroquinolone antibacterials or antiseptics were less clear and no additional benefit was noted by adding a systemic antibacterial to topical antibacterial treatment.

PREVENTION

Long-term antibacterial prophylaxis has been tried in children at high risk including those with *recurrent acute otitis media*,[31,32] but the evidence for its benefit is inconsistent. A meta-analysis[33] on the use of antibacterials to prevent recurrent AOM concluded that they appeared to have limited benefit and that 9 children would need to be treated to show an improved outcome in one. A later meta-analysis[34] concluded that antibacterials reduced the probability of disease recurring during the treatment period, but that the long-term benefits of treatment were unclear and that 5 children would need to be treated to show an improved outcome in one.

The use of xylitol, which inhibits the growth of *Str. pneumoniae*, as chewing gum[35,36] or as syrup for very young children[36,37] has been reported to reduce the incidence of AOM. Randomised studies[35,36] with xylitol chewing gum reported a 40% reduction in the incidence of AOM in children with recurrent AOM. However, xylitol was found to be ineffective when it was used only during an acute respiratory-tract infection[38] and the need for use 5 times daily may make this treatment impractical.[35,36]

Vaccination against AOM with pneumococcal vaccines has also been tried but unconjugated multivalent polysaccharide vaccines do not prevent AOM in children under 2 years of age[23,39] and their benefit in older children is minimal.[39] A meta-analysis[39] found that starting immunisation with the 7-valent pneumococcal conjugate vaccine during infancy has marginal beneficial effects in terms of reducing the incidence of recurrent AOM. Giving 7-valent pneumococcal conjugate vaccine, followed by 23-valent pneumococcal polysaccharide vaccine, to older children with recurrent infections appears to have no benefit in preventing further episodes.

Vaccination may also have a role in reducing the incidence and in preventing the development of antibacterial resistance[23] but use of conjugated pneumococcal vaccines was found to cause a shift in the pathogens responsible for AOM from vaccine-type pneumococci to nonvaccine-type strains and to *H. influenzae*.[23]

1. Wintermeyer SM, Nahata MC. Chronic suppurative otitis media. *Ann Pharmacother* 1994; **28**: 1089–99.
2. Hendley JO. Otitis media. *N Engl J Med* 2002; **347**: 1169–74.
3. Browning GG. Childhood otalgia: acute otitis media 1. *BMJ* 1990; **300**: 1005–6.
4. Majeed A, Harris T. Acute otitis media in children. *BMJ* 1997; **315**: 321–2.
5. Damoiseaux RAMJ, *et al.* Primary care based randomised, double blind trial of amoxicillin versus placebo for acute otitis media in children aged under 2 years. *BMJ* 2000; **320**: 350–4.
6. Rosenfeld RM, *et al.* Clinical efficacy of antimicrobial drugs for acute otitis media: metaanalysis of 5400 children from thirty-three randomized trials. *J Pediatr* 1994; **124**: 355–67.
7. Del Mar C, *et al.* Are antibiotics indicated as initial treatment for children with acute otitis media? A meta-analysis. *BMJ* 1997; **314**: 1526–9.
8. Froom J, *et al.* Antimicrobials for acute otitis media? A review from the International Primary Care Network. *BMJ* 1997; **315**: 98–102.
9. Takata GS, *et al.* Evidence assessment of management of acute otitis media: I— The role of antibiotics in treatment of uncomplicated acute otitis media. *Pediatrics* 2001; **108**: 239–47.
10. Rosenfeld RM, Kay D. Natural history of untreated otitis media. *Laryngoscope* 2003; **113**: 1645–57.
11. Glasziou PP, *et al.* Antibiotics for acute otitis media in children. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 22/05/07).
12. Rovers MM, *et al.* Antibiotics for acute otitis media: a meta-analysis with individual patient data. *Lancet* 2006; **368**: 1429–35.
13. Little P, *et al.* Pragmatic randomised controlled trial of two prescribing strategies for childhood acute otitis media. *BMJ* 2001; **322**: 336–42.
14. McCormick DP, *et al.* Nonsevere acute otitis media: a clinical trial comparing outcomes of watchful waiting versus immediate antibiotic treatment. *Pediatrics* 2005; **115**: 1455–65.
15. Chonmaitree T, *et al.* A randomized, placebo-controlled trial of the effect of antihistamine or corticosteroid treatment in acute otitis media. *J Pediatr* 2003; **143**: 377–85.
16. Foxlee R, *et al.* Topical analgesia for acute otitis media. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 22/05/07).
17. American Academy of Pediatrics. Clinical practice guideline: diagnosis and management of acute otitis media. *Pediatrics* 2004; **113**: 1451–65. Also available at: http://aappolicy.aappublications.org/cgi/reprint/pediatrics;113/5/1451.pdf (accessed 22/05/07)
18. UK National Library for Health. Clinical Knowledge Summaries. Otitis media—acute (issued Jan 2007; updated 2009). Available at: http://cks.library.nhs.uk/otitis_media_acute/view_whole_topic (accessed 30/04/10)
19. Kozyrskyj AL, *et al.* Short course antibiotics for acute otitis media. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2000 (accessed 22/05/07).
20. Klugman KP. Epidemiology, control and treatment of multiresistant pneumococci. *Drugs* 1996; **52** (suppl 2): 42–6.
21. Rovers MM, *et al.* Otitis media. *Lancet* 2004; **363**: 465–73. Correction. *ibid.*: 1080.
22. Pelton SI. New concepts in the pathophysiology and management of middle ear disease in childhood. *Drugs* 1996; **52** (suppl 2): 62–7.
23. Jacobs MR. Prevention of otitis media: role of pneumococcal conjugate vaccines in reducing incidence and antibiotic resistance. *J Pediatr* 2002; **141**: 287–93.
24. American Academy of Family Physicians, American Academy of Otolaryngology-Head and Neck Surgery, American Academy of Pediatrics Subcommittee on Otitis Media With Effusion. Otitis media with effusion. *Pediatrics* 2004; **113**: 1412–29. Also available at: http://pediatrics.aappublications.org/cgi/reprint/113/5/1412 (accessed 26/01/07)
25. UK National Library for Health. Clinical Knowledge Summaries. Otitis media with effusion (issued March 2007). Available at: http://cks.library.nhs.uk/otitis_media_with_effusion/view_whole_topic (accessed 18/08/08)
26. Griffin GH, *et al.* Antihistamines and/or decongestants for otitis media with effusion (OME) in children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 18/01/07).
27. Thomas CL, *et al.* Oral or topical nasal steroids for hearing loss associated with otitis media with effusion in children. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 18/01/07).
28. Cantekin EI, McGuire TW. Antibiotics are not effective for otitis media with effusion: reanalysis of meta-analyses. *Otorhinolaryngol Nova* 1998; **8**: 214–22.
29. Macfadyen CA, *et al.* Topical antibiotics without steroids for chronically discharging ears with underlying eardrum perforations. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 18/01/07).
30. Macfadyen CA, *et al.* Systemic antibiotics versus topical treatments for chronically discharging ears with underlying eardrum perforations. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 18/01/07).
31. Roark R, Berman S. Continuous twice daily or once daily amoxicillin prophylaxis compared with placebo for children with recurrent acute otitis media. *Pediatr Infect Dis J* 1997; **16**: 376–81.
32. Teele DW, *et al.* Antimicrobial prophylaxis for infants at risk for recurrent acute otitis media. *Vaccine* 2001; **19** (suppl 1): S140–S143.
33. Williams RL, *et al.* Use of antibiotics in preventing recurrent acute otitis media and in treating otitis media with effusion: a meta-analytic attempt to resolve the brouhaha. *JAMA* 1993; **270**: 1344–51. Correction. *ibid.* 1994; **271**: 430.
34. Leach AJ, Morris PS. Antibiotics for the prevention of acute and chronic suppurative otitis media in children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 18/01/07).
35. Uhari M, *et al.* Xylitol chewing gum in prevention of acute otitis media: double blind randomised trial. *BMJ* 1996; **313**: 1180–4.
36. Uhari M, *et al.* A novel use of xylitol sugar in preventing acute otitis media. *Pediatrics* 1998; **102**: 879–84.
37. Uhari M, *et al.* Xylitol in preventing acute otitis media. *Vaccine* 2001; **19**: S144–S147.
38. Tapiainen T, *et al.* Xylitol administered only during respiratory infections failed to prevent acute otitis media. Abstract: *Pediatrics* 2002; **109**: 302. Full version: http://pediatrics.aappublications.org/cgi/content/full/109/2/e19 (accessed 22/05/07)
39. Jansen AGSC, *et al.* Pneumococcal conjugate vaccines for preventing otitis media. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 30/04/10).

Pancreatitis

The overall management of pancreatitis is discussed on p. 2580.2. **Pancreatic necrosis** is the most serious local complication of acute pancreatitis. When necrosis is sterile, mortality is low and *treatment* is conservative.[1] Morbidity and mortality increase if the initially sterile pancreatic necrosis becomes infected by bacteria from the gut.[1,2] When infection is proven and cultures reveal the presence of Gram-negative bacteria, choices for antibacterial treatment include a carbapenem, a fluoroquinolone plus metronidazole, or a third generation cephalosporin plus metronidazole; vancomycin is a reasonable choice for Gram-positive bacteria.[3]

There has been considerable interest in the early *prevention* of infected necrosis with antibacterials; cephalosporins, carbapenems, and fluoroquinolones have been studied as they are considered to have the best penetration into the pancreas.[4] There is, however, uncertainty about their value in acute necrotising pancreatitis due to concerns about promoting antibacterial resistance and opportunistic fungal infections,[5] and conflicting results from studies. A systematic review[6] of 5 studies in patients with proven pancreatic necrosis found that, despite variations in drugs used (cefuroxime, imipenem, or metronidazole with ciprofloxacin or ofloxacin) and in the quality and methodology of studies conducted, intravenous antibacterial prophylaxis appeared to reduce the risk of death in patients with pancreatic necrosis, but with only a trend towards a reduced rate of infected pancreatic necrosis. A subsequent meta-analysis[4] of 7 studies, including the 5 studies in the previous systematic review, found no reduction in the risk of infected pancreatic necrosis or death, and suggested that routine prophylactic antibacterials may not be useful. Guidelines therefore vary in their recommendations. Those developed in the USA[3] do not recommend antibacterial prophylaxis in patients with necrotising pancreatitis; however, if signs of sepsis are present, antibacterials may be given while the source of infection is investigated. Treatment should be stopped if no source of infection is found. UK guidelines[2] do not make a recommendation as there is no consensus on the issue, but state that if antibacterial prophylaxis is used, it should be given for a maximum of 14 days.

1. Frossard J-L, *et al.* Acute pancreatitis. *Lancet* 2008; **371**: 143–52.
2. Working Party of the British Society of Gastroenterology. Association of Surgeons of Great Britain and Ireland. Pancreatic Society of Great Britain and Ireland. UK guidelines for the management of acute pancreatitis. *Gut* 2005; **54** (suppl III): iii1–iii9. Also available at: http://www.bsg.org.uk/pdf_word_docs/pancreatic.pdf (accessed 23/12/08)
3. Banks PA, Freeman ML. Practice Parameters Committee of the American College of Gastroenterology. Practice guidelines in acute pancreatitis. *Am J Gastroenterol* 2006; **101**: 2379–2400. Also available at: http://www.acg.gi.org/physicians/guidelines/AcutePancreatitis.pdf (accessed 23/12/08)
4. Bai Y, *et al.* Prophylactic antibiotics cannot reduce infected pancreatic necrosis and mortality in acute necrotizing pancreatitis: evidence from a meta-analysis of randomized controlled trials. *Am J Gastroenterol* 2008; **103**: 104–10.
5. Kingsnorth A, O'Reilly D. Acute pancreatitis. *BMJ* 2006; **332**: 1072–6.
6. Villatoro E, *et al.* Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 23/12/08).

Pelvic inflammatory disease

Pelvic inflammatory disease (PID) is a broad term for infectious disorders of the upper genital tract in women and may include endometritis, salpingitis, tubo-ovarian abscess, and pelvic peritonitis. It is generally due to ascending infection through the cervix and uterus to the fallopian tubes, resulting in salpingitis, and from there may extend to the ovaries and peritoneum. Long-term complications include infertility and ectopic pregnancy. The use of intrauterine contraceptive devices might increase the likelihood of PID although the risk may have been overstated;[1] it appears to be greatest during the first 20 days after insertion of the device.[2]

The majority of these infections are probably sexually transmitted and at one time were mainly due to *Neisseria gonorrhoeae*, but *Chlamydia trachomatis* is increasingly responsible and may be the commonest cause of PID in some areas. Other organisms that have been isolated include *Mycoplasma hominis; Ureaplasma urealyticum;* anaerobes such as *Bacteroides, Peptococcus,* and *Peptostreptococcus* spp.; Gram-negative enteric aerobes such as *Escherichia coli;* and Gram-positive aerobes such as group B streptococci. Some of these organisms occur in the abnormal vaginal flora associated with bacterial vaginosis (p. 174.1). Thus, the aetiology of PID appears to be polymicrobial; some think that primary infection with *N. gonorrhoeae* or *C. trachomatis*, or both, allows opportunistic infection with aerobic and anaerobic bacteria.[1]

Treatment regimens are of necessity broad spectrum and empirical and should include antibacterials active against the major pathogens. Many consider that treatment should be started in hospital so that drugs can be given parenterally. Guidelines produced by WHO,[3] by an expert group in the UK,[4] and by the CDC in the USA[5] are as follows, although recommendations may need to be localised because of differences in patterns of infection and drug resistance:

- **WHO:**
  - *inpatients:*
    - intramuscular ceftriaxone 250 mg daily, *plus* oral or intravenous doxycycline 100 mg twice daily (or oral tetracycline 500 mg four times daily), *plus*

oral or intravenous metronidazole 400 to 500 mg twice daily or chloramphenicol 500 mg four times daily
- intravenous clindamycin 900 mg every 8 hours, *plus* intravenous gentamicin 1.5 mg/kg every 8 hours
- oral ciprofloxacin 500 mg twice daily or intramuscular spectinomycin 1 g four times daily, *plus* oral or intravenous doxycycline 100 mg twice daily (or oral tetracycline 500 mg four times daily), *plus* oral or intravenous metronidazole 400 to 500 mg twice daily or chloramphenicol 500 mg four times daily

Therapy should be continued for at least 48 hours after clinical improvement, and *then* followed by doxycycline or tetracycline orally for 14 days.

- *outpatients*:
  - a single-dose treatment for uncomplicated gonorrhoea such as a single intramuscular dose of ceftriaxone 125 mg is recommended (see Gonorrhoea, p. 206.2) *plus* oral metronidazole 400 to 500 mg twice daily *and* oral doxycycline 100 mg twice daily (or oral tetracycline 500 mg four times daily) for 14 days.

- **UK:**
  - *inpatients*:

    with the regimens below intravenous therapy is continued until 24 hours after clinical improvement, and the oral regimen is *then* substituted until therapy has been given for at least 14 days.
    - intravenous ceftriaxone 2 g daily *plus* intravenous (or oral if tolerated) doxycycline 100 mg twice daily, until clinical improvement, *then* oral doxycycline 100 mg twice daily, *plus* oral metronidazole 400 mg twice daily
    - intravenous clindamycin 900 mg three times daily *plus* intravenous gentamicin (2 mg/kg as a loading dose, *then* 1.5 mg/kg three times daily *or* a single daily dose of 7 mg/kg) until clinical improvement, *then* either oral clindamycin 450 mg four times daily or oral doxycycline 100 mg twice daily *plus* oral metronidazole 400 mg twice daily

    alternative regimens, given for a total of 14 days, are:
    - intravenous ofloxacin 400 mg twice daily *plus* intravenous metronidazole 500 mg three times daily
    - intravenous ciprofloxacin 200 mg twice daily *plus* intravenous metronidazole 500 mg three times daily, *plus* intravenous or oral doxycycline 100 mg twice daily

    Metronidazole may be stopped in women with mild or moderate disease who tolerate it poorly, but the improved coverage of anaerobic infection that it provides is more important in women with severe disease.
  - *outpatients*:
    - a single intramuscular dose of ceftriaxone 500 mg, *then* oral doxycycline 100 mg twice daily plus oral metronidazole 400 mg twice daily for 14 days, *or*
    - oral ofloxacin 400 mg plus oral metronidazole 400 mg both twice daily for 14 days

    alternative regimens are:
    - a single intramuscular dose of ceftriaxone 500 mg, *then* azithromycin 1 g each week for 2 weeks, *or*
    - oral moxifloxacin 400 mg once daily for 14 days
- **USA:**
  - *parenteral* treatment:
    - (regimen A): intravenous cefoxitin 2 g every 6 hours or cefotetan 2 g every 12 hours *plus* oral or intravenous doxycycline 100 mg every 12 hours
    - (regimen B): intravenous clindamycin 900 mg every 8 hours *plus* parenteral gentamicin 2 mg/kg as a loading dose *then* 1.5 mg/kg every 8 hours; alternatively, a single daily dose regimen of 3 to 5 mg/kg daily can be used for maintenance

    In each case parenteral treatment is continued for 24 hours after substantial clinical improvement has occurred and *then* followed by oral therapy to complete a total of 14 days of treatment.
    - in regimen A, continuation is usually with oral doxycycline 100 mg twice daily; in patients with tubo-ovarian abscesses oral clindamycin *or* oral metronidazole should be added to doxycycline
    - in regimen B, continuation may be with oral clindamycin 450 mg four times daily *or* doxycycline; oral clindamycin is preferred in patients with tubo-ovarian abscesses

    Another parenteral regimen which has been tried is:
    - intravenous ampicillin/sulbactam 3 g every 6 hours *plus* oral or intravenous doxycycline 100 mg every 12 hours.
  - *oral* treatment:
    - a single intramuscular dose of cefoxitin 2 g *plus* oral probenecid 1 g, *or* a single intramuscular dose of ceftriaxone 250 mg (*or* an equivalent third-generation cephalosporin), *plus* oral doxycycline 100 mg twice daily, with or without oral metronidazole 500 mg twice daily, for 14 days

Pregnant women who have suspected PID disease should be hospitalised and treated with a parenteral regimen.[3]

Sexual partners of patients with PID should be tested and treated.[3]

Women co-infected with HIV appear to be more likely to develop tubo-ovarian abscesses but respond similarly to treatment compared with women who are HIV-negative.[3]

1. Pearce JM. Pelvic inflammatory disease. *BMJ* 1990; 300: 1090–1.
2. Farley TMM, *et al.* Intrauterine devices and pelvic inflammatory disease: an international perspective. *Lancet* 1992; 339: 785–8.
3. WHO. Guidelines for the management of sexually transmitted infections. Geneva: WHO, 2003. Also available at: http://whqlibdoc.who.int/publications/2003/9241546263.pdf (accessed 23/03/07)
4. Clinical Effectiveness Group (British Association for Sexual Health and HIV). UK national guideline for the management of pelvic inflammatory disease (updated June 2011). Available at: http://www.bashh.org/documents/3572 (accessed 30/07/12)
5. CDC. Sexually transmitted diseases treatment guidelines, 2010. *MMWR* 2010; 59 (RR-12): 1–110. Also available at: http://www.cdc.gov/STD/treatment/2010/STD-Treatment-2010-RR5912.pdf (accessed 08/01/11) Correction. *ibid.* 2011; 60: 18. [dose]

Peptic ulcer disease

The Gram-negative bacterium *Helicobacter pylori* is involved in the aetiology of gastritis and peptic ulceration, and treatment regimens to eradicate the organism are recommended in peptic ulcer disease (p. 1816.2).

Perinatal streptococcal infections

Group B streptococci are a major cause of perinatal infections, often leading to neonatal pneumonia or septicaemia, sometimes with meningitis, although the incidence varies in different parts of the world. Maternal colonisation with group B streptococci in the genito-urinary or gastrointestinal tracts is the main risk factor for disease and neonatal infections are acquired vertically through maternal genital carriage during pregnancy. Infection in newborns occurring within the first week of life is termed early-onset disease, while late-onset infections occur in infants more than 1 week of age.

It has been suggested that *prevention* of group B streptococcal infection in infants may be achieved by giving appropriate antibacterials to the mother during labour,[1] but a systematic review found a lack of high-quality clinical evidence to support this practice.[2] Ideally maternal carriers of group B streptococci would be identified during pregnancy, but this may not be practical. Factors that increase the risk of acquiring neonatal infection include premature labour, prolonged rupture of membranes, maternal fever, a previous child with neonatal group B streptococcal infection, and multiple pregnancy and they will influence the decision of whether or not to give intrapartum antibacterial prophylaxis to the mother. A penicillin is the preferred drug.

Guidelines to prevent early-onset disease from the USA[1] recommend prophylaxis based on universal prenatal screening. Where required, they recommend benzylpenicillin or, alternatively, ampicillin, given intravenously during labour. In women allergic to penicillin but who are not considered to be at high risk of anaphylaxis, intravenous cefazolin is recommended as an alternative; those considered to be at high risk of anaphylaxis should be given clindamycin intravenously or, where there is resistance to clindamycin or susceptibility is unknown, intravenous vancomycin. Erythromycin is no longer recommended as an alternative for prophylaxis for penicillin-allergic women at high risk for anaphylaxis.

In other parts of the world, including Europe, the incidence of neonatal streptococcal infections is much lower and the US model for prophylaxis may not be appropriate.[3]

Another strategy suggested for areas with a high incidence of neonatal group B streptococcal disease (above 1.5 per 1000 live births) is to give a single intramuscular dose of penicillin to all neonates at birth.[4] However, despite positive results in some uncontrolled, retrospective, and non-randomised studies, a systematic review[5] found that routine use of intramuscular penicillin in neonates did not reduce the incidence of early-onset group B streptococcal disease, or mortality.

As mentioned under Premature Labour, p. 203.3, the elimination of bacteria such as group B streptococci in pregnant women might also reduce the risk of premature labour.

Streptococcus group B vaccines are under investigation for use in pregnant women to prevent neonatal infection.

1. CDC. Prevention of perinatal group B streptococcal disease: revised guidelines from CDC, 2010. *MMWR* 2010; 59 (RR-10): 1–32. Also available at: http://www.cdc.gov/mmwr/pdf/rr/rr5910.pdf (accessed 28/11/10)
2. Ohlsson A, Shah VS. Intrapartum antibiotics for known maternal Group B streptococcal colonization. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2009 (accessed 18/02/10).
3. Simpson AJA, Heard SR. Group B Streptococcus. *Lancet* 1995; 346: 700.
4. Siegel JD, Cushion NB. Prevention of early-onset group B streptococcal disease: another look at single-dose penicillin at birth. *Obstet Gynecol* 1996; 87: 692–8.
5. Woodgate PG, *et al.* Intramuscular penicillin for the prevention of early onset group B streptococcal infection in newborn infants. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 18/02/10).

Peritonitis

Infective peritonitis, a type of intra-abdominal infection, is an inflammation of the peritoneum resulting from contamination of the peritoneal cavity with bacteria or fungi (for information on fungal peritonitis, see under Choice of Antifungal, p. 567.1). It may be primary or secondary or may be a complication of peritoneal dialysis (PD). Peritonitis may be complicated by intraperitoneal abscesses, and abscesses of the intra-abdominal viscera such as those of the liver (see under Abscess, Liver, p. 172.3), pancreas, and spleen.

Primary peritonitis. In primary or spontaneous bacterial peritonitis there is no specific focus of infection and it occurs most often as a complication of ascites, particularly in advanced liver disease. Infecting bacteria include *Escherichia coli*, other Enterobacteriaceae, and streptococci or enterococci; anaerobic bacteria are very rarely encountered. Infection is most often due to a single organism.

Because ascitic fluid cultures are often negative in primary peritonitis, initial antibacterial **treatment** is generally empirical and targeted towards the most likely pathogens. Historically, multidrug regimens such as ampicillin plus an aminoglycoside have been used, and more recently, other alternatives have included broad-spectrum penicillins, carbapenems, fluoroquinolones, and combinations of penicillins with beta-lactamase inhibitors.[1-4] Third-generation cephalosporins such as cefotaxime are considered by some to be the treatment of choice.[1,2,5] Current evidence, however, does not appear to show a significant advantage for the cephalosporins over other antibacterials in terms of resolution of infection or patient survival.[4]

Intravenous antibacterials are generally preferred, however, oral antibacterials such as amoxicillin-clavulanic acid, cefixime, and some fluoroquinolones[4] have been tried and may be as effective in patients with uncomplicated infection. The optimal duration of therapy is unclear. Intervals of 10 to 14 days have been used, but, in one study,[6] a 5-day regimen was noted to be as effective as a 10-day course. In most studies, however, length of treatment has been dictated by the resolution of signs and symptoms of disease, rather than completion of a predetermined course of therapy.[4]

Given the very high rate of recurrence in patients surviving an initial episode of primary peritonitis, long-term secondary **prophylaxis** has been advocated. In some studies, daily oral doses of norfloxacin have been associated with lower rates of subsequent peritonitis; in one, the probability of recurrent infection at 1 year was reduced from 68 to 20%.[7] Ciprofloxacin[8] and co-trimoxazole[9] are also reportedly effective.

In addition, long-term prophylaxis against first episodes of infection has also been suggested for some high-risk patient groups. Patients at highest risk appear to be those with low serum sodium or ascitic fluid protein concentration, as well as those with acute gastrointestinal bleeding, or very advanced liver disease.[4,10] A meta-analysis[8] examining efficacy of antibacterial prophylaxis in cirrhotic patients with advanced liver dysfunction or low ascitic fluid protein concentrations reported a 28% relative risk reduction for first-time incidence of primary peritonitis, but a trend towards survival benefit failed to reach statistical significance. It has been suggested that short courses of antibacterials may be of benefit in cirrhotic patients with ascites *without gastrointestinal bleeding*, but the body of evidence in support of this practice has been criticised.[11] Use of primary prophylaxis in such patients remains an area of controversy and is currently not routinely recommended.[2,3,10] In contrast, short courses of antibacterials have been associated with significantly reduced rates of subsequent infection, including peritonitis, and reductions in overall mortality, in cirrhotic patients *with acute gastrointestinal bleeds*;[12,13] as a result, routine antibacterial treatment for a minimum of 7 days has been recommended for all cirrhotic patients presenting with acute upper gastrointestinal haemorrhage.[2] Although most studies have involved the use of a fluoroquinolone, other drugs including third-generation cephalosporins, carbapenems, and amoxicillin-clavulanic acid have also been tried.[13]

Secondary peritonitis. Secondary peritonitis is associated with perforation of the gastrointestinal tract, conditions such as appendicitis and diverticulitis, and contamination at surgery. Infections are generally mixed and originate from the gastrointestinal tract. Bacteria responsible include *E. coli* and other Enterobacteriaceae, anaerobes (especially *Bacteroides fragilis*), enterococci, and sometimes *Pseudomonas aeruginosa*. Timely control of the source of infection, where possible, is critical for successful **treatment**, but antibacterial therapy is an important adjunct. Broad-spectrum antibacterial therapy is usually given, at least until the infecting organisms are known, and should generally include, at minimum, antibacterials effective against enteric Gram-negative aerobic and facultative bacilli, and enteric Gram-positive streptococci. Coverage for obligate anaerobic bacilli should also be included for infections derived from distal small-bowel, appendix, and colon, as well as for more proximal perforations in the presence of obstruction or paralytic ileus.[14] In addition, choice of regimen should take into account patient-specific risk factors for more resistant

infection. For patients with a history of antibacterial exposure or prolonged hospitalisation, a regimen with antipseudomonal activity should be considered.[15] Similarly, coverage for MRSA should be added for healthcare-associated infections in patients known to be colonised with MRSA, or who are at risk due to previous treatment failure and significant antibacterial exposure.[14] Coverage for enterococci has also been advocated in severely ill patients with a history of prolonged cephalosporin use or recurrent intra-abdominal infection, active immunosuppression, and in those with prosthetic heart valves.[16] Empirical antifungal treatment might also be considered in cases of gastrointestinal perforation, anastomotic leak, or severe necrotising pancreatitis.[15] For healthcare-associated infections, institution-specific resistance patterns are also an important consideration in the choice of therapy.

No empirical antibacterial regimen has been shown to be consistently superior or better tolerated than comparators,[17] and various single- and multidrug regimens have been suggested by the Infectious Diseases Society of America (IDSA) depending on infection severity and whether it is considered community-acquired or healthcare-associated.[14]

For *mild-to-moderate community-acquired infection*, the IDSA recommends the following regimens:

- monotherapy with ticarcillin-clavulanate, cefoxitin, ertapenem, moxifloxacin, or tigecycline
- combination therapy with metronidazole and either cefazolin, cefuroxime, ceftriaxone, cefotaxime, levofloxacin, or ciprofloxacin

For *high-severity community-acquired infection* a regimen with an expanded spectrum of activity against Gram-negative bacteria is suggested by the IDSA,[14] and suitable regimens include:

- monotherapy with meropenem, imipenem-cilastatin, doripenem, or piperacillin-tazobactam
- combination therapy with metronidazole and either ciprofloxacin, levofloxacin, ceftazidime, or cefepime (however, see below regarding *E.coli* resistance to quinolones)
- combination therapy with metronidazole, aztreonam, and another antibacterial effective against Gram-positive cocci

For *healthcare-associated infection*, empirical antibacterial regimens should be informed by hospital-specific microbiological and resistance data and may require drugs active against a wide spectrum of Gram-negative organisms. Multidrug regimens are suggested, and the IDSA recommends using metronidazole combined with either meropenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam, ceftazidime, or cefepime; use of colistin or an aminoglycoside may be required.[14]

Because *B. fragilis* has shown substantial acquired resistance to clindamycin, cefotetan, cefoxitin, and the fluoroquinolones, these drugs should not be used alone as initial therapy.[14] Given the high rate of fluoroquinolone-resistant *E. coli* in some communities, fluoroquinolones should not be used empirically unless hospital microbiological surveys indicate >90% susceptibility to fluoroquinolones.[14]

For patients with only mild or moderate community-acquired infection, drugs with the broadest spectrum of Gram-negative and Gram-positive coverage (such as ertapenem and tigecycline) have no advantage and may contribute to the emergence of more resistant organisms. Similarly, aminoglycosides are not routinely recommended due to their potential toxicity, although empirical use may be warranted in patients with healthcare-associated infection or intolerance to beta-lactam or fluoroquinolone-based regimens.[14]

The intravenous route is generally preferred, and therapy should be tailored to culture and susceptibility reports when available. Treatment is generally continued until clinical signs of infection and gastrointestinal function have returned to normal; where source control has been adequate, about 5 to 7 days has been suggested.[15]

For reference to the **prevention** of postoperative infection, see under Surgical Infection, p. 211.1.

PD peritonitis. Peritonitis is the main complication of peritoneal dialysis (PD). Like primary, and, unlike secondary peritonitis, above, a single infecting organism is often responsible. The most common infections have usually been due to Gram-positive organisms, especially staphylococci, but infections with Gram-negative bacteria (typically Enterobacteriaceae) are becoming more common, and fungi are an increasingly important cause of peritonitis in PD.[1] The origin of infection is often contamination of the dialysis catheter or the exit site.

The International Society for Peritoneal Dialysis recommends[18] that the choice of antibacterial for empirical **treatment** be based on the history of sensitivities of organisms causing peritonitis in the particular hospital or centre involved, and be active against both Gram-positive and Gram-negative organisms. In many cases, first-generation cephalosporins such as cefazolin or cefalotin provide adequate Gram-positive coverage, but in centres with high rates of meticillin-resistant infection empirical vancomycin may be needed. Drugs for Gram-negative coverage should possess activity against *Ps. aeruginosa* and may include the aminoglycosides, ceftazidime, cefepime, a carbapenem, or aztreonam. Fluoroquinolones are only appropriate for Gram-negative coverage if local susceptibility is shown.

Intraperitoneal dosage, by mixing the antibacterials with the dialysate, has been shown to be more effective than intravenous use. For many antibacterials, once-daily intermittent dosing regimens (in a single dialysate exchange) are appropriate and as effective as continuous regimens.[19] Intermittent doses of vancomycin are generally given once every 5 to 7 days.[18] Once the infecting organism is identified, an appropriate narrow-spectrum antibacterial can be substituted. Treatment is generally continued for 14 days in patients who have a clinical response. Treatment should be extended to 21 days in patients with severe infections (such as *Staph. aureus*, Gram-negative, or enterococcal peritonitis).

Exit-site infections can be treated with an oral penicillinase-resistant penicillin, a first-generation cephalosporin such as cefalexin, or co-trimoxazole for Gram-positive infections. Vancomycin should be avoided for routine use but may be needed if there is meticillin resistance. Rifampicin may be added in severe *Staph. aureus* infections. An oral fluoroquinolone such as ciprofloxacin may be used for Gram-negative infections.[18] Intraperitoneal ceftazidime may be added in cases of pseudomonal infection where resolution of infection is slow or where there is recurrence.

Long-term antibacterial **prophylaxis** is not generally effective, but intermittent use has been advocated in situations associated with higher risk of infection. Perioperative intravenous antibacterial prophylaxis during PD catheter insertion is recommended,[18] and has been shown to significantly reduce the risk of peritonitis in the first month after surgery.[20] *Staph. aureus* nasal carriage is associated with increased risk of exit-site infections and intranasal or exit-site mupirocin (cream, as ointment may damage the catheter) or exit-site gentamicin cream have been used to reduce them.[18] The results of a systematic review suggest that treating carriers with intranasal mupirocin significantly decreases overall rates of exit-site infections, although there does not appear to be an associated reduction in risk of peritonitis.[20] Dramatic reductions in peritonitis rates have been achieved with programmes based on stringent aseptic wound care and on minimising contact of the PD system with domestic water.[21]

1. Johnson CC, *et al.* Peritonitis: update on pathophysiology, clinical manifestations, and management. *Clin Infect Dis* 1997; **24**: 1035–47.
2. Rimola A, *et al.* Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. *J Hepatol* 2000; **32**: 142–53.
3. Koulaouzidis A, *et al.* Spontaneous bacterial peritonitis. *World J Gastroenterol* 2009; **15**: 1042–9.
4. Chavez-Tapia NC, *et al.* Antibiotics for spontaneous bacterial peritonitis in cirrhotic patients. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009 (accessed 15/04/09).
5. Gilbert JA, Kamath PS. Spontaneous bacterial peritonitis: an update. *Mayo Clin Proc* 1995; **70**: 365–70.
6. Runyon BA, *et al.* Short-course versus long-course antibiotic treatment of spontaneous bacterial peritonitis: a randomized controlled study of 100 patients. *Gastroenterology* 1991; **100**: 1737–42.
7. Ginés P, *et al.* Norfloxacin prevents spontaneous bacterial peritonitis recurrence in cirrhosis: results of a double-blind, placebo-controlled trial. *Hepatology* 1990; **12**: 716–24.
8. Saab S, *et al.* Oral antibiotic prophylaxis reduces spontaneous bacterial peritonitis occurrence and improves short-term survival in cirrhosis: a meta-analysis. *Am J Gastroenterol* 2009; **104**: 993–1001.
9. Singh N, *et al.* Trimethoprim–sulfamethoxazole for the prevention of spontaneous bacterial peritonitis in cirrhosis: a randomized trial. *Ann Intern Med* 1995; **122**: 595–8.
10. Prazee LA, *et al.* Long-term prophylaxis of spontaneous bacterial peritonitis in patients with cirrhosis. *Ann Pharmacother* 2005; **39**: 908–12.
11. Cohen MJ, *et al.* Antibiotic prophylaxis for spontaneous bacterial peritonitis in cirrhotic patients with ascites, without gastro-intestinal bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 13/04/10).
12. Bernard B, *et al.* Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding: a meta-analysis. *Hepatology* 1999; **29**: 1655–61.
13. Soares-Weiser K, *et al.* Antibiotic prophylaxis for cirrhotic patients with gastrointestinal bleeding. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2002 (accessed 15/04/09).
14. Solomkin JS, *et al.* Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Clin Infect Dis* 2010; **50**: 133–64. Also published in *Surg Infect (Larchmt)* 2010; **11**: 79–109. Also available at: http://www.idsociety.org/WorkArea/linkit.aspx?LinkIdentifier=id&ItemID=15966 (accessed 04/05/10)
15. Blot S, De Waele JJ. Critical issues in the clinical management of complicated intra-abdominal infections. *Drugs* 2005; **65**: 1611–20.
16. Harbarth S, Uckay I. Are there patients with peritonitis who require empiric therapy for enterococcus? *Eur J Clin Microbiol Infect Dis* 2004; **23**: 73–7.
17. Wong PF, *et al.* Antibiotic regimens for secondary peritonitis of gastrointestinal origin in adults. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 15/04/09).
18. Piraino B, *et al.* Peritoneal dialysis-related infections recommendations: 2005 update. *Perit Dial Int* 2005; **25**: 107–31. Also available at: http://www.ispd.org/guidelines/03Piraino42371SPD%20with%20watermark.pdf (accessed 27/06/06)
19. Wiggins KJ, *et al.* Treatment for peritoneal dialysis-associated peritonitis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 15/04/09).
20. Strippoli GF, *et al.* Antimicrobial agents for preventing peritonitis in peritoneal dialysis patients. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 15/04/09).
21. Ludlam H, *et al.* Prevention of peritonitis in continuous ambulatory peritoneal dialysis. *Lancet* 1990; **335**: 1161.

Pertussis

Pertussis or whooping cough[1] is caused by infection with the respiratory pathogen *Bordetella pertussis*, a Gram-negative aerobic bacterium. The related species *B. parapertussis* causes a similar but generally milder illness. Pertussis is very infectious and occurs most frequently in children, but may be more common in adults than once thought. The incidence of pertussis has been greatly reduced by the active immunisation of infants (see under Pertussis Vaccines, p. 2408.3) and effective prevention by the adequate uptake of vaccine remains the ultimate objective.

Erythromycin has been the antibacterial of choice, but the newer macrolides, clarithromycin and azithromycin, have similar efficacy and are also recommended for the **treatment** of pertussis.[1-3] Once infection has occurred antibacterial therapy is thought to render the patient non-infectious by eliminating nasopharyngeal carriage of *B. pertussis*. Such treatment is unlikely to affect the clinical course of pertussis because diagnosis is difficult until the paroxysmal stage, by which time the bacteria have already damaged the respiratory tract and released their toxins. Effective regimens include:[2,3]

- oral azithromycin 500 mg daily on the first day of treatment then 250 mg daily for 4 days; infants and children may be given oral azithromycin 10 mg/kg daily for 3 to 5 days, or 10 mg/kg daily on the first day of treatment then 5 mg/kg daily for 4 days
- oral clarithromycin 500 mg twice daily for 7 days; infants and children may be given oral clarithromycin 7.5 mg/kg twice daily for 7 days
- oral erythromycin 500 mg four times daily for 14 days; infants and children may be given oral erythromycin 40 to 50 mg/kg daily in 3 to 4 divided doses for 7 to 14 days, or 60 mg/kg daily in 3 divided doses for 14 days

Oral co-trimoxazole for 7 to 14 days may be given as an alternative treatment for patients unable to tolerate macrolides. Oxytetracycline or chloramphenicol are not recommended because of their potential adverse effects.

Macrolide antibacterials, given in the same doses as for treatment and within 3 weeks of onset of cough in the index patients, may also be given **prophylactically** to close contacts.[2] However, protection is limited and a systematic review[3] concluded there was insufficient evidence to determine the benefit of prophylactic treatment of healthy pertussis contacts.

1. Crowcroft NS, Pebody RG. Recent developments in pertussis. *Lancet* 2006; **367**: 1926–36.
2. CDC. Recommended antimicrobial agents for the treatment and postexposure prophylaxis of pertussis: 2005 CDC Guidelines. *MMWR* 2005; **54** (RR-14): 1–16. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5414.pdf (accessed 18/08/08)
3. Altunaiji S, *et al.* Antibiotics for whooping cough (pertussis). Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 27/06/08).

Pharyngitis

Pharyngitis and tonsillitis are upper respiratory-tract infections with similar causes and occur especially in children. Acute pharyngitis is an inflammatory syndrome of the oropharynx that may include the tonsils whereas tonsillitis is, strictly speaking, a more localised infection. The commonest causes are viral and a sore throat is often a symptom of the common cold as well as influenza and infectious mononucleosis. For further details of these viral infections, see under Choice of Antiviral, p. 953.1.

The most important bacterial cause of acute pharyngitis and tonsillitis is the group A beta-haemolytic *streptococcus*, *Streptococcus pyogenes*. An erythrogenic toxin-producing strain causes pharyngitis and tonsillitis in scarlet fever.

In view of the prevalence of a viral cause, opinions have differed over whether and when to treat pharyngitis with antimicrobial drugs. Some have advocated waiting until a definite diagnosis of *Str. pyogenes* infection is made, but others treat immediately if streptococcal pharyngitis is suspected because of the risk of longer term complications such as rheumatic fever and the need to eradicate *Str. pyogenes* from the throat.[1-3] The incidence of rheumatic fever has been low for many years in developed countries, but there was evidence of a resurgence in parts of the USA in the mid-1980s. Thus, in addition to shortening the illness and interrupting transmission, the antibacterial treatment of streptococcal pharyngitis also serves as primary prevention of rheumatic fever (see below). However, in countries in which the incidence of rheumatic fever remains low the routine use of antibacterials for the management of sore throats is discouraged.[4,5]

Penicillin is the standard **treatment** for streptococcal pharyngitis or tonsillitis,[6-8] generally as phenoxymethylpenicillin orally for 10 days or a single intramuscular injection of benzathine benzylpenicillin. Both options are advocated by WHO[7] and the American Heart Association[8] for the primary prevention of rheumatic fever (see under Rheumatic Fever, p. 204.3), the latter particularly where compliance with a 10-day course of oral penicillin is unlikely. Oral amoxicillin is also effective[7,9] and a further treatment option for confirmed streptococcal pharyngitis;[8] however, some suggest that empirical use of aminopenicillins (including amoxicillin and ampicillin) should probably be avoided because of the risk of maculopapular rash if the patient proves to have infectious mononucleosis.[10] Erythromycin or another macrolide may be given to penicillin-allergic patients, except where there is evidence of significant resistance,[7,8] as in some parts of Europe,[7] the USA,[11] Japan,[12] and Finland;[13] it may also be a better choice than penicillin if there is a likelihood of infection with *Arcanobacterium haemolyticum* (*Corynebacterium haemolyticum*), but should be avoided if there is risk of infection with *Fusobacterium necrophorum* (see below). Clindamycin may also be used.[8] Oral cephalosporins are another alternative, and a meta-analysis[14] has shown that the likelihood of treatment failure with oral cephalosporins may be about half that with penicillin; first-generation cephalosporins appear no less effective than later generations,[14] and are generally preferred due to their narrower antibacterial spectrum.[8,14]

Despite the general efficacy of penicillin a trend of increasing numbers of relapses and recurrent infections has been noted.[15] Some treatment failures have been attributed to poor patient compliance with a 10-day course of penicillin and attempts to overcome this have included giving fewer daily doses or shortening the length of treatment. Meta-analysis of studies supports the use of twice-daily dosing of phenoxymethylpenicillin which appears to be as effective as doses three or four times daily,[16] but a single daily dose is less effective. Courses of phenoxymethylpenicillin shorter than 10 days have not proved effective.[17,18] There is some evidence that shorter courses may be possible with other antibacterials.[19] Courses of 5 days or less of erythromycin,[20] amoxicillin with clavulanic acid,[21] azithromycin,[22,23] clarithromycin,[24] josamycin,[25] telithromycin,[26] or cephalosporins[27] have been given as alternatives to a 10-day course of phenoxymethylpenicillin. However, definitive studies have not been done, and the broader spectrum and higher cost of these regimens are drawbacks.[6]

Penicillin resistance in *Str. pyogenes* remains rare. In addition to poor compliance, treatment failures with penicillin, leading to recurrent infection, might be explained by the presence of beta-lactamase-producing oropharyngeal bacteria that are able to protect *Str. pyogenes* against penicillin,[28] although this theory was not supported by a study in 462 children.[29] Antibacterials less susceptible to beta lactamase have been effective, sometimes more so than phenoxymethylpenicillin. They include the oral cephalosporins cefaclor,[30] cefuroxime axetil,[31] cefixime,[32] cefprozil,[33] and cefadroxil[34] and the combined preparation amoxicillin with clavulanic acid[35,36] (however, see above regarding the risk of rash with aminopenicillins). Clindamycin has eradicated *Str. pyogenes* and beta-lactamase-producing bacteria in children aged 12 years and under with recurrent tonsillitis, but might be less effective in older patients.[37] It was also effective where penicillin and erythromycin had failed in an outbreak of streptococcal pharyngitis.[38]

Pharyngeal carriage of *Str. pyogenes* is common, especially in primary-school children and thus its presence does not necessarily reflect acute infection. **Eradication** is generally unnecessary[7,8] but may be beneficial in selected cases and has been achieved by a single intramuscular injection of benzathine benzylpenicillin together with a 4-day course of oral rifampicin;[39] a 10-day course of oral clindamycin has also been effective.[40] In order to ensure that outbreaks of *Str. pyogenes* are prevented in closely confined populations, some have recommended prophylactic antibacterials for *all* members of these populations, without exception.[41]

Other bacterial causes of pharyngitis include *Arcanobacterium haemolyticum* (*Corynebacterium haemolyticum*), *Chlamydophila pneumoniae* (*Chlamydia pneumoniae*), *Corynebacterium diphtheriae* (see under Diphtheria, p. 178.3), *Fusobacterium necrophorum*, *Neisseria gonorrhoeae* (see under Gonorrhoea, p. 206.2), groups C and G beta-haemolytic streptococci, and anaerobic bacteria.

A. haemolyticum is thought to be an important cause of pharyngitis in adolescents and young adults; there is often an accompanying scarlatiniform rash. It has been reported to respond to a single injection of benzathine benzylpenicillin or a 10-day course of oral erythromycin, but not to phenoxymethylpenicillin.[6]

F. necrophorum is also common in adolescents and young adults, and is thought to cause about 10% of acute pharyngitis within this age group.[42] Of particular concern is its association with Lemierre syndrome, a life-threatening condition characterised by bacteraemia, metastatic infections, and suppurative thrombophlebitis of the internal jugular vein. Although susceptible to penicillins and cephalosporins, *F. necrophorum* does not respond to treatment with macrolides; it has therefore been suggested that empirical use of macrolides be avoided in adolescents and young adults with acute pharyngitis.[42]

For pharyngitis associated with *C. pneumoniae* infection, tetracycline or erythromycin are effective antibacterials.[43]

Systemic corticosteroids have been tried for the symptomatic relief of acute pharyngitis and in a meta-analysis,[44] patients with severe or exudative sore throat who took corticosteroids in addition to antibacterials were 3 times more likely to have complete resolution of pain at 24 hours than those who did not. However, it remains unclear whether corticosteroids offer additional benefits over simple analgesics, or if they are safe for use in pharyngitis not requiring antibacterial therapy.

1. Anonymous. Bacterial pharyngitis. *Lancet* 1987; **1**: 1241–2.
2. Marcovitch H. Sore throats. *Arch Dis Child* 1990; **65**: 249–50.
3. Lang SDR, Singh K. The sore throat: when to investigate and when to prescribe. *Drugs* 1990; **40**: 854–62.
4. Little P, *et al.* Reattendance and complications in a randomised trial of prescribing strategies for sore throat: the medicalising effect of prescribing antibiotics. *BMJ* 1997; **315**: 350–2.
5. Del Mar CB, *et al.* Antibiotics for sore throat. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 18/08/08).
6. Bisno AL. Acute pharyngitis. *N Engl J Med* 2001; **344**: 205–11.
7. WHO. Rheumatic fever and rheumatic heart disease. *WHO Tech Rep Ser* 923 2004. Also available at: http://www.who.int/cardiovascular_diseases/resources/en/cvd_trs923.pdf (accessed 02/03/10)
8. Gerber MA, *et al.* Prevention of rheumatic fever and diagnosis and treatment of acute streptococcal pharyngitis: a scientific statement from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, the Interdisciplinary Council on Functional Genomics and Translational Biology, and the Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. *Circulation* 2009; **119**: 1541–51. Also available at: http://circ.ahajournals.org/cgi/reprint/119/11/1541 (accessed 02/03/10)
9. Lennon DR, *et al.* Once-daily amoxicillin versus twice-daily penicillin V in group A β-haemolytic streptococcal pharyngitis. *Arch Dis Child* 2008; **93**: 474–8.
10. Scottish Intercollegiate Guidelines Network. Management of sore throat and indications for tonsillectomy: a national clinical guideline (issued January 1999). Available at: http://www.sign.ac.uk/pdf/sign34.pdf (accessed 02/03/10)
11. Martin JM, *et al.* Erythromycin-resistant group A streptococci in schoolchildren in Pittsburgh. *N Engl J Med* 2002; **346**: 1200–6.
12. Maruyama S, *et al.* Sensitivity of group A streptococci to antibiotics: prevalence of resistance to erythromycin in Japan. *Am J Dis Child* 1979; **133**: 1143–5.
13. Seppälä H, *et al.* Resistance to erythromycin in group A streptococci. *N Engl J Med* 1992; **326**: 292–7.
14. Casey JR, Pichichero ME. Meta-analysis of cephalosporins versus penicillin for treatment of group A streptococcal tonsillopharyngitis in adults. *Clin Infect Dis* 2004; **38**: 1526–34.
15. Dillon HC. Streptococcal pharyngitis in the 1980s. *Pediatr Infect Dis J* 1987; **6**: 123–30.
16. Lan AJ, *et al.* The impact of dosing frequency on the efficacy of 10-day penicillin or amoxicillin therapy for streptococcal tonsillopharyngitis: a meta-analysis. Abstract: *Pediatrics* 2000; **105**: 414. Full version: http://pediatrics.aappublications.org/cgi/content/full/105/2/e19 (accessed 20/05/04)
17. Gerber MA, *et al.* Five vs ten days of penicillin V therapy for streptococcal pharyngitis. *Am J Dis Child* 1987; **141**: 224–7.
18. Strömberg A, *et al.* Five versus ten days treatment of group A streptococcal pharyngotonsillitis: a randomized controlled clinical trial with phenoxymethylpenicillin and cefadroxil. *Scand J Infect Dis* 1988; **20**: 37–46.
19. Altamimi S, *et al.* Short versus standard duration antibiotic therapy for acute streptococcal pharyngitis in children. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009 (accessed 03/03/10).
20. Adam D, *et al.* Five days of erythromycin estolate versus ten days of penicillin V in the treatment of group A streptococcal tonsillopharyngitis in children. *Eur J Clin Microbiol Infect Dis* 1996; **15**: 712–17.
21. Syrogiannopoulos GA, *et al.* Two dosages of clarithromycin for five days, amoxicillin/clavulanate for five days or penicillin V for ten days in acute group A streptococcal tonsillopharyngitis. *Pediatr Infect Dis J* 2004; **23**: 857–65.
22. O'Doherty B, *et al.* Azithromycin versus penicillin V in the treatment of paediatric patients with acute streptococcal pharyngitis/tonsillitis. *Eur J Clin Microbiol Infect Dis* 1996; **15**: 718–24.
23. Hooton TM. A comparison of azithromycin and penicillin V for the treatment of streptococcal pharyngitis. *Am J Med* 1991; **91** (suppl 3A): 23S–26S.
24. Portier H, *et al.* Five day clarithromycin modified release versus 10 day penicillin V for group A streptococcal pharyngitis: a multi-centre, open-label, randomized study. *J Antimicrob Chemother* 2002; **49**: 337–44.
25. Portier H, *et al.* Groupe d'étude de pathologie infectieuse pédiatrique. Traitement des angines aiguës à streptocoque beta-hémolytique du groupe A chez l'enfant par la josamycine pendant cinq jours. *Arch Pediatr* 2001; **8**: 700–6.
26. Norrby SR, *et al.* Evaluation of 5-day therapy with telithromycin, a novel ketolide antibacterial, for the treatment of tonsillopharyngitis. *Clin Microbiol Infect* 2004; **10**: 615–23.
27. Pichichero M, Casey J. Comparison of European and U.S. results for cephalosporin versus penicillin treatment of group A streptococcal tonsillopharyngitis. *Eur J Clin Microbiol Infect Dis* 2006; **25**: 354–64.
28. Brook I. The role of β-lactamase-producing bacteria in the persistence of streptococcal tonsillar infection. *Rev Infect Dis* 1984; **6**: 601–7.
29. Gerber MA, *et al.* Potential mechanisms for failure to eradicate group A streptococci from the pharynx. *Pediatrics* 1999; **104**: 911–17.
30. Stillerman M. Comparison of oral cephalosporins with penicillin therapy for group A streptococcal pharyngitis. *Pediatr Infect Dis* 1986; **5**: 649–54.
31. Gooch WM, *et al.* Efficacy of cefuroxime axetil suspension compared with that of penicillin V suspension in children with group A streptococcal pharyngitis. *Antimicrob Agents Chemother* 1993; **37**: 159–63.
32. Kiani R, *et al.* Comparative, multicenter studies of cefixime and amoxicillin in the treatment of respiratory tract infections. *Am J Med* 1988; **85** (suppl 3A): 6–13.
33. Milatovic D, *et al.* Cefprozil versus penicillin V in treatment of streptococcal tonsillopharyngitis. *Antimicrob Agents Chemother* 1993; **37**: 1620–3.
34. Milatovic D, Knauer J. Cefadroxil versus penicillin in the treatment of streptococcal tonsillopharyngitis. *Eur J Clin Microbiol Infect Dis* 1989; **8**: 282–8.
35. Brook I. Treatment of patients with acute recurrent tonsillitis due to group A β-haemolytic streptococci: a prospective randomized study comparing penicillin and amoxycillin/clavulanate potassium. *J Antimicrob Chemother* 1989; **24**: 227–33.
36. Dykhuizen RS, *et al.* Phenoxymethyl penicillin versus co-amoxiclav in the treatment of acute streptococcal pharyngitis, and the role of β-lactamase activity in saliva. *J Antimicrob Chemother* 1996; **37**: 133–8.
37. Foote PA, Brook I. Penicillin and clindamycin therapy in recurrent tonsillitis: effect of microbial flora. *Arch Otolaryngol Head Neck Surg* 1989; **115**: 856–9.
38. Raz R, *et al.* Clindamycin in the treatment of an outbreak of streptococcal pharyngitis in a kibbutz due to beta-lactamase producing organisms. *J Chemother* 1990; **2**: 182–4.
39. Tanz RR, *et al.* Penicillin plus rifampin eradicates pharyngeal carriage of group A streptococci. *J Pediatr* 1985; **106**: 876–80.
40. Tanz RR, *et al.* Clindamycin treatment of chronic pharyngeal carriage of group A streptococci. *J Pediatr* 1991; **119**: 123–8.
41. Gray GC, *et al.* Hyperendemic Streptococcus pyogenes infection despite prophylaxis with penicillin G benzathine. *N Engl J Med* 1991; **325**: 92–7.
42. Centor RM. Expand the pharyngitis paradigm for adolescents and young adults. *Ann Intern Med* 2009; **151**: 812–15.
43. Grayston JT, *et al.* A new respiratory tract pathogen: Chlamydia pneumoniae strain TWAR. *J Infect Dis* 1990; **161**: 618–25.
44. Hayward G, *et al.* Corticosteroids for pain relief in sore throat: systematic review and meta-analysis. Abridged version: *BMJ* 2009; **339**: 488–90. Full version: http://www.bmj.com/cgi/reprint/339/aug06_2/b2976 (accessed 02/03/10)

Pinta

See Syphilis, p. 207.2.

Plague

Plague[1,2] is caused by the Gram-negative bacillus *Yersinia pestis* (*Yersinia pseudotuberculosis* subsp. *pestis*) and is usually transmitted to man via rodents and their infected fleas. It has occurred as worldwide pandemics, for example, the Black Death in Europe in the Middle Ages. In the 1980s the largest numbers of cases reported were in Tanzania, Vietnam, Brazil, Peru and more recently in Madagascar. Plague may take several forms of which bubonic plague is the most common; others include pneumonic, septicaemic, and meningitic plague. Streptomycin, tetracycline, and chloramphenicol have traditionally been used in the treatment of plague[3] with streptomycin being the treatment of choice, although the possibility of a Jarisch-Herxheimer reaction resulting from the bactericidal effect of streptomycin must be borne in mind; it is also contra-indicated in pregnancy. Success has also been reported with aminoglycosides such as gentamicin and kanamycin. Although there is no clinical experience with fluoroquinolones, *in-vitro* susceptibilities and *animal* studies suggest that they would be effective.[3]

In the UK, the recommended treatment for adults is gentamicin (first choice in pregnancy); ciprofloxacin or doxycycline may be used if aminoglycosides are unsuitable and may also be used for first-line therapy in children, but doxycycline is only suitable for children over 8 years of age. If plague meningitis is suspected chloramphenicol should be used as it crosses the blood-brain barrier.[3] Similar information is provided by WHO,[4] with sulfonamides being mentioned as alternatives. European guidelines[5] consider either streptomycin or gentamicin to be appropriate for first-line treatment of plague in both adults and children, and suggest that ofloxacin and levofloxacin may be appropriate alternatives to ciprofloxacin for second-line treatment in adults.

In UK guidelines[3] ciprofloxacin is considered to be the drug of choice for prophylaxis in adults and children considered to be at risk after close contact with cases of pneumonic disease or after a deliberate release of *Y. pestis*; doxycycline may be used as an alternative in those over 12 years of age. European guidelines[5] offer similar advice, but consider levofloxacin and ofloxacin as possible options for prophylaxis in adults. Other suggested antibacterials include co-trimoxazole,[3,5] chloramphenicol,[3,5] and sulfadiazine.[5]

Commenting on the plague epidemic that occurred in India in 1994, workers from the US CDC[6] considered that prophylaxis should be given to those who have had face-to-face contact or who have occupied a closed space with someone who has pneumonic plague. For prophylaxis, tetracycline could be given to adults and older children or sulfonamides to children of 8 years or less; chloramphenicol was also effective.[6]

Infection with a strain of *Y. pestis* resistant to all the drugs usually effective against plague identified in a patient from Madagascar[7] responded to treatment with co-trimoxazole and streptomycin.

A vaccine is available for active immunisation.

1. Prentice MB, Rahalison L. Plague. *Lancet* 2007; **369**: 1196–1207.
2. Butler T. Plague into the 21st century. *Clin Infect Dis* 2009; **49**: 736–42.
3. Health Protection Agency. Guidelines for action in the event of a deliberate release: plague (issued April 2007). Available at: http://www.

hpa.org.uk/web/HPAwebFile/HPAweb_C/1194947396073 (accessed 18/08/08)
4. WHO. *Plague manual: epidemiology, distribution, surveillance and control.* Available at: http://www.who.int/csr/resources/publications/plague/WHO_CDS_CSR_EDC_99_2_EN/en/ (accessed 27/06/06)
5. Bossi P, *et al.* Task Force on Biological and Chemical Agent Threats of the European Commission. BICHAT guidelines for the clinical management of plague and bioterrorism-related plague. *Eur Surveill* 2004; 9: 1–6. Also available at: http://www.eurosurveillance.org/images/dynamic/em/v09n12/0912-230.pdf (accessed 04/02/10)
6. Campbell GL, Hughes JM. Plague in India: a new warning from an old nemesis. *Ann Intern Med* 1995; 122: 151–3.
7. Galimand M, *et al.* Multidrug resistance in Yersinia pestis mediated by a transferable plasmid. *N Engl J Med* 1997; 337: 677–80.

Pneumonia

Pneumonia[1] is a respiratory disease characterised by inflammation of the lung parenchyma with congestion. It is mostly due to bacterial or viral infection, but may be caused by fungi in immunocompromised patients or by the aspiration of chemical irritants. Pneumonia is a common illness occurring in all age groups and throughout the world; it is a major cause of death among the elderly and those who are chronically and/or terminally ill. Symptoms and signs of pneumonia include chills, cough, dyspnoea, fever, headache, myalgia, pleuritic chest pain, and sputum production. Treatment of pneumonia relies on prompt use of antibacterials and identification of the infecting organisms and their sensitivity to antibacterials. Cases of pneumonia are usually classified as community-acquired or hospital-acquired (nosocomial) pneumonia. Cases of community-acquired pneumonia can also be further sub-divided into those who can be treated in an ambulatory (outpatient) setting and those that need hospitalisation. Patients who need hospitalisation are generally infected with unusual pathogens and/or have more severe disease. Pneumonia occurring in long-term-care facilities can be treated as either community-acquired or hospital-acquired pneumonia. Cases of hospital-acquired pneumonia are generally classified according to the time of onset after hospital admission. These categories also provide a rough guide as to the likely pathogen and severity of the disease.

Other types of pneumonia include aspiration pneumonia and the various forms of interstitial pneumonia or pneumonitis (see also Aspiration Syndromes, p. 1807.2, and Interstitial Lung Disease, p. 1607.1). Interstitial pneumonitis is a common complication in cancer patients and has also been associated with certain drugs, for example amiodarone, bleomycin, and nitrofurantoin.

Community-acquired pneumonia. In community-acquired pneumonia (CAP)[2-7] the commonest pathogen in previously healthy subjects is *Streptococcus pneumoniae* (pneumococcus). Other common pathogens include *Haemophilus influenzae* and atypical pathogens such as *Chlamydophila pneumoniae* (*Chlamydia pneumoniae*), *Mycoplasma pneumoniae*, and *Legionella pneumophila* (see Legionnaires' Disease, p. 188.2).[2,5] Less common causes include *Staphylococcus aureus*, which usually occurs as a secondary bacterial infection after influenza and is associated with high mortality; *Moraxella catarrhalis* (*Branhamella catarrhalis*) occurs especially in patients with chronic lung disease; Gram-negative enteric bacilli; *Pseudomonas aeruginosa*; *Chlamydophila psittaci* (*Chlamydia psittaci*) (see Psittacosis, p. 204.1); and *Coxiella burnetii* (see Q Fever, p. 204.1). Gram-negative bacilli rarely cause pneumonia in the community, especially in previously healthy patients, although the frequency of such infections is increasing.[6] Anaerobic bacteria are associated with aspiration pneumonia. Viruses are the commonest pathogens in young children.

Pneumococcal pneumonia usually develops over several days and in elderly patients onset may be insidious. *Str. pneumoniae* has usually been considered to be sensitive to penicillins (benzylpenicillin, amoxicillin, or ampicillin), cephalosporins, erythromycin, or co-trimoxazole, but there is increasing prevalence of global resistance although there are marked geographical differences.[9,10] However, in clinical practice pneumococcal pneumonia frequently responds to high doses of penicillins or cephalosporins and the routine use of penicillin for CAP may still be reasonable in many countries.

The treatment of CAP is complicated by the increasing spectrum of causative organisms and prevalence of antibacterial resistance. Furthermore, since the causative pathogen is often unknown, initial antibacterial therapy is usually empirical. Guidelines for the treatment of pneumonia have been issued by bodies in many countries.[8,11-18] Although common principles can be identified, recommendations must be localised because of differences in patterns of infection and drug resistance, variations in the availability of antibacterials and local policies for their use, and differences in medical practice. Countries also vary in the degree to which such guidelines are accepted in practice. These guidelines generally give advice for differences associated with age, the severity of the infection, and the presence or absence of underlying or co-existent disorders.

In the UK, guidelines for the management of CAP have been produced by the British Thoracic Society (BTS).[8] For initial ***empirical treatment in the community*** oral amoxicillin is usually preferred. Alternatives in penicillin-allergic patients include doxycycline and the macrolides clarithromycin and erythromycin; clarithromycin is generally preferred to erythromycin due to better tolerance and more convenient dosing. The approach to treatment is similar for patients ***hospitalised with low-severity CAP***, many of whom are admitted to hospital for non-clinical reasons such as old age, family preference, inadequate home care, or adverse social circumstances; when oral therapy cannot be used in these patients, intravenous amoxicillin, benzylpenicillin, or clarithromycin are suitable alternatives.

In those patients ***hospitalised with moderately-severe CAP*** there is an increased likelihood of infection with atypical pathogens, or with *Legionella* spp.; consequently, combined empirical treatment orally with amoxicillin plus either erythromycin or clarithromycin is preferred.[8] When oral therapy is inappropriate, intravenous ampicillin or benzylpenicillin is given, with intravenous clarithromycin. For those intolerant of beta lactams and macrolides, oral doxycycline, levofloxacin, or moxifloxacin can be considered; intravenous alternatives include either monotherapy with levofloxacin, or the combination of a second- or third-generation cephalosporin (such as cefuroxime, cefotaxime, or ceftriaxone) with clarithromycin.[8]

Patients ***hospitalised with severe CAP*** should receive parenteral empirical treatment regardless of their ability to take oral medication. Since CAP caused by *Legionella* spp. is more likely to result in severe disease, the initial empirical regimen should include appropriate therapy. Current recommendations[8] are for combined intravenous treatment with a broad-spectrum beta-lactamase-stable antibacterial such as amoxicillin with clavulanic acid or a second- or third-generation cephalosporin such as cefuroxime, cefotaxime, or ceftriaxone, together with a macrolide (preferably clarithromycin). For life-threatening infection where *Legionella* is suspected, the further addition of levofloxacin should be considered. As an alternative to the above regimens, benzylpenicillin with either levofloxacin or ciprofloxacin can also be used.[8]

The following treatments are recommended in the UK,[8] along with local microbiological advice, for the minority of patients with CAP in whom the ***causative organism*** has been identified, usually in hospital:

- *Str. pneumoniae*: preferred treatment, oral amoxicillin or intravenous benzylpenicillin; alternatives, oral clarithromycin, or intravenous cefuroxime, cefotaxime, or ceftriaxone
- *M. pneumoniae* or *C. pneumoniae*: preferred treatment, oral or intravenous clarithromycin; alternatives, oral doxycycline or an oral or intravenous fluoroquinolone
- *C. psittaci* or *C. burnetii*: preferred treatment, oral doxycycline; alternatives, oral or intravenous clarithromycin
- *Legionella* spp.: preferred treatment, an oral or intravenous fluoroquinolone; alternatives, oral or intravenous clarithromycin (or azithromycin, if necessary)
- *H. influenzae* (non-beta-lactamase-producing): preferred treatment, oral or intravenous amoxicillin; alternatives, intravenous cefuroxime, cefotaxime, or ceftriaxone, or an oral or intravenous fluoroquinolone
- *H. influenzae* (beta-lactamase-producing): preferred treatment, oral or intravenous amoxicillin with clavulanic acid; alternatives, intravenous cefuroxime, cefotaxime, or ceftriaxone, or an oral or intravenous fluoroquinolone
- Gram-negative enteric bacilli: preferred treatment, intravenous cefuroxime, cefotaxime, or ceftriaxone; alternatives, intravenous fluoroquinolone, imipenem, or meropenem
- *Ps. aeruginosa*: preferred treatment, intravenous ceftazidime plus either gentamicin or tobramycin; alternatives, intravenous ciprofloxacin or piperacillin plus either gentamicin or tobramycin
- *Staph. aureus* (non-meticillin-resistant): preferred treatment, intravenous flucloxacillin with or without oral or intravenous rifampicin; alternatives, intravenous vancomycin, linezolid, or teicoplanin with or without oral or intravenous rifampicin
- *Staph. aureus* (meticillin-resistant): preferred treatment, intravenous vancomycin, linezolid, or teicoplanin with or without oral or intravenous rifampicin

In the USA, guidelines for the management of CAP in adults have been jointly produced by the Infectious Diseases Society of America (IDSA) and by the American Thoracic Society (ATS).[12] For previously healthy ***outpatients*** with no risk factors for drug-resistant *Str. pneumoniae* (DRSP) infection they recommend a macrolide (such as erythromycin, azithromycin, or clarithromycin); doxycycline may be given as an alternative. In those with co-existing cardiopulmonary disease and/or other complicating factors (such as renal disease, diabetes mellitus, alcoholism, malignancies, or asplenia), taking immunosuppressive drugs, those who have received antibacterial therapy within the previous 3 months, or those with other risks for DRSP infection a 'respiratory fluoroquinolone' (gemifloxacin, levofloxacin, or moxifloxacin) is recommended. Alternatively a beta-lactam (high-dose amoxicillin with or without clavulanic acid, or ceftriaxone, cefpodoxime, or cefuroxime) plus a macrolide (or doxycycline) may be given.

In ***hospitalised*** patients who are not in intensive care the preferred treatment is a beta lactam (cefotaxime, ceftriaxone, ampicillin, or ertapenem) plus a macrolide (or doxycycline). In penicillin-allergic patients a respiratory fluoroquinolone is recommended. In hospitalised patients who are in intensive care the preferred treatment is a beta lactam (cefotaxime, ceftriaxone, or ampicillin/sulbactam) plus either azithromycin or a respiratory fluoroquinolone. In penicillin-allergic patients a respiratory fluoroquinolone and aztreonam are recommended. For *Pseudomonas* infection, an antipneumococcal, antipseudomonal beta lactam (such as piperacillin/tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin are recommended. Alternative regimens include an antipneumococcal, antipseudomonal beta lactam plus an aminoglycoside and azithromycin, or an antipneumococcal, antipseudomonal beta lactam plus an aminoglycoside and an antipneumococcal fluoroquinolone. In penicillin-allergic patients aztreonam should be used in place of the beta lactam. For community-acquired meticillin-resistant *Staph. aureus* (MRSA) infection, vancomycin or linezolid should be added.

In **children** pneumonia is caused by a wider spectrum of organisms than in adults. Viruses, especially RSV, are very common pathogens in infants and children up to 4 years of age and, as in adults, pneumococci are very common bacterial pathogens. Guidelines for the management of CAP in children have been produced by the BTS.[11] Amoxicillin is considered the antibacterial of first choice for empirical oral therapy in children under 5 years of age because it is effective against the majority of causative organisms. Alternatives are amoxicillin with clavulanic acid, cefaclor, erythromycin, clarithromycin, or azithromycin. Macrolides should be given as first-line empirical therapy in children over 5 years since *M. pneumoniae* pneumonia is more prevalent in older children. Macrolides should also be used in children of any age if either *M. pneumoniae* or *C. pneumoniae* are suspected. Amoxicillin should be used as first-line treatment at any age if *Str. pneumoniae* is thought to be the likely pathogen. If *Staph. aureus* is suspected then a macrolide or a combination of flucloxacillin with amoxicillin is appropriate. Intravenous therapy should be given in severe infection or when the child is unable to absorb oral antibacterials, for example due to vomiting; appropriate intravenous drugs for severe pneumonia include amoxicillin with clavulanic acid, cefuroxime, or cefotaxime. If the causative organism is known to be *Str. pneumoniae* a penicillin may be used alone. *Chlamydia trachomatis* is another common cause in infants up to 3 months of age for which erythromycin may be used or, alternatively, sulfafurazole.

Pneumonia in neonates is usually due to organisms acquired from the mother's genital tract, especially group B streptococci, *Escherichia coli*, and *Klebsiella pneumoniae*; initial treatment with gentamicin and benzylpenicillin or ampicillin has been suggested. For prophylaxis against group B streptococci in neonates, see under Perinatal Streptococcal Infections, p. 197.2.

Similar guidelines for the empirical management of CAP in children have been developed in South Africa.[15] Additional recommendations have been made to take into account the high prevalence of HIV infection. The drug of choice is amoxicillin; although standard doses of amoxicillin will treat most cases of pneumococcal pneumonia the use of high-dose amoxicillin (30 mg/kg given 3 times daily) is recommended in order to overcome and limit the emergence of resistant pneumococci, and to successfully treat those few children with high-level pneumococcal resistance the following additional factors should be considered:

- children younger than 2 months have more Gram-negative infections and therefore need an intravenous aminoglycoside or an intravenous cephalosporin, while children older than 5 years have more infections caused by *M. pneumoniae* and *C. pneumoniae* and need a macrolide (erythromycin, clarithromycin, or azithromycin)
- HIV-infected children requiring hospitalisation and those with a high risk of being HIV-infected or who have symptomatic HIV disease or who are severely malnourished should be given an aminoglycoside plus their empirical antibacterial regimen; alternatively they may be given a regimen that provides effective treatment against Gram-negative bacteria
- if pneumocystis pneumonia is suspected, co-trimoxazole should be added. All hospitalised HIV-exposed children less than 6 months of age should be treated empirically with co-trimoxazole, unless HIV infection status is

negative and the child is not being breast-fed. Empirical treatment with co-trimoxazole plus amoxicillin and an aminoglycoside should also be given to older HIV-infected children with features of AIDS who are not on co-trimoxazole prophylaxis

- when *Staph. aureus* is suspected, cloxacillin is the drug of choice. In HIV-infected children, about 60% of community-acquired *Staph. aureus* may be resistant to cloxacillin and vancomycin should be given

For the **prevention** of CAP, pneumococcal (p. 2410.1) and influenza (p. 2393.3) vaccines are generally recommended for active immunisation of individuals considered to be at high risk of pneumonia-related complications.[8,12] However, a meta-analysis[19] of pneumococcal vaccination in adults (with unconjugated vaccine) has suggested that the practice may not effectively prevent pneumonia, even in high-risk populations. The role of influenza vaccination in reducing the risk of CAP in elderly, immunocompetent patients has also been questioned.[20]

Hospital-acquired and healthcare-associated pneumonia. Pneumonia occurring at least 48 hours after hospital admission that was not incubating at initial presentation is termed nosocomial or hospital-acquired pneumonia (HAP). Ventilator-associated pneumonia (VAP) is a specific subtype of HAP defined as pneumonia occurring at least 48 hours after endotracheal intubation and/or mechanical ventilation, usually resulting from aspiration of pathogenic material that colonises the oropharynx. While early-onset HAP (occurring within the first 4 days of hospital admission) is usually caused by typical community organisms, late-onset infection can be caused by a wide spectrum of possible pathogens, many of which may be resistant to multiple antibacterials; these can include opportunistic Gram-negative bacilli such as *Ps. aeruginosa, Acinetobacter* spp., *Stenotrophomonas maltophilia, Burkholderia cepacia,* and the Enterobacteriaceae, as well as *Staph. aureus.* More recently, an increased incidence of these potentially drug-resistant bacteria among patients with early-onset pneumonia, thought to be a consequence of previous hospital stays or antibacterial use, has led to the concept of healthcare-associated pneumonia (HCAP). This is pneumonia occurring in any patient who has been hospitalised for at least 2 days in the previous 3 months, lives in a long-term care or nursing facility, has received intravenous antibacterials, chemotherapy, or wound care in the previous month, or attends a hospital or haemodialysis clinic.[21,22] The spectrum of bacteria causing HCAP is similar to late-onset HAP, and patients are considered to be at high risk of multidrug-resistant infection. Other risk factors for multidrug-resistant pneumonia include immunosuppressive disease or therapy, and high frequency of antibacterial resistance within the community or specific hospital unit.

Broad spectrum antibacterial therapy is essential for treatment of HAP and HCAP, and most initial therapy is empirical. As in the treatment of CAP, selection of antibacterials must be localised. For initial empirical treatment of early-onset HAP or VAP in patients with no known risk factors for multidrug-resistant pathogens, and any disease severity, ATS recommends[21] the following drugs: ceftriaxone; levofloxacin, moxifloxacin, or ciprofloxacin; ampicillin/sulbactam; or ertapenem. Where there is late-onset infection or risk factors for multidrug resistance (including possible HCAP) the following are recommended: an antipseudomonal cephalosporin (cefepime or ceftazidime) or an antipseudomonal carbapenem (imipenem or meropenem) or piperacillin-tazobactam together with an antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) or an aminoglycoside (amikacin, gentamicin, or tobramycin); if MRSA is likely then linezolid or vancomycin should also be used. Intravenous therapy should be given to all patients initially, and changed to the oral or enteral route as soon as possible. Efforts should be made to shorten the duration of therapy from the traditional 14 to 21 days to as little as 7 days provided *Ps. aeruginosa* is absent and that the patient shows a good clinical response. Guidelines for the management of HAP, VAP, and HCAP have also been issued in the UK,[22] and emphasise the need to choose initial antibacterial therapy based on patient-specific factors (such as previous antibacterial use, length of hospital stay, and comorbidities) as well as local microbiology and resistance patterns. For intensive care patients requiring mechanical ventilation for 48 hours or more, selective decontamination of the digestive tract (see under Intensive Care, p. 187.3) is recommended to reduce the risk of VAP.

Immunocompromised patients. Immunosuppressed patients are at increased risk of pneumonia. In addition to the bacteria mentioned above they are susceptible to opportunistic infections with *Mycobacterium tuberculosis* (see Tuberculosis, p. 212.2); viruses such as CMV and fungi, in particular *Pneumocystis jirovecii* (see p. 567.2), are also causes of pneumonia in these patients.

Aspiration pneumonia. Aspiration of organisms present in the upper respiratory tract into the lungs, often as a result of loss of consciousness or difficulty in swallowing, can cause aspiration pneumonia.[23] When community acquired the organisms responsible are mainly anaerobes, but in hospital-acquired aspiration pneumonia Gram-negative bacilli and *Staph. aureus* are also found. Confusion has arisen over the term 'aspiration pneumonia' because it has also been applied more generally to aspiration, for example, of gastric acid (Mendelson's syndrome), resulting in chemical pneumonitis and not associated with bacterial infection. *Lung abscess* generally characterises late-stage aspiration pneumonia involving anaerobic bacteria. The aetiology is rarely established, but specific anaerobic bacteria involved include *Peptostreptococcus, Prevotella melaninogenica* (*Bacteroides melaninogenicus*), and *Fusobacterium nucleatum.* Nearly all patients with anaerobic pulmonary infections are treated empirically. Some[23] workers have expressed the view that penicillin and clindamycin are inadequate and that antibacterials with activity against Gram-negative organisms, such as third-generation cephalosporins, fluoroquinolones, and piperacillin are usually required even in community-acquired aspiration pneumonia. Most patients with lung abscess receive parenteral therapy until they become afebrile and show clinical improvement; oral therapy may then continue for weeks or months if necessary.

1. Hoare Z, Lim WS. Pneumonia: update on diagnosis and management. *BMJ* 2006; 332: 1077–9.
2. File TM. Community-acquired pneumonia. *Lancet* 2003; 362: 1991–2001.
3. Ostapchuk M, *et al.* Community-acquired pneumonia in infants and children. *Am Fam Physician* 2004; 70: 899–908.
4. Epstein BJ, Gums JG. Optimal pharmacological therapy for community-acquired pneumonia: the role of dual antibacterial therapy. *Drugs* 2005; 65: 1949–71.
5. Lutfiyya MN, *et al.* Diagnosis and treatment of community-acquired pneumonia. *Am Fam Physician* 2006; 73: 442–50.
6. Niederman MS. Recent advances in community-acquired pneumonia: inpatient and outpatient. *Chest* 2007; 131: 1205–15.
7. Garau J, Calbo E. Community-acquired pneumonia. *Lancet* 2008; 371: 455–8.
8. Lim WS, *et al.* Pneumonia Guidelines Committee of the British Thoracic Society Standards of Care Committee. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. *Thorax* 2009; 64 (suppl 3): iii1–iii55. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Pneumonia/Guidelines/CAPGuideline-full.pdf (accessed 24/02/10)
9. Garau J. Treatment of drug-resistant pneumococcal pneumonia. *Lancet Infect Dis* 2002; 2: 404–15.
10. Felmingham D, *et al.* Increasing prevalence of antimicrobial resistance among isolates of Streptococcus pneumoniae from the PROTEKT surveillance study, and comparative in vitro activity of the ketolide, telithromycin. *J Antimicrob Chemother* 2002; 50 (suppl S1): 25–37.
11. British Thoracic Society. BTS Guidelines for the management of community acquired pneumonia in childhood. *Thorax* 2002; 57 (suppl 1): i1–i24. Also available at: http://www.brit-thoracic.org.uk/portals/0/Clinical%20Information/Pneumonia/Guidelines/paediatriccap.pdf (accessed 18/08/08)
12. Mandell LA, *et al.* Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007; 44 (suppl 2): S27–S72. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/511159 (accessed 22/01/08)
13. Woodhead M, *et al.* European Respiratory Society, European Society of Clinical Microbiology and Infectious Diseases. Guidelines for the management of adult lower respiratory tract infections. *Eur Respir J* 2005; 26: 1138–80. Also available at: http://erj.ersjournals.com/cgi/reprint/26/6/1138.pdf (accessed 18/08/08)
14. Brink A, *et al.* South African Thoracic Society (SATS). Guideline for the management of nosocomial infections in South Africa. *S Afr Med J* 2006; 96: 642–52. Also available at: http://www.pulmonology.co.za/guidelines/nosocomial%20infections%20guideline.pdf (accessed 26/02/08)
15. Zar HJ, *et al.* Working Groups of the Paediatric Assembly of the South African Thoracic Society. Diagnosis and management of community-acquired pneumonia in childhood—South African Thoracic Society Guidelines. *S Afr Med J* 2005; 95: 977–81, 984–90. Also available at: http://blues.sabinet.co.za/WebZ/Authorize?sessionid=0:authow-pubmed:password=pubmed20046/AdvancedQuery?&format=F6next=images/ejour/m_samj/m_samj_v95_n12_a21.pdf (accessed 05/05/08)
16. Infectious Diseases Society of Taiwan, Taiwan Society of Pulmonary and Critical Medicine, and Medical Foundation in Memory of Dr. Deh-Lin Cheng. Guidelines on antimicrobial therapy of pneumonia in adults in Taiwan, revised 2006. *J Microbiol Immunol Infect* 2007; 40: 279–83. Also available at: http://www.jmii.org/content/pdf/v40n3p279.pdf (accessed 05/03/08)
17. Miyashita N, *et al.* Japanese Respiratory Society. The JRS guidelines for the management of community-acquired pneumonia in adults: an update and new recommendations. *Intern Med* 2006; 45: 419–28. Also available at: http://www.jstage.jst.go.jp/article/internalmedicine/45/7/419/_pdf (accessed 05/03/08)
18. Maxwell DJ, *et al.* Empiric management of community-acquired pneumonia in Australian emergency departments. *Med J Aust* 2005; 183: 520–4.
19. Huss A, *et al.* Efficacy of pneumococcal vaccination in adults: a meta-analysis. *CMAJ* 2009; 180: 48–58.
20. Jackson ML, *et al.* Influenza vaccination and risk of community-acquired pneumonia in immunocompetent elderly people: a population-based, nested case-control study. *Lancet* 2008; 372: 398–405.
21. American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005; 171: 388–416. Also available at: http://www.thoracic.org/sections/publications/statements/pages/mtpl/guide1-29.html (accessed 25/05/06)
22. Masterton RG, *et al.* Guidelines for the management of hospital-acquired pneumonia in the UK: report of the working party on hospital-acquired pneumonia of the British Society for Antimicrobial Chemotherapy. *J Antimicrob Chemother* 2008; 62: 5–34. Also available at: http://jac.oxfordjournals.org/cgi/reprint/62/1/5 (accessed 24/02/10)
23. Marik PE. Aspiration pneumonitis and aspiration pneumonia. *N Engl J Med* 2001; 344: 665–71.

Pregnancy and the neonate

For infections associated specifically with pregnancy, see Endometritis (p. 180.3), Perinatal Streptococcal Infections (p. 197.2), and Premature Labour (p. 203.3).

Premature labour

Preterm birth, with or without rupture of membranes, causes significant perinatal morbidity and mortality. There is evidence that infection appears to have an important role in the cause or as a consequence of ruptured membranes[1,2] and as many as 50% of spontaneous preterm births are due to infection, with *Mycoplasma* spp. being the most commonly isolated organisms from the amniotic cavity.[3] Other bacteria that have been implicated include group B streptococci, *Chlamydia trachomatis,* and those associated with bacterial vaginosis. The role of antibacterial treatment has been evaluated. However, it is possible that maternal antibacterial treatment may suppress the stimulation of labour without effectively treating fetal infection[2] and concerns have been expressed that delaying delivery in the presence of a subclinical infection may not produce the best outcome for the neonate.[4]

A meta-analysis[5] and a systematic review[1] of studies of the routine use of antibacterials as adjuncts in the management of premature labour in women with *intact membranes* have failed to show an overall improvement in neonatal morbidity; indeed, an increase in neonatal mortality was actually noted.[5] Furthermore, a long-term follow-up study[6] indicated an increased rate of functional impairment among 7-year-olds whose mothers had received erythromycin for spontaneous preterm labour; an increased incidence of cerebral palsy was also noted among children exposed to either erythromycin or amoxicillin with clavulanic acid.

In women with preterm premature *rupture of membranes,* meta-analyses[7,8] and a systematic review[2] have shown that antibacterials could delay delivery, and reduce both maternal morbidity (chorioamnionitis and postpartum infections) and some aspects of neonatal morbidity (sepsis, pneumonia, and intraventricular haemorrhage). No effects on neonatal mortality or gestational age-related morbidity were noted,[2,8] and a long-term follow-up study found no evidence of negative health effects on the child.[9] However, an increased incidence of neonatal necrotising enterocolitis has been found after maternal use of amoxicillin with clavulanic acid specifically and it is considered best avoided in women at risk of premature delivery; erythromycin may be the antibacterial of choice.[2] A systematic review and meta-analysis[3] evaluated the effect of antibacterials on the rate of preterm births when given in the second trimester of pregnancy to women at risk of preterm births. Giving macrolides or clindamycin was associated with a lower rate of preterm delivery, whereas giving metronidazole alone in the second trimester was associated with a greater risk of preterm delivery in a high-risk population.

Clinical infections of the genito-urinary tract during pregnancy are a cause of significant morbidity in the neonate and antimicrobial treatment is necessary (see Bacterial Vaginosis, p. 174.1, Chlamydial Infections, p. 177.1, and Perinatal Streptococcal Infections, p. 197.2).

1. King J, Flenady V. Prophylactic antibiotics for inhibiting preterm labour with intact membranes. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 16/05/05).
2. Kenyon S, *et al.* Antibiotics for preterm rupture of membranes. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 16/05/05).
3. Morency AM, Bujold E. The effect of second-trimester antibiotic therapy on the rate of preterm birth. *J Obstet Gynaecol Can* 2007; 29: 35–44.
4. Brocklehurst P. Infection and preterm delivery. *BMJ* 1999; 318: 548–9.
5. Egarter C, *et al.* Adjunctive antibiotic treatment in preterm labor and neonatal morbidity: a meta-analysis. *Obstet Gynecol* 1996; 88: 303–9.
6. Kenyon S, *et al.* Childhood outcomes after prescription of antibiotics to pregnant women with spontaneous preterm labour: 7-year follow-up of the ORACLE II trial. *Lancet* 2008; 372: 1319–27.
7. Mercer BM, Arheart KL. Antimicrobial therapy in expectant management of preterm premature rupture of the membranes. *Lancet* 1995; 346: 1271–9. Correction. *ibid.* 1996; 347: 410.
8. Egarter C, *et al.* Antibiotic treatment in preterm premature rupture of membranes and neonatal morbidity: a metaanalysis. *Am J Obstet Gynecol* 1996; 174: 589–97.
9. Kenyon S, *et al.* Childhood outcomes after prescription of antibiotics to pregnant women with preterm rupture of the membranes: 7-year follow-up of the ORACLE I trial. *Lancet* 2008; 372: 1310–18.

Proctitis

Proctitis is inflammation of the rectum that may be caused by sexually transmitted pathogens, most commonly *Neisseria gonorrhoeae, Chlamydia trachomatis, Treponema pallidum,* or herpes simplex virus.

For empirical **treatment** of sexually transmitted proctitis the CDC[1] in the USA recommends a single intramuscular dose of ceftriaxone 125 mg, plus oral doxycycline 100 mg twice daily for 7 days.

The specific treatment of rectal infections caused by *C. trachomatis* and *N. gonorrhoeae* is discussed under Chlamydial Infections (p. 177.1) and Gonorrhoea (p. 206.2) respec-

tively. Patients with herpes proctitis should be treated in the same way as those with genital herpes (p. 957.2).

1. CDC. Sexually transmitted diseases treatment guidelines, 2010. *MMWR* 2010; 59 (RR-12): 1–110. Also available at: http://www.cdc.gov/STD/treatment/2010/STD-Treatment-2010-RR5912.pdf (accessed 08/01/11) Correction. *ibid.* 2011; 60: 18. [dose]

Prostatitis

See under Urinary-tract Infections, p. 215.1.

Psittacosis

The causative organism of psittacosis[1,2] (ornithosis) is *Chlamydophila psittaci* (*Chlamydia psittaci*). It is usually transmitted to humans by direct or indirect contact with infected birds and the primary site of infection is the lung.[1] The clinical presentation of psittacosis can vary widely from a mild 'flu-like' illness to a fulminating toxic state with multiple organ involvement.[1] Most patients will have a cough, although this is not always prominent.[1] However, severe headache similar to that of meningitis is a characteristic symptom.[2] Tetracyclines are the treatment of choice[1,3] and early therapy may be life-saving; a 21-day course has been suggested since relapses have occurred after shorter periods,[1] although 14-day courses are also widely recommended.[2] An alternative is chloramphenicol.[3] Erythromycin or a similar macrolide have also been used successfully.[4,5]

1. Macfarlane JT, Macrae AD. Psittacosis. *Br Med Bull* 1983; 39: 163–7.
2. Stewardson AJ, Grayson ML. Psittacosis. *Infect Dis Clin North Am* 2010; 24: 7–25.
3. Abramowicz M, ed. The choice of antibacterial drugs. In: *Handbook of antimicrobial therapy*. 19th ed. New Rochelle NY: The Medical Letter,2011: 74.
4. Morrison WM, *et al.* An outbreak of psittacosis. *J Infect* 1991; 22: 71–5.
5. Chang KP, Veitch PC. Fever, haematuria, proteinuria, and a parrot. *Lancet* 1997; 350: 1674.

Q fever

Q fever[1,2] (or query fever) is a rickettsial infection (p. 205.2) caused by *Coxiella burnetii*. It is a zoonosis occurring worldwide and is transmitted to humans from domestic animals such as cattle and sheep, mainly by inhalation of infected dust. Q fever is asymptomatic in about 50 to 60% of infected persons. Symptomatic acute infection generally presents as a febrile flu-like illness and many patients may also have hepatitis or pneumonia that can progress to acute respiratory distress syndrome. Endocarditis is the most frequent form of chronic infection and the most serious form of Q fever; infection may be difficult to eradicate and prolonged treatment is generally needed. There is also evidence of long-term sequelae including lethargy and fatigue in patients who have not had cardiac involvement.

Subclinical **acute infections** should be treated if recognised and if possible treatment should be started within 3 days of the onset of symptoms. A tetracycline such as doxycycline for 14 days is the treatment of choice for acute Q fever. The role of macrolides in acute infection is unclear and clinical data on the use of fluoroquinolones are limited.[1,2] Co-trimoxazole is recommended for children younger than 8 years of age.[1] **Q fever endocarditis** is more difficult to treat and surgery may be required in addition to antibacterial treatment.[2] Monotherapy with tetracycline decreases symptoms but fails to eradicate *C. burnetii* and combination antibacterial therapy has been evaluated. Long-term treatment with doxycycline plus rifampicin or with ciprofloxacin alone[3] has been successful in individual patients with endocarditis, whereas pefloxacin alone[4] was not. A retrospective comparison of doxycycline alone or with rifampicin, fluoroquinolones (ofloxacin or pefloxacin), or co-trimoxazole, recommended treatment for at least 3 years with doxycycline plus a fluoroquinolone;[5] doxycycline plus rifampicin also appeared effective, but in most cases rifampicin had been stopped after a few months because of interactions with anticoagulants often prescribed at the same time. Patients given doxycycline plus hydroxychloroquine needed a shorter treatment course and had fewer relapses than those treated with doxycycline plus ofloxacin; mortality rate for both groups was 5%.[6] Successful treatment with doxycycline and chloroquine for 2 years has been reported in a patient with a biological prosthetic aortic valve and aortic homograft.[7] The combination of doxycycline 100 mg twice daily and hydroxychloroquine 200 mg three times daily, both given orally for at least 18 months, is considered to be the treatment of choice for Q fever endocarditis.[1,2] An alternative regimen for patients unable to tolerate hydroxychloroquine is doxycycline plus a fluoroquinolone for at least 3 to 4 years.[2]

Q fever during **pregnancy** may result in obstetric complications, such as spontaneous abortion, intra-uterine growth retardation, intra-uterine fetal death, and premature delivery.[8] Treatment with co-trimoxazole for at least 5 weeks during pregnancy was reported to protect against maternal chronic Q fever, placental infection, and obstetric complications (in particular intra-uterine fetal death).[8]

A vaccine is available in some countries for **prophylaxis** in occupational groups who regularly handle potentially infected animal tissues.

1. Parker NR, *et al.* Q fever. *Lancet* 2006; 367: 679–88.
2. Hartzell JD, *et al.* Q fever: epidemiology, diagnosis, and treatment. *Mayo Clin Proc* 2008; 83: 574–9.
3. Yebra M, *et al.* Ciprofloxacin in a case of Q fever endocarditis. *N Engl J Med* 1990; 323: 614.
4. Cacoub P, *et al.* Q-fever endocarditis and treatment with the fluoroquinolones. *Arch Intern Med* 1991; 151: 816, 818.
5. Levy PY, *et al.* Comparison of different antibiotic regimens for therapy of 32 cases of Q fever endocarditis. *Antimicrob Agents Chemother* 1991; 35: 533–7.
6. Raoult D, *et al.* Treatment of Q fever endocarditis: comparison of 2 regimens containing doxycycline and ofloxacin or hydroxychloroquine. *Arch Intern Med* 1999; 159: 167–73.
7. Caliza L, *et al.* Doxycycline and chloroquine as treatment for chronic Q fever endocarditis. *J Infect* 2002; 45: 127–9.
8. Carcopino X, *et al.* Managing Q fever during pregnancy: the benefits of long-term cotrimoxazole therapy. *Clin Infect Dis* 2007; 45: 548–55.

Relapsing fever

Relapsing fever is caused by spirochaetes of the *Borrelia* genus that are transmitted to humans by body lice or *Ornithodoros* ticks. *B. recurrentis* causes louse-borne relapsing fever (LBRF). Global distribution and incidence of LBRF have reduced substantially due to improvements in sanitation and hygiene; however, it is endemic in some areas such as northeastern Africa, and can occur elsewhere in populations affected by war or natural disasters. Many species of *Borrelia* may cause tick-borne relapsing fever (TBRF), which has a global distribution, but is highly endemic in sub-Saharan Africa.

Clinical manifestations of LBRF and TBRF are similar. The onset is typically sudden, with high fever (sometimes with delirium), headache, chills, sweating, myalgia, arthralgia, and gastrointestinal disturbances. Complications include epistaxis, and gastrointestinal and CNS haemorrhage. Without treatment, symptoms intensify, resulting in a crisis. This comprises two phases: a chill phase characterised by rigors, increasing temperature, and hypermetabolism, and a flush phase of decreasing temperature, diaphoresis, and hypotension, which may be fatal. Death due to TBRF is rare. However, untreated LBRF has a high fatality rate, especially in malnourished populations.

The treatment of choice for relapsing fever is a tetracycline such as doxycycline; benzylpenicillin or erythromycin are alternatives; treatment is given orally where possible[1,2] Therapy with single oral doses of tetracycline, erythromycin, or chloramphenicol has been effective for LBRF, whereas treatment for 7 to 10 days is usually given for tick-borne disease,[2] because of the higher rate of treatment failure and relapses in these patients. Antibacterial treatment often causes a Jarisch-Herxheimer reaction within 4 hours of the first dose, and associated with a release of cytokines, the symptoms of which resemble the crisis phase of untreated patients;[2] this reaction tends to be more severe in LBRF. Attempts to prevent this reaction include use of paracetamol, NSAIDS, and corticosteroids, to little effect.[2] Antibodies against tumour necrosis factor α have also been tried.[3]

1. Abramowicz M, ed. The choice of antibacterial drugs. In: *Handbook of antimicrobial therapy*. 19th ed. New Rochelle NY: The Medical Letter,2011: 75.
2. Roscoe C, Epperly T. Tick-borne relapsing fever. *Am Fam Physician* 2005; 72: 2039–44.
3. Pekade D, *et al.* Prevention of Jarisch-Herxheimer reactions by treatment with antibodies against tumor necrosis factor α . *N Engl J Med* 1996; 335: 311–15.

Respiratory-tract infections

Principal community-acquired bacterial pathogens in the respiratory tract are *Streptococcus pneumoniae* and *Haemophilus influenzae*, although *Moraxella catarrhalis* (*Branhamella catarrhalis*) is increasingly important in some areas. Other respiratory pathogens include *Chlamydophila pneumoniae* (*Chlamydia pneumoniae*), *Legionella pneumophila*, and *Mycoplasma pneumoniae*. *Streptococcus pyogenes* is the predominant cause of pharyngitis. *Staphylococcus aureus* and aerobic Gram-negative bacilli such as *Pseudomonas aeruginosa* and *Klebsiella* spp. may be responsible for hospital-acquired (nosocomial) infections.

Non-specific, community-acquired respiratory-tract infections are very common and usually viral in origin. Because these infections are generally self-limiting, US[1] and UK[2] guidelines suggest that antibacterials should not be routinely given, although they may be appropriate for some patients based on severity of illness or risk factors for serious complications.[2,3]

For details on infections of the upper respiratory tract, see under Epiglottitis (p. 181.3), Pharyngitis (p. 198.3), and Sinusitis (p. 208.2); see also Otitis Media (p. 195.2). For infections of the lower respiratory tract, see under Bronchitis (p. 175.3), Cystic Fibrosis (p. 177.2), and Pneumonia (p. 200.1); those with a specific cause include Legionnaires' Disease (p. 188.2), Nocardiosis (p. 193.3), Pertussis (p. 198.3), and Tuberculosis (p. 212.2). For discussion on the eradication of nasal staphylococci carriage, see Staphylococcal Infections, p. 210.2.

For details on the symptomatic management of respiratory-tract infection, see under Cough (p. 1651.2) and Fever and Hyperthermia (p. 11.3).

1. Snow V, *et al.* American College of Physicians, American Society of Internal Medicine, American Academy of Family Physicians, Centers for Disease Control. Principles of appropriate antibiotic use for treatment of nonspecific upper respiratory tract infections in adults. *Ann Intern Med* 2001; 134: 487–9. Also available at: http://www.annals.org/cgi/reprint/134/6/487 (accessed 05/08/08)
2. NICE. Respiratory-tract infections—antibiotic prescribing: prescribing of antibiotics for self-limiting respiratory tract infections in adults and children in primary care (issued July 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/CG69FullGuideline.pdf (accessed 03/03/10)
3. Petersen I, *et al.* Protective effect of antibiotics against serious complications of common respiratory tract infections: retrospective cohort study with the UK General Practice Research Database. Abridged version: *BMJ* 2007; 335: 982–4. Full version: http://www.bmj.com/cgi/reprint/335/7627/982 (accessed 03/03/10)

Rheumatic fever

Acute rheumatic fever[1] occurs especially in children aged 6 to 15 years as a consequence of upper respiratory-tract infections, such as pharyngitis or tonsillitis, with rheumatogenic strains of the group A beta-haemolytic streptococcus, *Streptococcus pyogenes*. The pathogenesis of rheumatic fever is unknown, but an immune mechanism may be involved. There may be a latent period of 1 to 5 weeks after the initial infection, before clinical manifestations of rheumatic fever appear. The major ones are arthritis, carditis, chorea, erythema marginatum, and subcutaneous nodules. Those affecting the heart are the most serious and are a major cause of cardiovascular death in children and young adults in developing countries. Rheumatic fever has been associated with poverty and overcrowding and has declined dramatically in developed countries, but is still a major problem in the developing world. However, in the 1980s there was evidence of a resurgence in the USA with outbreaks of rheumatic fever reported in middle-class children[2] and military recruits.[3] Increased pathogenicity of *Str. pyogenes* serotypes might have contributed to this resurgence.[4] A high incidence is also seen among indigenous populations in Australia and New Zealand.[5]

Guidelines for the management and prevention of rheumatic fever have been published by sources including the American Heart Association,[6] WHO,[7] and expert groups from Australia and New Zealand[8] as well as India.[9] Rheumatic fever can usually be prevented by *primary prophylaxis*, that is, by the prompt treatment of streptococcal upper respiratory-tract infection with eradication of group A streptococci (GAS) from the throat. Penicillin is the drug of choice, either as a single intramuscular injection of benzathine benzylpenicillin or as an oral course of phenoxymethylpenicillin (or alternatively, amoxicillin) for 10 days.[6,7] An injection containing benzathine benzylpenicillin and procaine benzylpenicillin, which is less painful than benzathine benzylpenicillin alone, is a suitable alternative for use in children.[6] For patients who are intolerant of penicillin, a narrow-spectrum oral cephalosporin such as cefadroxil or cefalexin may be considered in those who do not have type I penicillin hypersensitivity. Further treatment options include oral clindamycin, and the macrolides erythromycin, clarithromycin, and azithromycin; however, because macrolide-resistant GAS are common in some areas of the world, there may be a higher risk of treatment failure when these drugs are used.[6] For further details on the treatment of streptococcal sore throat, see under Pharyngitis, p. 198.3. Failure to eradicate GAS is more common after oral antibacterials and in the USA many of these patients are asymptomatic, chronic streptococcal carriers;[6] re-treatment of these patients is usually unnecessary,[6,7] and should only be considered in those with a personal or family history of rheumatic fever.[6] Symptomatic individuals can be re-treated either with the same, or an alternative antibacterial regimen; where initial treatment with penicillin has failed, a narrow-spectrum cephalosporin, clindamycin, amoxicillin with clavulanic acid, or penicillin with rifampicin are all reasonable alternatives.[6] Broad-based primary prophylaxis in communities rather than individuals has been tried[10,11] but a study in military recruits showed that *Str. pyogenes* infection could not be prevented in closely confined communities unless all individuals in the population received prophylaxis.[11]

If acute rheumatic fever occurs, a full therapeutic course of penicillin should be given initially, as for primary prevention, to eradicate GAS.[6,8] Treatment then comprises bed rest and anti-inflammatory drugs, usually corticosteroids or salicylates, in an attempt to prevent valvular scarring. However, it is unclear whether anti-inflammatory treatment has any influence on such long-term sequelae.[12] Carbamazepine or valproate may be given for severe and distressing chorea.[8] *Secondary prevention* is then continued with prolonged antibacterial prophylaxis because of the high risk of recurrent attacks of rheumatic fever after subsequent streptococcal upper respiratory-tract infections.

Again, penicillin is the preferred antibacterial, the usual recommendation being an intramuscular injection of benzathine benzylpenicillin every 4 weeks, although injections every 3 weeks may be warranted where the risk of recurrence is high.[6-8] This advice has been influenced by reports of high recurrence rates with the monthly regimen in such situations.[13] A 12-year study in Taiwan[14] confirmed that prophylaxis with benzathine benzylpenicillin injections every 3 weeks is more effective than injections every 4 weeks and it was recommended that the 3-week regimen should be used in adults and children with a recent episode of rheumatic fever, especially in developing countries where exposure to streptococci is still intense. In addition, pharmacokinetic studies have indicated relatively low serum concentrations of penicillin in the fourth week after an intramuscular injection of benzathine benzylpenicillin,[15,16] despite the successful use of monthly injections in most patients. However, Australian and New Zealand guidelines consider the 4-week regimen suitable in most patients.[8] Alternatively, oral prophylaxis with phenoxymethylpenicillin or sulfadiazine may be given, although, over the long time scale involved, compliance is likely to be a problem;[5,7,8] a macrolide is suggested for the rare patient who is allergic to penicillin and sulfonamides.[6] Sulfonamides should *not* be used for primary prevention because they do not eradicate the streptococci.[6,7] The duration of secondary prophylaxis depends on the individual patient, but in those who have not had rheumatic carditis it should generally continue for a minimum of 5 years after the last attack of rheumatic fever, or until early adulthood (18 to 21 years of age), whichever is longer.[6,7] Those who have had rheumatic carditis but without residual valvular disease should perhaps receive prophylaxis at least until the age of 21[6] or 25 years,[7] or for 10 years after the last attack,[6] whichever is longer. For those with carditis and persistent valvular disease, prophylaxis should continue at least until the age of 40 years, or sometimes for life.[6,7] Fears of serious allergic reactions associated with long-term benzathine benzylpenicillin prophylaxis appear to be unfounded.[17]

Household contacts of rheumatic fever patients who themselves have positive streptococcal cultures should be treated.[6]

Some patients with rheumatic valvular heart disease as a result of rheumatic fever are at risk of developing infective endocarditis and those at highest risk may need additional appropriate short-term antibacterial prophylaxis when undergoing dental and some surgical procedures (see Endocarditis, p. 179.2).

1. Carapetis JR, *et al.* Acute rheumatic fever. *Lancet* 2005; 366: 155–68.
2. Veasy LG, *et al.* Resurgence of acute rheumatic fever in the intermountain area of the United States. *N Engl J Med* 1987; 316: 421–7.
3. Wallace MR, *et al.* The return of acute rheumatic fever in young adults. *JAMA* 1989; 262: 2557–61.
4. Schwartz B, *et al.* Changing epidemiology of group A streptococcal infection in the USA. *Lancet* 1990; 336: 1167–71.
5. Cilliers AM. Rheumatic fever and its management. *BMJ* 2006; 333: 1153–6.
6. Gerber MA, *et al.* Prevention of rheumatic fever and diagnosis and treatment of acute streptococcal pharyngitis: a scientific statement from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, the Interdisciplinary Council on Functional Genomics and Translational Biology, and the Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. *Circulation* 2009; 119: 1541–51. Also available at: http://circ.ahajournals.org/cgi/reprint/119/11/1541 (accessed 26/02/10)
7. WHO. Rheumatic fever and rheumatic heart disease. *WHO Tech Rep Ser* 923 2004. Also available at: http://www.who.int/cardiovascular_diseases/resources/en/cvd_trs923.pdf (accessed 05/08/08)
8. Heart Foundation of Australia, Cardiac Society of Australia and New Zealand. Diagnosis and management of acute rheumatic fever and rheumatic heart disease in Australia - an evidence-based review (issued June 2006). Available at: http://www.heartfoundation.org.au/document/NHF/PP-590_Diagnosis-Management_ARF-RHD_Evidence-Based%20Review_Sep06Update_FINAL.pdf (accessed 05/08/08)
9. Saxena A, *et al.* Working Group on Pediatric Acute Rheumatic Fever and Cardiology Chapter of Indian Academy of Pediatrics. Consensus guidelines on pediatric acute rheumatic fever and rheumatic heart disease. *Indian Pediatr* 2008; 45: 565–73.
10. Colling A, *et al.* Minimum amount of penicillin prophylaxis required to control Streptococcus pyogenes epidemic in closed community. *BMJ* 1982; 285: 95–6.
11. Gray GC, *et al.* Hyperendemic Streptococcus pyogenes infection despite prophylaxis with penicillin G benzathine. *N Engl J Med* 1991; 325: 92–7.
12. Cilliers AM, *et al.* Anti-inflammatory treatment for carditis in acute rheumatic fever. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 06/08/08).
13. Ayoub EM. Prophylaxis in patients with rheumatic fever: every three or every four weeks? *J Pediatr* 1989; 115: 89–91.
14. Lue H-C, *et al.* Long-term outcome of patients with rheumatic fever receiving benzathine penicillin G prophylaxis every three weeks versus every four weeks. *J Pediatr* 1994; 125: 812–16.
15. Kaplan EL, *et al.* Pharmacokinetics of benzathine penicillin G: serum levels during the 28 days after intramuscular injection of 1,200,000 units. *J Pediatr* 1989; 115: 146–50.
16. Meira ZMA, *et al.* Evaluation of secondary prophylactic schemes, based on benzathine penicillin G, for rheumatic fever in children. *J Pediatr* 1993; 123: 156–8.
17. International Rheumatic Fever Study Group. Allergic reactions to long-term benzathine penicillin prophylaxis for rheumatic fever. *Lancet* 1991; 337: 1308–10.

Rickettsial infections

Bacteria of the Rickettsiaceae family that infect man include *Rickettsia* spp. (see under Spotted Fevers, p. 210.1 and Typhus, p. 214.3) and *Coxiella burnetii* (see under Q fever, p. 202.1). *Ehrlichia* spp. (see under Ehrlichiosis, p. 179.1) and *Bartonella quintana* (*Rochalimaea quintana*) (see under Trench Fever, p. 212.2) are no longer classified as a rickettsia. The treatment of choice for rickettsial infections is doxycycline; chloramphenicol or a fluoroquinolone are alternatives.[1]

1. Abramowicz M, ed. The choice of antibacterial drugs. In: *Handbook of antimicrobial therapy*. 19th ed. New Rochelle NY: The Medical Letter, 2011: 74.

Salmonella enteritis

See p. 185.2.

Salpingitis

See under Pelvic Inflammatory Disease, p. 196.3.

Septicaemia

Traditionally, transient bacteraemia (the presence of bacteria in the blood) has been regarded as a fairly common condition which does not usually cause complications, whereas uncontrolled bacteraemia leads to septicaemia with serious symptoms such as fever and shock. This distinction has not always been adhered to in published sources and the terms have sometimes been used interchangeably. Added to this, the identification of the cascade of inflammatory mediators involved and the realisation that what had been called 'sepsis' could arise in the absence of infection have prompted reassessment of the terminology used both in the UK and in the USA.[1] In the UK, some authorities[2] considered that the term 'septicaemia' should no longer be used since it does not distinguish between mild and severe disease. The term 'sepsis syndrome' was preferred for patients with a generalised systemic response together with evidence of organ dysfunction and 'septic shock' to describe patients who also have hypotension not due to hypovolaemia or cardiac causes. The American College of Chest Physicians and Society of Critical Care Medicine proposed the following series of definitions to cover the spectrum of syndromes resulting from this inflammatory response:[1,3]

- **systemic inflammatory response syndrome** (SIRS), the systemic inflammatory response to infection or various other severe clinical insults including pancreatitis, ischaemia, trauma, and haemorrhagic shock
- **sepsis**, the SIRS caused specifically by infection
- **severe sepsis**, sepsis associated with organ dysfunction, perfusion abnormalities (such as lactic acidosis, oliguria, or an acute alteration in mental status), or hypotension
- **septic shock**, sepsis with hypotension, despite adequate fluid resuscitation, together with perfusion abnormalities
- **multiple organ dysfunction syndrome** (MODS), the presence of altered organ function in an acutely ill patient such that homoeostasis cannot be maintained without intervention; it may be a cause as well as a consequence of SIRS.

Septicaemia can be caused by many bacteria.[4] **Community-acquired** primary septicaemia is often associated with a specific infectious disease, such as meningococcal septicaemia with meningococcal meningitis (p. 191.1) or streptococcal septicaemia with pneumonia (p. 200.1). *Streptococcus pneumoniae* and *Haemophilus influenzae* are common causes of primary septicaemia in children (although this pattern is changing in countries where immunisation against *H. influenzae* type b is routine); Gram-negative rods and group B streptococci are commonest in neonates. **Hospital-acquired** septicaemia is often iatrogenic and may occur as a complication of surgery or indwelling catheters[5] or may be associated with neutropenia in immunocompromised patients (see under Infections in Immunocompromised Patients, p. 186.3). Hospital-acquired septicaemia is often associated with acute respiratory distress syndrome (p. 1599.3).

Whatever the cause, septicaemia requires prompt empirical treatment.[6-8] Choice of antibacterial depends on the probable source of infection. For example, urinary-tract infection is likely to be associated with Gram-negative septicaemia due to *Escherichia coli*; abdominal sepsis with Gram-negative septicaemia due to mixed infection with *E. coli*, enterococci, and anaerobic bacteria; and skin sepsis, bacterial arthritis, acute osteomyelitis, and cardiovascular shunts with Gram-positive septicaemia due to staphylococci. The antibacterials used should also reflect current patterns of bacterial resistance in the community or hospital. International guidelines[9] have recommended starting intravenous antibacterial therapy as early as possible, and within the first hour of recognition of septic shock; the initial choice of therapy should be broad enough to cover all likely pathogens, and it should be reassessed daily to optimise activity and prevent the development of resistance. De-escalation of combination therapy to the most appropriate single therapy should be carried out as soon as susceptibility of the infection is known. The typical duration of therapy will be 7 to 10 days. *Empirical treatment* has often begun with a penicillin and an aminoglycoside, metronidazole being added if anaerobic infection is suspected. In the UK, the *BNF* recommends that initial empirical treatment for community-acquired septicaemia is with either a broad-spectrum antipseudomonal penicillin (such as piperacillin with tazobactam or ticarcillin with clavulanic acid) or a broad-spectrum cephalosporin (such as cefuroxime); if other resistant micro-organisms are suspected, a more broad-spectrum beta-lactam antibacterial such as meropenem should be used. For hospital-acquired septicaemia a broad-spectrum antipseudomonal beta-lactam antibacterial (such as ceftazidime, piperacillin with tazobactam, ticarcillin with clavulanic acid, imipenem, or meropenem) is recommended. In both cases, metronidazole should be added if anaerobic organisms are suspected, and vancomycin or teicoplanin if meticillin-resistant staphylococci are suspected. US guidelines[10] recommend a third- or fourth-generation cephalosporin (cefotaxime, ceftriaxone, ceftazidime, or cefepime), or piperacillin with tazobactam, or imipenem, or meropenem, in each case with vancomycin and sometimes also an aminoglycoside (gentamicin, tobramycin, or amikacin) for the initial treatment of life-threatening sepsis in adults. When there is some information on which to base choice of treatment, but before the infecting organisms are definitely known, the following treatment is suggested:

- suspected bacterial endocarditis—ceftriaxone with vancomycin, possibly with gentamicin as well
- suspected meticillin-resistant staphylococci—vancomycin, alone or with gentamicin and/or rifampicin

Once the infecting organisms have been identified, choice of treatment will again depend on their sensitivity and current patterns of resistance in the community or hospital. For comments on the consequences of emerging multidrug-resistant strains of enterococci and staphylococci, see Enterococcal Infections, p. 181.1, and Staphylococcal Infections, p. 210.2.

In addition to antimicrobial therapy, patients with sepsis or septic shock require rigorous supportive measures (p. 1279.3). Specific supportive treatment aimed at inhibiting endogenous mediators released in response to sepsis has been tried with little clinical success, and includes adjunctive therapy with endotoxin antibodies, anticytokines such as anakinra and tumour necrosis factor antibodies, soluble tumour necrosis factor receptor, bactericidal permeability increasing protein, nitric oxide synthase inhibitors, guanylate cyclase inhibitors such as methylthioninium chloride, and platelet-activating factor antagonists.[11-13] A systematic review[14] of the use of intravenous polyclonal immunoglobulin concluded that it had a promising role as adjuvant therapy in sepsis and septic shock. Specific monoclonal immunoglobulins were not effective.[14] Reduced mortality was reported[15] after the treatment of patients with severe sepsis with recombinant activated protein C [drotrecogin alfa (activated)] which has antithrombotic, anti-inflammatory, and pro-fibrinolytic properties. However, a systematic review[16] of this and subsequent studies found no mortality benefit, and a higher risk of bleeding. Drotrecogin alfa (activated) was withdrawn from the market in October 2011. Although deficiency of adrenal corticosteroid production has been described in severe sepsis, high-dose corticosteroid treatment was found to be of no benefit, but improved outcomes have been reported with the use of lower doses of corticosteroids.[6] International guidelines developed by the Surviving Sepsis Campaign[9] consider that low-dose intravenous hydrocortisone may be given to adults with septic shock who remain hypotensive despite adequate fluid resuscitation and vasopressor therapy; the addition of oral fludrocortisone is optional but dexamethasone is not recommended. The addition of daily oral fludrocortisone is suggested if an alternative corticosteroid is used that lacks significant mineralocorticoid activity.[9] However, since these guidelines were published a multicentre, randomised, double-blind, placebo-controlled study[17] of 499 patients with septic shock reported that low-dose hydrocortisone did not significantly affect survival rate at 28 days or the rate of reversal of shock either overall or in patients who did not have a response to corticotropin, but a decrease in time to reversal was noted in those patients in whom shock was reversed. Studies with other physiological anticoagulants such as antithrombin III[18] and tissue factor pathway inhibitor (tifacogin)[19] have not been successful.

Neonatal septicaemia may be divided into **early-onset**, which is acquired from the mother's genital tract and manifests itself during the first few days after birth, and **late-onset** which may be nosocomially acquired. Bacteria commonly causing early-onset sepsis include enterococci, *E. coli*, *H. influenzae*, *Listeria monocytogenes*, and streptococci. Some of these organisms may also produce meningitis in the neonate (p. 191.1). Empirical treatment for both early- and

late-onset sepsis is based on similar principles to those in other patients, giving consideration to local patterns of infection and resistance and to the suitability of individual antibacterials for this age group. However, early-onset sepsis is usually best controlled by prenatal treatment of the mother or by perinatal prophylaxis. Prophylaxis for group B streptococcal infections is discussed under Perinatal Streptococcal Infections, p. 197.2. While vancomycin has been shown to prevent infections with coagulase-negative staphylococci and to reduce the incidence of neonatal sepsis, widespread prophylactic use of this drug is not recommended.[20] Intravenous normal immunoglobulin (see Neonatal Infection, p. 2406.2) and filgrastim (see Neutropenia, p. 1152.3) have been tried for the prevention of septicaemia in preterm neonates with variable results.

1. Bone RC. Why new definitions of sepsis and organ failure are needed. *Am J Med* 1993; **95**: 348–50.
2. Lynn WA, Cohen J. Management of septic shock. *J Infect* 1995; **30**: 207–12.
3. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992; **20**: 864–74.
4. Eykyn SJ, *et al.* The causative organisms of septicaemia and their epidemiology. *J Antimicrob Chemother* 1990; **25** (suppl C): 41–58.
5. Mermel LA, *et al.* Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009; **49**: 1–45. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/599376 (accessed 11/05/10) Correction. *ibid.* 2010; **50**: 457.
6. Mackenzie I, Lever A. Management of sepsis. *BMJ* 2007; **335**: 929–32.
7. Lever A, Mackenzie I. Sepsis: definition, epidemiology, and diagnosis. *BMJ* 2007; **335**: 879–83.
8. O'Brien JM, *et al.* Sepsis. *Am J Med* 2007; **120**: 1012–22.
9. Dellinger RP, *et al.* Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 2008; **36**: 296–327.
10. Anonymous. The choice of antibacterial drugs. In: *Handbook of antimicrobial therapy*. 18th ed. New York: The Medical Letter, 2008: 48–57.
11. Baumgartner J-D, Calandra T. Treatment of sepsis: past and future avenues. *Drugs* 1999; **57**: 127–32.
12. Verhoef J, *et al.* Issues in the adjunct therapy of severe sepsis. *J Antimicrob Chemother* 1996; **38**: 167–82.
13. Opal SM, Yu RL. Antiendotoxin strategies for the prevention and treatment of septic shock: new approaches and future directions. *Drugs* 1998; **55**: 497–508.
14. Alejandria MM, *et al.* Intravenous immunoglobulin for treating sepsis and septic shock. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2002 (accessed 16/05/05).
15. Bernard GR, *et al.* Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001; **344**: 699–709.
16. Martí-Carvajal AJ, *et al.* Human recombinant activated protein C for severe sepsis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2011 (accessed 31/10/11).
17. Sprung CL, *et al.* Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008; **358**: 111–24.
18. Warren BL, *et al.* High-dose antithrombin III in severe sepsis: a randomized controlled trial. *JAMA* 2001; **286**: 1869–78. Correction. *ibid.* 2002; **287**: 192.
19. Abraham E, *et al.* Efficacy and safety of tifacogin (recombinant tissue factor pathway inhibitor) in severe sepsis: a randomized controlled trial. *JAMA* 2003; **290**: 238–47.
20. Craft AP, *et al.* Vancomycin for prophylaxis against sepsis in preterm neonates. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2000 (accessed 16/05/05).

Sexually transmitted diseases

The sexually transmitted diseases, formerly termed venereal diseases, are defined as a group of communicable diseases that are transferred mainly by sexual contact. Many pathogens are known to be transmitted sexually including:

- bacteria:
  - *Chlamydia trachomatis* (see Lymphogranuloma Venereum, p. 207.2 and Chlamydial Infections, p. 177.1)
  - *Haemophilus ducreyi* (see Chancroid, p. 206.2)
  - *Klebsiella granulomatis* (see Granuloma Inguinale, p. 207.1)
  - *Neisseria gonorrhoeae* (see Gonorrhoea, p. 206.2)
  - *Treponema pallidum* (see Syphilis, p. 207.2)
  - *Ureaplasma urealyticum*
- protozoa:
  - *Trichomonas vaginalis* (see Trichomoniasis, p. 927.1).
- viruses:
  - human immunodeficiency virus (see HIV Infection and AIDS, p. 959.2)
  - hepatitis viruses (see Hepatitis, p. 954.1)
  - herpesviruses (see Herpesvirus Infections, p. 956.1)

Clinical syndromes associated with sexually transmitted diseases, and which are discussed in this section, include urethritis (p. 214.3) and epididymitis (p. 181.2) in men; cervicitis (p. 177.1), pelvic inflammatory disease (p. 196.3), and bacterial vaginosis (p. 174.1) in women; and proctitis (p. 201.3). Perinatal transmission of sexually transmitted pathogens from the mother can result in neonatal conjunctivitis (p. 193.2) or pneumonia (p. 200.1).

General guidelines for the management of sexually transmitted diseases have been published[1-3] although recommendations may need to be localised because of differences in patterns of infection and drug resistance. Early detection and treatment are required to prevent long-term complications, including infertility, still-births and neonatal infections, genital cancers, and an increased risk of acquiring and transmitting HIV.

The suggestion that spermicidal contraceptives may provide some protection against sexually transmitted diseases is discussed under Nonoxinols, p. 2199.1.

1. WHO. Guidelines for the management of sexually transmitted infections. Geneva: WHO, 2003. Also available at: http://whqlibdoc.who.int/publications/2003/9241546263.pdf (accessed 23/03/07)
2. Clinical Effectiveness Group (British Association for Sexual Health and HIV). United Kingdom national guideline on the management of sexually transmitted infections and related conditions in children and young people (2009). Available at: http://www.bashh.org/documents/2275 (accessed 05/03/10)
3. CDC. Sexually transmitted diseases treatment guidelines, 2010. *MMWR* 2010; **59** (RR-12): 1–110. Also available at: http://www.cdc.gov/STD/treatment/2010/STD-Treatment-2010-RR5912.pdf (accessed 08/01/11) Correction. *ibid.* 2011; **60**: 18. [dose]

Chancroid. Chancroid is a sexually transmitted disease caused by the Gram-negative bacterium *Haemophilus ducreyi*. It occurs worldwide, but is endemic in parts of Africa and South East Asia, where it is a frequent cause of painful genital ulcers and a risk factor in the transmission of HIV.

Specific treatment guidelines have been provided by WHO,[1] by expert groups in the UK,[2] and by the CDC in the USA.[3] Treatment failure may be more common in patients also infected with HIV[1] (see below), but in other patients single-dose treatment regimens might be preferable if compliance is a problem. Guideline regimens are as follows:

- **WHO:**
  - oral ciprofloxacin 500 mg twice daily for 3 days, *or*
  - oral erythromycin 500 mg four times daily for 7 days, *or*
  - a single oral dose of azithromycin 1 g

  an alternative regimen is:
  - a single intramuscular injection of ceftriaxone 250 mg
- **UK:**
  - a single oral dose of azithromycin 1 g, *or*
  - a single intramuscular dose of ceftriaxone 250 mg, *or*
  - oral ciprofloxacin 500 mg twice daily for 3 days *or* as a single oral dose, *or*
  - oral erythromycin 500 mg four times daily for 7 days

  further alternatives are:
  - single oral doses of other fluoroquinolones such as fleroxacin 400 mg *or* norfloxacin 800 mg
  - a single intramuscular injection of spectinomycin 2 g
- **USA:**
  - a single oral dose of azithromycin 1 g, *or*
  - a single intramuscular dose of ceftriaxone 250 mg, *or*
  - oral ciprofloxacin 500 mg twice daily for 3 days, *or*
  - oral erythromycin 500 mg three times daily for 7 days

Sexual partners of patients with chancroid should also be tested and treated.[2,3]

Patients co-infected with HIV have ulcers that heal more slowly and may need to be treated for longer to prevent treatment failure;[3] treatment failure is common with single-dose regimens.[1]

1. WHO. Guidelines for the management of sexually transmitted infections. Geneva: WHO, 2003. Also available at: http://whqlibdoc.who.int/publications/2003/9241546263.pdf (accessed 23/03/07)
2. Clinical Effectiveness Group (British Association for Sexual Health and HIV). 2007 National guideline for the management of chancroid. Available at: http://www.bashh.org/documents/85/85.pdf (accessed 05/03/10)
3. CDC. Sexually transmitted diseases treatment guidelines, 2010. *MMWR* 2010; **59** (RR-12): 1–110. Also available at: http://www.cdc.gov/STD/treatment/2010/STD-Treatment-2010-RR5912.pdf (accessed 08/01/11) Correction. *ibid.* 2011; **60**: 18. [dose]

Gonorrhoea. Gonorrhoea is a sexually transmitted disease caused by infection of mucosa with *Neisseria gonorrhoeae* (gonococcus), a Gram-negative bacterium. It occurs mainly in the lower genital tract as urethritis (p. 214.3) in men and cervicitis (p. 177.1) in women, but also as pharyngitis, proctitis (p. 201.3), or conjunctivitis. Infection may sometimes ascend to the upper genital tract to cause complications such as pelvic inflammatory disease (p. 196.3) in women and epididymitis (p. 181.2) in men. In the USA[1] routine screening is recommended for all sexually active women with an increased risk of infection. Disseminated gonococcal infection resulting from gonococcal bacteraemia is rare and may lead to septic arthritis, an arthritis-dermatitis syndrome (not to be confused with Reiter's disease which has been associated with non-gonococcal or non-specific urethritis), and more rarely to conditions such as endocarditis or meningitis. Gonorrhoea in pregnant women may cause neonatal gonococcal conjunctivitis (ophthalmia neonatorum).

Antibacterial drug resistance is a problem in the management of gonococcal infection. Penicillins were once the treatment of choice for *N. gonorrhoeae* but are no longer recommended. High-level plasmid-mediated and chromosomally mediated resistances have also been reported with tetracycline, and chromosomally mediated resistance to other antibacterials may occur. Gonococcal resistance is now monitored in England and Wales via the Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP)[2] and in the USA by the Gonococcal Isolate Surveillance Project (GISP).[3] Worldwide resistance to fluoroquinolones has resulted in revision of treatment guidelines; in the UK fluoroquinolones are no longer recommended as first-line drugs and should only be used if the infection is known or anticipated to be sensitive, while in the USA they are no longer recommended for any gonococcal infections. Reports are also emerging of decreasing gonococcal susceptibility to extended-spectrum cephalosporins and verified treatment failures to oral cefixime have been reported.[4]

Infection with *Chlamydia trachomatis* (see under Chlamydial Infections, p. 177.1) often occurs along with gonorrhoea and should be tested for or treated presumptively usually with either oral azithromycin or doxycycline. WHO[5] generally recommends that unless infection with *C. trachomatis* has been excluded by a laboratory test, all patients with anogenital or pharyngeal gonorrhoea should be given concurrent anti-chlamydia treatment. UK[6] and US[1] guidelines recommend routine treatment, irrespective of the results of chlamydia testing, in order to delay the onset of widespread cephalosporin resistance.

Guidelines produced by WHO,[5] by an expert group in the UK,[6] and by the CDC in the USA[1,7] for the **treatment** of gonorrhoea are as follows, although recommendations may need to be localised because of differences in patterns of infection and drug resistance:

- UNCOMPLICATED ANOGENITAL GONOCOCCAL INFECTIONS IN ADULTS.
  - **WHO:**
    - a single oral dose of ciprofloxacin 500 mg, *or*
    - a single oral dose of cefixime 400 mg, *or*
    - a single intramuscular dose of ceftriaxone 125 mg, *or*
    - a single intramuscular dose of spectinomycin 2 g
  - **UK:**

    All the treatment options given below should be given with a single oral 1-g dose of azithromycin.
    - a single intramuscular dose of ceftriaxone 500 mg

    alternative regimens are:
    - a single intramuscular dose of spectinomycin 2 g
    - a single oral dose of cefixime 400 mg
    - a single intramuscular dose of cefotaxime 500 mg
    - a single intramuscular dose of cefoxitin 2 g plus oral probenecid 1 g
    - a single oral dose of ciprofloxacin 500 mg
    - a single oral dose of ofloxacin 400 mg
    - a single oral dose of cefpodoxime 400 mg
    - a single oral dose of azithromycin to a total of 2 g
  - **USA:**
    - a single intramuscular dose of ceftriaxone 250 mg *plus* either a single oral 1-g dose of azithromycin *or* oral doxycycline 100 mg twice daily for 7 days

    alternative regimens are:
    - a single oral dose of cefixime 400 mg, if ceftriaxone is not available, *plus* either a single oral 1-g dose of azithromycin *or* oral doxycycline 100 mg twice daily for 7 days
    - in patients with severe cephalosporin allergy, a single oral dose of azithromycin 2 g
- PHARYNGEAL INFECTIONS.
  - **UK:**
    - a single intramuscular dose of ceftriaxone 500 mg *plus* a single oral 1-g dose of azithromycin, *or*
    - a single oral dose of ciprofloxacin 500 mg, *or*
    - a single oral dose of ofloxacin 400 mg
  - **USA:**
    - a single intramuscular dose of ceftriaxone 250 mg *plus* either a single oral 1-g dose of azithromycin *or* oral doxycycline 100 mg twice daily for 7 days
- GONOCOCCAL INFECTIONS IN PREGNANT WOMEN.
  - **WHO:**
    - a single oral dose of cefixime 400 mg, *or*
    - a single intramuscular dose of ceftriaxone 125 mg, *or*
    - a single intramuscular dose of spectinomycin 2 g
  - **UK:**

    Both regimens below should be given with a single oral 1-g dose of azithromycin.
    - a single intramuscular dose of ceftriaxone 500 mg, *or*
    - a single intramuscular dose of spectinomycin 2 g
  - **USA:**
    - an intramuscular cephalosporin *plus* either a single oral 1-g dose of azithromycin *or* oral amoxicillin 500 mg three times daily for 7 days
    - azithromycin 2 g orally can be considered for women who are intolerant of cephalosporins
- GONOCOCCAL EYE INFECTIONS IN ADULTS.
  - **WHO:** frequent irrigation of the infected eye with saline together with:
    - a single intramuscular dose of ceftriaxone 125 mg, *or*
    - a single intramuscular dose of spectinomycin 2 g, *or*
    - a single oral dose of ciprofloxacin 500 mg

    a further alternative is:
    - a single intramuscular dose of kanamycin 2 g
  - **UK:** irrigation of the infected eye with saline together with:
    - intramuscular ceftriaxone 500 mg daily for 3 days, *or*
    - intramuscular spectinomycin 2 g daily for 3 days, *or*
    - a single oral dose of azithromycin 2 g, *plus* oral doxycycline 100 mg twice daily for 7 days, *plus* oral ciprofloxacin 250 mg daily for 3 days
  - **USA:** irrigation of the infected eye with saline together with:
    - a single intramuscular dose of ceftriaxone 1 g
- DISSEMINATED GONOCOCCAL INFECTIONS IN ADULTS.
  - **WHO:**
    - parenteral ceftriaxone 1 g once daily for 7 days, *or*
    - intramuscular spectinomycin 2 g twice daily for 7 days

Another third-generation cephalosporin may be substituted if neither of these drugs is available. Treatment for endocarditis should continue for 28 days.

- **UK:**
  - parenteral ceftriaxone 1 g daily, *or*
  - intravenous cefotaxime 1 g 8 hourly, *or*
  - intravenous ciprofloxacin 500 mg 12 hourly, *or*
  - intramuscular spectinomycin 2 g 12 hourly

  Treatment should continue for 7 days but once improvement has been established for 24 to 48 hours, oral therapy with cefixime 400 mg twice daily *or* ciprofloxacin 500 mg twice daily *or* ofloxacin 400 mg twice daily, may be substituted for the remaining period.
- **USA:**
  - parenteral ceftriaxone 1 g every 24 hours

  alternatives are:
  - intravenous ceftizoxime 1 g every 8 hours
  - intravenous cefotaxime 1 g every 8 hours

  Once improvement has been established for 24 to 48 hours, oral therapy with cefixime 400 mg twice daily may be substituted until at least a 1-week treatment period is complete.

  For gonococcal meningitis and endocarditis, intravenous ceftriaxone 1 to 2 g every 12 hours is recommended; treatment for meningitis should continue for 10 to 14 days and for endocarditis for at least 4 weeks.

- GONOCOCCAL INFECTIONS IN NEONATES AND CHILDREN.

  Neonates born to mothers with gonorrhoea are at high risk of infection and require *prophylaxis*:
  - **WHO:**
    - a single intramuscular injection of ceftriaxone 50 mg/kg (maximum 125 mg)

    alternatives are:
    - a single intramuscular dose of spectinomycin 25 mg/kg (maximum 75 mg)
    - a single intramuscular dose of kanamycin 25 mg/kg (maximum 75 mg)
  - **USA:**
    - a single parenteral dose of ceftriaxone 25 to 50 mg/kg (maximum 125 mg)

  For those neonates with *disseminated gonococcal infection* (sepsis, arthritis, meningitis) or gonococcal scalp abscesses, US recommendations are:
  - parenteral ceftriaxone 25 to 50 mg/kg once daily for 7 days, *or*
  - parenteral cefotaxime 25 mg/kg every 12 hours for 7 days

  Treatment should be extended to 10 to 14 days if meningitis is present.

  Treatment for *children* with uncomplicated gonococcal infections, most commonly due to sexual abuse in pre-adolescents, is as for adults in those weighing more than 45 kg. For those weighing 45 kg or less a single intramuscular dose of ceftriaxone 125 mg is recommended. For disseminated infection in all children an intramuscular or intravenous dose of ceftriaxone 50 mg/kg once daily for 7 days, up to a maximum dose of 1 g in those weighing 45 kg or less is recommended.

The prevention and treatment of neonatal gonococcal conjunctivitis is discussed under Neonatal Conjunctivitis, p. 193.2.

Sexual partners of patients with gonococcal infection should be tested and treated.[1]

Patients co-infected with HIV should receive the same treatment as those who are HIV-negative.[1]

1. CDC. Sexually transmitted diseases treatment guidelines, 2010. *MMWR* 2010; **59** (RR-12): 1–110. Also available at: http://www.cdc.gov/STD/treatment/2010/STD-Treatment-2010-RR5912.pdf (accessed 08/01/11) Correction. *ibid.* 2011; **60**: 18. [dose]
2. Health Protection Agency. GRASP 2010 report: The Gonococcal Resistance to Antimicrobials Surveillance Programme. Available at: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1316016752917 (accessed 18/07/12)
3. CDC. Gonococcal Isolate Surveillance Project (GISP). Available at: http://www.cdc.gov/std/gisp (accessed 18/07/12)
4. WHO. Emergence of multi-drug resistant *Neisseria gonorrhoeae*—threat of global rise in untreatable sexually transmitted infections. Geneva: WHO, 2011. Available at: http://whqlibdoc.who.int/hq/2011/WHO_RHR_11.14_eng.pdf (accessed 26/07/12)
5. WHO. Guidelines for the management of sexually transmitted infections. Geneva: WHO, 2003. Also available at: http://whqlibdoc.who.int/publications/2003/9241546263.pdf (accessed 20/06/07)
6. Clinical Effectiveness Group (British Association for Sexual Health and HIV). UK national guideline for the management of gonorrhoea in adults 2011. Available at: http://www.bashh.org/documents/3611 (accessed 18/07/12)
7. CDC. Update to CDC's sexually transmitted diseases treatment guidelines, 2010: oral cephalosporins no longer a recommended treatment for gonococcal infections. *MMWR* 2012; **61**: 590–4. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6131a3.htm (accessed 13/08/12)

Granuloma inguinale. Granuloma inguinale or donovanosis is caused by the Gram-negative bacterium *Klebsiella granulomatis* (formerly known as *Calymmatobacterium granulomatis*) and occurs most commonly in the tropics and subtropics, especially Papua New Guinea and India. It is characterised by genital ulcers and is generally considered to be a sexually transmitted disease.

Guidelines produced by WHO,[1] by an expert group in the UK,[2] and by the CDC in the USA[3] for the treatment of granuloma inguinale are as follows:

- **WHO:**
  - oral azithromycin 1 g on the first day then 500 mg once daily, *or*
  - oral doxycycline 100 mg twice daily

  alternatives include:
  - oral erythromycin 500 mg four times daily
  - oral tetracycline 500 mg four times daily
  - oral co-trimoxazole 960 mg twice daily

  Treatment is continued until all lesions have completely resolved. The addition of parenteral gentamicin should be considered for HIV-infected patients. Streptomycin is no longer recommended because of its toxicity and the need to reserve it for tuberculosis.
- **UK:**
  - oral azithromycin 1 g once weekly or 500 mg daily, *or*
  - parenteral ceftriaxone 1 g once daily, *or*
  - oral co-trimoxazole 960 mg twice daily, *or*
  - oral doxycycline 100 mg twice daily, *or*
  - oral erythromycin 500 mg four times daily, *or*
  - oral norfloxacin 400 mg twice daily

  Duration of treatment should be until lesions have healed; the addition of parenteral gentamicin 1 mg/kg every 8 hours should be considered if lesions do not respond during the first few days of treatment.
- **USA:**
  - oral doxycycline 100 mg twice daily for a minimum of 3 weeks and until all lesions have completely healed

  alternatives are:
  - oral ciprofloxacin 750 mg twice daily, *or*
  - oral erythromycin 500 mg four times daily, *or*
  - oral azithromycin 1 g once weekly, *or*
  - oral co-trimoxazole 960 mg twice daily

  In each case treatment is for at least 3 weeks, and until all lesions have completely healed. The addition of an aminoglycoside may be considered if lesions do not respond during the first few days of treatment, in pregnant women, and in those co-infected with HIV.

Sexual partners of patients with granuloma inguinale should be tested and treated.[2,3]

Patients co-infected with HIV should receive the same treatment as those who are HIV-negative.[3]

1. WHO. Guidelines for the management of sexually transmitted infections. Geneva: WHO, 2003. Also available at: http://whqlibdoc.who.int/publications/2003/9241546263.pdf (accessed 23/03/07)
2. Clinical Effectiveness Group (British Association for Sexual Health and HIV). United Kingdom national guideline for the management of donovanosis (granuloma inguinale) 2011. Available at: http://www.bashh.org/documents/3194 (accessed 24/07/12)
3. CDC. Sexually transmitted diseases treatment guidelines, 2010. *MMWR* 2010; **59** (RR-12): 1–110. Also available at: http://www.cdc.gov/STD/treatment/2010/STD-Treatment-2010-RR5912.pdf (accessed 08/01/11) Correction. *ibid.* 2011; **60**: 18. [dose]

Lymphogranuloma venereum. Lymphogranuloma venereum or chlamydial lymphogranuloma is an invasive, systemic infection caused by certain serotypes of *Chlamydia trachomatis* and is endemic in tropical and subtropical areas, but may also occur in the developed world. It is a sexually transmitted disease and in the early phase may cause genital ulceration although the commonest clinical manifestation is unilateral inguinal and/or femoral lymphadenopathy. Multisystem involvement occurs, and late complications, including those related to fibrosis and abnormal lymphatic drainage, may require surgery.

Guidelines produced by WHO,[1] by an expert group in the UK,[2] and by the CDC in the USA[3] for the treatment of lymphogranuloma venereum are as follows:

- **WHO:** treatment for 2 weeks with:
  - oral doxycycline 100 mg twice daily, *or*
  - oral erythromycin 500 mg four times daily

  an alternative is:
  - oral tetracycline 500 mg four times daily
- **UK and USA:** treatment for 3 weeks with:
  - oral doxycycline 100 mg twice daily, *or*
  - oral tetracycline 2 g daily, *or*
  - oral minocycline 300 mg as a loading dose *then* 200 mg twice daily, *or*
  - oral erythromycin 500 mg four times daily

  Sexual partners of patients with lymphogranuloma venereum should be treated with:
  - a single oral dose of azithromycin 1 g *or*
  - oral doxycycline 100 mg twice daily for 7 days

Patients co-infected with HIV should receive the same treatment as those who are HIV-negative, although longer therapy may be required.[3]

1. WHO. Guidelines for the management of sexually transmitted infections. Geneva: WHO, 2003. Also available at: http://whqlibdoc.who.int/publications/2003/9241546263.pdf (accessed 23/03/07)
2. Clinical Effectiveness Group (British Association for Sexual Health and HIV). 2006 National guideline for the management of lymphogranuloma venereum (LGV). Available at: http://www.bashh.org/documents/92/92.pdf (accessed 18/08/08)
3. CDC. Sexually transmitted diseases treatment guidelines, 2010. *MMWR* 2010; **59** (RR-12): 1–110. Also available at: http://www.cdc.gov/STD/treatment/2010/STD-Treatment-2010-RR5912.pdf (accessed 08/01/11) Correction. *ibid.* 2011; **60**: 18. [dose]

Syphilis. Syphilis is a sexually transmitted disease caused by the spirochaete *Treponema pallidum* and occurs worldwide. Non-venereal treponematoses include endemic syphilis or bejel, also caused by *T. pallidum*; pinta, caused by *T. carateum*; and yaws, caused by *T. pertenue*.

Syphilis may be classified as acquired or congenital and in each case has early and late stages. Syphilis may be described as latent, when serological tests are positive but the patient is asymptomatic.

- In acquired sexually transmitted disease the *early* stage includes primary and secondary syphilis and early latent infection; early latent infection is defined in the UK[1] and by WHO[2] as of not more than 2 years in duration or of less than 1 year in duration by the CDC in the USA.[3]
- *Late* stage disease includes late latent infection and all late clinical stages. The late clinical stages fall broadly into three types: *neurosyphilis* manifesting as neurological symptoms, commonly including dorsal column loss (tabes dorsalis), dementia, or meningovascular involvement; *cardiovascular* syphilis, characterised by aortitis which may manifest as aortic regurgitation, aortic aneurysm, or angina; and *gummata*, inflammatory fibrous nodules or plaques which may be locally destructive and which commonly affect the bone and skin but may occur in any organ. Some term all these late clinical stages tertiary syphilis whereas others use tertiary for benign gummatous syphilis and quaternary for the more serious complications of cardiovascular syphilis and neurosyphilis. The term neurosyphilis has generally been applied to late-stage symptomatic neurological disease, although it is recognised that CNS invasion by *T. pallidum* is common in early syphilis and that CNS involvement may occur at any stage.
- *Congenital syphilis* may result from transplacental infection at any stage of pregnancy and any stage of maternal syphilis.

The incidence of syphilis fell dramatically after the introduction of penicillin and *T. pallidum* remains sensitive to it. There has, however, been a resurgence of syphilis, linked in part with HIV infection. In HIV-infected patients syphilis appears more virulent and neurosyphilis occurs more quickly. Like other diseases causing genital ulcers, syphilis is a risk factor for HIV infection.

The treatment of choice for both early and late syphilis is still penicillin and long-acting injections are generally used. Treatment for late syphilis is less well-established than that for early disease and is usually given for longer. A Jarisch-Herxheimer reaction may occur after the first dose of antibacterial, especially in patients with early syphilis, and corticosteroid cover may be beneficial, especially in patients with cardiovascular or neurological involvement.

Guidelines produced by WHO,[2] by an expert group in the UK,[1] and by the CDC in the USA[3] for the treatment of acquired and congenital syphilis are as follows:

- EARLY SYPHILIS
  - **WHO:**
    - intramuscular benzathine benzylpenicillin 1.8 g (2.4 million units) usually given as 2 injections at separate sites in a single session, *or*
    - intramuscular procaine benzylpenicillin 1.2 g (1.2 million units) daily for 10 days

    alternatives for non-pregnant penicillin-allergic patients are:
    - oral doxycycline 100 mg twice daily for 14 days, *or*
    - oral tetracycline 500 mg four times daily for 14 days

    Pregnant women allergic to penicillin may be given:
    - oral erythromycin 500 mg four times daily for 14 days (but see Syphilis in Pregnancy, below)
  - **UK:**
    - intramuscular benzathine benzylpenicillin 1.8 g (2.4 million units) as a single dose, *or*
    - intramuscular procaine benzylpenicillin 600 mg (600 000 units) daily for 10 days

    An additional alternative if parenteral therapy is refused is:
    - oral amoxicillin 500 mg *plus* oral probenecid 500 mg, both four times daily for 14 days

    alternatives for penicillin-allergic patients are:
    - oral doxycycline 100 mg twice daily for 14 days
    - oral erythromycin 500 mg four times daily for 14 days
    - oral azithromycin 2 g as a single dose
    - oral azithromycin 500 mg daily for 10 days
    - intramuscular ceftriaxone 500 mg daily for 10 days (in the absence of anaphylaxis to penicillin)
  - **USA:**
    - a single intramuscular dose of benzathine benzylpenicillin 1.8 g (2.4 million units)

    alternatives for penicillin-allergic patients are:
    - oral doxycycline 100 mg twice daily for 14 days
    - oral tetracycline 500 mg four times daily for 14 days

    Preliminary data suggest that azithromycin 2 g orally as a single dose may also be effective, *or* parenteral ceftriaxone 1 g daily for 10 to 14 days may also be considered.
- LATE SYPHILIS
  - **WHO:**
    - intramuscular benzathine benzylpenicillin 1.8 g (2.4 million units) once weekly for 3 consecutive weeks, *or*
    - intramuscular procaine benzylpenicillin 1.2 g (1.2 million units) daily for 20 consecutive days

alternatives for non-pregnant penicillin-allergic patients are:
- oral doxycycline 100 mg twice daily for 30 days, *or*
- oral tetracycline 500 mg four times daily for 30 days

Pregnant women allergic to penicillin may be given:
- oral erythromycin 500 mg four times daily for 30 days

For those with *neurosyphilis*:
- intravenous benzylpenicillin 1.2 to 2.4 g (2 to 4 million-units) every 4 hours for 14 days, *or*
- if outpatient compliance can be ensured, intramuscular procaine benzylpenicillin 1.2 g (1.2 million units) daily *plus* oral probenecid 500 mg four times daily each for 10 to 14 days

alternatives for non-pregnant penicillin-allergic patients are:
- oral doxycycline 200 mg twice daily for 30 days
- oral tetracycline 500 mg four times daily for 30 days

- **UK:**
  - intramuscular benzathine benzylpenicillin 1.8 g (2.4 million units) weekly for 3 doses, *or*
  - intramuscular procaine benzylpenicillin 600 mg (600 000 units) daily for 17 days

  alternatives for patients allergic to penicillin and those declining parenteral therapy are:
  - oral doxycycline 100 mg twice daily for 28 days, *or*
  - if penicillin can be tolerated, oral amoxicillin 2 g three times daily *plus* oral probenecid 500 mg four times daily, both for 28 days

  For those with *neurosyphilis* recommendations are:
  - intramuscular procaine benzylpenicillin 1.8 to 2.4 g (1.8 to 2.4 million units) once daily *plus* oral probenecid 500 mg four times daily for 17 days, *or*
  - intravenous benzylpenicillin 1.8 to 2.4 g (3 to 4 million-units) every 4 hours for 17 days

  alternatives are:
  - oral doxycycline 200 mg twice daily for 28 days
  - oral amoxicillin 2 g three times daily *plus* oral probenecid 500 mg four times daily, both for 28 days
  - intramuscular or intravenous ceftriaxone 2 g daily for 10 to 14 days (in the absence of anaphylaxis to penicillin)
- **USA:**
  - intramuscular benzathine benzylpenicillin 1.8 g (2.4 million units) weekly for 3 consecutive weeks

  alternatives in penicillin-allergic patients are:
  - oral doxycycline 100 mg twice daily for 28 days, *or*
  - oral tetracycline 500 mg four times daily for 28 days

  For those with *neurosyphilis*:
  - intravenous benzylpenicillin 1.8 to 2.4 g (3 to 4 million-units) every 4 hours for 10 to 14 days (or the total daily dose may be given by continuous infusion), *or*
  - if outpatient compliance can be ensured, then intramuscular procaine benzylpenicillin 2.4 g (2.4 million units) daily *plus* oral probenecid 500 mg four times daily, both for 10 to 14 days

  Since the duration of treatment for neurosyphilis is shorter than that for late syphilis in the absence of neurosyphilis, some clinicians give intramuscular benzathine benzylpenicillin 1.8 g (2.4 million units) once weekly for up to 3 weeks after completion of neurosyphilis treatment to provide a comparable total duration of treatment.

- SYPHILIS IN PREGNANCY

All guidelines recommend penicillin as under early and late syphilis, together with close surveillance. In the USA, CDC[3] notes that some recommend a second dose of benzathine benzylpenicillin a week after the initial dose for patients with early syphilis. In the UK[1] it is recommended that when the first dose is given in the third trimester a second dose should be given one week later. According to CDC,[3] pregnant patients who are allergic to penicillin should be given penicillin, after desensitisation if necessary, since the alternatives, tetracyclines, are contra-indicated during pregnancy and the macrolides (azithromycin and erythromycin) cannot be relied upon to cure an infected fetus. WHO,[2] on the other hand, advises against desensitisation in a primary care setting and suggest that erythromycin, although inferior, should be given in these circumstances; consideration should probably be given to use of a third-generation cephalosporin in the absence of anaphylaxis. After treatment, the mother should be re-treated if there is serological evidence of re-infection or relapse, and the infant treated.[2] UK guidelines[1] list alternative antibacterials that may be given as: amoxicillin, ceftriaxone, erythromycin or azithromycin. they also state that desensitisation should be considered in those allergic to penicillin.

- CONGENITAL SYPHILIS
  - **WHO:**

    for early congenital syphilis, infants up to 2 years of age and having abnormal CSF may be given:
    - intravenous benzylpenicillin 30 mg/kg (50 000 units/kg) twice daily for the first 7 days of life and then three times daily for a total of 10 days, *or*
    - intramuscular procaine benzylpenicillin 50 mg/kg (50 000 units/kg) once daily for 10 days

    For infants with normal CSF (although some treat all infants as if the CSF were abnormal):
    - a single intramuscular dose of benzathine benzylpenicillin 37.5 mg/kg (50 000 units/kg)

    Children older than 2 years may be given:
    - parenteral benzylpenicillin 30 mg/kg (50 000 units/kg) every 4 to 6 hours for 10 to 14 days

    For penicillin-allergic infants aged over 1 month:
    - oral erythromycin 7.5 to 12.5 mg/kg four times daily for 30 days
  - **UK:** recommended doses are as for infants up to 2 years with abnormal CSF in WHO guidelines, above.
  - **USA:**

    Neonates (up to 4 weeks of age) and having proven or probable disease:
    - intravenous benzylpenicillin 30 mg/kg (50 000 units/kg) twice daily for the first 7 days of life and then three times daily for a total of 10 days, *or*
    - intramuscular procaine benzylpenicillin 50 mg/kg (50 000 units/kg) once daily for 10 days

    Neonates who have a normal physical examination and a nontreponemal serum titre the same as or less than 4 times the maternal titre may be given, depending on how successfully the mother was treated during pregnancy:
    - one of the above treatment regimens *or*
    - a single intramuscular dose of benzathine benzylpenicillin 37.5 mg/kg (50 000 units/kg)

    Infants and children may be given:
    - intravenous benzylpenicillin 30 mg/kg (50 000 units/kg) every 4 to 6 hours for 10 days.

    Those who are allergic to penicillin should be desensitised if necessary.

Sexual partners of patients with syphilis in any stage should be examined, tested, and treated.[2,3]

Guidelines[1-3] advise that all cases of syphilis in HIV-infected patients be treated as for the appropriate stage of infection as in HIV-negative patients; in the UK, some experts recommend treatment as for neurosyphilis but the UK guidelines note that evidence for this policy is lacking.

1. Clinical Effectiveness Group (British Association for Sexual Health and HIV). 2008 UK national guidelines on the management of syphilis. http://www.bashh.org/documents/1771 (accessed 18/08/08)
2. WHO. Guidelines for the management of sexually transmitted infections. Geneva: WHO, 2003. Also available at: http://whqlibdoc.who.int/publications/2003/9241546263.pdf (accessed 23/03/07)
3. CDC. Sexually transmitted diseases treatment guidelines, 2010. *MMWR* 2010; **59** (RR-12): 1–110. Also available at: http://www.cdc.gov/STD/treatment/2010/STD-Treatment-2010-RR5912.pdf (accessed 08/01/11) Correction. *ibid.* 2011; **60**: 18. [dose]

Shigellosis

See p. 186.1.

Sickle-cell disease

For prophylaxis against pneumococcal infection in sickle-cell disease, see under Spleen Disorders, p. 209.3.

Sinusitis

Sinusitis or inflammation of the paranasal sinuses can be caused by viral, bacterial, or fungal infection or may be secondary to other disorders such as allergy. Sinusitis rarely occurs without rhinitis (rhinosinusitis).

Acute sinusitis often results from viral upper respiratory-tract infections. About 2% of cases are complicated by bacterial infection;[1] the most frequent bacterial pathogens are *Streptococcus pneumoniae* and unencapsulated *Haemophilus influenzae*, with *Moraxella catarrhalis* (*Branhamella catarrhalis*) increasingly important in children. Other bacterial causes, especially in adults, include mixed anaerobic bacteria (usually associated with dental disease and more frequent in chronic sinusitis), *Staphylococcus aureus*, *Streptococcus pyogenes*, and Gram-negative bacteria including Enterobacteriaceae and *Pseudomonas aeruginosa* (in nosocomial sinusitis). About 5% of primary sinusitis in young adults has been associated with *Chlamydophila pneumoniae* (*Chlamydia pneumoniae*).

Acute sinusitis usually resolves spontaneously, and symptomatic relief with simple analgesics is considered the mainstay of treatment.[1] Although antibacterials are widely prescribed for acute sinusitis, their use is controversial given the self-limiting nature of the condition and the relatively small proportion of cases where bacterial infection is confirmed. A systematic review of 57 studies concluded that any treatment effect of antibacterial therapy was small.[2] In the UK, guidance issued by NICE[3] suggests that antibacterial prescribing should be avoided or delayed, unless the patient is systemically very unwell or has signs or symptoms of, or is at high risk of developing, serious complications. US guidelines[4] suggest that appropriate criteria for use of antibacterials include symptoms of sinusitis for 10 to 14 days or severe symptoms (including fever with purulent nasal discharge, facial pain or tenderness, and periorbital swelling). However, a meta-analysis concluded that for immunocompetent adults with acute sinusitis, antibacterials could not be justified, even in patients who reported symptoms for longer than 7 or 10 days, and that the only reason for antibacterial treatment was the presence of signs suggestive of serious complications.[5] Guidelines from the American Academy of Pediatrics for the management of sinusitis in children[6] recommend that antibacterials be given to children clinically diagnosed with persistent or severe acute bacterial sinusitis in order to achieve a more rapid clinical cure.

If antibacterials are considered necessary, treatment should be given for an adequate length of time, usually 10 to 14 days;[4,6,7] however, in a meta-analysis[8] of 12 studies, no significant difference in efficacy was found between short-course (defined in various studies as 3 to 7 days) and long-course (6 to 10 days) treatment in patients with acute, uncomplicated, bacterial sinusitis. When antibacterial therapy is used, choosing the drug with the narrowest spectrum against the most probable pathogens is prudent to minimise the risk of resistance.[9] US guidelines[4] recommend amoxicillin as first-choice therapy in adults and children; co-trimoxazole can be used as an alternative in adults. Increased resistance has been noted among causative organisms, however, and local resistance patterns should be considered. For patients who do not respond to amoxicillin, high-dose amoxicillin plus clavulanic acid (90 mg/kg based on the amoxicillin component, to a maximum of 4 g daily) is recommended. For those intolerant of amoxicillin, alternatives include oral cephalosporins (such as cefpodoxime, cefdinir, and cefuroxime), macrolides, or fluoroquinolones. If associated with dental disease, coverage for anaerobes and Gram-negative bacteria is indicated.[9] Tetracycline or erythromycin are the most effective antibacterials against *Chlamydophila pneumoniae*.[10]

Intranasal corticosteroids reduce inflammation in the nasal mucosa. A systematic review[11] supported the use of intranasal corticosteroids for acute, uncomplicated sinusitis confirmed by radiology or nasal endoscopy, either as monotherapy or adjuncts to antibacterial treatment although the authors noted that data were limited and the observed effects were modest.

Failure to treat acute sinusitis that does not resolve spontaneously can result in ***chronic sinusitis*** or rarely in complications such as orbital cellulitis, intraorbital abscesses (which may lead to blindness), cavernous sinus thrombosis osteomyelitis of the frontal bone, extradural and subdural empyema, brain abscess, or meningitis.[1]

Management of chronic sinusitis is based on reducing obstruction of the sinus cavity using antihistamines decongestants, anti-inflammatory drugs (including corticosteroids), and saline washes as appropriate.[1,7] A systematic review[12] concluded that intranasal saline irrigations, either as monotherapy or as adjuvant treatment, are beneficial for symptomatic management of chronic sinusitis, although they appear to be less effective than intranasal corticosteroids. The usefulness of antibacterials is more contentious,[13] although some clinicians advocate prolonged courses as part of initial treatment.[7] As well as their established antibacterial effect, it has been suggested that macrolides also have immunomodulatory effects that could be useful in the management of respiratory diseases including chronic sinusitis but large placebo-controlled studies are needed. Surgical intervention may be necessary for selected patients if medical treatment fails.

Exacerbations of chronic sinusitis are treated as for acute infection.

1. Ah-See KW, Evans AS. Sinusitis and its management. *BMJ* 2007; **334**: 358–61.
2. Ahovuo-Saloranta A, *et al.* Antibiotics for acute maxillary sinusitis. Available in The Cochrane Database of Systematic Reviews: Issue 2. Chichester: John Wiley; 2008 (accessed 19/08/08).
3. NICE. Respiratory tract infections—antibiotic prescribing: prescribing of antibiotics for self-limiting respiratory tract infections in adults and children in primary care (issued July 2008). Available at: http://www.nice.org.uk/nicemedia/live/12015/41323/41323.pdf (accessed 26/04/10)
4. Slavin RG, *et al.* American College of Allergy, Asthma and Immunology. Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of sinusitis: a practice parameter update. *J Allergy Clin Immunol* 2005; **116** (suppl): S13–S47. Also available at: http://www.aaaai.org/professionals/resources/pdf/sinusitis2005.pdf (accessed 05/05/10)
5. Young J, *et al.* Antibiotics for adults with clinically diagnosed acute rhinosinusitis: a meta-analysis of individual patient data. *Lancet* 2008; **371**: 908–14.
6. American Academy of Pediatrics: Subcommittee on Management of Sinusitis and Committee on Quality Improvement. Clinical practice guideline: management of sinusitis. *Pediatrics* 2001; **108**: 798–808. Corrections. *ibid.* **108** (5): A24 and *ibid.* 2002; **109** (5): A40. Also available at: http://pediatrics.aappublications.org/cgi/reprint/108/3/798 (accessed 19/08/08)
7. Scadding GK, *et al.* British Society for Allergy and Clinical Immunology. BSACI guidelines for the management of rhinosinusitis and nasal polyposis. *Clin Exp Allergy* 2008; **38**: 260–75. Also available at: http://www3.interscience.wiley.com/cgi-bin/fulltext/119410083/PDFSTART (accessed 05/05/10)
8. Falagas ME, *et al.* Effectiveness and safety of short vs. long duration of antibiotic therapy for acute bacterial sinusitis: a meta-analysis of randomized trials. *Br J Clin Pharmacol* 2009; **67**: 161–71.
9. Hwang PH. A 51-year-old woman with acute onset of facial pressure, rhinorrhea, and tooth pain: review of acute rhinosinusitis. *JAMA* 2009; **301**: 1798–1807.
10. Grayston JT, *et al.* A new respiratory tract pathogen: Chlamydia pneumoniae strain TWAR. *J Infect Dis* 1990; **161**: 618–25.
11. Zalmanovici A, Yaphe J. Intranasal steroids for acute sinusitis. Available in The Cochrane Database of Systematic Reviews: Issue 4. Chichester: John Wiley; 2009 (accessed 28/04/10).

12. Harvey R, *et al.* Nasal saline irrigations for the symptoms of chronic rhinosinusitis. Available in The Cochrane Database of Systematic Reviews: Issue 3. Chichester: John Wiley; 2007 (accessed 28/04/10).
13. Cherry WB, Li JT. Chronic rhinosinusitis in adults. *Am J Med* 2008; 121: 185–9.

Skin infections

Bacterial infections of the skin and soft tissue (skin structures) may result from invasion of skin structures by endogenous skin flora or by exogenous pathogenic organisms. They may involve any or all layers of the skin, fascia, and muscle, and can spread giving rise to complications such as endocarditis, Gram-negative sepsis, or streptococcal glomerulonephritis.

Clinical assessment of the infection is important for management and several classification schemes have been developed. Primary bacterial skin infections usually involve areas of previously healthy skin and are typically caused by a single organism. Secondary infections occur in areas of previously damaged skin and are frequently polymicrobial. Skin infections have also been classified as uncomplicated or complicated (when they involve deeper skin structures, need surgical treatment, or occur in immunocompromised patients). Another classification system divides skin and soft tissue infections into 4 classes based on the severity of local and systemic signs and symptoms of infection, and the presence and stability of any comorbidities.[1]

- Class 1 patients: are afebrile and otherwise healthy and usually can be managed with topical or oral antibacterials on an outpatient basis
- Class 2 patients: are febrile and have an ill appearance, but have no unstable comorbidities. Oral antibacterials may be helpful in some of these patients but most will need parenteral antibacterial treatment
- Class 3 patients: have a toxic appearance, at least one unstable comorbidity, or a limb-threatening infection and need treatment with parenteral antibacterials
- Class 4 patients: have sepsis syndrome or serious life-threatening infections, such as necrotising fasciitis (see p. 193.1) and always need treatment with parenteral antibacterials; some patients will also need surgical treatment

Treatment of skin infections is based on knowledge of the likely infecting organisms and patterns of resistance.[1,2] The majority of skin and soft tissue infections are caused by aerobic Gram-positive cocci, such as *Staphylococcus aureus* and streptococci. Increasing drug resistance of Gram-positive organisms and the rising incidence of nosocomial and more recently community-acquired MRSA is causing concern and complicating treatment options. Treatment alternatives for infections with these organisms are discussed under Staphylococcal Infections, p. 210.2. Guidelines and recommendations for the management and diagnosis of skin and soft-tissue infections have been developed in the USA.[1,3]

Impetigo is a superficial skin infection that consists of discrete purulent lesions usually on exposed areas of the body, most frequently the face and extremities and occurs most commonly in children aged 2 to 5 years. It is caused by β-haemolytic streptococci and/or *Staph. aureus*, and is highly contagious. The infection may be nonbullous or bullous in appearance; bullous impetigo is caused by *Staph. aureus*. Staphylococcal scalded skin syndrome is a severe manifestation of bullous impetigo caused by infection with strains of *Staph. aureus* producing exfoliative exotoxins. The term toxic epidermal necrolysis is used to cover both this syndrome and a morphologically identical syndrome of more varied aetiology. A syndrome resembling scarlet fever may also occur.

For patients with a limited number of lesions, topical therapy with mupirocin may be considered;[3,4] other topical antibacterials, such as bacitracin and neomycin are considerably less effective.[3] Topical retapamulin is licensed for the treatment of impetigo[5] due to either *Staph. aureus* or *Streptococcus pyogenes*.

Patients with many lesions or those who do not respond to topical drugs should be given oral antibacterials. Penicillinase-resistant penicillins (dicloxacillin, flucloxacillin, or cloxacillin) or a first-generation cephalosporin (cefalexin) are preferred;[3,4] alternatives include macrolides, clindamycin, and amoxicillin with clavulanic acid.[1,3] Intravenous benzylpenicillin, intramuscular benzathine benzylpenicillin, or oral phenoxymethylpenicillin may be given for infections likely to be caused only by streptococci.[1,6]

Cutaneous abscesses are collections of pus within the dermis and deeper skin tissues and are typically polymicrobial (containing normal skin bacteria and organisms from adjacent mucous membranes). *Staph. aureus* is found as a single pathogen in about 25% of cases. Treatment includes incision and drainage, and systemic antibacterials are rarely necessary but may be needed for those with multiple lesions, cutaneous gangrene, severely impaired host defences, extensive surrounding cellulitis, or severe systemic symptoms of infection.[3]

Folliculitis is an inflammation of the hair follicle which may result in superficial infection with pus only present in the epidermis. **Furuncles** (abscess or boil) are infections of the hair follicle in which suppuration extends through the dermis into the subcutaneous tissue, forming a small abscess.[3] **A carbuncle** forms when the infection extends to involve several adjacent follicles, producing a coalescent inflammatory mass with pus draining from multiple follicular orifices.[3] These skin infections are usually caused by *Staph. aureus*. Folliculitis and small furuncles may respond to the application of moist heat to promote localisation and drainage of pus. Topical antibacterials such as mupirocin, clindamycin, erythromycin, or benzoyl peroxide may also be used for management of folliculitis. Larger furuncles and all carbuncles require incision and drainage.[3] Patients who are febrile or also have extensive cellulitis may be treated with systemic antibacterials as for impetigo.[3,4] In patients at risk of recurrent furunculosis topical or systemic antibacterial therapy has been tried for eradicating nasal or extra-nasal *Staph. aureus* carriage (see under Staphylococcal Infections, p. 210.2).

Erysipelas (also known as St. Anthony's fire) is an infection of the more superficial layers of the skin and cutaneous lymphatics characterised by abrupt onset of fiery-red swelling of the face or extremities; it is mostly caused by β-haemolytic streptococci (usually group A). The treatment of choice is a penicillin, e.g. intravenous benzylpenicillin, intramuscular procaine benzylpenicillin, or oral phenoxymethylpenicillin depending on the severity of the infection.[3,6] Clindamycin or erythromycin are alternatives for those allergic to penicillin.[6] If *Staph. aureus* is suspected a penicillinase-resistant penicillin or a first-generation cephalosporin should be chosen.[3]

Cellulitis is an acute infection, initially affecting the epidermis and dermis, but may spread within the superficial fascia. It may also spread through the lymphatic tissue and to the bloodstream. Cellulitis is most commonly caused by beta-haemolytic streptococci and *Staph. aureus* although many other bacteria may cause infection. Parenteral drug abusers are most often infected with *Staph. aureus*, while mixed aerobic and anaerobic infections generally occur in diabetic patients. Mild infections caused by unidentified Gram-positive organisms or staphylococci may be treated with oral penicillinase-resistant penicillins or first-generation cephalosporins, while intravenous nafcillin, oxacillin, or cefazolin are given for moderate to severe infections.[3,6] Clindamycin and vancomycin are alternatives in those with life-threatening penicillin allergy.[3] Documented mild streptococcal infections are treated with oral phenoxymethylpenicillin or amoxicillin or intramuscular procaine benzylpenicillin; intravenous benzylpenicillin is given to those with moderate to severe infections. Infections due to Gram-negative bacilli may be treated with an oral second-generation cephalosporin (cefaclor or cefuroxime), an intravenous first- or second-generation cephalosporin, or an aminoglycoside depending on the severity of the infection. Those with polymicrobial infections (without anaerobes) may be treated with an aminoglycoside plus either intravenous benzylpenicillin (if streptococci are cultured) or a penicillinase-resistant penicillin (if staphylococci are cultured). Ceftazidime and the fluoroquinolones are effective against both Gram-positive and Gram-negative bacteria.[6] Patients with mild, polymicrobial infections (with anaerobes) may be treated with oral amoxicillin plus clavulanic acid or a fluoroquinolone (ciprofloxacin or levofloxacin) plus either oral clindamycin or oral metronidazole. Moderate to severe infections may be treated intravenously with an aminoglycoside plus clindamycin or metronidazole, or monotherapy with a second- or third-generation cephalosporin (cefoxitin or ceftizoxime), a carbapenem (imipenem, meropenem, or ertapenem), a beta lactam with a beta-lactamase inhibitor (piperacillin with tazobactam), or tigecycline.[6] Antibacterial treatment is usually continued for 10 to 14 days or until inflammation resolves,[6] but uncomplicated cellulitis may be treated for 5 days.[3,7]

Antibacterial resistance among *Staph. aureus* (meticillin resistance) and *Str. pyogenes* (erythromycin resistance) is problematic because both of these organisms commonly cause a variety of skin and soft-tissue infections.[3] Generally meticillin-sensitive *Staph. aureus* (MSSA) infections may be treated with oral antibacterials such as cloxacillin, flucloxacillin, dicloxacillin, or cefalexin; for penicillin-allergic patients clindamycin or a macrolide (erythromycin, clarithromycin, or azithromycin) may be given.[4] If parenteral antibacterial treatment is needed a penicillinase-resistant penicillin (nafcillin or oxacillin) or a cephalosporin (cefazolin, cefuroxime, or ceftriaxone) may be given; clindamycin may be used in penicillin-allergic patients. MRSA infections may be treated with oral antibacterials such as co-trimoxazole, doxycycline, minocycline, clindamycin, or linezolid.[4,5] Oral rifampicin with either doxycycline or co-trimoxazole has also been used.[5] The fluoroquinolones (levofloxacin and moxifloxacin) have been used in patients who could not tolerate any of the other drug choices,[4] but some advise against their use as resistance to them develops rapidly in *Staph. aureus*.[5] Parenteral vancomycin is the drug of choice for moderate to severe infections; appropriate parenteral alternatives may include clindamycin, daptomycin, tigecycline, linezolid, and quinupristin/dalfopristin depending on whether the infection is hospital- or community-acquired.[4,5]

For details on other skin and soft tissue infections, see under Acne (p. 1682.2), Bites and Stings (p. 174.2), Rosacea (p. 1688.3) and Surgical Infections (p. 211.1); systemic infections with cutaneous involvement include Anthrax (p. 173.2), Diphtheria (p. 178.3), and Mycetoma (p. 193.1).

1. Eron LJ, *et al.* Managing skin and soft tissue infections: expert panel recommendations on key decision points. *J Antimicrob Chemother* 2003; 52 (suppl 1): i3–i17.
2. Breen JO. Skin and soft tissue infections in immunocompetent patients. *Am Fam Physician* 2010; 81: 893–9.
3. Stevens DL, *et al.* Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. *Clin Infect Dis* 2005; 41: 1373–1406. Corrections. *ibid.*: 1830 and *ibid.* 2006; 42: 1219. [dose error] Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/497143 (accessed 06/08/08)
4. Eron LJ, *et al.* Cellulitis and soft-tissue infections. *Ann Intern Med* 2009; 150: ITC1-1–ITC1-15.
5. Daum RS. Skin and soft-tissue infections caused by methicillin-resistant *Staphylococcus aureus*. *N Engl J Med* 2007; 357: 380–90. Correction. *ibid.*: 1357. [dose error]
6. Fish DN, *et al.* Skin and soft-tissue infections. In: DiPiro JT, *et al.* eds. *Pharmacotherapy: a pathophysiologic approach*. 7th ed. New York: McGraw-Hill, 2008: 1801–17.
7. Hepburn MJ, *et al.* Comparison of short-course (5 days) and standard (10 days) treatment for uncomplicated cellulitis. *Arch Intern Med* 2004; 164: 1669–74.

Spleen disorders

Patients with asplenia (due to splenectomy or congenital defect) or functional hyposplenism (associated with, for example, coeliac disease, haematopoietic stem cell transplantation, or haemoglobinopathies such as thalassaemia major or sickle-cell disease) have impaired immunity and, like other immunocompromised patients (p. 186.3), are at increased risk of infection.[1] Children are at special risk. Frequently, infection is caused by encapsulated bacteria such as *Haemophilus influenzae, Neisseria meningitidis,* and most commonly, *Streptococcus pneumoniae*,[1-4] which may cause severe overwhelming infection that is rapid in onset and sometimes fatal. *Salmonella* spp. are also important pathogens in children with sickle-cell disease.[4] More unusual organisms include *Capnocytophaga canimorsus* (formerly called DF-2), which may cause opportunistic infections in splenectomised patients after animal bites,[2] *Bordetella holmesii*, and tick-borne *Ehrlichia* spp.[3] There may also be an increased risk of falciparum malaria and babesiosis.[2,4]

Infections in asplenic or hyposplenic individuals are largely preventable, the general approach being through vaccination and the use of antibacterial prophylaxis. Practice guidelines based on published evidence and expert opinion have been published in countries including Australia and New Zealand[3] and the UK.[2,3]

Immunoprophylaxis. Immunisation with polyvalent pneumococcal vaccine is recommended for all asplenic patients and those with functional hyposplenism. *Haemophilus influenzae* (Hib) vaccine is recommended for all patients who have not previously received this vaccine, and influenza vaccination should be given annually.[1,3] Meningococcal vaccine is also recommended; however, the group C conjugate vaccine routinely used in some countries (including the UK) does not protect against *N. meningitidis* serotypes A, W135, or Y; therefore, patients travelling abroad to areas where these serotypes are endemic should receive additional vaccination with an appropriate polyvalent meningococcal vaccine.[1,3]

Antibacterial prophylaxis. Prophylaxis with a suitable antibacterial should be offered to asplenic and hyposplenic patients, and although opinion varies on the optimal duration, UK guidelines[2,3] consider that prophylaxis should be lifelong; it is considered particularly important in patients with underlying immunodeficiency, in children up to the age of 16 years, and for the first 2 years after splenectomy.[2] Phenoxymethylpenicillin is usually given, but amoxicillin (with or without clavulanic acid)[2,3] may also be used, particularly in adults, as amoxicillin is better absorbed after oral doses and has a broader spectrum of activity. Erythromycin is a suitable alternative in those unable to tolerate penicillins;[2,3] roxithromycin, moxifloxacin, cefuroxime, and co-trimoxazole have also been suggested[3] although specific choices should also be informed by local resistance patterns. On a practical level, compliance with lifelong prophylaxis is difficult, and guidelines from Australia and New Zealand[3] have therefore suggested that, in the absence of impaired patient immunity, the need for ongoing prophylaxis can be reconsidered after 2 years of use. There is also evidence to suggest that, in children who have received pneumococcal immunisation, there is no benefit in continuing penicillin prophylaxis beyond the age of 5 years,[6] although indefinite prophylaxis has been recommended for those who have had a previous

pneumococcal septic event.[7] Fears that prolonged prophylaxis could encourage the emergence of resistant pneumococci have not been substantiated,[8] although the prevalence of beta-lactam-resistant pneumococci continues to increase. Patients who are not otherwise taking antibacterial prophylaxis should be advised to do so during periods of travel abroad, with resistance patterns in travel destinations being used to guide the specific choice of antibacterial.[2] Malaria prophylaxis is also necessary if travel to endemic areas cannot be avoided.[2,3]

Antibacterial prophylaxis reduces, but does not completely eliminate the risk of infection, and progression to overwhelming sepsis can be rapid. Patients should therefore be advised to keep a supply of a suitable antibacterial for immediate use should symptoms of infection occur, and be instructed to seek medical advice urgently.[3,5] Suggested drugs are generally similar to those used for prophylaxis.

1. Melles DC, de Marie S. Prevention of infections in hyposplenic and asplenic patients: an update. *Neth J Med* 2004; 62: 45–52.
2. Working Party of the British Committee for Standards in Haematology Clinical Haematology Task Force. Guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen. *BMJ* 1996; 312: 430–4.
3. Spelman D, *et al.* Australasian Society for Infectious Diseases. Guidelines for the prevention of sepsis in asplenic and hyposplenic patients. *Intern Med J* 2008; 38: 349–56.
4. William BM, *et al.* Hyposplenism: a comprehensive review. Part II: clinical manifestations, diagnosis, and management. *Hematology* 2007; 12: 89–98.
5. British Committee for Standards in Haematology Working Party of the Haemato-Oncology Task Force. Update of guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen. *Clin Med* 2002; 2: 440–3. Also available at: http://www.bcshguidelines.com/pdf/SPLEEN21.pdf (accessed 21/05/04)
6. Falletta JM, *et al.* Discontinuing penicillin prophylaxis in children with sickle cell anemia. *J Pediatr* 1995; 127: 685–90.
7. Hongeng S, *et al.* Recurrent Streptococcus pneumoniae sepsis in children with sickle cell disease. *J Pediatr* 1997; 130: 814–16. Correction. *ibid.*; 131: 232.
8. Norris CF, *et al.* Pneumococcal colonization in children with sickle cell disease. *J Pediatr* 1996; 129: 821–7.

Spotted fevers

Rickettsial infections of the spotted fever group are transmitted to man mostly by ticks and have also been called tick typhus. They include Rocky Mountain spotted fever, due to *Rickettsia rickettsii* and occurring especially in the USA but also in Canada, Mexico, and Central and South America; boutonneuse or Mediterranean spotted fever, due to *R. conorii* and occurring in Mediterranean countries including the Middle East, Africa, and India; African tick-bite fever, due to *R. africae* and occurring in sub-Saharan Africa and the Caribbean islands; Queensland tick typhus or Australian spotted fever, due to *R. australis* and occurring in Australia; north Asian or Siberian tick typhus, due to *R. sibirica* and occurring in Siberia and Mongolia; and oriental spotted fever, due to *R. japonica* and occurring in Japan and Korea. Rickettsialpox, due to *R. akari* is transmitted from mice by mites and occurs in the USA, Russia, and Africa. Flea-borne spotted fever is due to *R. felis*. It is transmitted by cat fleas and probably occurs worldwide.

Infection occurs after exposure to tick-infested environments or animals. The rickettsiae concentrate in the walls of small to medium blood vessels causing vasculitis. Generally, symptoms begin 4 to 10 days after a tick bite and may vary depending on the rickettsial species. Fever and headache are characteristic. As the infection progresses, an eschar at the tick bite site and/or a rash may develop. Myalgia, malaise, nausea and vomiting, and lymphadenopathy can also occur. Sequelae may include thrombocytopenia, encephalopathy, respiratory and renal failure, and myocarditis. Rocky Mountain spotted fever is the most severe of these fevers, but others are also potentially life-threatening.

The treatment of choice for all tick-borne rickettsioses is oral or intravenous doxycycline in both adults and children.[1] Tetracyclines are generally contra-indicated in young children; however, the risk of tooth staining with a single short course of doxycycline is considered negligible.[1-3] Susceptibility to rifampicin varies by species.[3]

- Chloramphenicol is a less effective alternative for *Rocky Mountain spotted fever*, used when doxycycline is not available or contra-indicated.[1-3] A fluoroquinolone has also been suggested,[4] although experience is limited.[1]
- Alternatives to doxycycline in patients with *Mediterranean spotted fever* include chloramphenicol[3] (although relapses have been reported after treatment[5]) and ciprofloxacin.[1] Macrolides such as azithromycin and clarithromycin are alternatives in children;[1,3,6] josamycin is also useful for pregnant women.[1] Short 2-day courses of ciprofloxacin or doxycycline were also curative for Mediterranean spotted fever in adults whose disease was not severe, although there was a more rapid response to doxycycline.[7]
- Infection with *R. australis* has been treated successfully with ciprofloxacin.[8]
- *Rickettsialpox* can be mistaken for chickenpox. It will respond to tetracycline although patients have generally recovered without treatment.[9]

1. Parola P, *et al.* Tick-borne rickettsioses around the world: emerging diseases challenging old concepts. *Clin Microbiol Rev* 2005; 18: 719–56.
2. Chapman AS, *et al.* Tickborne Rickettsial Diseases Working Group. CDC. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever, ehrlichioses, and anaplasmosis—United States. A practical guide for physicians and other health-care and public health professionals. *MMWR* 2006; 55: 1–27. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5504.pdf (accessed 28/01/09)
3. Buckingham SC. Tick-borne infections in children: epidemiology, clinical manifestations, and optimal management strategies. *Pediatr Drugs* 2005; 7: 163–76.
4. Abramowicz M, ed. The choice of antibacterial drugs. In: *Handbook of antimicrobial therapy*. 19th ed. New Rochelle NY: The Medical Letter, 2011: 74.
5. Shaked Y, *et al.* Relapse of rickettsial Mediterranean spotted fever and murine typhus after treatment with chloramphenicol. *J Infect* 1989; 18: 35–7.
6. Cascio A, *et al.* Clarithromycin versus azithromycin in the treatment of Mediterranean spotted fever in children: a randomized controlled trial. *Clin Infect Dis* 2002; 34: 154–8.
7. Gudiol F, *et al.* Randomized double-blind evaluation of ciprofloxacin and doxycycline for Mediterranean spotted fever. *Antimicrob Agents Chemother* 1989; 33: 987–8.
8. Hudson BJ, *et al.* Ciprofloxacin treatment for Australian spotted fever. *Med J Aust* 1996; 165: 588.
9. Kass EM, *et al.* Rickettsialpox in a New York City hospital, 1980 to 1989. *N Engl J Med* 1994; 331: 1612–17.

Staphylococcal infections

Staphylococci are Gram-positive bacteria pathogenic to man. Species may be differentiated by various methods, including the coagulase test. Those species of clinical importance are *Staphylococcus aureus*, which is usually coagulase-positive, and *Staph. epidermidis* and *Staph. saprophyticus*, which are coagulase-negative.

Staph. aureus colonises the skin and mucous membranes naturally and many people, including neonates, may be staphylococcal carriers from time to time. Localised *Staph. aureus* infections may follow surgery or trauma and commonly result in abscess formation. Staphylococcal skin infections include impetigo, carbunculosis, and furunculosis. Conditions associated with staphylococcal extracellular toxin production include staphylococcal scalded skin syndrome, toxic shock syndrome, and staphylococcal food poisoning. Staphylococcal septicaemia is usually a consequence of local infection and may sometimes be associated with intravascular or intraperitoneal catheters or with intravenous drug abuse. Septicaemia often results in staphylococcal endocarditis. Other possible complications of septicaemia are pneumonia and bone and joint infections, although in these cases aspiration or local trauma, respectively, may be the cause.

Staph. epidermidis is also a natural inhabitant of skin and mucous membranes and an important nosocomial pathogen. Many infections are hospital-acquired and are often associated with indwelling catheters. There has been an increased incidence of bacteraemia due to *Staph. epidermidis* in neonatal units.

Staph. saprophyticus is a common cause of urinary-tract infections in young women.

Staphylococci were sensitive to benzylpenicillin when it was first introduced, but the majority of strains are now resistant as a result of penicillinase production. Meticillin and other penicillinase-resistant penicillins such as flucloxacillin were developed because of their activity against these resistant staphylococci. However, meticillin-resistant staphylococci soon emerged. Both coagulase-negative staphylococci and *Staph. aureus* resistant to meticillin are generally resistant to all beta lactams and often have multiple resistance to other antibacterials (see Meticillin, Antimicrobial Action, p. 325.3). More studies have been published on MRSA than meticillin-resistant coagulase-negative staphylococci, but both types are a serious problem in hospitals around the world. Resistant strains may be endemic to a single hospital or may be epidemic causing outbreaks of infection at more than one hospital. Colonisation of hospital staff and patients with meticillin-resistant staphylococci is an important factor in the spread of these infections. Current trends are towards healthcare at home rather than in hospital and there are reports suggesting that MRSA is becoming more prevalent in the community.[1-4] Community-associated (community-acquired or community-onset; CA-MRSA) MRSA has clinical, epidemiologic, and bacteriologic characteristics distinct from hospital-associated (hospital-acquired) infections (HA-MRSA).[5] CA-MRSA refers to an MRSA infection with onset in the community in a person with no established risk factors for HA-MRSA, such as recent hospitalisation, surgery, residence in a long-term care facility, dialysis, or the presence of invasive medical devices.[3,5] The spectrum of disease caused by CA-MRSA appears to be similar to that of other *Staph. aureus* infections, although some manifestations such as skin and soft tissue infections are more common.[4,5]

Guidelines for the control of MRSA are available in many countries.[6] In the UK, revised guidelines[7] for the control of HA-MRSA were produced by a joint working party of the British Society for Antimicrobial Chemotherapy, the Hospital Infection Society, and the Infection Control Nurses Association in 2006. They advise prompt isolation of infected or colonised patients, screening of patients and staff in contact with such patients, the use of protective clothing, handwashing with an antiseptic detergent, and the use by all patients of an antiseptic detergent for washing and bathing.

Although ciprofloxacin may be used to treat infection, the emergence of widespread resistance in meticillin-sensitive and meticillin-resistant *Staph. aureus* limits its usefulness (see p. 267.2). Combination therapy may be helpful. Rifampicin is highly active against MRSA, but it must always be used with another drug to prevent the emergence of resistance. Combinations of rifampicin with gentamicin, vancomycin, co-trimoxazole, fusidic acid, quinolones, or novobiocin have been tried.

Guidelines for the management of CA-MRSA have been developed in the USA[5] and in the UK.[8] Skin and soft tissue infections associated with CA-MRSA can usually be treated with incision and drainage, with or without topical antibacterials; in some cases systemic antibacterials may be needed.[3] CA-MRSA infections appear to be resistant to fewer antibacterials than HA-MRSA infections; CA-MRSA isolates are generally resistant to beta lactam penicillins and cephalosporins and macrolides (erythromycin, clarithromycin, and azithromycin). Resistance to fluoroquinolones and tetracyclines occurs, and may be increasing.[3,5] Most CA-MRSA isolates are susceptible to co-trimoxazole, gentamicin, tetracycline, and clindamycin.[3,5] For more serious infections vancomycin is the drug of choice.[2,4]

For eradication of nasal carriage UK guidelines for the control of MRSA in healthcare facilities recommend mupirocin nasal ointment. Eradication at other colonised sites is more difficult: antiseptic detergents may be used for skin and hair washing.[7] A systematic review[9] has concluded that there is insufficient evidence to support the use of topical or systemic antimicrobial therapy for eradicating nasal or extra-nasal MRSA in colonised patients. A later systematic review[10] to determine the efficacy of topical or oral antibacterials, or both, for eradicating MRSA carriage found that short-term nasal application of mupirocin was the most effective treatment, with an estimated success rate of 90% 1 week after treatment and about 60% after a longer follow-up period. Drug resistance during treatment was reported in 1% and 9% of patients receiving mupirocin and oral antibacterials, respectively. Another systematic review[11] found that in those who are nasal carriers of *Staph. aureus*, use of mupirocin ointment significantly reduced the level of *Staph. aureus* infections. A randomised, double-blind, placebo-controlled study[12] concluded that rapid identification of *Staph. aureus* nasal carriers followed by treatment of nasal and extranasal sites with mupirocin nasal ointment and chlorhexidine soap respectively, significantly reduced the risk of HA-MRSA infection, especially among surgical patients. Although there is no data to support the use of mupirocin with or without chlorhexidine body washes to eliminate colonisation in people with CA-MRSA,[2,4,5] decolonisation treatment may be used in those with recurrent infections, or in high-risk patients.[2,5]

Isolated reports from around the world of MRSA with intermediate resistance or reduced susceptibility to vancomycin initially emerged in the late 1990s,[13-15] and in response the CDC produced interim[16] and later[17] guidelines for preventing the spread of vancomycin-intermediate *Staph. aureus* (VISA) and vancomycin-resistant *Staph. aureus* (VRSA). Newer antibacterials such as daptomycin, linezolid, quinupristin/dalfopristin, or tigecycline may be effective and may assume increasing importance.[4,18] Other antibacterials, either recently approved for use or in development, that may be effective alternatives to vancomycin are the glycopeptides (dalbavancin, oritavancin, or telavancin), ceftobiprole, and iclaprim.[18]

Staphylococcal vaccines have been used for the prophylaxis and treatment of staphylococcal infections.

For the management of staphylococcal infections in general, see under the specific disease headings.

1. Salgado CD, *et al.* Community-acquired methicillin-resistant Staphylococcus aureus: a meta-analysis of prevalence and risk factors. *Clin Infect Dis* 2003; 36: 131–9.
2. Zetola N, *et al.* Community-acquired meticillin-resistant *Staphylococcus aureus*: an emerging threat. *Lancet Infect Dis* 2005; 5: 275–86.
3. Herman RA, *et al.* Etiology and treatment of community-associated methicillin-resistant *Staphylococcus aureus*. *Am J Health-Syst Pharm* 2008; 65: 219–25.
4. Patel M. Community-associated meticillin-resistant *Staphylococcus aureus* infections: epidemiology, recognition and management. *Drugs* 2009; 69: 693–716.
5. Gorwitz RJ, *et al.* Strategies for clinical management of MRSA in the community: summary of an experts' meeting convened by the Centers for Disease Control and Prevention (March 2006). Available at: http://www.cdc.gov/ncidod/dhqp/pdf/ar/CAMRSA_ExpMtgStrategies.pdf (accessed 24/05/10)
6. Humphreys H. National guidelines for the control and prevention of methicillin-resistant Staphylococcus aureus—what do they tell us? *Clin Microbiol Infect* 2007; 13: 846–53.

All cross-references refer to entries in Volume A

7. Joint Working Party of the British Society for Antimicrobial Chemotherapy, the Hospital Infection Society and the Infection Control Nurses Association. Guidelines for the control and prevention of meticillin-resistant Staphylococcus aureus infection in healthcare facilities. *J Hosp Infect* 2006; 63S: S1–S44. Correction. *ibid.*; 64: 97–8.
8. Nathwani D, *et al.* British Society for Antimicrobial Chemotherapy Working Party on Community-onset MRSA Infections. Guidelines for UK practice for the diagnosis and management of methicillin-resistant Staphylococcus aureus (MRSA) infections presenting in the community. *J Antimicrob Chemother* 2008; 61: 976–94.
9. Loeb M, *et al.* Antimicrobial drugs for treating methicillin-resistant Staphylococcus aureus colonization. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 16/05/05).
10. Ammerlaan HS, *et al.* Eradication of methicillin-resistant *Staphylococcus aureus* carriage: a systematic review. *Clin Infect Dis* 2009; 48: 922–30.
11. van Rijen M, *et al.* Mupirocin ointment for preventing Staphylococcus aureus infections in nasal carriers. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 24/05/10).
12. Bode LGM, *et al.* Preventing surgical-site infections in nasal carriers of *Staphylococcus aureus*. *N Engl J Med* 2010; 362: 9–17.
13. CDC. Update: Staphylococcus aureus with reduced susceptibility to vancomycin—United States, 1997. *MMWR* 1997; 46: 813–15.
14. Smith TL, *et al.* Emergence of vancomycin resistance in Staphylococcus aureus. *N Engl J Med* 1999; 340: 493–501.
15. Rybak MJ, Akins RL. Emergence of methicillin-resistant Staphylococcus aureus with intermediate glycopeptide resistance: clinical significance and treatment options. *Drugs* 2001; 61: 1–7.
16. CDC. Interim guidelines for prevention and control of staphylococcal infection associated with reduced susceptibility to vancomycin. *MMWR* 1997; 46: 626–8, 635. Also available at: http://www.cdc.gov/mmwr//preview/mmwrhtml/00048384.htm (accessed 21/05/04)
17. CDC. Investigation and control of vancomycin-intermediate and resistant *Staphylococcus aureus* (VISA/VRSA): a guide for health departments and infection control personnel (updated September 2006). Available at: http://www.cdc.gov/ncidod/dhqp/pdf/ar/visa_vrsa_guide.pdf (accessed 20/05/10)
18. Micek ST. Alternatives to vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus* infections. *Clin Infect Dis* 2007; 45 (suppl 3): S184–S190.

Surgical infection

Infection is an important cause of postoperative surgical morbidity and mortality and *antimicrobial prophylaxis* is one of several strategies used to reduce the risk of infection. The value of infection prophylaxis is well established in certain types of surgery, especially abdominal surgery and where prostheses are implanted, although recommendations as to the choice of antibacterial and the route, timing, and duration of treatment may vary. Surgical wounds are classified as following clean, clean-contaminated (potentially contaminated), contaminated, and dirty operations. Clean operations exclude those involving the gastrointestinal, genital, urinary, or respiratory tracts. Clean-contaminated operations include those where the gastrointestinal, genital, urinary, or respiratory tracts are opened, but without unusual contamination. Contaminated operations include those where there is acute inflammation or spillage from a hollow viscus. Dirty operations include those where there is pus, gangrene, or perforated viscera. In addition, surgery to repair compound fractures and lacerations due to animal or human bites is considered dirty.

ANTIMICROBIAL PROPHYLAXIS. Strictly speaking the term 'prophylaxis' should be confined to elective procedures with no evidence of sepsis at the time of operation. If possible any pre-existing infections should be treated before admission for surgery. For prophylaxis it is customary to give antibacterials systemically as a single pre-operative dose whereas more prolonged use is necessary when they are given therapeutically. Antimicrobial prophylaxis is used in clean-contaminated operations and in clean operations that involve the insertion of prosthetic materials or when an infection, however unlikely, would be catastrophic. The use of antibacterials for the management of contaminated or dirty surgery is considered to be therapeutic rather than prophylactic and should continue for several days postoperatively.

Guidelines for the management of surgical infections have been developed in the USA[1,2] and in the UK.[3,4] Additional guidelines for the diagnosis and management of complicated intra-abdominal infections have been produced in the USA by the Surgical Infection Society and the Infectious Disease Society of America.[5]

Contaminating organisms. The choice of prophylactic antibacterial will be influenced by the likely contaminants for a particular surgical procedure. The most frequently isolated pathogens include *Staphylococcus aureus*, coagulase-negative staphylococci, *Enterococcus* spp., and *Escherichia coli*. Infections with antimicrobial-resistant pathogens including *Candida albicans* and MRSA are increasing. The most common source of infection is the endogenous flora of the patient's skin, mucous membranes, or viscera. Thus, aerobic Gram-positive organisms (for example staphylococci) are common infecting organisms when the source is the skin and mucous membranes, while infections with enterococci, Gram-negative aerobes (for example *E. coli*), and anaerobic bacteria (for example *Bacteroides fragilis*) can arise from the gastrointestinal tract.

Route of administration. Systemic dosage, usually by the intravenous route, is generally preferred. The chosen antibacterial is usually given as a single dose intravenously just before operation at the induction of anaesthesia. The pharmacokinetic properties should be such that adequate serum concentrations are maintained throughout the surgical procedure. Additional doses may be necessary when surgery is prolonged, when there is massive blood loss, or when an antibacterial with a short half-life is used. More controversial routes have included topical or intra-incisional use and peritoneal lavage. Giving non-absorbable antibacterials orally to suppress the intestinal flora was traditional before large bowel surgery, and neomycin with erythromycin is still given for this purpose in the USA. For reference to selective digestive tract decontamination (SDD), see under Intensive Care, p. 187.3. Other dosage forms include bone cement and chains of beads for implantation, both containing gentamicin and used prophylactically in orthopaedic surgery, and topical and sometimes subconjunctival antibacterials for ophthalmic surgery.

Certain categories of patient continue to be at long-term risk of infection after surgery and include splenectomised patients who have impaired immunity and are at risk of pneumococcal and other infections (see under Spleen Disorders, p. 207.3). Opinion has changed as to whether patients at special risk of endocarditis require prophylaxis before dental and surgical procedures (see Endocarditis, p. 179.2).

1. Bratzler DW, *et al.* American Society of Health-System Pharmacists. Infectious Disease Society of America. Surgical Infection Society. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Am J Health-Syst Pharm* 2013; 70: 195–283. Also available at: http://www.idsociety.org/uploadedFiles/IDSA/Guidelines-Patient_Care/PDF_Library/2013%20Surgical%20Prophylaxis%20ASHP,%20IDSA,%20SHEA,%20SIS(1).pdf (accessed 12/09/13)
2. Abramowicz M, ed. Antimicrobial prophylaxis for surgery. In: *Handbook of antimicrobial therapy*. 19th ed. New Rochelle NY: The Medical Letter. 2011: 119–34.
3. Scottish Intercollegiate Guidelines Network. Antibiotic prophylaxis in surgery: a national clinical guideline (issued July 2008). Available at: http://www.sign.ac.uk/pdf/sign104.pdf (accessed 25/05/10)
4. NICE. Surgical site infection: prevention and treatment of surgical site infection (issued October 2008). Available at: http://www.nice.org.uk/nicemedia/live/11743/42379/42379.pdf (accessed 25/05/10)
5. Solomkin JS, *et al.* Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Clin Infect Dis* 2010; 50: 133–64. Also published in *Surg Infect (Larchmt)* 2010; 11: 79–109. Also available at: http://www.idsociety.org/WorkArea/linkit.aspx?LinkIdentifier=id&ItemID=15966 (accessed 28/05/10)

Syphilis

See under Sexually Transmitted Diseases, p. 205.2.

Tetanus

Tetanus (or lockjaw)[1-3] is caused by the neurotoxin, tetanospasmin, produced by *Clostridium tetani*, a Gram-positive anaerobic spore-forming bacillus present in soil and faeces. The spores are resistant to heat, desiccation, and disinfectants and can survive for many years. Tetanus can be prevented by active immunisation with tetanus vaccine or passive immunisation with tetanus immunoglobulin. Nowadays it occurs mostly in those who are unimmunised or partially immunised; it may also occur in those who have been fully immunised but have not received further booster doses. Tetanus generally follows trauma, particularly deep penetrating injuries; patients with burns, surgical wounds, body piercings, or a history of injected drug abuse are at increased risk of developing tetanus. Infection may also develop postpartum in the uterus (maternal tetanus) and in the newborn (tetanus neonatorum). The mortality rate in mild to moderate tetanus is about 6% and increases to about 60% in severe disease; it may be 80 to 90% in newborns even if treated.

The goal of treatment is to relieve muscle spasm, prevent respiratory and metabolic complications, neutralise unbound or circulating toxin, and eliminate the source of toxin. Treatment includes the use of tetanus immunoglobulin to neutralise any circulating toxin (p. 2420.3) and the use of antibacterials to stop the production and release of toxins. Benzylpenicillin has traditionally been used, given intravenously or intramuscularly for 7 to 10 days, but many consider metronidazole to be the drug of choice;[1,2] given rectally it causes fewer spasms than when given parenterally.[1] Erythromycin, a tetracycline such as doxycycline, clindamycin, vancomycin, or chloramphenicol are second-line alternatives.[1,2]

Wounds should be cleaned and debrided. Drugs used to treat muscle spasm, rigidity, and seizures include sedative-hypnotic agents, general anaesthetics, centrally acting muscle relaxants, and neuromuscular blocking agents. For further information on the treatment of rigidity and spasms, see p. 2029.2.

1. Farrar JJ, *et al.* Tetanus. *J Neurol Neurosurg Psychiatry* 2000; 69: 292–301.
2. Cook TM, *et al.* Tetanus: a review of the literature. *Br J Anaesth* 2001; 87: 477–87.
3. Brook I. Current concepts in the management of Clostridium tetani infection. *Expert Rev Anti Infect Ther* 2008; 6: 327–36.

Tonsillitis

See Pharyngitis, p. 198.3.

Toxic shock syndrome

Toxic shock syndrome (TSS) is an acute, toxin-mediated, systemic illness often leading to multi-organ failure;[1] it may be characterised by shock, fever, rash, and gastrointestinal or CNS disturbances,[2] although bacteraemia is not always present.[1] TSS has most commonly been associated with *Staphylococcus aureus* and its bacterial exotoxin, toxic shock syndrome toxin-1 (TSST-1), or with group A streptococci (which produce streptococcal pyrogenic exotoxins A, B, and C).[2] More recently however, other bacteria including *Clostridium* spp.,[3] *Pseudomonas* spp., and *Klebsiella* spp. have also been implicated, and TSS is now considered to be a global immune response that may be caused by several different triggers.[2] In the early 1980s, TSS was reported mainly in menstruating women using high-absorbency tampons, but it is now appreciated that other foci of infection such as surgical wounds, burns, abscesses, and sinuses are often responsible.[4,5] Non-menstrual cases now occur more frequently than menstrual,[2] and mortality may be higher.[6]

As with any case of septic shock, the first consideration in the management of patients with acute TSS is **resuscitation and stabilisation.** For the general principles used in the treatment of shock, see p. 1279.3. A thorough investigation to find the infective focus, followed by effective **source control** is also necessary, and may include local measures such as removal of tampons or packing, wound debridement, or drainage of abscesses.

Appropriate, immediate antibacterial therapy is essential to **eliminate toxin-producing bacteria.** Where the infecting organism is unknown, initial regimens must cover both *Staph. aureus* and *S. pyogenes*; generally a beta lactam plus a lincosamide is considered appropriate. Where the causative organism has been identified, the following pathogen-specific regimens have been suggested:[1]

- Group A streptococcus: benzylpenicillin plus clindamycin
  beta-lactam intolerant patients: either a macrolide or fluoroquinolone plus clindamycin
- Macrolide-lincosamide-streptogramin-B-resistant (MLS_B phenotype) group A streptococcus: benzylpenicillin, plus either vancomycin or teicoplanin
  beta lactam intolerant patients: vancomycin or teicoplanin
- Meticillin-sensitive *Staph. aureus*: either cloxacillin, nafcillin, or cefazolin, plus clindamycin
  beta-lactam intolerant patients: clarithromycin plus clindamycin
- MRSA: clindamycin or linezolid plus vancomycin or teicoplanin
- Glycopeptide-resistant or intermediate *Staph. aureus* linezolid plus clindamycin (if sensitive)

Newer antibacterials such as linezolid, daptomycin, and tigecycline, that are effective against Gram-positive organisms, may be considered for third-line use.[1]

Continuing antibacterial treatment for 10 days during the convalescent phase to reduce the risk of recurrence has been recommended.[4] The use of prophylactic antibacterial therapy has been suggested in burns patients,[7] but this is controversial.

Provision of passive immunity through the use of fresh frozen plasma or intravenous normal immunoglobulins is considered by some to be one of the most important measures to stop the inflammatory escalation associated with TSS and prevent further tissue damage.[2] In a comparative observational study, improved 30-day survival was noted among patients with streptococcal TSS who were given intravenous immunoglobulins.[8] It has been suggested that such therapy be considered in cases where there has been no clinical response within the first 6 hours of aggressive supportive therapy.[1]

Toxic shock syndromes may be associated with necrotising fasciitis (see p. 193.1).

1. Lappin E, Ferguson AJ. Gram-positive toxic shock syndromes. *Lancet Infect Dis* 2009; 9: 281–90.
2. Young AE, Thornton KL. Toxic shock syndrome in burns: diagnosis and management. *Arch Dis Child Educ Pract Ed* 2007; 92: ep97–ep100.
3. Cohen AL, *et al.* Toxic shock associated with Clostridium sordellii and Clostridium perfringens after medical and spontaneous abortion. *Obstet Gynecol* 2007; 110: 1027–33.
4. Todd JK. Therapy of toxic shock syndrome. *Drugs* 1990; 39: 856–61.
5. Williams GR. The toxic shock syndrome. *BMJ* 1990; 300: 960.
6. Descloux E, *et al.* One in five mortality in non-menstrual toxic shock syndrome versus no mortality in menstrual cases in a balanced French series of 55 cases. *Eur J Clin Microbiol Infect Dis* 2008; 27: 37–43.
7. Rashid A, *et al.* On the use of prophylactic antibiotics in prevention of toxic shock syndrome. *Burns* 2005; 31: 981–5.
8. Kaul R, *et al.* Intravenous immunoglobulin therapy for streptococcal toxic shock syndrome—a comparative observational study. *Clin Infect Dis* 1999; 28: 800–7.

Trachoma

Trachoma[1,2] results from chronic eye infection with certain *Chlamydia trachomatis* serotypes and is an important cause of preventable blindness. It is endemic mainly in Africa and the Middle East, and also in parts of Asia, Latin America, and the western Pacific. The reservoir is chronic eye infection and transmission occurs easily via contaminated fingers, personal effects, and flies that come in contact with the eyes or nose. Infection tends to cluster in families and communities, particularly where water shortage, poor sanitary conditions, and overcrowding occur. Although trachoma is not a sexually transmitted disease, inclusion conjunctivitis in infants (see under Neonatal Conjunctivitis, p. 193.2) and in adults is associated with sexually transmitted genital *C. trachomatis* infection and can progress to trachoma when there is persistent or recurrent eye infection.

First infection generally occurs early in life, leading to a usually self-limiting conjunctivitis. Re-infection is common, and over many years leads to conjunctival scarring, causing the eyelashes to turn inwards and scratch the cornea (trichiasis); eventually irreversible corneal damage and visual loss may occur.

Blindness can be prevented by several interventions, and an Alliance for the Global Elimination of Trachoma (GET 2020) was launched under WHO leadership in 1998 with the goal of eliminating blinding trachoma by 2020. Interventions are also promoted by the International Trachoma Initiative and follow the WHO recommended SAFE strategy: lid surgery for trichiasis, antibacterials to treat infection and suppress transmission, facial cleanliness, and environmental improvements.[3,4] In endemic areas, community-wide antibacterial treatment is recommended where the prevalence of active trachoma in children aged 1 to 9 years is 10% or higher;[3,4] where prevalence is between 5 and 10%, targeted treatment may be considered.[3]

Active treatment. Oral azithromycin regimens (usually a single oral dose or 3 oral doses at weekly intervals) have been shown to be at least as effective as topical tetracycline in resolving active infection.[5,6] Azithromycin 1.5% eye drops used twice daily for 2 or 3 days have been shown to be as effective as treatment with oral azithromycin.[7]

Mass treatment of communities with oral azithromycin once weekly for 3 weeks resulted in a lower incidence of trachoma at one-year follow-up than topical tetracycline given daily for 6 weeks.[8,9] This may be in part due to the fact that topical tetracycline does not treat extra-ocular reservoirs of infection, and its long treatment schedule has led to poor compliance. WHO therefore recommends the use of azithromycin, given as a single annual oral dose of 20 mg/kg (to a maximum of 1 g) for a minimum of 3 years. After that, the prevalence of active disease in the community should be re-assessed to determine whether treatment may be stopped. For those who cannot take azithromycin (including infants less than 6 months old) or where it is unavailable, tetracycline 1% eye ointment can be used twice daily for 6 weeks.[1-4] Pregnancy and breast feeding are not considered to be contra-indications to the use of oral azithromycin.[4] Azithromycin 1.5% eye drops have also been used successfully[10,11] and may present a possible alternative to the standard WHO-recommended treatments.

It is uncertain how often, and for how long mass treatment needs to be given in endemic communities to achieve disease control.[1] Although several studies have reported significant reductions in the prevalence of disease and infection after mass treatment with a single oral dose of azithromycin,[12,13] recurrence of infection within 12 to 24 months has been reported.[14,15] Infection may have been eliminated in a Tanzanian community 3 years after the completion of 2 rounds of mass azithromycin treatment, given at 24-month intervals;[16] the authors concluded that one or two rounds of high-coverage mass treatment might be sufficient to eliminate infection in communities with moderate disease burden. A comparative study[17] of annual versus twice-yearly mass treatment with oral azithromycin in pre-school children living in communities with a high prevalence of infection found that, after 24 months, twice-yearly treatment was significantly more effective in reducing ocular chlamydial infection prevalence than annual treatment. However, a subsequent comparative study[18] found that after 42 months, the prevalence of infection in children aged 0 to 9 years was similar for both annual and twice-yearly treatment groups. The mean elimination of infection in those treated twice yearly was, however, 7.5 months earlier than those treated annually.[18]

1. Burton MJ. Trachoma: an overview. *Br Med Bull* 2007; 84: 99–116.
2. Wright HR, *et al.* Trachoma. *Lancet* 2008; 371: 1945–54.
3. WHO. Report of the 2nd global scientific meeting on trachoma (WHO/PBD/GET 03.1). Geneva: WHO, 2003. Available at: http://www.who.int/blindness/2nd%20GLOBAL%20SCIENTIFIC%20MEETING.pdf (accessed 06/04/09)
4. WHO. Trachoma control: a guide for programme managers. Geneva: WHO, 2006. Available at: http://whqlibdoc.who.int/publications/2006/9241546905_eng.pdf (accessed 06/04/09)
5. Bailey RL, *et al.* Randomised controlled trial of single-dose azithromycin in treatment of trachoma. *Lancet* 1993; 342: 453–6.
6. Evans JR, Solomon AW. Antibiotics for trachoma. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2011 (accessed 27/06/12).
7. Cochereau I, *et al.* Efficacy and safety of short duration azithromycin eye drops versus azithromycin single oral dose for the treatment of trachoma in children: a randomised, controlled, double-masked clinical trial. *Br J Ophthalmol* 2007; 91: 667–72.
8. Schachter J, *et al.* Azithromycin in control of trachoma. *Lancet* 1999; 354: 630–5.
9. Fraser-Hurt N, *et al.* Efficacy of oral azithromycin versus topical tetracycline in mass treatment of endemic trachoma. *Bull WHO* 2001; 79: 632–40.
10. Huguet P, *et al.* Mass treatment of trachoma with azithromycin 1.5% eye drops in the Republic of Cameroon: feasibility, tolerance and effectiveness. *Br J Ophthalmol* 2010; 94: 157–60.
11. Amza A, *et al.* Elimination of active trachoma after two topical mass treatments with azithromycin 1.5% eye drops. *PLoS Negl Trop Dis* 2010; 4: e895.
12. Solomon AW, *et al.* Mass treatment with single-dose azithromycin for trachoma. *N Engl J Med* 2004; 351: 1962–71.
13. Burton MJ, *et al.* Re-emergence of Chlamydia trachomatis infection after mass antibiotic treatment of a trachoma-endemic Gambian community: a longitudinal study. *Lancet* 2005; 365: 1321–8.
14. Chidambaram JD, *et al.* Effect of a single mass antibiotic distribution on the prevalence of infectious trachoma. *JAMA* 2006; 295: 1142–6.
15. West SK, *et al.* Infection with Chlamydia trachomatis after mass treatment of a trachoma hyperendemic community in Tanzania: a longitudinal study. *Lancet* 2005; 366: 1296–300.
16. Solomon AW, *et al.* Two doses of azithromycin to eliminate trachoma in a Tanzanian community. *N Engl J Med* 2008; 358: 1870–1.
17. Melese M, *et al.* Comparison of annual and biannual mass antibiotic administration for elimination of infectious trachoma. *JAMA* 2008; 299: 778–84.
18. Gebre T, *et al.* Comparison of annual versus twice-yearly mass azithromycin treatment for hyperendemic trachoma in Ethiopia: a cluster-randomised trial. *Lancet* 2012; 379: 143–51.

Trench fever

Trench fever is a louse-borne Gram-negative bacterial infection so named because of its prevalence among soldiers in the First World War. It is caused by *Bartonella quintana* (formerly *Rochalimaea quintana*) which was previously classified as a rickettsia. *B. quintana* and *B. henselae* have also been implicated in bacillary angiomatosis, especially in immunocompromised patients, and *B. henselae* is considered to be a cause of cat scratch disease (p. 176.3). Contemporary *B. quintana* infections (also known as urban trench fever) have a global distribution and are mainly associated with poverty, alcoholism, homelessness or displacement, and body-lice infestation.

The disease varies from asymptomatic to severe. Clinical manifestations include fever, headache, weight loss, and leg pain. Many patients have been found to have chronic bacteraemia, and some patients have been diagnosed with *Bartonella* endocarditis.

Mild or uncomplicated infection can be treated with a 4- to 6-week course of an oral tetracycline such as doxycycline, oral erythromycin, or oral azithromycin.[1] Patients with chronic bacteraemia should receive oral doxycycline for 4 weeks plus intravenous gentamicin for 2 weeks,[2,3] mainly to prevent the development of endocarditis. The recommended treatment for documented *Bartonella* endocarditis is oral doxycycline for 6 weeks plus intravenous gentamicin for 2 weeks.[2,3] If gentamicin cannot be used, rifampicin is an alternative. For suspected *Bartonella* endocarditis, intravenous gentamicin is given for 2 weeks with intramuscular or intravenous ceftriaxone for 6 weeks; this regimen may be given with or without a 6-week course of oral doxycycline.[2]

1. Ohl ME, Spach DH. Bartonella quintana and urban trench fever. *Clin Infect Dis* 2000; 31: 131–5.
2. Rolain JM, *et al.* Recommendations for treatment of human infections caused by Bartonella species. *Antimicrob Agents Chemother* 2004; 48: 1921–33.
3. Foucault C, *et al.* Bartonella quintana characteristics and clinical management. *Emerg Infect Dis* 2006; 12: 217–23.

Tuberculosis

Tuberculosis[1] refers to disease caused mainly by *Mycobacterium tuberculosis* and occasionally by *M. bovis* or *M. africanum*. Infection results from inhalation of infected droplet nuclei. Primary infection is usually asymptomatic and in more than 95% of immunocompetent individuals is controlled by acquired (cell mediated) immunity. The immune response, however, is unable to eradicate the tubercle bacilli, and these bacilli may give rise to progressive primary infection (if disease occurs within 2 years of initial infection) or post-primary (reactivated) tuberculosis (if disease occurs years to decades after initial infection). Young children and immunocompromised patients are at increased risk of developing active disease. The most common manifestation of tuberculosis is pulmonary disease, although almost any organ may be affected. Patients usually present with cough, fever, night sweats, and weight loss.

During recent years the incidence of tuberculosis in many countries has increased along with the increasing prevalence of HIV infection. Supervised rifampicin-based (short-course) therapy, using fixed-dose combination tablets, is recommended by WHO to improve cure rates and reduce the emergence of drug-resistant tuberculosis.[2] WHO applies the term **DOTS** (Directly Observed Therapy – Short Course) to its tuberculosis control strategy, which includes standards for diagnosis, supervised therapy, ensuring secure drug supplies, and regular evaluation of the tuberculosis control programme. The feasibility of implantable dosage forms has also been investigated.

First-line treatment. Multidrug treatment for 6 to 8 months is required to cure tuberculosis, reduce the risk of relapse, and prevent the emergence of drug-resistant disease. Treatment regimens recommend an initial intensive phase of 2 to 3 months that is aimed at achieving rapid sputum conversion followed by a continuation phase of 4 to 6 months to eliminate residual bacilli and prevent relapse. The choice of regimen depends on local patterns of drug resistance and the availability of drugs, and are embodied in national and regional treatment protocols in many countries including those in Europe,[3] the UK,[4,5] and USA.[6] WHO recommended treatment regimens[7] are based on disease severity and history of previous tuberculosis treatment:

- **new cases** of pulmonary or extrapulmonary tuberculosis are generally treated with an initial phase consisting of rifampicin (R), isoniazid (H), pyrazinamide (Z), and ethambutol (E) for 2 months, followed by a continuation phase with rifampicin and isoniazid for 4 months, such a regimen being described as: 2HRZE/4HR. Although a regimen using ethambutol in the continuous phase instead of rifampicin (2HRZE/6HE) has been used to reduce costs, it is no longer recommended by WHO due to an increased risk of relapse and death. All first-line drugs can be given intermittently if doses are directly observed (3 times each week), however, WHO advises that daily use is considered optimal. For tuberculous meningitis WHO recommends that ethambutol be replaced with streptomycin for the initial phase (although ethambutol is considered suitable by other authorities[5,6,8]); an extended continuation phase of up to 10 months with rifampicin and isoniazid is often recommended. Cure rates of greater than 90% are typically achieved in patients infected with drug-susceptible organisms who adhere to therapy.
- patients **previously treated** for tuberculosis are at higher risk for drug-resistant infection, and wherever possible, treatment should be guided by drug susceptibility testing (DST). Where DST is not available or is delayed, an initial empirical regimen should be chosen based on the perceived risk of multidrug-resistant infection, which is based on both patient-specific factors and the degree of resistance seen in the community. Those considered to be at low or medium risk may be empirically re-treated with first-line drugs; the initial treatment phase includes rifampicin, isoniazid, pyrazinamide, and ethambutol given for 3 months with streptomycin being added for the first 2 months, while the continuation phase includes 3 drugs (rifampicin, isoniazid, and ethambutol) and is extended to 5 months (2HRZES/1HRZE/5HRE). For those considered to be at high risk for multidrug-resistant infection, a regimen incorporating the use of second-line drugs is recommended (see below).

First-line drugs such as isoniazid, rifampicin, and particularly pyrazinamide may cause severe and possibly fatal drug-induced hepatitis. Further details covering hepatotoxicity and special precautions for use in patients with liver disorders are given in the respective drug monographs—see Isoniazid, p. 315.1; Rifampicin, p. 354.3; and Pyrazinamide, p. 348.2. UK[4] and US[6] guidelines recommend stopping all potentially hepatotoxic drugs if serum transaminases rise to more than 5 times the upper limit of normal or 3 times in the presence of symptoms of hepatitis or elevated bilirubin. Cautious sequential re-introduction of the same drugs (with or without pyrazinamide) after resolution of the biochemical abnormalities is often possible.[4,6,7] Patients in whom therapy is interrupted may be given streptomycin, ethambutol, and a fluoroquinolone until hepatotoxicity has resolved.[7]

Management of drug-resistant disease. The incidence of drug resistance amongst *M. tuberculosis* strains has increased over recent years typically in countries with poor tuberculosis control programmes.[9,10] Isoniazid and streptomycin resistance are the most prevalent. **Multidrug-resistant tuberculosis** (MDR-TB), caused by strains resistant to both isoniazid and rifampicin, requires a combination of first- and second-line drugs for at least 18 to 24 months (see below).[4,6,7,9] Drug-resistant tuberculosis is a reflection of poor tuberculosis management, control, and unreliable drug supply; it is difficult to treat, and not infrequently fatal, particularly in HIV-infected patients. Whereas the WHO DOTS programme may limit the development of MDR-TB, different strategies are required in areas where multidrug resistance is already established. These have been formulated by WHO in the **DOTS-plus** strategy for countries with well functioning tuberculosis control programmes.[11]

Patients with suspected or confirmed MDR-TB should receive a DOTS-plus regimen, which includes second-line

antituberculous drugs. These drugs are generally less effective and more toxic than standard therapy and need to be taken daily. They include injectable drugs such as the aminoglycosides (amikacin and kanamycin) and the polypeptide capreomycin, as well as further oral drugs such as the fluoroquinolones (levofloxacin, moxifloxacin, and ofloxacin), the diarylquinolines (bedaquiline fumarate), and bacteriostatic agents (aminosalicylic acid, cycloserine, ethionamide, protionamide, and terizidone). WHO advises that regimens should consist of at least 4 drugs with certain or almost certain efficacy, based on factors such as previous antituberculosis therapy, DST (where available), and country-specific drug-resistance patterns. Specific drugs should be chosen in hierarchical order based on potency and likely effectiveness; any suitable first-line oral drugs should be considered first, then addition of an injectable drug, a fluoroquinolone, and if necessary, 1 or more oral bacteriostatic drugs. Drugs that have potential for cross-resistance should not be used together.[7,9] Cross-resistance between rifampicin and rifabutin is common and rifabutin is therefore not recommended as a second-line drug. Cross-resistance between amikacin and kanamycin is also common, while cross-resistance is variable between the fluoroquinolones. Cross-resistance is complete between ethionamide and protionamide, and between cycloserine and terizidone.

Extensively drug-resistant tuberculosis (XDR-TB) is defined as tuberculosis that is resistant to isoniazid and rifampicin and also resistant to fluoroquinolones and at least one of three injectable second-line drugs (amikacin, capreomycin, or kanamycin).[12,13] XDR-TB can develop when the second-line drugs are misused or mismanaged and by early 2006 cases were being reported from every region in the world.[14] A report from the KwaZulu-Natal province of South Africa highlighted the risk for rapid death in HIV-infected persons with XDR-TB.[15] In this local case series, all but one of 53 patients died, and where the date of death could be confirmed the median survival was 16 days from the time of diagnosis. There are very limited clinical data available to guide treatment of XDR-TB, and management should always involve expert consultation. Although WHO[9] guidance for choice of treatment follows similar principles to those for MDR-TB, it may be impossible to construct an adequate regimen from among the usual first- and second-line drugs. Additional drugs such as clofazimine, linezolid, amoxicillin with clavulanic acid, thioacetazone, imipenem with cilastatin, or clarithromycin may have some activity against tuberculosis and should be considered in these cases, although their benefit remains unclear.

Children and infants can be treated with generally similar regimens to adults but with appropriate dose adjustments for age or body-weight.[4,6,16] While ethambutol is not usually given to young children because of the perceived difficulty in detecting ocular toxicity (see p. 299.1), a literature review[17] on its use in children found almost no ocular toxicity at daily doses of 15 to 30 mg/kg and it was considered safe in children of all ages.

Pregnancy, breast feeding, and the neonate. Tuberculosis, and especially drug-resistant tuberculosis, during pregnancy poses a serious risk to the mother, fetus, and neonate if not detected early and treated properly.[18] WHO recommends that pregnant women with tuberculosis are treated similarly to non-pregnant patients.[7] Fluoroquinolones, aminoglycosides, ethionamide, and protionamide are best avoided. Liver enzymes and symptoms of drug-induced hepatitis should be monitored.[4,6,18] Most antituberculous drugs may be used during breast feeding, but drug concentrations in the breast milk are too low to prevent or treat tuberculosis in infants. WHO recommends that once active neonatal tuberculosis is ruled out, neonates of mothers with tuberculosis should receive preventative treatment with isoniazid for 6 months;[7,16] alternatively, isoniazid may be given for 3 months after which time the need for further treatment can be evaluated.[16] BCG vaccination is recommended when isoniazid is stopped.[7,16]

Co-infection with HIV increases the risk of patients developing both pulmonary and extrapulmonary tuberculosis, and mortality is higher than in HIV-negative patients in the absence of antiretroviral therapy. HIV patients (including children) with active pulmonary tuberculosis respond to short-course chemotherapy similarly to HIV-negative tuberculosis patients, and most can be treated with the standard 6-month regimen.[4,19-22] For most extrapulmonary infections, 6 to 9 months of therapy is recommended; 9 to 12 months is suggested for infections involving the bones and joints or CNS.[21] Although some experts endorse the use of either daily or intermittent dosing schedules in HIV-infected patients,[20,21] WHO[7] advises against intermittent dosing due to higher risk of treatment failure and relapse; dosing three times a week may be acceptable during the continuous phase of treatment if doses are directly observed. Treatment failures in HIV-infected patients have also been associated with reduced drug concentrations due to malabsorption of antimycobacterials.[23]

In HIV-infected patients with tuberculosis, adjunctive preventative therapy with co-trimoxazole has been associated with substantially lower mortality; WHO therefore recommends that co-trimoxazole be started as soon as possible after a diagnosis of tuberculosis, and continued for the duration of treatment.[7] Thioacetazone should not be used in HIV-positive patients because of the potential for severe skin toxicity.

In antiretroviral-naive patients, the issue of when to start antiretroviral treatment is controversial.[7,20-22] Although WHO has advised that antiretroviral treatment should be started a soon as possible after, and within the first 8 weeks of starting, tuberculosis treatment,[7] concerns include overlapping drug toxicity, drug interactions, pill burden, and risk for immune reconstitution syndrome; some clinicians may instead choose to base the decision on when to start antiretrovirals on the immune status of the patient.[20,21] In an open-label, randomised, controlled study[24] of 642 HIV-infected patients with CD4+ T lymphocyte counts < 500 cells/mm^3, starting antiretroviral therapy during tuberculosis treatment (during, or up to 4 weeks after completion of the intensive phase) led to significantly improved survival. The use of rifamycin-based regimens to treat tuberculosis is recommended as response rates are better compared with non-rifamycin-based regimens. However, drug interactions between rifamycins and antiretrovirals complicate the co-administration of HIV and tuberculosis treatment,[21,22,25] and certain combinations may require dose adjustment or be contra-indicated (for details of the interactions of rifampicin and antiretrovirals, see p. 355.2, and for those with rifabutin, see p. 352.1). It is important to note that guideline recommendations are based on pharmacokinetic studies, often performed in healthy subjects, rather than on studies of treatment outcome in patients. Paradoxical worsening of tuberculosis symptoms is common in HIV-infected patients who start antiretroviral therapy[26] and incidences of up to 35% have been noted.[25]

Adjunctive therapy. The inflammatory response to tuberculosis can cause considerable tissue damage and adjunctive corticosteroid therapy may be used to counter this. Corticosteroids are of little benefit in uncomplicated pulmonary tuberculosis. However, a systematic review[27] found that in tuberculous meningitis, adjunctive corticosteroids reduced the risk of death and disabling residual neurological deficit in HIV-negative patients. Systematic reviews of tuberculous pleurisy[28] and pericarditis,[29] have concluded that there is insufficient evidence to support the use of corticosteroids in these conditions. Nevertheless, WHO[19] suggests that corticosteroids may be useful adjuvants to antituberculous therapy for the management of tuberculous meningitis, pericarditis, pleural effusion, laryngitis, tuberculosis of the renal tract, adrenocortical insufficiency due to adrenal gland tuberculosis, and massive lymph node enlargement in both HIV-positive and -negative patients. Corticosteroids may also be useful for hypersensitivity reactions to antituberculous drugs. For further details on the possible role of corticosteroids as an adjunct to antituberculous therapy, see p. 1614.3.

Studies have suggested that injection of suspensions of killed *Mycobacterium vaccae* improved immune responsiveness in patients with pulmonary tuberculosis, although a systematic review[30] concluded that *M. vaccae* immunotherapy was of no benefit.

Prevention. Studies have found that *BCG vaccine* offers protection against serious forms of tuberculosis in children, such as miliary and meningeal tuberculosis, but has variable efficacy against pulmonary tuberculosis in adults. In high prevalence areas, vaccination is recommended for children at birth, except for children with HIV infection. For further information on BCG vaccine, see p. 2378.1.

Tuberculosis skin testing may identify persons with *latent M. tuberculosis* infection. Treatment of tuberculosis skin test-positive persons (also referred to as preventative therapy or chemoprophylaxis) reduces the risk of developing (reactivation) tuberculosis. Treatment is beneficial in HIV-infected patients, contacts of active cases, persons who have recently become tuberculosis skin test positive, and persons at high risk of disease. Chemoprophylaxis is not recommended routinely in developing countries where the priority is to detect and treat patients with active tuberculosis.[19,31] Latent tuberculosis has been treated with isoniazid or rifampicin given alone, or with rifampicin given with either isoniazid or pyrazinamide. Daily isoniazid for 6 to 12 months reduces the risk of active tuberculosis by 60 to 90%[1,32] and in HIV-infected, tuberculosis skin test-positive persons isoniazid for 6 months has also been shown to provide short-term protection against tuberculosis.[33] However, the combination of rifampicin and pyrazinamide has resulted in severe and fatal liver damage in HIV-negative persons and is no longer recommended for tuberculosis prophylaxis.[32,34,35] The American Thoracic Society and the CDC,[32,34] and NICE[5] have issued detailed recommendations for treatment of latent tuberculosis infection. Briefly, UK recommendations for HIV-negative adults and children over 2 years old are for either isoniazid alone for 6 months or isoniazid with rifampicin for 3 months; isoniazid alone for 6 months should be given to all HIV-positive patients. In the USA either isoniazid alone for 9 months (or 6 months in HIV-negative patients) or rifampicin alone for 4 months is recommended.

1. Frieden TR, *et al.* Tuberculosis. *Lancet* 2003; 362: 887–99.
2. Blomberg B, Fourie B. Fixed-dose combination drugs for tuberculosis: application in standardised treatment regimens. *Drugs* 2003; 63: 535–553.
3. Broekmans JF, *et al.* European framework for tuberculosis control and elimination in countries with a low incidence. Recommendations of the World Health Organization (WHO), International Union Against Tuberculosis and Lung Disease (IUATLD) and Royal Netherlands Tuberculosis Association (KNCV) Working Group. *Eur Respir J* 2002; 19: 765–75. Also available at: http://erj.ersjournals.com/cgi/reprint/19/4/765.pdf (accessed 02/03/06)
4. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; 53: 536–48.[Although these guidelines were replaced by ones issued by NICE in 2006 the latter do not *"explain tuberculosis or its treatment in detail"* and therefore reference to the earlier guidelines has been retained] Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Tuberculosis/Guidelines/Chemotherapy.pdf (accessed 29/07/08)
5. National Collaborating Centre for Chronic Conditions/NICE. Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control (issued March 2011). Available at: http://www.nice.org.uk/nicemedia/live/13422/53642/53642.pdf (accessed 11/05/11)
6. American Thoracic Society, CDC, and the Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; 52 (RR-11): 1–77. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf (accessed 24/05/04) Correction. *ibid.* 2005: 53: 1203. [dose]
7. WHO. *Treatment of tuberculosis: guidelines—4th edition.* Geneva: WHO, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf (accessed 08/02/10)
8. Thwaites G, *et al.* British Infection Society. British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children. *J Infect* 2009; 59: 167–87. Also available at: http://www.britishinfection.org/drupal/sites/default/files/CNS%20TB%202009%20Thwaites.pdf (accessed 11/05/11)
9. WHO. *Guidelines for the programmatic management of drug-resistant tuberculosis: emergency update 2008.* Geneva: WHO, 2008. Available at: http://whqlibdoc.who.int/publications/2008/9789241547581_eng.pdf (accessed 08/02/10)
10. WHO. *Anti-tuberculosis drug resistance in the world: 4th global report.* Geneva: WHO, 2008. Available at: http://whqlibdoc.who.int/hq/2008/WHO_HTM_TB_2008.394_eng.pdf (accessed 08/02/10)
11. Sterling TR, *et al.* Impact of DOTS compared with DOTS-plus on multidrug resistant tuberculosis and tuberculosis deaths: decision analysis. *BMJ* 2003; 326: 574–9.
12. CDC. Notice to readers: revised definition of extensively drug-resistant tuberculosis. *MMWR* 2006; 55: 1176. Also available at: http://www.cdc.gov/mmwr/PDF/wk/mm5543.pdf (accessed 07/12/06)
13. Madariaga MG, *et al.* Extensively drug-resistant tuberculosis. *Am J Med* 2008; 121: 835–44.
14. CDC. Emergence of Mycobacterium tuberculosis with extensive resistance to second-line drugs—worldwide, 2000–2004. *MMWR* 2006; 55: 301–5. Also available at: http://www.cdc.gov/mmwr/PDF/wk/mm5511.pdf (accessed 07/12/06)
15. Gandhi NR, *et al.* Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. *Lancet* 2006; 368: 1575–80.
16. WHO. *Guidance for national tuberculosis programmes on the management of tuberculosis in children.* Geneva: WHO, 2006. Available at: http://whqlibdoc.who.int/hq/2006/WHO_HTM_TB_2006.371_eng.pdf (accessed 19/08/08)
17. WHO. *Ethambutol efficacy and toxicity: literature review and recommendations for daily and intermittent dosage in children.* Geneva: WHO, 2006. Available at: http://whqlibdoc.who.int/hq/2006/WHO_HTM_TB_2006.365_eng.pdf (accessed 08/12/06)
18. Bothamley G. Drug treatment for tuberculosis during pregnancy: safety considerations. *Drug Safety* 2001; 24: 553–65.
19. WHO. *TB/HIV. A clinical manual.* 2nd ed. Geneva: WHO, 2004. Available at: http://whqlibdoc.who.int/publications/2004/9241546344.pdf (accessed 02/03/06)
20. CDC. Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. *MMWR* 2009; 58 (RR-11): 1–166. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5811.pdf (accessed 08/02/10)
21. CDC. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR* 2009; 58: (RR-4): 1–207. Also available at: http://www.cdc.gov/mmwr/pdf/rr/rr5804.pdf (accessed 08/02/10)
22. CDC. Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis (issued December 2007). Available at: http://www.cdc.gov/tb/TB_HIV_Drugs/PDF/tbhiv.pdf (accessed 29/07/08)
23. Gurumurthy P, *et al.* Decreased bioavailability of rifampin and other antituberculosis drugs in patients with advanced human immunodeficiency virus disease. *Antimicrob Agents Chemother* 2004; 48: 4473–5.
24. Abdool Karim SS, *et al.* Timing of initiation of antiretroviral drugs during tuberculosis therapy. *N Engl J Med* 2010; 362: 697–706.
25. Pozniak AL, *et al.* British HIV Association. BHIVA treatment guidelines for TB/HIV infection, February 2005. Available at: http://www.bhiva.org/files/file1001577.pdf (accessed 05/10/07)
26. Breen RAM, *et al.* Paradoxical reactions during tuberculosis treatment in patients with and without HIV co-infection. *Thorax* 2004; 59: 704–7.
27. Prasad K, Singh MB. Corticosteroids for managing tuberculous meningitis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 11/02/10).
28. Engel ME, *et al.* Corticosteroids for tuberculous pleurisy: Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 19/08/08).
29. Mayosi BM, *et al.* Interventions for treating tuberculous pericarditis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 02/03/06).

30. de Bruyn G, Garner P. Mycobacterium vaccae immunotherapy for treating tuberculosis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 02/03/06).
31. Akolo C, *et al.* Treatment of latent tuberculosis infection in HIV infected persons. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 11/02/10).
32. American Thoracic Society. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000; 49: 1–51. Also published in *Am J Respir Crit Care Med* 2000; 111: S221–S247. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4906a1.htm (accessed 07/06/10)
33. Johnson JL, *et al.* Duration of efficacy of treatment of latent tuberculosis infection in HIV-infected adults. *AIDS* 2001; 15: 2137–47.
34. CDC. Update: adverse event data and revised American Thoracic Society/CDC recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection—United States, 2003. *MMWR* 2003; 52: 735–9. Also available at: http://www.cdc.gov/mmwr/PDF/wk/mm5231.pdf (accessed 05/10/07)
35. Jasmer RM, *et al.* Short-course rifampin and pyrazinamide compared with isoniazid for latent tuberculosis infection: a multicenter clinical trial. *Ann Intern Med* 2002; 137: 640–7.

Tularaemia

Tularaemia[1-4] is caused by the Gram-negative bacillus *Francisella tularensis*, an organism that mainly affects rodents and rabbits but may be transmitted to man, usually by handling infected animals or carcasses, or by the bites of insect vectors, or by ingestion of contaminated food or water. Tularaemia may also be caused by inhalation of airborne bacteria; there has been some concern about the potential use of airborne tularaemia as a biological weapon.

Symptoms usually appear 2 to 6 days after exposure, but can take up to 3 weeks. They depend on the route of exposure and may take several forms, the most common of which is the ulceroglandular. This is characterised by rash, ulceration at the site of inoculation, sudden onset of fever, chills, headache, muscle and joint pains, and lymphadenopathy. A glandular form without skin ulcers and a typhoidal (septicaemic) form are also seen, as are oculoglandular, oropharyngeal, and pneumonic forms. Possible complications of infection include endocarditis, hepatitis, meningitis, pericarditis, peritonitis, pneumonia, osteomyelitis, and sepsis and septic shock.

Parenteral streptomycin or gentamicin are considered the antibacterials of choice; treatment is usually given for about 10 days.[1-4] Tobramycin is not recommended. A tetracycline (such as doxycycline) or chloramphenicol have been given as alternatives but clinical relapses are more frequent than with the recommended aminoglycosides;[1-3] chloramphenicol is generally not recommended except in the treatment of tularaemia meningitis.[3] Fluoroquinolones have shown promise in treating tularaemia and ciprofloxacin, usually given orally for 10 days, is another suitable alternative,[1-4] especially for those patients who are allergic or intolerant of other treatments.

Oral doxycycline or oral ciprofloxacin given for 14 days are recommended for postexposure prophylaxis.[1]

A tularaemia vaccine is available in some countries for active immunisation against the disease.

1. Dennis DT, *et al.* Tularemia as a biological weapon: medical and public health management. *JAMA* 2001; 285: 2763–73.
2. Ellis J, *et al.* Tularemia. *Clin Microbiol Rev* 2002; 15: 631–46.
3. Eliasson H, *et al.* Tularemia: current epidemiology and disease management. *Infect Dis Clin North Am* 2006; 20: 289–311.
4. Hepburn MJ, Simpson AJH. Tularemia: current diagnosis and treatment options. *Expert Rev Anti Infect Ther* 2008; 6: 231–40.

Typhoid and paratyphoid fever

Typhoid and paratyphoid fever are systemic infections caused respectively by *Salmonella typhi* and *S. paratyphi* A, B, or C, Gram-negative bacteria belonging to the Enterobacteriaceae family. They are sometimes termed collectively 'enteric fever' but, although initial infection is intestinal, dissemination in the blood leads to more widespread systemic effects. Typhoid and paratyphoid are endemic in many developing countries in Asia (particularly the southern regions), Africa, the Caribbean, and Central and South America, where they are associated with poor water supply and sanitary conditions. Most cases occurring in developed countries are contracted abroad. Infection is usually transmitted by ingestion of food or water contaminated with the faeces of infected individuals and the incubation period is generally 7 to 14 days. As well as non-specific symptoms such as fever and disturbances of bowel function, characteristic rose-coloured skin lesions may appear on the chest, abdomen, and back, and neuropsychiatric symptoms may occur. Severe typhoid reportedly develops in up to 10 to 15% of patients[1,2] and may be associated with serious complications including gastrointestinal bleeding, intestinal perforation, and typhoid encephalopathy.[1-3]

Treatment of typhoid fever has traditionally been with chloramphenicol or alternatively amoxicillin, ampicillin, or co-trimoxazole.[1] However, there has been a spread of *S. typhi* strains simultaneously resistant to all of these drugs (termed MDR strains)[4,5] in virtually all typhoid-endemic areas.[2] With widespread use of the fluoroquinolones to treat typhoid, resistance to these drugs is an increasing problem as well, particularly in Asia. Resistance may be total or partial; in the latter case, nalidixic acid-resistant (NAR) isolates typically appear sensitive to fluoroquinolones, however therapeutic use often results in clinical failure. As a result, some experts recommend nalidixic-acid resistance testing as a means of predicting reduced fluoroquinolone susceptibility.[2] Interestingly, there is some evidence that as fluoroquinolone resistance spreads, sensitivity to some of the older drugs used to treat the disease, such as chloramphenicol, may be returning.[6,7]

Treatment recommendations[2,5,8] emphasise the use of a fluoroquinolone such as ciprofloxacin or ofloxacin for initial treatment of both fully-sensitive, and MDR typhoid. Chloramphenicol, amoxicillin, and co-trimoxazole are now considered second-line drugs against fully susceptible strains, although there appears to be little sound evidence that fluoroquinolones are more effective against such isolates.[8,9]

Azithromycin, or third generation cephalosporins such as cefixime, cefotaxime, and ceftriaxone, are possible alternatives for both MDR and fluoroquinolone-resistant infections.[10] A systematic review found that azithromycin was associated with reduced clinical failure and shorter hospitalisation times than the fluoroquinolones, and reduced rate of relapse compared with ceftriaxone.[11] For infections caused by NAR isolates, the fluoroquinolones are still second-line alternatives, but higher doses and longer courses of treatment are advocated. Combination regimens have been investigated,[8] but a study in patients infected with strains showing both multidrug resistance and reduced susceptibility to fluoroquinolones found that azithromycin alone was preferable to azithromycin plus ofloxacin.[12]

Most treatment options used for uncomplicated typhoid are also considered suitable for severe cases, but again higher doses and longer treatment are recommended, and initial parenteral therapy is advised until at least 5 days after fever subsides.[2]

Although fluoroquinolones are not generally indicated in children because of potential toxicity, WHO considers that their benefits in typhoid fever outweigh any putative risk.[5] Azithromycin may also be given.[5] In pregnancy a beta-lactam such as ampicillin or one of the cephalosporins may be preferable,[5] although there are reports of the successful use of fluoroquinolones. WHO also suggests that although there is no evidence to suggest harm, azithromycin should not be used in pregnant or nursing women if alternatives are available.[5]

Patients who develop mental changes should be evaluated for meningitis; if typhoid meningitis is suspected, high-dose intravenous dexamethasone should be given in addition to antibacterial treatment.[5]

On recovery, typhoid patients may continue to excrete *S. typhi* in the faeces or urine for several weeks. Unlike these convalescent carriers, some 1 to 5% of patients become chronic carriers[5] who may excrete *S. typhi* for years without any symptoms. Eradication is difficult and prolonged treatment is necessary, but regimens using ciprofloxacin or norfloxacin for 4 weeks, or co-trimoxazole or a combination of probenecid with either amoxicillin or ampicillin for 6 to 12 weeks have all reportedly been effective.[1-3,5]

Typhoid vaccines are used for the **prevention** of typhoid fever, for details see p. 2422.2. No vaccine provides complete protection, however, and strict attention to personal, food, and water hygiene is important in preventing infection.[3]

Paratyphoid fever is less common and generally milder than typhoid fever. Treatment is similar; no licensed vaccines are currently available for prevention.

1. Parry CM, *et al.* Typhoid fever. *N Engl J Med* 2002; 347: 1770–82.
2. Bhan MK, *et al.* Typhoid and paratyphoid fever. *Lancet* 2005; 366: 749–62.
3. Basnyat B, *et al.* Enteric (typhoid) fever in travelers. *Clin Infect Dis* 2005; 41: 1467–72.
4. Rowe B, *et al.* Multidrug-resistant Salmonella typhi: a worldwide epidemic. *Clin Infect Dis* 1997; 24 (suppl 1): S106–S109.
5. WHO. Background document: the diagnosis, treatment and prevention of typhoid fever (issued May 2003). Available at: http://www.who.int/vaccine_research/documents/en/typhoid_diagnosis.pdf (accessed 20/04/09)
6. Gogia A, *et al.* Quinolone-resistant typhoid fever. *Indian J Med Sci* 2006; 60: 389–90.
7. Chinnis S, *et al.* Ciprofloxacin therapy for typhoid fever needs reconsideration. *J Infect Chemother* 2006; 12: 402–4.
8. Bhutta ZA. Current concepts in the diagnosis and treatment of typhoid fever. *BMJ* 2006; 333: 78–82.
9. Thaver D, *et al.* Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever). Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 20/04/09).
10. Threlfall EJ, *et al.* Alternatives to ciprofloxacin use for enteric fever. United Kingdom. *Emerg Infect Dis* 2008; 14: 860–1.
11. Effa EE, Bukirwa H. Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever). Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 20/04/09).
12. Parry CM, *et al.* Randomized controlled comparison of ofloxacin, azithromycin, and an ofloxacin-azithromycin combination for treatment of multidrug-resistant and nalidixic acid-resistant typhoid fever. *Antimicrob Agents Chemother* 2007; 51: 819–25.

Typhus

Rickettsial infections or fevers of the typhus group are transmitted to man by various insect vectors. Louse-borne or epidemic typhus, due to *Rickettsia prowazekii*, and flea-borne or murine typhus, due to the closely related *R. typhi* (*R. mooseri*), have occurred worldwide. Scrub typhus is due to *Orientia tsutsugamushi* (*R. tsutsugamushi*), transmitted by mites, and occurs mainly in Asia, Australia, and the Pacific Islands.

A tetracycline, often doxycycline, or chloramphenicol is the treatment of choice for these infections although strains of *O. tsutsugamushi* resistant to doxycycline and chloramphenicol have been reported in Thailand.[1,2] Ciprofloxacin may be an effective alternative,[3] and rifampicin has been shown to be more effective against scrub typhus than doxycycline.[4] Azithromycin[5,6] and telithromycin[7] have also been reported to be effective. Prophylaxis for scrub typhus with doxycycline has shown promise when started before exposure to infection.[8]

1. Watt G, *et al.* Scrub typhus infections poorly responsive to antibiotics in northern Thailand. *Lancet* 1996; 348: 86–9.
2. Panpanich R, Garner P. Antibiotics for treating scrub typhus. Available in The Cochrane Database of Systematic Reviews: Issue 3. Chichester: John Wiley; 2002 (accessed 16/05/05).
3. Eaton M, *et al.* Ciprofloxacin treatment of typhus. *JAMA* 1989; 262: 772–3.
4. Watt G, *et al.* Doxycycline and rifampicin for mild scrub-typhus infections in northern Thailand: a randomised trial. *Lancet* 2000; 356: 1057–61.
5. Kim Y-S, *et al.* A comparative trial of a single dose of azithromycin versus doxycycline for the treatment of mild scrub typhus. *Clin Infect Dis* 2004; 39: 1329–35.
6. Phimda K, *et al.* Doxycycline versus azithromycin for treatment of leptospirosis and scrub typhus. *Antimicrob Agents Chemother* 2007; 51: 3259–63.
7. Kim D-M, *et al.* Controlled trial of a 5-day course of telithromycin versus doxycycline for treatment of mild to moderate scrub typhus. *Antimicrob Agents Chemother* 2007; 51: 2011–15.
8. Twartz JC, *et al.* Doxycycline prophylaxis for human scrub typhus. *J Infect Dis* 1982; 146: 811–18.

Urethritis

Urethritis or urethral inflammation can result from infectious or noninfectious conditions. Infectious urethritis is a sexually transmitted disease seen most frequently in men. The most common causes are *Neisseria gonorrhoeae* and *Chlamydia trachomatis* (termed nongonococcal urethritis or non-specific urethritis). Other organisms implicated have included *Mycoplasma genitalium* and *Ureaplasma urealyticum*. Gonococcal and chlamydial infections frequently occur together and if a specific clinical diagnosis cannot be made treatment for both infections should be given together otherwise postgonococcal urethritis due to *C. trachomatis* may follow the cure of gonorrhoea. For the treatment of gonococcal urethritis see Gonorrhoea (p. 204.2). For general management of chlamydial infections see p. 177.1.

Guidelines produced by WHO,[1] by an expert group in the UK,[2] and by the CDC in the USA[3] for the **treatment** of urethritis are as follows:

- **WHO:** for chlamydial urethritis:
  - oral doxycycline 100 mg twice daily for 7 days, *or*
  - a single oral dose of azithromycin 1 g

  alternative regimens for 7 days, are:
  - oral amoxicillin 500 mg three times daily
  - oral erythromycin 500 mg four times daily
  - oral ofloxacin 300 mg twice daily
  - oral tetracycline 500 mg four times daily

  Unless it can be excluded, patients should also be treated concurrently for gonorrhoea (p. 204.2)
- **UK:** for nongonococcal urethritis:
  - a single oral dose of azithromycin 1 g, *or*
  - oral doxycycline 100 mg twice daily for 7 days

  alternative regimens are:
  - oral erythromycin 500 mg twice daily for 14 days
  - oral ofloxacin 400 mg daily in one single or two divided doses for 7 days

  Persistent or recurrent nongonococcal urethritis should be treated with:
  - oral azithromycin 500 mg to start then 250 mg daily for 4 days *plus* oral metronidazole 400 mg twice daily for 5 days, *or*
  - oral erythromycin 500 mg four times daily for 21 days *plus* oral metronidazole 400 mg twice daily for 5 days

  An alternative, second-line regimen is:
  - oral moxifloxacin 400 mg once daily for 10 days *plus* oral metronidazole 400 mg twice daily for 5 days
- **USA:** for nongonococcal urethritis:
  - as for the UK

  alternative regimens for 7 days, are:
  - oral erythromycin 500 mg four times daily
  - oral erythromycin ethylsuccinate 800 mg four times daily
  - oral ofloxacin 300 mg twice daily
  - oral levofloxacin 500 mg once daily

  Persistent or recurrent nongonococcal urethritis should be treated with:
  - a single oral dose of either metronidazole 2 g or tinidazole 2 g *plus* oral azithromycin 1 g (if it was not used in the initial treatment regimen)

Sexual partners of patients with urethritis should be tested and treated.[2,3]

1. WHO. Guidelines for the management of sexually transmitted infections. Geneva: WHO, 2003. Also available at: http://whqlibdoc.who.int/publications/2003/9241546263.pdf (accessed 23/03/07)
2. Clinical Effectiveness Group (British Association for Sexual Health and HIV). 2007 UK national guideline on the management of non-gonococcal urethritis—updated December 2008. Available at: http://www.bashh.org/documents/1955 (accessed 05/03/10)
3. CDC. Sexually transmitted diseases treatment guidelines. 2010. *MMWR* 2010; 59 (RR-12): 1–110. Also available at: http://www.cdc.gov/STD/treatment/2010/STD-Treatment-2010-RR5912.pdf (accessed 08/01/11) Correction. *ibid.* 2011; 60: 18. [dose]

Urinary-tract infections

Infections of the urinary tract are especially common in women. They are frequently due to enteric bacteria, in particular *Escherichia coli*, although a common cause in young women is *Staphylococcus saprophyticus*, a coagulase-negative staphylococcus. Other urinary pathogens include *Staph. epidermidis*, enterococci, and *Pseudomonas* spp. An arbitrary definition of urinary-tract infection has been significant bacteriuria with 10^5 or more colony forming units/mL of a midstream urine specimen; some also consider lower counts to be indicative of infection. Most urinary-tract infections are isolated uncomplicated infections of the lower urinary tract. Recurrent infections may be due to relapse, or more often, re-infection, and are more serious. Patients with complicated urinary-tract infections associated with urinary-tract abnormalities or diseases such as diabetes mellitus may be at risk of kidney damage.

Infections of the lower urinary tract in *women* generally present as cystitis (inflammation of the bladder) and symptoms include dysuria, frequency, and urgency with pyuria and significant bacteriuria; the urethral syndrome is similar, but there is no significant bacteriuria. In the upper urinary tract, acute pyelonephritis may occur as a complication of cystitis or, more rarely, may result from septicaemia. Asymptomatic bacteriuria may progress to acute pyelonephritis in *pregnant women* and should therefore be treated.

Urinary-tract infections in *men* are less common and are often associated with abnormalities of the genito-urinary tract such as prostatic hyperplasia. Acute bacterial prostatitis is usually caused by organisms similar to those responsible for cystitis in women. Chronic bacterial prostatitis is difficult to treat; the antibacterials used must be able to penetrate into the prostatic fluid. For other genito-urinary infections in men, see under Epididymitis, p. 181.2, and under Urethritis, p. 212.3.

In preschool *children*, especially girls, asymptomatic bacteriuria with vesicoureteric reflux can result in renal scarring and should be treated; the use of prophylactic antibacterials is complex and controversial. Long-term follow-up of girls who have had asymptomatic bacteriuria suggests that new kidney damage does not occur after 4 years of age, but highlights the importance of diagnosis and treatment in younger children.

The significance of asymptomatic bacteriuria in *old age* is disputed, but most consider treatment to be unnecessary.

Infections associated with *indwelling bladder catheters* occur in both men and women and probably account for the majority of hospital-acquired urinary-tract infections.

Treatment. Antibacterials used to treat urinary-tract infections need to be excreted in adequate concentrations in the urine. For *acute uncomplicated infections* oral amoxicillin, ampicillin, co-trimoxazole, nalidixic acid, nitrofurantoin, or trimethoprim (preferred to co-trimoxazole in the UK) have been given, although the choice will depend on local patterns of bacterial resistance; *E. coli* resistant to ampicillin and amoxicillin is widespread. Alternatives when resistance is prevalent include amoxicillin with clavulanic acid, oral cephalosporins, fluoroquinolones, or fosfomycin. In pregnant women, nitrofurantoin or a beta-lactam antibacterial can be used. Standard treatment schedules have been for 5 to 7 days; 3-day or single-dose regimens can also be effective and may be preferred in women. Single-dose treatment may be associated with reduced efficacy compared with 3-day regimens. Urinary alkalinising agents such as potassium citrate and sodium citrate have been given orally to relieve the pain of cystitis caused by lower urinary-tract infections. Recurrent infections may require long-term low-dose antibacterial prophylaxis.

Acute pyelonephritis may require broad-spectrum parenteral treatment initially with, for example, aztreonam, ceftazidime, cefuroxime, ciprofloxacin, or gentamicin.

Chronic bacterial prostatitis may require treatment for several weeks with trimethoprim, erythromycin, or a fluoroquinolone.

Catheter-related bladder infections may sometimes respond to localised treatment with bladder washouts containing chlorhexidine.

General references.

1. Nicolle LE. Urinary tract infection: traditional pharmacologic therapies. *Am J Med* 2002; 113 (suppl 1A): 35S–44S.
2. Nicolle L. Best pharmacological practice: urinary tract infections. *Expert Opin Pharmacother* 2003; 4: 693–704.
3. Miller LG, Tang AW. Treatment of uncomplicated urinary tract infections in an era of increasing antimicrobial resistance. *Mayo Clin Proc* 2004; 79: 1048–53.
4. Carson C, Naber KG. Role of fluoroquinolones in the treatment of serious bacterial urinary tract infections. *Drugs* 2004; 64: 1359–73.
5. Blondeau JM. Current issues in the management of urinary tract infections: extended-release ciprofloxacin as a novel treatment option. *Drugs* 2004; 64: 611–28.
6. Hooton TM, *et al.* Acute uncomplicated cystitis in an era of increasing antibiotic resistance: a proposed approach to empirical therapy. *Clin Infect Dis* 2004; 39: 75–80.
7. Nicolle LE, *et al.* Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. *Clin Infect Dis* 2005; 40: 643–54. Correction. *ibid.*; 1556. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/427507 (accessed 03/06/10)
8. Geerlings SE, *et al.* Optimaliseren van het antibioticabeleid in Nederland X: SWAB-richtlijn voor antimicrobiële therapie bij gecompliceerde urineweginfecties. *Ned Tijdschr Geneeskd* 2006; 150: 2370–6.
9. Pohl A. Modes of administration of antibiotics for symptomatic severe urinary tract infections. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 07/08/08).
10. Nicolle LE. Short-term therapy for urinary tract infection: success and failure. *Int J Antimicrob Agents* 2008; 31 (suppl 1): S40–S45.
11. Nicolle LE. Uncomplicated urinary tract infection in adults including uncomplicated pyelonephritis. *Urol Clin North Am* 2008; 35: 1–12.
12. Norris DL, Young JD. Urinary tract infections: diagnosis and management in the emergency department. *Emerg Med Clin North Am* 2008; 26: 413–30.
13. Masson P, *et al.* Meta-analyses in prevention and treatment of urinary tract infections. *Infect Dis Clin North Am* 2009; 23: 355–85.

Catheter-related. References to catheter-related urinary-tract infections and their management.

1. Tambyah PA, Maki DG. The relationship between pyuria and infection in patients with indwelling urinary catheters: a prospective study of 761 patients. *Arch Intern Med* 2000; 160: 673–7.
2. Tambyah PA, Maki DG. Catheter-associated urinary tract infection is rarely symptomatic: a prospective study of 1497 catheterized patients. *Arch Intern Med* 2000; 160: 678–82.
3. Hooton TM, *et al.* Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 international clinical practice guidelines from the Infectious Diseases Society of America. *Clin Infect Dis* 2010; 50: 625–63. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/650482 (accessed 03/06/10)

The elderly. References to urinary-tract infections in the elderly and their management.

1. Abrutyn E, *et al.* Does asymptomatic bacteriuria predict mortality and does antimicrobial treatment reduce mortality in elderly ambulatory women? *Ann Intern Med* 1994; 120: 827–33. Correction. *ibid.*; 121: 901.
2. Nicolle LE. Urinary tract infection in the elderly. *J Antimicrob Chemother* 1994; 33 (suppl A): 99–109.
3. Ouslander JG, *et al.* Does eradicating bacteriuria affect the severity of chronic urinary incontinence in nursing home residents? *Ann Intern Med* 1995; 122: 749–54.
4. Abrutyn E, *et al.* Does treatment of asymptomatic bacteriuria in older ambulatory women reduce subsequent symptoms of urinary tract infection? *J Am Geriatr Soc* 1996; 44: 293–5.
5. Shortliffe LMD, McCue JD. Urinary tract infection at the age extremes: pediatrics and geriatrics. *Am J Med* 2002; 113 (suppl 1A): 55S–66S.
6. Lutters M, Vogt-Ferrier NB. Antibiotic duration for treating uncomplicated, symptomatic lower urinary tract infections in elderly women. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 19/08/08).

Infants and children. References to urinary-tract infections in infants and children, and their management.

1. Williams G, *et al.* Antibiotics for the prevention of urinary tract infection in children: a systematic review of randomized controlled trials. *J Pediatr* 2001; 138: 868–74.
2. Tran D, *et al.* Short-course versus conventional length antimicrobial therapy for uncomplicated lower urinary tract infections in children: a meta-analysis of 1279 patients. *J Pediatr* 2001; 139: 93–9.
3. Shortliffe LMD, McCue JD. Urinary tract infection at the age extremes: pediatrics and geriatrics. *Am J Med* 2002; 113 (suppl 1A): 55S–66S.
4. Michael M, *et al.* Short versus standard duration oral antibiotic therapy for acute urinary tract infection in children. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 16/05/05).
5. Williams GJ, *et al.* Long-term antibiotics for preventing recurrent urinary tract infection in children. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 07/08/08).
6. Hodson EM, *et al.* Antibiotics for acute pyelonephritis in children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 19/08/08).
7. Beetz R, *et al.* Harnwegsinfektionen im Säuglings- und Kindesalter: Konsensusempfehlungen zu Diagnostik, Therapie und Prophylaxe. *Urologe A* 2007; 46: 112–23.
8. Wolff O, Maclennan C. Evidence behind the WHO guidelines: hospital care for children: what is the appropriate empiric antibiotic therapy in uncomplicated urinary tract infections in children in developing countries? *J Trop Pediatr* 2007; 53: 150–2.
9. Agence française de sécurité sanitaire des produits de santé. Diagnostic et antibiothérapie des infections urinaires bactériennes communautaires du nourrisson et de l'enfant. *Med Mal Infect* 2007; 37: 645–63.
10. Ochoa Sangrador C, Málaga Guerrero S. Recomendaciones de la Conferencia de Consenso "Manejo Diagnóstico y Terapéutico de las Infecciones del Tracto Urinario en la Infancia". *An Pediatr (Barc)* 2007; 67: 517–25.
11. National Collaborating Centre for Womens and Childrens Health/NICE. Urinary tract infection in children: diagnosis, treatment and long-term management (issued August 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/CG54fullguideline.pdf (accessed 20/05/10)
12. Conway PH, *et al.* Recurrent urinary tract infections in children: risk factors and association with prophylactic antimicrobials. *JAMA* 2007; 298: 179–86.
13. Sedberry-Ross S, Pohl HG. Urinary tract infections in children. *Curr Urol Rep* 2008; 9: 165–71.
14. Montini G, *et al.* Prophylaxis after first febrile urinary tract infection in children? A multicenter, randomized, controlled, noninferiority trial. *Pediatrics* 2008; 122: 1064–71.
15. Merguerian PA, *et al.* Urinary tract infections in children: recommendations for antibiotic prophylaxis and evaluation; an evidence-based approach. *Curr Urol Rep* 2010; 11: 98–108.
16. Dai B, *et al.* Long-term antibiotics for the prevention of recurrent urinary tract infection in children: a systematic review and meta-analysis. *Arch Dis Child* 2010; 95: 499–508.

Men. References to urinary-tract infections in men and their management.

1. Joly-Guillou M-L, Lasry S. Practical recommendations for the drug treatment of bacterial infections of the male genital tract including urethritis, epididymitis and prostatitis. *Drugs* 1999; 57: 743–50.
2. Ulleryd P. Febrile urinary tract infection in men. *Int J Antimicrob Agents* 2003; 22 (suppl 2): 89–93.
3. Lipsky BA, *et al.* Treatment of bacterial prostatitis. *Clin Infect Dis* 2010; 50: 1641–52.

Pregnancy. References to urinary-tract infections in pregnancy and their management.

1. Maclean AB. Urinary tract infection in pregnancy. *Int J Antimicrob Agents* 2001; 17: 273–6.
2. Kremery S, *et al.* Treatment of lower urinary tract infection in pregnancy. *Int J Antimicrob Agents* 2001; 17: 279–82.
3. Wing DA. Pyelonephritis in pregnancy: treatment options for optimal outcomes. *Drugs* 2001; 61: 2087–96.
4. Vazquez JC, Villar J. Treatments for symptomatic urinary tract infections during pregnancy. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 20/05/10).
5. Mittal P, Wing DA. Urinary tract infections in pregnancy. *Clin Perinatol* 2005; 32: 749–64.
6. Macejko AM, Schaeffer AJ. Asymptomatic bacteriuria and symptomatic urinary tract infections during pregnancy. *Urol Clin North Am* 2007; 34: 35–42.
7. Smaill F, Vazquez JC. Antibiotics for asymptomatic bacteriuria in pregnancy. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 07/08/08).

Women. References to urinary-tract infections in women and their management.

1. Warren JW, *et al.* Infectious Diseases Society of America. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. *Clin Infect Dis* 1999; 29: 745–58.
2. Hooton TM. Recurrent urinary tract infection in women. *Int J Antimicrob Agents* 2001; 17: 259–68.
3. Fihn SD. Acute uncomplicated urinary tract infection in women. *N Engl J Med* 2003; 349: 259–66.
4. Albert X, *et al.* Antibiotics for preventing recurrent urinary tract infection in non-pregnant women. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 20/05/10).
5. Milo G, *et al.* Duration of antibacterial treatment for uncomplicated urinary tract infection in women. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 07/08/08).
6. Katchman EA, *et al.* Three-day vs longer duration of antibiotic treatment for cystitis in women: systematic review and meta-analysis. *Am J Med* 2005; 118: 1196–207.
7. Nicolle L, *et al.* Uncomplicated urinary tract infection in women: current practice and the effect of antibiotic resistance on empiric treatment. *Can Fam Physician* 2006; 52: 612–8.
8. Falagas ME, *et al.* Probiotics for prevention of recurrent urinary tract infections in women: a review of the evidence from microbiological and clinical studies. *Drugs* 2006; 66: 1253–61.
9. Car J. Urinary tract infections in women: diagnosis and management in primary care. *BMJ* 2006; 332: 94–7.
10. Foster RT. Uncomplicated urinary tract infections in women. *Obstet Gynecol Clin North Am* 2008; 35: 235–48.
11. André M, Mölstad S. Nya riktlinjer för urinvägsinfektion hos kvinnor. *Lakartidningen* 2008; 105: 1107–9.
12. Perrotta C, *et al.* Oestrogens for preventing recurrent urinary tract infection in postmenopausal women. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 20/05/10).
13. Guay DRP. Contemporary management of uncomplicated urinary tract infections. *Drugs* 2008; 68: 1169–205.
14. Falagas ME, *et al.* Antibiotics versus placebo in the treatment of women with uncomplicated cystitis: a meta-analysis of randomized controlled trials. *J Infect* 2009; 58: 91–102.

Whipple's disease

Whipple's disease[1-3] (also known as intestinal lipodystrophy) is a rare, chronic, multisystem condition associated with infection with the Gram-positive bacillus *Tropheryma whipplei* (formerly *T. whippelii*). It most often affects the gastrointestinal system but other organs that may also be infected include the CNS, heart, joints, and eyes.

Whipple's disease mainly affects middle-aged white men and clinical signs and symptoms vary depending on the organ system affected. Symptoms include diarrhoea, steatorrhoea, abdominal pain, loss of appetite, weight loss, malabsorption, fever, and weakness. Arthritis, arthralgia, and myalgia often occur several years before gastrointestinal symptoms develop. About 10 to 40% of patients may also have neurological symptoms such as confusion, dementia, headache, memory impairment, or decreased level of consciousness.

Undiagnosed and untreated disease is progressive and fatal. However, appropriate long-term treatment with antibacterials results in rapid symptomatic improvement and lasting remission. Tetracycline was once considered the treatment of choice but relapse rates, especially CNS relapse, were high (up to 35%) and antibacterials that cross the blood-brain barrier are now generally recommended.[1-3] Induction treatment consists of a 2-week course of an

intravenous third-generation cephalosporin such as ceftriaxone, or a penicillin (either as intravenous benzylpenicillin or intramuscular procaine benzylpenicillin) with or without intramuscular streptomycin.[1-3] Intravenous meropenem has also been used successfully.[4] Patients allergic to ceftriaxone or penicillins may be treated with oral co-trimoxazole plus intramuscular streptomycin for 2 weeks.[3] The induction course is followed by long-term maintenance treatment with oral co-trimoxazole for 1 to 2 years.[1-3] An alternative oral maintenance regimen for those allergic to sulphonamides is doxycycline and hydroxychloroquine for more than 1 year.[3] Other alternative oral antibacterials that have been used for maintenance treatment are minocycline, tetracycline, phenoxymethylpenicillin,[1] or chloramphenicol. An exclusively oral treatment regimen of doxycycline and hydroxychloroquine for more than 1 year has been tried in some patients without CNS involvement; it has been suggested that in those with CNS involvement high dose sulfamethoxazole (which may be given as co-trimoxazole) or sulfadiazine should be added to the treatment regimen.[2,3]

Patients who relapse as a result of inadequate treatment may be re-treated with intravenous ceftriaxone or intravenous benzylpenicillin for 4 weeks, followed by an oral maintenance regimen for more than 1 year.[3] A patient with chronic Whipple's disease involving the CNS and refractory to antibacterial therapy was successfully treated with an induction course of ceftriaxone and chloramphenicol followed by long-term maintenance treatment with co-trimoxazole supplemented with interferon gamma.[5] Adjunctive treatment with interferon gamma has been suggested for patients who relapse despite appropriate treatment and who do not have inflammatory focal cerebral lesions.[3] Corticosteroids may be given to patients with cerebral lesions and to those with continued high fever after starting antibacterial treatment.[3]

1. Marth T, Raoult D. Whipple's disease. *Lancet* 2003; **361**: 239–46.
2. Fenollar F, *et al.* Whipple's disease. *N Engl J Med* 2007; **356**: 55–66.
3. Schneider T, *et al.* Whipple's disease: new aspects of pathogenesis and treatment. *Lancet Infect Dis* 2008; **8**: 179–90.
4. Feurle GE, *et al.* Efficacy of ceftriaxone or meropenem as initial therapies in Whipple's disease. *Gastroenterology* 2010; **138**: 478–86.
5. Schneider T, *et al.* Treatment of refractory Whipple disease with interferon-γ. *Ann Intern Med* 1998; **129**: 875–7.

Yaws

See Syphilis, p. 205.2.

Yersinia enteritis

See p. 186.2.

Acediasulfone Sodium *(rINN)*

Acediasulfona sódica; Acédiasulfone Sodique; Acediasulfonnatrium; Acediasulfonum Natricum; Asediasulfoninatrium; Sodium Diaphenylsulphonacetate; Ацедиасульфон Натрий.

N-p-Sulphanilylphenylglycine sodium.

$C_{14}H_{13}N_2NaO_4S$=328.3

CAS — 127-60-6.

UNII — M45G7BJL52.

Profile

Acediasulfone sodium is reported to have antibacterial properties and is an ingredient of preparations used topically in the treatment of local infections of the ear.

Amikacin *(BAN, rINN)*

Amicacina; Amikacina; Amikacinas; Amikacine; Amikacinum; Amikacyna; Amikasiini; Амикацин.

6-*O*-(3-Amino-3-deoxy-α-D-glucopyranosyl)-4-*O*-(6-amino-6-deoxy-α-D-glucopyranosyl)-*N*^{1}-[(2*S*)-4-amino-2-hydroxybutyryl]-2-deoxystreptamine.

$C_{22}H_{43}N_5O_{13}$=585.6

CAS — 37517-28-5.

ATC — D06AX12; J01GB06; S01AA21.

ATC Vet — QD06AX12; QJ01GB06; QS01AA21.

UNII — 84319SGC3C.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Amikacin). An antimicrobial substance obtained from kanamycin A. A white or almost white powder. Sparingly soluble in water; practically insoluble in alcohol and in acetone; slightly soluble in methyl alcohol. A 1% solution in water has a pH of 9.5 to 11.5.

USP 36: (Amikacin). A white crystalline powder. Sparingly soluble in water. pH of a 1% solution in water is between 9.5 and 11.5. Store in airtight containers.

Amikacin Sulfate *(BANM, USAN, rINNM)*

Amikacin Sulphate; Amikacina, sulfato de; Amikacin-disulfát; Amikacine, Sulfate d'; Amikacini Disulfas; Amikacini Sulfas; Amikacino sulfatas; Amikacinsulfat; Amikacin-szulfát; Amikacyny siarczan; Amikasiinisulfaatti; Amikasin Sülfat; BB-K8; Sulfato de amikacina; Амикацина Сульфат.

$C_{22}H_{43}N_5O_{13}.2H_2SO_4$=781.8

CAS — 39831-55-5.

ATC — D06AX12; J01GB06; S01AA21.

ATC Vet — QD06AX12; QJ01GB06; QS01AA21.

UNII — N6M33094FD.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 8: (Amikacin Sulfate). A white or almost white powder. It loses not more than 13.0% of its weight on drying. Freely soluble in water; practically insoluble in alcohol and in acetone. The pH of a 1% solution in water is between 2.0 and 4.0. Store in airtight containers.

USP 36: (Amikacin Sulfate). Amikacin sulfate, having a molar ratio of amikacin to H_2SO_4 of 1:2 contains the equivalent of not less than 674 micrograms and not more than 786 micrograms of amikacin per mg, calculated on the dried basis. Amikacin sulfate having a molar ratio of amikacin to H_2SO_4 of 1:1.8 contains the equivalent of not less than 691 micrograms and not more than 806 micrograms of amikacin per mg, calculated on the dried basis.

A white crystalline powder. Freely soluble in water. pH of a 1% solution in water is between 2.0 and 4.0 (1:2 salt) and 6.0 to 7.3 (1:1.8 salt). Store in airtight containers.

Incompatibility. For discussion of the incompatibility of aminoglycosides, including amikacin, with beta lactams, see under Gentamicin Sulfate, p. 306.3. Amikacin is also reported to be incompatible with various other drugs. However, reports are contradictory in many cases, and other factors, such as the strength and composition of the vehicles used, may play a role.

Stability. Solutions may darken from colourless to pale yellow but this does not indicate a loss of potency.

Uses and Administration

Amikacin is a semisynthetic aminoglycoside antibacterial derived from kanamycin and is used similarly to gentamicin (p. 306.3) in the treatment of severe Gram-negative and other infections. It is given as the sulfate, and is generally reserved for the treatment of severe infections caused by susceptible bacteria that are resistant to gentamicin and tobramycin. Amikacin has also been given with antimycobacterials in the treatment of nontuberculous mycobacterial infections (p. 194.1) and multidrug-resistant tuberculosis (p. 210.2). As with gentamicin, amikacin may be used with penicillins and with cephalosporins; the injections should be given at separate sites.

Doses of amikacin sulfate are expressed in terms of amikacin base; 1.3 g of amikacin sulfate is equivalent to about 1 g of amikacin. Adults may be given 15 mg/kg daily in equally divided doses every 8 or 12 hours by intramuscular injection. In life-threatening infections, the dose may be increased up to a maximum of 500 mg every 8 hours. A dose of 7.5 mg/kg daily in two divided doses (equivalent to 250 mg twice daily) may be given for the treatment of uncomplicated urinary-tract infections. The same doses may be given by slow intravenous injection over 2 to 3 minutes, or by intravenous infusion.

For details of doses in children, see p. 216.3.

Treatment should preferably not continue for longer than 7 to 10 days, and the total dose given to adults should not exceed 15 g. Peak plasma concentrations greater than 30 to 35 micrograms/mL or trough plasma concentrations greater than 5 to 10 micrograms/mL should be avoided. Dosage should be adjusted in all patients according to plasma-amikacin concentrations, and this is particularly important where factors such as age, renal impairment, or prolonged therapy may predispose to toxicity, or where there is a risk of subtherapeutic concentrations. For discussion of the methods of calculating aminoglycoside dosage requirements, see Administration and Dosage, under Gentamicin, p. 307.2. See also Administration, p. 216.2. As with some other aminoglycosides, once-daily and extended-interval dose regimens have been used successfully with amikacin without increasing toxicity, but local guidelines should be consulted (see also Once-daily and Extended-interval Dose Regimens, p. 307.2).

A 0.25% solution has been instilled into body cavities in adults.

An inhaled liposomal formulation of amikacin is under investigation for the management of chronic lung infections such as nontuberculous mycobacteria and those caused by *Pseudomonas*.

Administration. It has been suggested that in patients with severe sepsis or septic shock, in whom the volume of distribution may be markedly increased, an initial intravenous loading dose of amikacin 25 mg/kg total body weight should be given, since standard doses of 15 mg/kg may not achieve therapeutic peak concentrations; however, evidence from a prospective open study in ICU patients[1] suggested that even with the higher dose, serum concentrations of amikacin were too low in about one-third of the patients. Subsequent doses should be determined on the basis of therapeutic drug monitoring.

1. Taccone FS, *et al.* Revisiting the loading dose of amikacin for patients with severe sepsis and septic shock. *Crit Care* 2010; **14**: R53.

Administration in children. Amikacin is licensed for use in neonates, infants, and children and may be given by intramuscular or intravenous injection or by intravenous infusion. For *severe infections caused by susceptible* bacteria in children beyond the newborn period, the American Academy of Pediatrics (AAP)[1] suggests an intravenous or intramuscular dose of amikacin of 15 to 22.5 mg/kg daily, in 3 divided doses.

For the treatment of *serious Gram-negative infections resistant to gentamicin* in infants and children the *BNFC* suggests:

- **a multiple daily dose regimen** of amikacin by slow intravenous injection over at least 3 to 5 minutes
  - in those 1 month to 12 years of age: 7.5 mg/kg every 12 hours
  - children 12 years of age and older: 7.5 mg/kg every 12 hours; in severe infections the dose may be increased to 7.5 mg/kg every 8 hours to a maximum dose of 500 mg every 8 hours for up to 10 days, *or*
- **a once-daily dose regimen** (other than for endocarditis or meningitis) given by intravenous injection or infusion of 15 mg/kg adjusted according to serum-amikacin concentration in those from 1 month of age

In the management of pseudomonal lung infection in *cystic fibrosis* the *BNFC* suggests a multiple daily dose regimen of amikacin given by slow intravenous injection or infusion, of 10 mg/kg every 8 hours (to a maximum dose of 500 mg every 8 hours) in those from 1 month of age.

For *neonatal sepsis* the *BNFC* suggests:

- **an extended-interval dose regimen** of 15 mg/kg every 24 hours by slow intravenous injection or intravenous infusion, *or*
- **a multiple daily dose regimen** of 10 mg/kg as a loading dose, followed by 7.5 mg/kg every 12 hours by intramuscular or slow intravenous injection or by infusion

An alternative regimen based on the age and birth-weight of the neonate is suggested by the AAP:[1] doses may be given by intramuscular or intravenous injection:

- for neonates aged ⩽7 days and weighing ⩽2 kg: 15 mg/kg every 48 hours
- for neonates aged ⩽7 days and weighing >2 kg: 15 mg/kg every 24 hours
- for neonates aged 8 to 28 days and weighing ⩽2 kg: 15 mg/kg every 24 to 48 hours; a dosing interval of 48 hours may be used until 2 weeks of life in extremely low birth-weight neonates (those weighing less than 1 kg)
- for neonates aged 8 to 28 days and weighing >2 kg: 15 mg/kg every 12 to 24 hours

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Adverse Effects, Treatment, and Precautions

As for Gentamicin Sulfate, p. 308.2. Peak plasma concentrations of amikacin greater than 30 to 35 micrograms/mL or trough concentrations greater than 5 to 10 micrograms/mL should be avoided. Comparisons with equipotent doses found that amikacin affects auditory (cochlear) function to about the same extent as gentamicin.

Effects on the eyes. A report of retinal damage after intravitreal injection of amikacin.[1]

1. Jackson TL, Williamson TH. Amikacin retinal toxicity. *Br J Ophthalmol* 1999; **83**: 1199–1200.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies amikacin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

As for Gentamicin Sulfate, p. 309.2.

Antimicrobial Action

As for Gentamicin Sulfate, p. 309.2. Amikacin is active against a similar range of organisms although it is also reported to have some activity against *Nocardia asteroides*, *Mycobacterium tuberculosis*, and some atypical mycobacterial

strains. Amikacin is not degraded by many of the common enzymes often responsible for acquired aminoglycoside resistance. In consequence, cross-resistance with gentamicin and other aminoglycosides is infrequent and amikacin may be effective against strains resistant to other aminoglycosides. However, resistant strains of Gram-negative bacteria and staphylococci have been reported, and it is generally reserved for infections resistant to other aminoglycosides, although reports differ as to the extent and speed of the development of amikacin resistance where it has been widely used.

References.
1. Ho YH, *et al.* In-vitro activities of aminoglycoside-aminocyclitols against mycobacteria. *J Antimicrob Chemother* 1997; 40: 27–32.

Pharmacokinetics

As for Gentamicin Sulfate, p. 309.3.

On intramuscular injection, peak plasma-amikacin concentrations of about 20 micrograms/mL occur 1 hour after a 500-mg dose, reducing to about 2 micrograms/mL 10 hours after injection. A plasma concentration of 38 micrograms/mL has been reported after the intravenous infusion of 500 mg over 30 minutes, reducing to 18 micrograms/mL 1 hour later. Amikacin has been detected in body tissues and fluids after injection; it crosses the placenta but does not readily penetrate into the CSF, although substantial penetration of the blood-brain barrier has been reported in children with meningitis.

A plasma half-life of about 2 to 3 hours has been reported in patients with normal renal function. Most of a dose is excreted by glomerular filtration in the urine within 24 hours.

References.
1. Vanhaeverbeek M, *et al.* Pharmacokinetics of once-daily amikacin in elderly patients. *J Antimicrob Chemother* 1993; 31: 185–7.
2. Gaillard J-L, *et al.* Cerebrospinal fluid penetration of amikacin in children with community-acquired bacterial meningitis. *Antimicrob Agents Chemother* 1995; 39: 253–5.
3. Bressolle F, *et al.* Population pharmacokinetics of amikacin in critically ill patients. *Antimicrob Agents Chemother* 1996; 40: 1682–9.
4. Canis F, *et al.* Pharmacokinetics and bronchial diffusion of single daily dose amikacin in cystic fibrosis patients. *J Antimicrob Chemother* 1997; 39: 431–3.
5. Tod M, *et al.* Population pharmacokinetic study of amikacin administered once or twice daily to febrile, severely neutropenic adults. *Antimicrob Agents Chemother* 1998; 42: 849–56.
6. Tréluyer JM, *et al.* Nonparametric population pharmacokinetic analysis of amikacin in neonates, infants, and children. *Antimicrob Agents Chemother* 2002; 46: 1381–7.
7. Okusanya OO, *et al.* Pharmacokinetic and pharmacodynamic evaluation of liposomal amikacin for inhalation in cystic fibrosis patients with chronic pseudomonal infection. *Antimicrob Agents Chemother* 2009; 53: 3847–54.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Biklin†; Greini; Riklinak; *Austral.*: Amikin†; *Austria*: Biklin; *Belg.*: Amukin; *Braz.*: Amicilon; Klebicil; Novamin; *China*: Mi Li Xian (米丽先); Mi Ying Jie (米英杰); *Cz.*: Amikin; *Fin.*: Biklin; *Fr.*: Amiklin†; *Ger.*: Biklin†; *Gr.*: Amicagel; Amicasil; Amikan; Biorisan; Briklin; Brucelin; Cinegel; Consumonit; Durocin; Farcyclin; Flexelite; Fromentyl; Kancin-Gap; Lanomycin; Lifermycin; Likacin; Medilen; Micalpha; Orlobin; Remikin; Roveridin; Selaxa; Uzix; Xylanal; *Hong Kong*: Amikin; *Hung.*: Amikin†; Likacin; *India*: Acil; Afcin; Alkanit; Alnamik; Amcin; Amexel; Amiact; Amibiotic Amic; Amicaba; Amicin; Amicip; Amicom; Amijet; Amikable; Amikas; Amikater; Amikavel; Amikcin; Amikef; Amikin; Amilab; Amimac; Amimax; Aminocin; Amiron; Amistar; Amister; Amisulf; Amitax; Amivir; Amiz; Amiza; AMK; Amoka; Amricin; Amtop; Amzo; Anamika; Antinag; Arimic; Atmika; Avikacin; Avmik; Axcin; Bekacin; Blocin; Cadicin; Cinamica; Cinas; Coskacin; Curesin; D-Cin; Elcin; Elmik; Emcin; Emica; Emka; Endocin; Erkacin; Erocin; Erymik; Estacin; Eumik; Fokin; Fymika; Gabacin; Gekacin; Gemka; Glomika; Glykacin; Hosik; Icin; Ideg; Ikacin; Ikka; Inkacin; Ivimicin; Jyomik; Kacina; Kam; Kamsa; Kasino; Kawacin; Lemicin; Lexcin; Litomik; Lupamik; M-Cinn; Malaracin; MBKacin; Medcin; Megamica; Mepcin; Mica; Micare; Micin; Mikabit; Mikacin; Mikafine; Mikaject; Mikaphar; Mikastar; Mikatax; Miker; Mikif; Mikka; Mini; Mishacin; MKCN; Narish; NBCin; Nicin; Niksin; Nimicin; Nimika; Niskacin; Nosomik; Orkacin; Osin; *Indon.*: Alostil; Amikin†; Glybotic; Mikasin; *Irl.*: Amikin; *Ital.*: Amicasil; Amik†; Amikan; BB-K8†; Chemacin; Dramigel; Likacin; Lukadin; Mediamik; Migracin; Mikan; Mikavir†; Nekacin; *Malaysia*: Apalin; *Mex.*: Agnicin; Akacin; Amicina; Amikafur; Amikalem†; Amikasons; Amikavl; Amikayect; Amikin; Amiyec; AMK; Beramikin; Biclin; Biokacin; Gamikal; Kafran†; Kana; Karmikin; Libamic; Lisobac; Mikazul†; Oprad; Plokim†; Sermicina; Tetralin; Yectamid†; *NZ*: Amikin†; *Philipp.*: Amikacide; Amikin†; Amitax; Cidacid; Cinmik; Kamin; Kormakin; Mikasul; Nica; Panmikin; *Pol.*: Amikin; Biodacyna; *Port.*: Amic; Biclin†; Kamina; *Rus.*: Amikozit (Амикозит)†; Chemacin (Хемацин); Selemycin (Селемицин); *S.Afr.*: Amikin; Kacinth-A†; *Spain*: Biclin†; *Swed.*: Biklin; *Switz.*: Amikin; *Thal.*: Akacin; Akicin; Amikin†; Anbikin†; Siamik; Tipkin; Tybikin; *Turk.*: Amijeksin; Amiketem†; Amiklin; Amikozit; Mikasin†; *UAE*: Mikacin; *UK*: Amikin; *Ukr.*: Amicil (Амицил); *USA*: Amikin†; *Venez.*: Amikavax; Behkacin; Biklin; Likacin.

Multi-ingredient Preparations. *India*: Mikapime; Nicpime-AM; *Ukr.*: Inflarax (Инфларакс).

Pharmacopoeial Preparations
BP 2014: Amikacin Injection;
USP 36: Amikacin Sulfate Injection.

Aminosalicylic Acid

Acidum Aminosalicylicum; Aminosalicílico, ácido; 4-Aminosalicylic Acid; Aminosalicylsyra; Aminosalisyylihappo; Aminosalylum; Para-aminosalicylic Acid; PAS; Pasalicylum; Аминосалициловая Кислота.

4-Amino-2-hydroxybenzoic acid.

$C_7H_7NO_3$=153.1

CAS — 65-49-6.

ATC — J04AA01.

ATC Vet — QJ04AA01.

UNII — 5B2658E0N2.

NOTE. Distinguish from 5-aminosalicylic acid (Mesalazine, p. 1862.2).

Pharmacopoeias. In *US.*

USP 36: (Aminosalicylic Acid). A white or practically white, bulky powder that darkens on exposure to light and air; it is odourless or has a slight acetous odour. Slightly soluble in water and in ether; soluble in alcohol; practically insoluble in benzene. Under no circumstances should a solution be used if its colour is darker than that of a freshly prepared solution. pH of a saturated solution in water is between 3.0 to 3.7. Store in airtight containers at a temperature not exceeding 30 degrees. Protect from light.

Calcium Aminosalicylate

Aminosalicilato cálcico; Aminosalicylate calcium; Aminosalylcalcium; Aminosalylkalcium; Aminosalyylikalsium; Calcii Aminosalicylas; Calcii Para-aminosalicylas; Calcium Para-aminosalicylate; Calcium PAS; Kalciumaminosalicylat; Kalsiumaminosalisylaatti; Аминосалицилат Кальция.

Calcium 4-amino-2-hydroxybenzoate trihydrate.

$(C_7H_6NO_3)_2Ca,3H_2O$=398.4

CAS — 133-15-3 (anhydrous calcium aminosalicylate).

ATC — J04AA03.

ATC Vet — QJ04AA03.

UNII — 9VF16M7FWU.

Pharmacopoeias. *Jpn* includes the heptahydrate.

Sodium Aminosalicylate

Aminosalicilato sódico; Aminosalicylan sodný dihydrát; Aminosalicylate Sodium; Aminosalylnatrium; Monosódium 4-Aminosalicylate Dihydrate; Natrii Aminosalicylas; Natrii Aminosalicylas Dihydricus; Natrii Para-aminosalicylas; Natrii Paraaminosalicylas; Natrio aminosalicilatas dihidratas; Natriumaminosalicylat; Natriumaminosalicylatdihydrat; Natriumaminosalisylaatti; Natriumaminosalisylaattidihydraatti; Pasalicylum Solubile; Sodium (aminosalicylate de) dihydraté; Sodium Para-aminosalicylate; Sodium PAS; Sodu aminosalicylan; Аминосалицилат Натрия.

Sodium 4-amino-2-hydroxybenzoate dihydrate.

$C_7H_6NNaO_3,2H_2O$=211.1

CAS — 133-10-8 (anhydrous sodium aminosalicylate); 6018-19-5 (sodium aminosalicylate dihydrate).

ATC — J04AA02.

ATC Vet — QJ04AA02.

UNII — S38B9W6AXW.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Sodium Aminosalicylate Dihydrate). A slightly hygroscopic, white or almost white, crystalline powder, or white or almost white crystals. Freely soluble in water; sparingly soluble in alcohol, practically insoluble in dichloromethane. A 2% solution in water has a pH of 6.5 to 8.5. Store in airtight containers. Protect from light.

USP 36: (Aminosalicylate Sodium). A white to cream-coloured, practically odourless crystalline powder. Soluble 1 in 2 of water; sparingly soluble in alcohol; very slightly soluble in chloroform and in ether. Its solutions decompose slowly and darken in colour. Prepare solutions within 24 hours of use. Under no circumstances should a solution be used if its colour is darker than that of a freshly prepared solution. pH of a 2% solution in water is between 6.5 and 8.5. Store in airtight containers at a temperature not exceeding 40 degrees. Protect from light.

Stability. Aqueous solutions of aminosalicylates are unstable and should be freshly prepared.

Solutions of sodium aminosalicylate in sorbitol or syrup degraded more quickly to *m*-aminophenol than those in glycerol or propylene glycol.[1] Colour developed in all solutions but was not found to be an accurate indicator of decomposition of sodium aminosalicylate as it reflected only oxidation of *m*-aminophenol.

1. Blake ML *et al.* Effect of vehicle on the stability of sodium aminosalicylate in liquid dosage forms. *Am J Hosp Pharm* 1973; 30: 441–3.

Uses and Administration

Aminosalicylic acid and its salts are second-line antimycobacterials given orally in the treatment of multidrug-resistant **tuberculosis** (p. 210.2). They should always be given with other antituberculous drugs.

Aminosalicylic acid may be given as the acid or as the sodium salt. Sodium aminosalicylate 1.38 g is equivalent to about 1 g of aminosalicylic acid. However, a usual daily oral dose of 8 to 12 g in 2 or 3 divided doses has been recommended both for products containing the acid and those containing the sodium salt.

For details of doses in children, see p. 217.3.

Like 5-aminosalicylic acid (see Mesalazine, p. 1862.2), sodium aminosalicylate is also used in the treatment of **ulcerative colitis** (see Inflammatory Bowel Disease, p. 217.3). It is given rectally in a usual dose of 2 g once daily.

Attempts have been made in formulation to overcome the bulk and exceedingly unpleasant taste of the aminosalicylates. The salts appear to be better tolerated than the free acid and solutions in iced water prepared immediately before use may be less unpleasant to take.

References.
1. Anonymous. Para-aminosalicylic acid. *Tuberculosis (Edinb)* 2008; 88: 137–8.

Administration. A small study suggested that giving aminosalicylic acid in a dose of 4 g twice daily produced adequate serum concentrations (well in excess of 1 microgram/mL, a typical MIC against *Mycobacterium tuberculosis*) for up to 12 hours after each dose.[1] The drug was taken with an acidic beverage such as fruit juice to prevent early release in the stomach. A single 4-g dose was not sufficient to maintain serum concentrations for the full 24-hour dosage interval. The authors had subsequently changed their practice to use a twice-daily regimen for aminosalicylic acid in patients with multidrug-resistant tuberculosis.

1. Peloquin CA, *et al.* Once-daily and twice-daily dosing of p-aminosalicylic acid granules. *Am J Respir Crit Care Med* 1999; 159: 932–4.

Administration in children. For the treatment of drug-resistant tuberculosis in infants, children, and adolescents the American Academy of Pediatrics[1] and WHO[2] suggest an oral dose of para-aminosalicylic acid 200 to 300 mg/kg daily, given in 2 to 4 divided doses, to a maximum dose of 10 g daily.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases.* 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.
2. WHO. *Guidelines for the programmatic management of drug-resistant tuberculosis: emergency update 2008.* Geneva: WHO, 2008. Available at: http://whqlibdoc.who.int/publications/2008/9789241547581_eng.pdf (accessed 08/06/10)

Administration in renal impairment. It has been recommended that aminosalicylic acid should be avoided in patients with renal impairment.[1] An increase in plasma clearance of aminosalicylic acid (attributed to increased hepatic metabolism) has been noted in patients with renal impairment, hence attempting to give aminosalicylate in reduced doses to such patients may lead to subtherapeutic serum concentrations.[2]

1. Appel GB, Neu HC. The nephrotoxicity of antimicrobial agents (first of three parts). *N Engl J Med* 1977; 296: 663–70.
2. Holdiness MR. Clinical pharmacokinetics of the antituberculosis drugs. *Clin Pharmacokinet* 1984; 9: 511–44.

Inflammatory bowel disease. Derivatives of 5-aminosalicylic acid and corticosteroids are the mainstays of the treatment of inflammatory bowel disease (p. 1811.3). However, aminosalicylic acid (4-aminosalicylic acid) has also been investigated, and beneficial results have been reported with both enemas[1-4] and oral dose forms[5] in ulcerative colitis. Three patients who developed acute pancreatitis while taking mesalazine (5-aminosalicylic acid) for inflammatory bowel disease, later tolerated treatment with 4-aminosalicylic acid enemas.[6]

1. Campieri M, *et al.* 4-Aminosalicylic acid (4-ASA) and 5-aminosalicylic acid (5-ASA) in topical treatment of ulcerative colitis patients. *Gastroenterology* 1984; 86: 1039.
2. Ginsberg AL, *et al.* Treatment of left-sided ulcerative colitis with 4-aminosalicylic acid enemas: a double-blind, placebo-controlled trial. *Ann Intern Med* 1988; 108: 195–9.
3. Sharma MP, Duphare HV. 4-Aminosalicylic acid enemas for ulcerative colitis. *Lancet* 1989; i: 450.
4. O'Donnell LJD, *et al.* Double blind, controlled trial of 4-aminosalicylic acid and prednisolone enemas in distal ulcerative colitis. *Gut* 1992; 33: 947–9.
5. Beeken W, *et al.* Controlled trial of 4-ASA in ulcerative colitis. *Dig Dis Sci* 1997; 42: 354–8.
6. Daniel F, *et al.* Tolerance of 4-aminosalicylic acid enemas in patients with inflammatory bowel disease and 5-aminosalicylic-induced acute pancreatitis. *Inflamm Bowel Dis* 2004; 10: 258–60.

Manganese toxicity. Intravenous aminosalicylic acid, given as the sodium salt in a course of 6 g daily for 4 days a week, for fifteen courses, produced significant benefit in a patient with parkinsonism induced by chronic occupational manganese exposure.[1] The patient remained well on prolonged follow-up. Other cases of benefit had been reported in the Chinese literature.

1. Jiang Y-M, *et al.* Effective treatment of manganese-induced occupational Parkinsonism with p-aminosalicylic acid: a case of 17-year follow-up study. *J Occup Environ Med* 2006; 48: 644–9.

Adverse Effects and Treatment

Aminosalicylic acid and its salts may cause the adverse effects of salicylates (see Aspirin, p. 24.2).

Gastrointestinal effects are common and include nausea, vomiting, and diarrhoea; they may be reduced by giving doses with food or with an antacid but occasionally may be severe enough that therapy has to be stopped. Alteration of gastrointestinal function may lead to malabsorption of vitamin B_{12}, folate, and lipids.

Hypersensitivity reactions have been reported in 5 to 10% of adults, usually during the first few weeks of treatment, and include fever, and rashes; arthralgia, lymphadenopathy, and hepatosplenomegaly are less common and a syndrome resembling infectious mononucleosis occurs rarely. Other adverse effects which have been attributed to a hypersensitivity reaction to aminosalicylate include jaundice and encephalitis. Blood disorders reported include haemolytic anaemia in patients with G6PD deficiency, agranulocytosis, eosinophilia, leucopenia, and thrombocytopenia. Psychosis may occasionally occur. Prolonged treatment may induce goitre and hypothyroidism. Crystalluria may occur.

Effects on the liver. Drug-induced hepatitis occurred in 0.32% of 7492 patients receiving antituberculous drugs; aminosalicylic acid was the most common cause.[1]

1. Rossouw JE, Saunders SJ. Hepatic complications of antituberculous therapy. *Q J Med* 1975; 44: 1–16.

Precautions

Aminosalicylic acid and its salts should be used with great care in patients with hepatic or renal impairment and in patients with gastric ulcer. They should be given with caution to patients with G6PD deficiency. The sodium salt should be used with caution in patients with heart failure.

Aminosalicylates interfere with tests for glycosuria using copper reagents and for urobilinogen using Ehrlich's reagent.

Breast feeding. Small amounts of aminosalicylic acid are present in breast milk. A maximum concentration of 1.1 microgram/mL has been reported in the breast milk of a woman 3 hours after a 4-g dose of aminosalicylic acid.[1]

1. Holdiness MR. Antituberculosis drugs and breast feeding. *Arch Intern Med* 1984; 144: 1888.

Pregnancy. The use of aminosalicylic acid or its salts is not recommended in pregnant patients due to gastrointestinal intolerance.[1] In addition it has been noted that a study published in 1964 suggested first-trimester exposure might be associated with congenital defects, although other studies had not found similar effects.[2]

1. Snider D. Pregnancy and tuberculosis. *Chest* 1984; 86: 10S–13S.
2. *et al. Drugs in pregnancy and lactation,* 8th ed. Philadelphia, USA: Lippincott Williams and Wilkins, 2008.

Interactions

The adverse effects of aminosalicylates and salicylates may be additive. Probenecid may also increase toxicity by delaying renal excretion and enhancing plasma concentrations of aminosalicylate. The activity of aminosalicylic acid may be antagonised by ester-type local anaesthetics such as procaine.

Antimicrobial Action

Aminosalicylic acid is bacteriostatic and is active against *M. tuberculosis*. Other mycobacteria are usually resistant. It has a relatively weak action compared with other antituberculous drugs. Resistance develops quickly if aminosalicylic acid is used alone.

References.

1. Rengarajan J, *et al.* The folate pathway is a target for resistance to the drug para-aminosalicylic acid (PAS) in mycobacteria. *Mol Microbiol* 2004; 53: 275–82.

Pharmacokinetics

When given orally, aminosalicylic acid and its salts are readily absorbed, and peak plasma concentrations occur after about 1 to 4 hours.

Aminosalicylate diffuses widely through body tissues and fluids, although diffusion into the CSF occurs only if the meninges are inflamed. About 15% of the sodium salt, and 50 to 70% of the acid, is bound to plasma proteins.

Aminosalicylate is metabolised in the intestine and liver mainly by acetylation. Urinary excretion is rapid, and 80% or more of a dose is excreted within 24 hours; 50% or more of the dose is excreted as the acetylated metabolite. The half-life of aminosalicylic acid is about 1 hour.

Aminosalicylate is distributed into breast milk (see under Precautions, above, for more details).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Chile*: Aflogol; *Fr.*: Paser; Quadrasa; *Ger.*: Pas-Fatol N; *Gr.*: Paser; *India*: Monopas; *Ital.*: Salf-Pas; *Port.*: Paramino-Corazida; *Rus.*: Aquapask (Аквапаск); Mac-Pas (Мак-Пас); Monopas (Монопас); Pas-Fatol N (Пас-Фатол Н); Pasconat (Пасконат); Paser (Пазер); Pask (ПАСК); Pask-Akri (Паск-Акри); *Thai.*: PAS Sodium; *Turk.*: PAS; *Ukr.*: Pasconat (Пасконат); *USA*: Paser.

Multi-ingredient Preparations. *India*: Inapas; Mycospas; *Rus.*: Isopask (Изопаск); Mac-Pas Plus (Мак-Пас Плюс).

Pharmacopoeial Preparations

USP 36: Aminosalicylate Sodium Tablets; Aminosalicylic Acid Tablets.

Amoxicillin *(BAN, rINN)*

Amoksisilin; Amoksisilliini; Amoxicilina; Amoxicilline; Amoxicillinum; Amoxycillin; Амоксициллин.

(6*R*)-6-[α-D-(4-Hydroxyphenyl)glycylamino]penicillanic acid.

$C_{16}H_{19}N_3O_5S$=365.4

CAS — 26787-78-0.

ATC — J01CA04.

ATC Vet — QG51AX01; QJ01CA04.

UNII — 9EM05410Q9.

Amoxicillin Sodium *(BANM, USAN, rINNM)*

Amoksicilino natrio druska; Amoksisilin Sodyum; Amoksisilliininatrium; Amoksycylina sodowa; Amoxicilin sodná sůl; Amoxicilina sódica; Amoxicillin-Natrium; Amoxicilline Sodique; Amoxicillinnatrium; Amoxicillin-nátrium; Amoxicillinum natricum; Amoxycillin Sodium; BRL-2333AB-B; Natrii Amoxicillinum; Натрий Амоксициллин.

$C_{16}H_{18}N_3NaO_5S$=387.4

CAS — 34642-77-8.

ATC — J01CA04.

ATC Vet — QJ01CA04.

UNII — 544Y3D6MYH.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Ph. Eur. 8: (Amoxicillin Sodium). A white or almost white, very hygroscopic powder. Very soluble in water; sparingly soluble in dehydrated alcohol; very slightly soluble in acetone. A 10% solution in water has a pH of 8.0 to 10.0. Store in airtight containers.

Amoxicillin Trihydrate *(BANM, rINNM)*

Amoksicilinas trihidratas; Amoksisilin Trihidrat; Amoksisilliinitrihydraatti; Amoksycylina trójwodna; Amoxicilin trihydrát; Amoxicilina trihidrato; Amoxicillin (USAN); Amoxicillin-Trihydrat; Amoxicilline Trihydratée; Amoxicillin-trihidrát; Amoxicillintrihydrat; Amoxicillinum Trihydricum; Amoxycillin Trihydrate; BRL-2333; Амоксициллин Тригидрат.

$C_{16}H_{19}N_3O_5S,3H_2O$=419.4

CAS — 61336-70-7.

ATC — J01CA04.

ATC Vet — QJ01CA04.

UNII — 804826J2HU.

NOTE. Compounded preparations of amoxicillin may be represented by the following names:

- Co-amoxiclav *x/y* (*BAN*)—amoxicillin (as the trihydrate or the sodium salt) and potassium clavulanate; *x* and *y* are the strengths in milligrams of amoxicillin and clavulanic acid respectively
- Co-amoxiclav (*PEN*)—amoxicillin trihydrate and potassium clavulanate.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Amoxicillin Trihydrate). A white or almost white, crystalline powder. Slightly soluble in water; very slightly soluble in alcohol; practically insoluble in fatty oils. It dissolves in dilute acids and in dilute solutions of alkali hydroxides. A 0.2% solution in water has a pH of 3.5 to 5.5. Store in airtight containers.

USP 36: (Amoxicillin). A white, practically odourless crystalline powder. Slightly soluble in water and in methyl alcohol; insoluble in carbon tetrachloride, in chloroform, and in benzene. pH of a 0.2% solution in water is between 3.5 and 6.0. Store in airtight containers.

Uses and Administration

Amoxicillin is the 4-hydroxy analogue of ampicillin (p. 220.3) and is used similarly in susceptible infections. These include actinomycosis, anthrax, biliary-tract infections, bronchitis, endocarditis (particularly for prophylaxis), gastro-enteritis (including salmonella enteritis, but not shigellosis), gonorrhoea, Lyme disease, mouth infections, otitis media, pneumonia, spleen disorders (pneumococcal infection prophylaxis), typhoid and paratyphoid fever, and urinary-tract infections. The beta-lactamase inhibitor clavulanic acid (p. 270.3) widens amoxicillin's antimicrobial spectrum and a combined preparation (co-amoxiclav) can be used when resistance to amoxicillin is prevalent, for example in respiratory-tract infections due to *Haemophilus influenzae* or *Moraxella catarrhalis* (*Branhamella catarrhalis*), in the empirical treatment of animal bites, or in melioidosis. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Amoxicillin is also given as part of treatment regimens to eradicate *Helicobacter pylori* infection in patients with peptic ulcer disease (p. 1816.2).

Amoxicillin is given orally as the trihydrate and by injection as the sodium salt. Doses are expressed in terms of the equivalent amount of amoxicillin; 1.06 g of amoxicillin sodium and 1.15 g of amoxicillin trihydrate are each equivalent to about 1 g of amoxicillin.

The usual *oral* dose is 250 to 500 mg every 8 hours, or 500 to 875 mg every 12 hours. Higher oral doses of amoxicillin, either as a single dose or in short courses, are used in some conditions. For example, a dose of 3 g repeated once after 8 hours may be used for dental abscesses. A 3-g dose may be given for uncomplicated acute urinary-tract infections, and repeated once after 10 to 12 hours.

A high-dose regimen of 3 g twice daily may be used in patients with severe or recurrent infections of the respiratory tract. Amoxicillin has also been given as a single dose of 3 g, with probenecid 1 g, in the treatment of uncomplicated gonorrhoea in areas where gonococci remain sensitive.

For the prophylaxis of endocarditis in patients at risk, amoxicillin 2 or 3 g may be given about 1 hour before dental procedures. However, in the UK, NICE suggests that such prophylaxis is unnecessary (see p. 179.2).

For the eradication of *H. pylori*, amoxicillin is given with either metronidazole or clarithromycin and a proton pump inhibitor; usual doses of amoxicillin are 0.75 or 1 g twice daily or 500 mg three times daily.

An extended-release formulation containing 775 mg of amoxicillin as the trihydrate is available in the USA for the treatment of tonsillitis and pharyngitis due to *Streptococcus pyogenes* in patients aged 12 years or older. It is given orally in a dose of 775 mg daily for 10 days.

Amoxicillin is given by *intramuscular* or slow *intravenous* injection in doses of 500 mg every 8 hours. In severe infections, 1 g of amoxicillin may be given every 6 hours by slow intravenous injection over 3 to 4 minutes or by infusion over 30 to 60 minutes.

For details of doses in children, see p. 218.3.

Doses may need to be reduced in moderate to severe renal impairment (see p. 219.1).

Amoxicillin with clavulanic acid. Amoxicillin combined with clavulanic acid (co-amoxiclav) is given orally in a ratio of amoxicillin (as the trihydrate) 2, 4, 7, or 14 parts to 1 part of clavulanic acid (as the potassium salt), or intravenously in a ratio of 5 parts of amoxicillin (as the sodium salt) to 1 part of clavulanic acid (as the potassium salt). Doses of the combination, calculated on amoxicillin content, are similar to those for amoxicillin used alone.

References.

1. Speller DCE, *et al.*, eds. Clavulanate/β-lactam antibiotics: further experience. *J Antimicrob Chemother* 1989; 24 (suppl B): 1–226.
2. Todd PA, Benfield P. Amoxicillin/clavulanic acid: an update of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1990; 39: 264–307.
3. Malik ZA, Litman N. Ampicillin and amoxicillin. *Pediatr Rev* 2006; 27: 434–6.
4. Geddes AM, *et al.* Introduction: historical perspective and development of amoxicillin/clavulanate. *Int J Antimicrob Agents* 2007; 30 (suppl 2): S109–S112.
5. Ball P. The clinical development and launch of amoxicillin/clavulanate for the treatment of a range of community-acquired infections. *Int J Antimicrob Agents* 2007; 30 (suppl 2): S113–S117.
6. Thanaviratananich S, *et al.* Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media. Available in The Cochrane Database of Systematic Reviews: Issue 4. Chichester: John Wiley; 2008 (accessed 06/08/09).
7. Salvo F, *et al.* Amoxicillin and amoxicillin plus clavulanate: a safety review. *Expert Opin Drug Safety* 2009; 8: 111–8.

Administration in children. Amoxicillin may be given to neonates and children for the treatment of infections caused by susceptible organisms. It may be given orally, by intramuscular injection, by slow intravenous injection over 3 to 4 minutes, or by intermittent intravenous infusion over 30 to 60 minutes.

For the treatment of susceptible infections including urinary-tract infections, sinusitis, uncomplicated community-acquired pneumonia, oral infections, Lyme disease, and salmonellosis, the *BNFC* suggests the following *oral* doses for neonates and children; these may be doubled in severe or serious infections:

- 7 to 28 days of age: 30 mg/kg (to a maximum of 62.5 mg) 3 times daily
- 1 month to 1 year of age: 62.5 mg 3 times daily
- 1 to 5 years of age: 125 mg 3 times daily
- from 5 years of age: 250 mg 3 times daily The *BNFC* also recommends the following *intravenous* dose ranges for neonates and children which may be doubled in severe or serious infections:
- neonates: 30 mg/kg, given every 12 hours for neonates less than 7 days of age and every 8 hours for those 7 to 28 days of age
- from 1 month of age: 20 to 30 mg/kg (to a maximum of 500 mg) every 8 hours; the maximum recommended dose in severe infections is 4 g daily

In the USA, the following licensed *oral* doses are recommended for amoxicillin depending on infection severity:

- neonates and infants less than 12 weeks of age: a maximum of 30 mg/kg daily in divided doses every 12 hours
- children from 3 months of age weighing less than 40 kg: 25 to 45 mg/kg daily in divided doses every 12 hours, or 20 to 40 mg/kg in divided doses every 8 hours
- children from 3 months weighing 40 kg or more: as for adults (see Uses and Administration, p. 216.3)

Alternatively, for children from 1 month of age the American Academy of Pediatrics (AAP)[1] recommends *oral* doses of 25 to 50 mg/kg daily in 3 divided doses for most infections.

For **otitis media**, the *BNFC* recommends that children from 1 month of age may be given *oral* amoxicillin 40 mg/kg (to a maximum of 1.5 g) daily in 3 divided doses; alternatively the AAP recommends 90 mg/kg daily in 2 divided doses. Where compliance may be a challenge, UK licensed product information suggests an alternative course of 750 mg twice daily for 2 days for children from 3 to 10 years of age.

In patients with **cystic fibrosis** for the treatment of asymptomatic *Haemophilus influenzae* carriage or mild exacerbations, the *BNFC* recommends that the following oral doses may be given 3 times daily:

- children 1 month to 1 year of age: 125 mg
- children 1 to 7 years of age: 250 mg
- children from 7 years of age: 500 mg

For the treatment of **listerial meningitis, group B streptococcal infection, or enterococcal endocarditis**, the *BNFC* recommends the following intravenous doses:

- neonates: 50 mg/kg given every 12 hours for those less than 7 days of age and every 8 hours for those 7 to 28 days of age; doses may be doubled in meningitis
- children from 1 month of age: 50 mg/kg every 4 to 6 hours (to a maximum dose of 2 g every 4 hours)

For **prophylaxis of endocarditis** in children at risk, US experts[2] suggest a single *oral* dose of 50 mg/kg 30 to 60 minutes before high risk procedures.

For doses in children with renal impairment see p. 219.1.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.
2. Wilson W, *et al.* Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation* 2007; 116: 1736–54. Correction. *ibid.*: e376–7. Also available at: http://circ.ahajournals.org/cgi/reprint/116/15/1736 (accessed 13/08/09)

Administration in renal impairment. Oral doses of amoxicillin should be reduced in patients with moderate to severe renal impairment according to creatinine clearance (CC):

- CC 10 to 30 mL/minute: maximum 500 mg every 12 hours
- CC less than 10 mL/minute: maximum 500 mg every 24 hours
- haemodialysis patients: 250 to 500 mg every 24 hours and an additional dose both during and after the dialysis session.

In children weighing less than 40 kg and up to 10 years of age with renal impairment, UK licensed product information recommends dosage as follows:

- CC 10 to 30 mL/minute: 15 mg/kg (maximum 500 mg) every 12 hours
- CC less than 10 mL/minute: 15 mg/kg (maximum 500 mg) once daily

Dose reduction should also be considered when giving amoxicillin by parenteral routes.

Adverse Effects and Precautions

As for Ampicillin, p. 221.2.

The incidence of diarrhoea is less with amoxicillin than ampicillin.

Hepatitis and cholestatic jaundice have been reported with amoxicillin plus clavulanic acid (see p. 219.2); the clavulanic acid component has been implicated. Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and exfoliative dermatitis have also been attributed occasionally to the use of amoxicillin with clavulanic acid.

Use of amoxicillin with clavulanic acid during pregnancy for premature rupture of the fetal membrane has been associated with an increased risk of neonatal necrotising enterocolitis. For further information, see under Premature Labour, p. 201.3.

Breast feeding. Although amoxicillin is excreted in breast milk in small amounts,[1] the American Academy of Pediatrics considers that it is usually compatible with breast feeding.[2]

1. Kafetzis DA, *et al.* Passage of cephalosporins and amoxicillin into the breast milk. *Acta Paediatr Scand* 1981; 70: 285–8.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 24/05/04)

Effects on the liver. Hepatitis and cholestatic jaundice associated with the combination amoxicillin with clavulanic acid (co-amoxiclav) have been reported[1-4] and by 1993 the UK CSM had received 138 reports of hepatobiliary disorders, 3 of which were fatal.[5] It warned that, although usually reversible, the reaction often occurred after stopping therapy with a delay of up to 6 weeks. It appeared that the clavulanic acid was probably responsible. Retrospective analysis of cases reported in Australia[6] and a cohort study in the UK[7] found increasing age and prolonged treatment to be major risk factors for jaundice after co-amoxiclav; male sex is also a risk factor. By 1997 the CSM considered that cholestatic jaundice occurred with a frequency of about 1 in 6000 adult patients and that the risk of acute liver injury was about 6 times greater with co-amoxiclav than with amoxicillin alone. Therefore it recommended that co-amoxiclav should be reserved for bacterial infections likely to be caused by amoxicillin-resistant strains, and that treatment should not usually exceed 14 days.[8] Use is also considered contra-indicated in patients with a history of jaundice or hepatic dysfunction associated with co-amoxiclav or other penicillins.

1. Stricker BHC, *et al.* Cholestatic hepatitis due to antibacterial combination of amoxicillin and clavulanic acid (Augmentin). *Dig Dis Sci* 1989; 34: 1576–80.
2. Wong FS, *et al.* Augmentin-induced jaundice. *Med J Aust* 1991; 154: 698–701.
3. Larrey D, *et al.* Hepatitis associated with amoxycillin-clavulanic acid combination report of 15 cases. *Gut* 1992; 33: 368–71.
4. Hebbard GS, *et al.* Augmentin-induced jaundice with a fatal outcome. *Med J Aust* 1992; 156: 285–6.
5. CSM/MCA. Cholestatic jaundice with co-amoxiclav. *Current Problems* 1993; 19: 2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024454&RevisionSelectionMethod=LatestReleased (accessed 28/07/08)
6. Thomson JA, *et al.* Risk factors for the development of amoxycillin-clavulanic acid associated jaundice. *Med J Aust* 1995; 162: 638–40.
7. Rodriguez LAG, *et al.* Risk of acute liver injury associated with the combination of amoxicillin and clavulanic acid. *Arch Intern Med* 1996; 156: 1327–32.
8. CSM/MCA. Revised indications for co-amoxiclav (Augmentin). *Current Problems* 1997; 23: 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023305&RevisionSelectionMethod=LatestReleased (accessed 11/07/06)

Effects on the teeth. Tooth discoloration associated with the use of amoxicillin with clavulanic acid has been reported in 3 children.[1]

1. García-López M, *et al.* Amoxycillin-clavulanic acid-related tooth discoloration in children. *Pediatrics* 2001; 108: 819–20.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies amoxicillin and co-amoxiclav as not porphyrinogenic; they may be used as drugs of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Sodium content. Each g of amoxicillin sodium contains about 2.6 mmol of sodium.

Interactions

As for Ampicillin, p. 221.2.

Antimicrobial Action

As for Ampicillin, p. 221.3.

Amoxicillin has been reported to be more active *in vitro* than ampicillin against *Enterococcus faecalis*, *Helicobacter pylori*, and *Salmonella* spp., but less active against *Shigella* spp.

Amoxicillin is inactivated by beta lactamases and complete cross-resistance has been reported between amoxicillin and ampicillin. The spectrum of activity of amoxicillin may be extended by use with a beta-lactamase inhibitor such as clavulanic acid (p. 270.3). As well as reversing resistance to amoxicillin in beta-lactamase-producing strains of species otherwise sensitive, clavulanic acid has also been reported to enhance the activity of amoxicillin against several species not generally considered sensitive. These have included *Bacteroides*, *Legionella*, and *Nocardia* spp., *Haemophilus influenzae*, *Moraxella catarrhalis* (*Branhamella catarrhalis*), and *Burkholderia pseudomallei* (*Pseudomonas pseudomallei*). However, *Ps. aeruginosa*, *Serratia marcescens*, and many other Gram-negative bacteria remain resistant. Transferable resistance has been reported in *H. pylori*.

Pharmacokinetics

Amoxicillin is resistant to inactivation by gastric acid. It is more rapidly and more completely absorbed than ampicillin when given orally. Peak plasma-amoxicillin concentrations of about 5 micrograms/mL have been seen 1 to 2 hours after a dose of 250 mg, with detectable amounts present for up to 8 hours. Doubling the dose can double the concentration. The presence of food in the stomach does not appear to reduce the total amount absorbed.

Concentrations of amoxicillin after intramuscular injection are similar to those achieved with oral doses.

About 20% is bound to plasma proteins and plasma half-lives of 1 to 1.5 hours have been reported. The half-life may be prolonged in neonates, the elderly, and patients with renal impairment; in severe renal impairment the half-life may be 7 to 20 hours. Amoxicillin is widely distributed at varying concentrations in body tissues and fluids. It crosses the placenta; small amounts are distributed into breast milk. Little amoxicillin passes into the CSF unless the meninges are inflamed.

Amoxicillin is metabolised to a limited extent to penicilloic acid which is excreted in the urine. About 60% of an oral dose of amoxicillin is excreted unchanged in the urine in 6 hours by glomerular filtration and tubular secretion. Urinary concentrations above 300 micrograms/mL have been reported after a dose of 250 mg. Probenecid reduces renal excretion. Amoxicillin is removed by haemodialysis. High concentrations have been reported in bile; some may be excreted in the faeces.

Amoxicillin with clavulanic acid. The pharmacokinetics of amoxicillin and clavulanic acid are broadly similar and neither appears to affect the other to any great extent.

References.

1. Sánchez Navarro A. New formulations of amoxicillin/clavulanic acid: a pharmacokinetic and pharmacodynamic review. *Clin Pharmacokinet* 2005; 44: 1097–115.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Abiotyl; Abramox†; Almorsan; Amixen Duo; Amixen; Amox-G; Amoxi Duo; Amoxi; Amoxibiot†; Amoxicina; Amoxicler; Amoxidal Duo; Amoxidal; Amoxigrand; Amoxipenil; Amoxipoten†; Amoxitenk; Amoxol Duo; Amoxol; Antiamox†; Biotamoxal†; Bioxilina Duo; Bioxilina; Clofamox; Darzitil; Dunox; Fabamox; Flemoxon; Fulcilina†; Grinsil Duo; Grinsil; Mixcilin†; Moxitral; Nobactam; Optamox; Oximar†; Plamox†; Telmox; Trifamox Duo; Trifamox; *Austral.*: Alphamox; Amohexal†; Amoxil; Bgramin; Cilamox; Fisamox; Ibiamox; Maxamox; Moxacin†; Moxiclav; Ranmoxy; *Austria*: Amoxihexal; Amoxilan; Amoxistad; Clamoxyl; Ospamox; *Belg.*: Amoxypen; Bactimed; Clamoxyl; Docamoxicit; Flemoxin; Moxitop†; *Braz.*: Amofluxt; Amox; Amoxadene; Amoxi-Ped; Amoxibron†; Amoxidil; Amoxifar†; Amoxil; Amoximed; Amoxina; Amoxitan; Ductocilina; Farmoxil†; Hiconcil; Hincomox; Licilon; Moxiplus; Neo Moxicilin†; Neo Moxilin; Novocilin; Ocylin; Pharmox; Polimoxil; Probenil†; Prodoxil†; Sinot; Trimox; Ultramox; Uni Amox; Velamox; *Canad.*: Amox; Apo-Amoxi; Novamoxin; Nu-Amoxi; Pro Amox; *Chile*: Abiolex; Amobiotic; Amoval Duo; Amoval; Amoxipenil; Moxilanic Optamox; *China*: A Lin Xin (阿林新); Akelin (阿克林); Amoling (阿莫灵)†; Amoxian (阿莫仙)†; Amoxilin (阿莫西林); Amoxy (阿莫仙); Hypher (海夫安); Qingdi (青帝); Ri Ao (日奥); Xindabeining (新达贝宁); Yabao Like (亚宝力可); Yi Sa Lin (益萨林); Zai Lin (再林); *Cz.*: Amoclen†; Amoxihexal; Duomox; Ospamox; *Denm.*: Flemoxin; Imacillin; Imadrax; *Fin.*: Amorion; Amoxin; *Fr.*: Amodex; Bactox; Bristamox†; Clamoxyl; Hiconcil†; *Ger.*: Amagesan†; Amoxi-Diolan†; Amoxi-Hefa†; Amoxi-saar; Amoxi-Tablinen†; Amoxi-Wolff†; Amoxi†; Amoxibeta; Amoxidoc†; Amoxihexal†; Amoxypen†; Baktocillin; Flui-Amoxicillin†; InfectoMox; Jutamox†; *Gr.*: Amospes; Amoxil; Amoximycin; Aproxal; Bimoxal; Chromoxyl; Daminopen; Dipenocin; Drinus; Flemoxin; Geymocillina; Izolil; Lamberin; Matasedrin; Ospamox; Paradroxil; Prevasal; Princimox; Selevistine; Stevencillin; Surmagal; Triodanin; Wesfem; *Hong Kong*: Amon†; Amox†; Amoxapen; Amoxon†; Amoxy†; Aroxin; Edamox; Hamoxillin†; Hiconcil†; Moxicillin†; Moxcin†; Moxen†; Moxilen; Moxipen†; Moxlin; Ospamox; Promox;

Ranoxyl†; Reichamox†; Setmoxil†; Unimox; *Hung.*: Clonamox; Duomox; Ospamox; *India*: Actimox; Allmox; Amosym; Amox; Amoxil; Amoxinga; Amoxipen; Amoxivan; Amoxybid; Amoxyn; Amoxypen; Amyn; Antimox; Apimox; Aristomox; Atmox; Axcel; Axl; Betacillin; Betmox; Big Mox; Biomoxil; Bitamox; Blismox; Blumox; Brimox; Cidomex; Cipmox; Clearmox; Damoxy; Delamin; Dicimox; Dormox; Dynamox; E-Amox; Edomox; Erox P; Erox; Euphomox; Finemox; Flemoxin; Fydomox; Genmox; Glamoxin; Glymox; Gutenmox; Hipen; Hycimox; Idimox; Imox; Inmox; Jetmox; Kemox; Labmox; Lakmox; Lamoxy; Lexmox; Linmox; Lomox; Loxyn; Lupimox; Magcil; Max; Maxmox; Mokcan; Monamox; Mopen; Mormox; Mox; Moxi; Moxibact; Moxidat Kid; Moxiday; Moxileb; Moxilup; Moximet; Moximon; Moxind; Moxinova; Moxinta; Moxipal; Moxipil; Moxiplus; Moxitrac; Moxspen; Moxtid; Moxybiotic; Moxycarb; Moxydil; Moxylong; Moxystat; Natamox; Nepomox; Novamox; O-Moxy; Octamox; Olymox; Onamox; Optimox; Osomox; Ronemox; Symoxyl; *Indon.*: Abdimox†; Adam; Amobiotic; Amosine; Amoxil; Amoxillin; Amoxsan; Arcamox; Bellacid; Bintamox†; Bioxyllin†; Bufamoxy; Corsamox; Danoxilin; Dexymox; Erphamoxy; Ethimox; Farmoxyl; Ikamoxyl; Intermoxil; Kalmoxillin; Kimoxil; Lactamox; Lapimox; Leomoxyl; Medimox†; Medocyl†; Mestamox; Mexylin; Mokbios; Moxlin†; Moxtid†; Novax; Nufamox; Opimox; Ospamox; Pehamoxil; Penmox; Primoxil†; Pritamox; Rindomox; Robamox; Scannoxyl; Silamox†; Solpenox; Supramox; Topcillin; Vibramox; Wiamox; Widecillin; Xiltrop; *Irl.*: Amoxil; Clonamox; Geramox; Oramox; Pinamox; Rimoxallin†; *Israel*: Amoxi; Moxypen; Moxyvit; *Ital.*: Alfamox; Amoflux; Amosol; Amox; Amoxillin†; Amoxina; Bradimox†; Hydramox; Mopen; Moxiren†; Neotetranase; Oralmox; Pamocil; Posmox; Sievert; Sintopen; Velamox; Zimox; *Jpn*: Pasetocin; *Malaysia*: Beamoxy; Betamox; Moxilen; Ospamox; *Mex.*: Acimox; Acroxil; Ameclina†; Amicil; Amobay; Amoxifur; Amoxil; Amoxinovag†; Amoxisol; Amoxivet; Ampliron; Amsaxilina; Armoxin; Betabiot; Bimoxan†; Biotaxil; Biovicam; Brenoxil; Dimopen; Doxamil; Examolin; Flemoxon; Gimalxina; Grunicina†; Hidramox; Limoxin; Lorexil M; Lumox; Micro Mox; Micromox; Mocimed; Moxiclina; Moxlin; Penamox; Penticlox; Polymox; Prodomix; Servamox-P; Servamox; Solcidina; Vandix†; Xalyn-Or; *Neth.*: Amoxi†; Flemoxin; *Norw.*: Amoxillin; Imacillin; *NZ*: Alpha-Amoxi; Alphamox; Amoxi; Amoxil; Apo-Amoxi; Flemoxin; Ibiamox; Ospamox; *Philipp.*: Agpen; Amelox; Amoxico; Amoxil; Amusa†; AMX; Ardent; Axmel; Bactigent; Benemox; Bradoxil; Cartrimox; Cilamox; Cilfam; Clearamox; Cycamil; Daisamox; Eleomox; Eppitrexil; Essenmox†; Gexcil; Globamox; Globapen; Harbimox; Himox; Koact; Kramollex; Lewixin; Littmox; Maelenoxyl; Maroxil; Medimoxil; Medvox; Megamox; Moks; Montramox†; Moxillin; Moxiped†; Neomox; Novamox; Pediamox; Pediaxil; Penbiosyn; Pharmamox; Promox; Roddexil; Sterimox; Sumoxil; Syndoxil; Taimox; Telsimox; Teramoxyl; Termox; Trexil; Valmox†; Valzimox; Vastamox; Vaxman†; Vbellox; Westfimox; Xazexy†; Xybatron; Yugoxil; Zedroxyn; Zerrsox; Zymoxyl; *Pol.*: Amotaks; Apo-Amoxi†; Duomox; Hiconcil; Novamox; Ospamox; *Port.*: Amoxil; Amplamox; Cipamox; Clamoxyl; Flemoxin; Moxadent; Oraminax; Ospamox; *Rus.*: Amosin (Амосин); Flemoxin (Флемоксин); Gramox (Грамокс); Hiconcil (Хиконцил); Ospamox (Оспамокс); Ranoxyl (Раноксил); *S.Afr.*: A-Lennon†; Acucil†; Allmox; Amocas; Amocillin; Amoxicap; Amoxil; Amoxyfizz†; Betamox; C-Mox†; Ipcamox; Maxcil†; Moxan; Moxymax; Moxypen; Mymox; Promoxil; Ranmoxy; Saltermox; Spectramox; Xeracil†; Yomax; Zaloxy; Zoxil; *Singapore*: Amoxa; Amoxapen; Amoxicap; Amoxigran; Amoxil; Apo-Amoxi; Aroxin; Betamox; Moxilen; Moxipen; Ospamox; Pulmoxy; Strimox; Synamox; Unimox; *Spain*: Amitron; Amoxaren†; Amoxi Gobens; Apamox; Borbalan†; Britamox; Brondix†; Clamoxyl; Co Amoxin†; Dobriciclin†; Flubiotic†; Hosboral; *Swed.*: Amimox; Imacillin; *Switz.*: Amoxi-Mepha; Azilline; Clamoxyl; Spectroxyl†; Supramox†; *Thai.*: Acticillin; Amacin; Amox; Amoxa†; Amoxicillin; Amoxi; Amoxidon; Amoxil; Amoxin; Amoxlin; Amoxy; Amoxylin†; Amoxypac; Asiamox; Augxil-G; Bomox; Camox; Clanoxy; Coamox; Dymoxin; Ibiamox; Kamoxin†; Manmox; Meixil; Milamox; Mox; Moxapen†; Moxcil; Moxcillin; Moxcin; Moxilcap; Moxilin; Moximed; Moxitab†; Moxno†; Moxodyl; Moxxo†; Moxycillin; Moxyno; Moxypac; Pondnoxcil; Promoxy; Pulmoxyl†; Pyramox; Rancil; Ranoxyl; Rapiclav; Samox; Samoxil†; Samoxin; Sanomox; Servamox; Sia-Mox; Sumoxcin; TO Cillin; TV Mox; U-Amox; Unimox; *Turk.*: Alfoxil; Amoksilav; Amoksilin; Amoksina; Amosin; Atoksilin; Bioksil; Demoksil; Largopen; Moksilin; Neoamox; Remoxil; Topramoxin; Trimosin; Xibac; *UAE*: Julphamox; *UK*: Amix†; Amoram; Amoxident; Amoxil; Galenamox; Rimoxallin; *Ukr.*: Amoxil (Амоксил-КМП); Flemoxin (Флемоксин); Gramox (Грамокс); Hiconcil (Хиконцил); Ospamox (Оспамокс); *USA*: Amoxil; DisperMox; Moxatag; Trimox; *Venez.*: Amitrexyl; Amofar; Amoxal; Amoxiduo; Amoxiga; Amoxilan; Amoxival; Amylin; Ospamox; Sentapen; Strimox; Sumopen; Trimoxal.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

BP 2014: Amoxicillin Capsules; Amoxicillin Injection; Amoxicillin Oral Suspension; Co-amoxiclav Injection; Co-amoxiclav Oral Suspension; Co-amoxiclav Tablets; Dispersible Co-amoxiclav Tablets;

USP 36: Amoxicillin and Clavulanate Potassium for Oral Suspension; Amoxicillin and Clavulanate Potassium Tablets; Amoxicillin and Clavulanic Acid Extended-Release Tablets; Amoxicillin Capsules; Amoxicillin for Oral Suspension; Amoxicillin Tablets for Oral Suspension; Amoxicillin Tablets.

Ampicillin *(BAN, USAN, rINN)*

Aminobenzylpenicillin; Ampicilin; Ampicilina; Ampicilinas; bevandenis; Ampicillin, vattenfritt; Ampicilline; Ampicilline anhydre; Ampicillinum; Ampicillinum Anhydricum; Ampicylina bezwodna; Ampisilin; Ampisilliini; Ampisilliini, vedetön; Anhydrous Ampicillin; AY-6108; BRL-1341; NSC-528986; P-50; Vízmentes ampicillin; Wasserfreies Ampicillin; Ампициллин. (6*R*)-6-(α-D-Phenylglycylamino)penicillanic acid.

$C_{16}H_{19}N_3O_4S$=349.4

CAS — 69-53-4.

ATC — J01CA01; S01AA19.

ATC Vet — QJ01CA01; QJ51CA01; QS01AA19.

UNII — 7C782967RD.

NOTE. Compounded preparations of ampicillin may be represented by the following names:

- Co-fluampicil *(BAN)*—flucloxacillin 1 part and ampicillin 1 part (w/w).

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *Viet.*

Int. and *US* permit anhydrous or the trihydrate.

Ph. Eur. 8: (Ampicillin, Anhydrous; Ampicillin BP 2014). A white or almost white, crystalline powder. It exhibits polymorphism. Sparingly soluble in water; practically insoluble in alcohol, in acetone, and in fatty oils. It dissolves in dilute solutions of acids and of alkali hydroxides. A 0.25% solution in water has a pH of 3.5 to 5.5. Store at a temperature not exceeding 30 degrees in airtight containers.

USP 36: (Ampicillin). It is anhydrous or contains three molecules of water of hydration. A white, practically odourless crystalline powder. Slightly soluble in water and in methyl alcohol; insoluble in carbon tetrachloride, in chloroform, and in benzene. pH of a 1% solution in water is between 3.5 and 6.0. Store in airtight containers.

Ampicillin Sodium *(BANM, USAN, rINNM)*

Aminobenzylpenicillin Sodium; Ampicilin sodná sůl; Ampicilina sódica; Ampicilino natrio druska; Ampicillin-Natrium; Ampicilline Sodique; Ampicillinnatrium; Ampicillinnátrium; Ampicillinum Natricum; Ampicylina sodowa; Ampisilliininatrium; Natrii Ampicillinum; Sodyum Ampisilin; Натрий Ампициллин.

$C_{16}H_{18}N_3NaO_4S$=371.4

CAS — 69-52-3.

ATC — J01CA01; S01AA19.

ATC Vet — QJ01CA01; QS01AA19.

UNII — JFN36L5S8K.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Ampicillin Sodium). A white or almost white hygroscopic powder. Freely soluble in water; sparingly soluble in acetone; practically insoluble in liquid paraffin and in fatty oils. A 10% solution in water has a pH of 8.0 to 10.0. Store in airtight containers.

USP 36: (Ampicillin Sodium). A white to off-white, odourless or practically odourless, hygroscopic, crystalline powder. Very soluble in water and in isotonic sodium chloride and glucose solutions. pH of a solution in water containing the equivalent of ampicillin 1% is between 8.0 and 10.0. Store in airtight containers.

Incompatibility. The incompatibility of ampicillin sodium and aminoglycosides is well established. Incompatibilities have also been reported with many other drugs, including other antibacterials, and appear to be more pronounced at higher concentrations and in solutions also containing glucose.

Stability. The stability of solutions of ampicillin sodium is dependent on many factors including concentration, pH, temperature, and the nature of the vehicle. Stability decreases in the presence of glucose, fructose, invert sugar, dextrans, hetastarch, sodium bicarbonate, and lactate. It is recommended that reconstituted solutions of ampicillin sodium for injection should be given within 24 hours of preparation, and should be stored at 2 degrees to 8 degrees but should not be frozen. Solutions for infusion are stable for varying periods and details are given in licensed product information.

References.

1. Lynn B. The stability and administration of intravenous penicillins. *Br J Intraven Ther* 1981; 2(Mar): 22–39.

Ampicillin Trihydrate *(BANM, rINNM)*

Ampicilin trihydrát; Ampicilina trihidrato; Ampicilinas trihidratas; Ampicillin; Ampicillin-Trihydrat; Ampicilline Trihydratée; Ampicillin-trihidrát; Ampicillintrihydrat; Ampicillinum Trihydricum; Ampicylina trójwodna; Ampisilliinitrihydraatti; Ампициллин Тригидрат.

$C_{16}H_{19}N_3O_4S.3H_2O$=403.4

CAS — 7177-48-2.

ATC — J01CA01; S01AA19.

ATC Vet — QJ01CA01; QS01AA19.

UNII — HXQ6A1N7R6.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *Viet.* In *Chin.* under the title Ampicillin. *Int.* and *US* permit anhydrous or the trihydrate under the title Ampicillin.

Ph. Eur. 8: (Ampicillin Trihydrate). A white or almost white, crystalline powder. Slightly soluble in water; practically insoluble in alcohol and in fatty oils. It dissolves in dilute solutions of acids and of alkali hydroxides. A 0.25% solution in water has a pH of 3.5 to 5.5. Store in airtight containers.

USP 36: (Ampicillin). It is anhydrous or contains three molecules of water of hydration. A white, practically odourless crystalline powder. Slightly soluble in water and in methyl alcohol; insoluble in carbon tetrachloride, in chloroform, and in benzene. pH of a 1% solution in water is between 3.5 and 6.0. Store in airtight containers.

Uses and Administration

Ampicillin is used in the treatment of a variety of infections due to susceptible organisms (see Antimicrobial Action, p. 221.3). They include biliary-tract infections, bronchitis, endocarditis, gastro-enteritis (including salmonella enteritis and shigellosis), gonorrhoea, listeriosis, meningitis, perinatal streptococcal infections (intrapartum prophylaxis against group B streptococci), peritonitis, pneumonia, septicaemia, typhoid and paratyphoid fever, and urinary-tract infections. Resistance to ampicillin is increasingly a problem in some infections, for example, gonorrhoea, pneumococcal infections, respiratory-tract infections due to *Haemophilus influenzae* or *Moraxella catarrhalis* (*Branhamella catarrhalis*), *Salmonella* infections, shigellosis, and infections due to *Escherichia coli*. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

If beta-lactamase-producing organisms are present, ampicillin can be given with a beta-lactamase inhibitor such as sulbactam (see below) or a penicillinase-resistant drug such as cloxacillin, dicloxacillin, or flucloxacillin (known as co-fluampicil). It may also be used with an aminoglycoside to increase the spectrum of organisms covered; it is advisable to give the injections separately.

The dosage of ampicillin will depend on the severity of the disease, the age of the patient, and renal function. Ampicillin is usually given orally as the trihydrate and by injection as the sodium salt. Doses are expressed in terms of the equivalent amount of ampicillin; 1.06 g of ampicillin sodium and 1.15 g of ampicillin trihydrate are each equivalent to about 1 g of ampicillin.

The usual oral dose is 0.25 to 1 g every 6 hours taken at least 30 minutes before or 2 hours after food. For urinary-tract infections, ampicillin 500 mg is given orally every 8 hours. The usual dose by injection is 500 mg every 4 to 6 hours intramuscularly or by slow intravenous injection over 3 to 5 minutes or by infusion, although for severe infections higher doses are often used.

For typhoid and paratyphoid fever where *Salmonella typhi* strains remain sensitive to ampicillin, an oral dose of 1 to 2 g may be given every 6 hours for 2 weeks for acute infections, and for 4 to 12 weeks in carriers.

Ampicillin 2 g given with probenecid 1 g, as a single oral dose, has been used in the treatment of uncomplicated gonorrhoea in areas where gonococci remain sensitive; repeated doses are recommended in females.

In meningitis, higher parenteral doses may be used; 12 g daily given intravenously in divided doses every 4 or 6 hours has been suggested for listerial meningitis.

For intrapartum prophylaxis against group B streptococcal infection in the neonate, a maternal dose of 2 g by intravenous injection initially then 1 g every 4 hours until delivery has been suggested.

For details of doses in children, see p. 221.1.

Ampicillin has been given by other routes, usually as a supplement to systemic therapy. Intraperitoneal or intrapleural injections have been given in a dose of 500 mg daily dissolved in 5 to 10 mL of water. For intra-articular injection, ampicillin 500 mg daily has been given dissolved in up to 5 mL of water or a solution of procaine hydrochloride 0.5%.

Ampicillin benzathine has also been given by intramuscular injection.

Ampicillin with sulbactam. The sodium salts of ampicillin and sulbactam (p. 362.1) may be given intramuscularly or intravenously in the treatment of infections due to beta-lactamase-producing organisms. Doses are expressed in terms of the equivalent amounts of ampicillin and sulbactam; available injections contain ampicillin and sulbactam in the ratio 2:1, respectively. The usual dose is

ampicillin 1 g with sulbactam 500 mg every 6 hours; doses may be doubled in severe infections.

For oral use sultamicillin (p. 371.1), a mutual prodrug of ampicillin and sulbactam, may be given.

References.

1. Malik ZA, Litman N. Ampicillin and amoxicillin. *Pediatr Rev* 2006; 27: 434–6.
2. Rafailidis PI, *et al.* Ampicillin/sulbactam: current status in severe bacterial infections. *Drugs* 2007; 67: 1829–49.
3. Lode HM. Rational antibiotic therapy and the position of ampicillin/sulbactam. *Int J Antimicrob Agents* 2008; 32: 10–28.

Administration in children. Ampicillin may be given to neonates and children for the treatment of infections caused by susceptible bacteria and may be given orally, by intramuscular injection, by slow intravenous injection over 3 to 5 minutes, or by intermittent intravenous infusion over 30 minutes.

For the treatment of susceptible infections including urinary-tract infections, otitis media, sinusitis, uncomplicated community-acquired pneumonia, and salmonellosis, the *BNFC* suggests the following *oral* doses for neonates and children; these may be doubled in severe or serious infections:
- neonates: 30 mg/kg (to a maximum of 62.5 mg) given 3 times daily for neonates 7 to 21 days old and 4 times daily for those 21 to 28 days old
- 1 month to 1 year of age: 62.5 mg 4 times daily
- 1 to 5 years of age: 125 mg 4 times daily
- from 5 to 12 years of age: 250 mg 4 times daily
- from 12 years of age: 250 to 500 mg 4 times daily

The *BNFC* also recommends the following *intravenous* dose ranges in neonates and children which may be doubled in severe or serious infections:
- neonates: 30 mg/kg, given every 12 hours for neonates less than 7 days old, every 8 hours for those 7 to 21 days old, and every 6 hours for those 21 to 28 days old
- children from 1 month of age: 25 mg/kg (to a maximum of 500 mg) every 6 hours

For listerial meningitis, group B streptococcal infection, and enterococcal endocarditis, the *BNFC* suggests the following *intravenous* doses;
- neonates: 50 mg/kg, given every 12 hours for neonates less than 7 days old, every 8 hours for those 7 to 21 days old, and every 6 hours for those 21 to 28 days old; the dose is doubled for the treatment of meningitis
- from 1 month of age: 50 mg/kg every 4 to 6 hours (to a maximum of 2 g every 4 hours) is recommended

In the USA, the American Academy of Paediatrics[1] suggests the following doses given *intramuscularly* or *intravenously*, although higher doses may be needed for the treatment of meningitis in neonates:
- for neonates aged ⩽7 days and weighing ⩽2 kg: 50 mg/kg every 12 hours; for the treatment of presumed early-onset group B streptococcal septicaemia, 100 mg/kg every 12 hours is also suggested
- for neonates aged ⩽7 days and weighing >2 kg: 50 mg/kg every 8 hours; for the treatment of presumed early-onset group B streptococcal septicaemia, 100 mg/kg every 12 hours is also suggested
- for neonates aged 8 to 28 days and weighing ⩽2 kg: 50 mg/kg every 8 hours; a dosing interval of 12 hours may be used until 2 weeks of life in extremely low birthweight neonates (those weighing <1 kg)
- for neonates aged 8 to 28 days and weighing >2 kg: 50 mg/kg every 6 hours
- for group B streptococcal meningitis in all the above weight groups: 75 mg/kg every 6 hours
- children 1 month and older: 100 to 150 mg/kg daily in 4 divided doses (to a maximum of 4 g daily). For severe infections, a total daily dose of 200 to 400 mg/kg (to a maximum of 12 g) is recommended

Alternatively, for mild to moderate infections in children from 1 month of age, a daily dose of 50 to 100 mg/kg *orally*, in 4 divided doses (to a maximum of 4 g daily), may also be used.

Ampicillin is also used in some countries in children to eradicate chronic carriage of *Salmonella typhi* and *S. paratyphi*, which can cause typhoid and paratyphoid fever respectively; an *intramuscular* dose of 10 mg/kg (to a maximum of 250 mg) every 6 hours for 4 to 6 weeks has been recommended.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Administration in renal impairment. UK licensed product information advises that the dose of ampicillin should be reduced, or the dose interval increased, in severe renal impairment (creatinine clearance less than 10 mL/minute). Patients undergoing dialysis should receive an additional dose after the session.

A review[1] of antimicrobial dosing in critically ill patients receiving renal replacement therapy recommends that patients undergoing continuous renal replacement therapy (CRRT) receive a loading dose of 2 g, followed by maintenance doses of 1 to 2 g at intervals depending on the type of CRRT:
- continuous venovenous haemofiltration (CVVH): every 8 to 12 hours
- continuous venovenous haemodialysis (CVVHD): every 8 hours
- continuous venovenous haemodiafiltration (CVVHDF): every 6 to 8 hours

For critically ill patients undergoing intermittent haemodialysis, the authors suggest a dosing regimen of 1 to 2 g every 12 to 24 hours.[1]

1. Heintz BH, *et al.* Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy* 2009; 29: 562–77.

Adverse Effects

As for Benzylpenicillin, p. 231.2.

Skin rashes are among the most common adverse effects and are generally either urticarial or maculopapular; the urticarial reactions are typical of penicillin hypersensitivity, while the erythematous maculopapular eruptions are characteristic of ampicillin and amoxicillin and often appear more than 7 days after starting treatment. Such rashes may be due to hypersensitivity to the beta-lactam moiety or to the amino group in the side-chain, or to a toxic reaction. The occurrence of a maculopapular rash during ampicillin use does not necessarily preclude the subsequent use of other penicillins. However, since it may be difficult in practice to distinguish between hypersensitive and toxic responses, skin testing for hypersensitivity may be advisable before another penicillin is used in patients who have had ampicillin rashes. Most patients with infectious mononucleosis develop a maculopapular rash when treated with ampicillin, and patients with other lymphoid disorders such as lymphatic leukaemia, and possibly those with HIV infection, also appear to be at higher risk. More serious skin reactions may occur and erythema multiforme associated with ampicillin has occasionally been reported.

Gastrointestinal adverse effects, particularly diarrhoea and nausea and vomiting, occur quite often, usually after oral use. Pseudomembranous colitis has also been reported.

Effects on the liver. Ampicillin has been associated with hepatic injury. Self-limiting cholestasis was reported in a 23-year-old man who received oral ampicillin;[1] recurrence followed each of 2 subsequent exposures to the drug. A case of chronic cholestasis associated with ampicillin use has also been reported.[2]

Severe and prolonged cholestasis has also been reported after treatment with ampicillin plus sulbactam; gradual resolution of the condition occurred over 7 months.[3]

1. Köklü S, *et al.* Recurrent cholestasis due to ampicillin. *Ann Pharmacother* 2003; 37: 395–7.
2. Cavanzo FJ, *et al.* Chronic cholestasis, paucity of bile ducts, red cell aplasia, and the Stevens-Johnson syndrome: an ampicillin-associated case. *Gastroenterology* 1990; 99: 854–6.
3. Köklü S, *et al.* Probable sulbactam/ampicillin-associated prolonged cholestasis. *Ann Pharmacother* 2004; 38: 2055–8.

Precautions

As for Benzylpenicillin, p. 231.3.

Ampicillin should be stopped if a skin rash occurs. It should preferably not be given to patients with infectious mononucleosis since they are especially susceptible to ampicillin-induced skin rashes; patients with lymphatic leukaemia or possibly HIV infection may also be at increased risk of developing skin rashes.

Myasthenia gravis. The symptoms of a woman with myasthenia gravis were exacerbated when she was given ampicillin.[1]

1. Argov Z, *et al.* Ampicillin may aggravate clinical and experimental myasthenia gravis. *Arch Neurol* 1986; 43: 255–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ampicillin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Sodium content. Each g of ampicillin sodium contains about 2.7 mmol of sodium.

Interactions

As for Benzylpenicillin, p. 232.1.

Antigout drugs. An increased frequency of skin rashes has been reported in patients receiving ampicillin or amoxicillin, with *allopurinol*, compared with those receiving the antibacterial alone,[1] but this could not be confirmed in a subsequent study.[2]

1. Jick H, Porter JB. Potentiation of ampicillin skin reactions by allopurinol or hyperuricemia. *J Clin Pharmacol* 1981; 21: 456–8.
2. Hoigné R, *et al.* Occurrence of exanthems in relation to aminopenicillin preparations and allopurinol. *N Engl J Med* 1987; 316: 1217.

Antimalarials. The absorption of ampicillin has been reduced in healthy subjects taking *chloroquine*.[1]

1. Ali HM. Reduced ampicillin bioavailability following oral coadministration with chloroquine. *J Antimicrob Chemother* 1985; 15: 781–4.

Antimicrobial Action

Ampicillin is a beta-lactam antibacterial. It is bactericidal and has a similar mode of action to that of benzylpenicillin (p. 232.1), but as an aminopenicillin with an amino group side-chain attached to the basic penicillin structure, ampicillin is better able to penetrate the outer membrane of some Gram-negative bacteria and has a broader spectrum of activity.
- Ampicillin resembles benzylpenicillin in its action against Gram-positive organisms, including *Streptococcus pneumoniae* and other streptococci, but, with the possible exception of activity against *Enterococcus faecalis*, it is slightly less potent than benzylpenicillin.
  Listeria monocytogenes is highly sensitive.
- The Gram-negative cocci *Moraxella catarrhalis* (*Branhamella catarrhalis*), *Neisseria gonorrhoeae*, and *N. meningitidis* are sensitive.
- Ampicillin is more active than benzylpenicillin against some Gram-negative bacilli, including *Haemophilus influenzae* and Enterobacteriaceae such as *Escherichia coli*, *Proteus mirabilis*, *Salmonella* and *Shigella* spp. It is inactive against *Pseudomonas aeruginosa*.
- Ampicillin also has activity similar to benzylpenicillin against other organisms including many anaerobes and *Actinomyces* spp.

Activity with other antimicrobials. There is synergy against some beta-lactamase-producing organisms between ampicillin and beta-lactamase inhibitors such as clavulanic acid or sulbactam, and also penicillinase-stable drugs such as cloxacillin or flucloxacillin. Synergy has also been shown between ampicillin and aminoglycosides against a range of organisms, including enterococci. Variable effects ranging from synergy to antagonism have been reported between ampicillin and other beta lactams, bacteriostatic drugs such as chloramphenicol, and rifampicin.

Resistance. Like benzylpenicillin, ampicillin is inactivated by beta lactamases, although other mechanisms may be responsible for resistance in some species. There are geographical variations in the incidence of resistance, but most staphylococci and many strains of *E. coli*, *H. influenzae*, *M. catarrhalis*, *N. gonorrhoeae*, and *Salmonella* and *Shigella* spp. are resistant.

Pharmacokinetics

Ampicillin is relatively resistant to inactivation by gastric acid and is moderately well absorbed from the gastrointestinal tract after oral doses. Food can interfere with the absorption of ampicillin so doses should preferably be taken at least 30 minutes before meals. Peak concentrations in plasma occur in about 1 to 2 hours and after a 500-mg oral dose are reported to range from 3 to 6 micrograms/mL.

Peak plasma concentrations of ampicillin after a 500-mg intramuscular dose given as the sodium salt occur within about 1 hour and are reported to range from 7 to 14 micrograms/mL.

Ampicillin is widely distributed and therapeutic concentrations can be achieved in ascitic, pleural, and joint fluids. It crosses the placenta and small amounts are distributed into breast milk. There is little diffusion into the CSF except when the meninges are inflamed. About 20% is bound to plasma proteins and the plasma half-life is about 1 to 1.5 hours, but this may be increased in neonates, the elderly, and patients with renal impairment; in severe renal impairment half-lives of 7 to 20 hours have been reported.

Ampicillin is metabolised to some extent to penicilloic acid which is excreted in the urine.

Renal clearance of ampicillin occurs partly by glomerular filtration and partly by tubular secretion; it is reduced by probenecid. About 20 to 40% of an oral dose may be excreted unchanged in the urine in 6 hours; urinary concentrations have ranged from 0.25 to 1 mg/mL after a dose of 500 mg. After parenteral use about 60 to 80% is excreted in the urine within 6 hours. Ampicillin is removed by haemodialysis. High concentrations are reached in bile; it undergoes enterohepatic recycling and some is excreted in the faeces.

Ampicillin with sulbactam. The pharmacokinetics of ampicillin and sulbactam are broadly similar and neither appears to affect the other to any great extent.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Alpovex; Ampi-Bis; Ampiclen†; Ampigen; Ampigrand†; Ampinox; Ampitenk; Ampixen†; Atecilina; Bactilina; Fabopcilina†; Galciclina; Histopen†; Trifacilina; Trimicro†; Weldcilina†; *Austral.*: Alphacin†; Ampicyn; Austrapen; Ibimicyn; *Austria*: Standacillin; *Belg.*: Pentrexyl; *Braz.*: Ampi†; Ampicilan; Ampicil†; Ampicilab; Ampicilase; Ampicilil; Ampicilon; Ampigran; Ampilozin; Amplaclina; Amplacin; Amplibac†; Binotal; Cilinon; Cilipen†; Emicilin; Expectocilin; Gonol; Gramcilina†; Parenzyme Ampicilina; *Canad.*: Apo-Ampi; Nu-Ampi; *China*: Ai Luo Di (艾罗迪); An Tai Lin (安泰林); Anbixian (安必仙); Bixianshu (必仙素); En Pu Luo (恩普洛); Lingxu (灵旭); Yixide (伊西德); *Denm.*: Pentrexyl; *Fin.*: A-Pen; *Ger.*: Binotal†; *Gr.*: Abetathen; Adelcopen; Allomycin; Ampicipen; Competor; Comrarilin; Copercilex; Extrapen; Prateline; Praxicilline; Isticilline; Pentrexyl; Piclin; Spiracillin; Stopan; Toscapen; Xanline; *Hong Kong*: Ampisul†; Amprexyl; Apo-Ampi†; Pamecil; Penodil†; Pentrexyl†; Uni-Ampicin†; *Hung.*: Semicillin; Standacillin; *India*: Albercilin; Alfacillin; Ampijet; Ampilin; Ampipen; Ampisyn; Ampy; Aristocillin; Bacipen; Biocilin; Broacil; Broadicilin; Campicillin; Cincillin; Dabclin; Dynacil; Eskaycillin; Ingacillin; JP-Cilin; Maxamp; Megasyn; Monocilin; Natcocillin; Neocillin; Nepocil; Osocillin; Roscillin; Synthocilin; *Indon.*: Ambiopi; Amcillin†; Ampi; Arcocillin†; Binotal; Biopensyn†; Cetacillin†; Corsacillin; Kalpicilin; Opicillin; Parpicillin†; Penbiotic†; Penbritin†; Phapin; Polypen; Primacillin†; Sanpicillin; Standacillin; Ultrapen†; Viccillin; Xepacillin; *Irl.*: Clonamp; Novapen†; Penbritin†; Rimacillin†; *Israel*: Penibrin; *Ital.*: Ampilux; Ampiplus Simplex†; Amplital; Amplizer†; Pentrexyl; *Malaysia*: Ampilin; Pamecil; Standacillin; *Mex.*: Acilmed; Alphapen; Alvedrin†; Am-An; Ambidrin†; Ambiosol; Ampex; Ampi-Quim; Ampi-Tecno; Ampigrin†; Ampimex; Amprexyn†; Amsapen; Anglopen†; Azpencil†; Besticilina-A; Binotal; Bremecina†; Brupen; Deamcilina†; Dibacilina; Diferin; Expicin; Flamicina; Gramipen-P; Iqfacilina; Lampicin†; Luzampil; Marovilina; Meprizina†; Mexapin†; Mibiot; Omnipen; Pebiot; Penbritin; Pentiver; Pentrexyl; Procilina; Prodifer†; Promecilina; Sinaplin; Tronex; Yapamicin†; Zumorin; *Norw.*: Pentrexyl; *Philipp.*: Aldribid; Ampicin; Ampiclin; Ampico; Ampinex; Ampisan; Ampitrex; Ampizef; Bactimed†; Cilisod; Clovillin; Dincil; Dinpen; Eurocin; Excillin; Famacin; Gramcil; Mapciril; Microcilin; Obocil; Panacta; Penbritin; Pentrexyl†; Picaplin; Polypen; Rotocin; Shinapen; Sodampen; Trumepen; Vatacil; *Port.*: Amplifar†; Estreptobroncol†; Hiperbiotico Retard; Hiperbiotico; *Rus.*: Standacillin (Стандациллин); Zetsyl (Зетсил); *S.Afr.*: Acupillin†; Ampimax†; Ampipen; Ampisalt†; Be-Ampicil; M-P-Cil; Penbritin†; Penrite†; Petercillin†; Ranamp; Spectracil†; *Singapore*: Ampicap; Ampilin; Dhacillin; Pamecil†; Standacillin; *Spain*: Britapen; Gobemicina; *Swed.*: Doktacillin; *Thai.*: Amicilin; Amilin†; Ampac; Ampi Frx; Ampi-Oral; Ampi; Ampicin; Ampicyn†; Ampihof; Ampilin; Ampillin; Ampimycin; Ampipac; Ampra; Amprexyl; Eracillin†; Medicillin; Penbritin†; Pencotrex†; Pentrexyl†; Siampicil†; Sumapen†; Utocillin; Vacillin†; Viccillin†; *Turk.*: Alfasilin; Ampisid; Ampistna; Neosilin; Penbisin†; Seskasilin; Silina; *UAE*: Julphapen; *UK*: Magnapen†; Magnapen; Magnapen; Penbritin; Rimacillin; *USA*: Principen; *Venez.*: Alampen; Ampenina; Ampilan; Arcocilin.

Multi-ingredient Preparations. *Arg.*: Aminoxidin Sulbactam; Ampi-Bis Plus; Ampigen SB; Amplibenzatin Bronquial; Cronopen Balsamico; Meticil; Prixin; Unasyna†; *Austria*: Unasyn; *Braz.*: Ambezetal; Amplotal†; Benzotal; Combactan; Durapen†; Optacilin; Unasyn; Uropielon; *Chile*: Auropennz; Unasyn; *China*: Fumaixin (孚麦欣); Jielite (洁利特); Kaila (凯法); Pu Shu (普舒); Shu An Xin (舒氨新); Shuanxilin (舒氧西林); Shudi (舒敌); Shutabituo (舒他必妥); Stanyn (施坦宁); Unasyn (优立新); Xin An Lin (欣安林); Zhuo Tong (卓彤); *Cz.*: Bitammon; Unasyn; *Fr.*: Unacim; *Ger.*: Ampicillin comp†; Unacid; *Gr.*: Begalin-P; Demotine; *Hong Kong*: Cloxamp†; Cloxampi†; Cloxampilin†; Co-Amclox†; Lampicin†; Pamedox†; Roscilox†; Unasyn; *Hung.*: Unasyn; *India*: ADC; Adilox; AK-60; Alcilox; Amci-Clox; Amclominus; Amclox; Amiclox Plus; Amisul; Amklok; Ampicloxa; Ampilong; Ampilox-LB; Ampilox; Ampitum; Amplus; Amplus; Ampoxin-LB; Ampoxin; Ampy C; Ampy S; Ampylox; Ampysul; Amsat; Baciclox; Bactimox Plus; Bactimox; Baxin-D-LB; Baxin-D; Baxin-LB; Baxin; Betamp; Biclopen; Bilactam; Broadiclox-LB; Broadiclox; Campicillin Plus; Campilox-LB; Campilox; Cilclox; Cinclox-S; Clacin; Clax; Climpen; Clomentin; Clompic; Clotrop; Cloxapene; Cloxcin; Combilox-LB; Combilox; Combipen; D-Clox; Dabcilox; DC-Ped; DC; Duoclox; Elclox Plus; Elclox; Emulox; Eradiclox; Euphoclox; G-Clox; Hclox; Intaclox-D; Kloxamp; Magnacillin; Mediclox Plus; Megaclox LB; Megaclox; Megapen; Napi-D; Nepoclox; Omnipen; Osocillin-S; Sulbacin; *Israel*: Unasyn; *Ital.*: Amplium; Bethacil; Loricin; Unasyn; *Jpn*: Unasyn-S; *Malaysia*: Easyn; Shinasyn; Sulbacin; Sulbamp; Unasyn; *Mex.*: Ampiclox-D†; Anglotex†; Bisolvon A; Brucilina; Brupen Compuesto; Diamprex†; Doxapen†; Mucolin; Panac K†; Panac; Penbritin Ex; Pentibrom; Pentidix; Penttexyl Expec; Unasyna; *Philipp.*: Ambacitam; Ampimax; Ampisul; Dinocin; Silgram; Subacillin; Sulbacin; Sultacillin; Unasan; Unasyn; *Pol.*: Unasyn; *Rus.*: Libakcil (Либакцил); Oxamp (Оксамп); Oxampicine (Оксампицин); Oxamsar (Оксамсар); Sulbacin (Сульбацин); Sultasin (Сультасин); Unasyn (Уназин)†; *S.Afr.*: Ampiclox†; Ampoxin; Apen; Cloxam; Megamox; *Singapore*: Unasyn; *Spain*: Ampilevel†; Gobemicina Retard†; Retarpen; *Thai.*: Ampcoxin; Ampiclox†; Sulam; Sulbaccin; Sulbacilline; Unasyn; Viccillin-S†; *Turk.*: Alfasid; Azosilin; Combicid; Devasid; Duobak; Duobaktam; Duocid; Nobecid; Probicid; Sulbaksit; Sulcid; Sultasid; Sultibac; *UK*: Magnapen†; Magnapen; Magnapen; *Ukr.*: Ampisid (Амписид); Ampisulbin (Амписульбин); Unasyn (Уназин)†; *USA*: Unasyn; *Venez.*: Ampibactan; Fipexiam; Sinif; Unasyn.

Pharmacopoeial Preparations

BP 2014: Ampicillin Capsules; Ampicillin Injection; Ampicillin Oral Suspension; Co-fluampicil Capsules; Co-fluampicil Oral Suspension;

USP 36: Ampicillin and Probenecid for Oral Suspension; Ampicillin and Sulbactam for Injection; Ampicillin Capsules; Ampicillin for Injectable Suspension; Ampicillin for Injection; Ampicillin for Oral Suspension; Ampicillin Tablets.

Apramycin *(BAN, USAN, rINN)*

47657; Apramicina; Apramycine; Apramycinum; EL-857; EL-857/820; Nebramycin Factor 2; Апрамицин.

4-*O*-[(2*R*,3*R*,4a*S*,6*R*,7*S*,8*R*,8a*R*)-3-Amino-6-(4-amino-4-deoxy-α-D-glucopyranosyloxy)-8-hydroxy-7-methylaminoperhydropyrano[3,2-*b*]pyran-2-yl]-2-deoxystreptamine.

$C_{21}H_{41}N_5O_{11}$=539.6

CAS — 37321-09-8.

ATC Vet — QA07AA92; QJ01GB90; QJ51GB90.

UNII — 388K3TR36Z.

Apramycin Sulfate *(BANM, rINNM)*

Apramicina, sulfato de; Apramycin Sulphate; Apramycine, Sulfate d'; Apramycini Sulfas; Apramycinsulfat; Apramysiinisulfaatti; Sulfato de apramicina; Апрамицина Сульфат.

$C_{21}H_{41}N_5O_{11}.2½H_2SO_4$=784.8

CAS — 41194-16-5.

UNII — 8UYL6NAZ3Q.

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2014: (Apramycin Sulfate). The sulfate of an antibiotic produced by certain strains of *Streptomyces tenebrarius* or by other means. The potency is not less than 430 units per mg, calculated with reference to the anhydrous substance. A light brown hygroscopic powder or granular material. Freely soluble in water; practically insoluble in alcohol, in acetone, in ether, and in methyl alcohol.

Profile

Apramycin is an aminoglycoside antibacterial used as the sulfate in veterinary practice for the treatment of susceptible infections.

Arbekacin Sulfate *(rINNM)*

ABK (arbekacin); AHB-DBK (arbekacin); Arbekacin Sulphate; Arbekacina, sulfato de; Arbékacine, Sulfate d'; Arbekacini Sulfas; HABA-Dibekacin (arbekacin); Sulfato de arbekacina; Арбекацина Сульфат.

O-3-Amino-3-deoxy-α-D-glucopyranosyl-(1→4)-*O*-[2,6-diamino-2,3,4,6-tetradeoxy-α-D-*erythro*-hexopyranosyl-(1→6)]-*N*^{1}-[(2*S*)-4-amino-2-hydroxybutyryl]-2-deoxy-L-streptamine sulphate.

$C_{22}H_{44}N_6O_{10}xH_2SO_4$

CAS — 51025-85-5 (arbekacin).

ATC — J01GB12.

ATC Vet — QJ01GB12.

UNII — G7395HZ992.

Pharmacopoeias. In *Jpn*.

Profile

Arbekacin is an aminoglycoside antibacterial derived from dibekacin and has general properties similar to those of gentamicin (p. 306.2). It has been used as the sulfate in the treatment of serious infections due to meticillin-resistant *Staphylococcus aureus*.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Habekacin.

Arsanilic Acid *(BAN, rINN)*

Acide Arsanilique; Ácido arsanílico; Acidum Arsanilicum; Aminarsonic Acid; Arsanílico, ácido; AS-101; Арсаниловая Кислота.

p-Aminobenzenearsonic acid; 4-Aminophenylarsonic acid.

$C_6H_8AsNO_3$=217.1

CAS — 98-50-0.

UNII — UDX9AKS7GM.

NOTE. The code AS-101 has also been used for an immunomodulator investigated as an antineoplastic and antiviral.

Pharmacopoeias. In *US* for veterinary use only.

USP 36: (Arsanilic Acid). A white to off-white crystalline powder. Soluble in hot water, in amyl alcohol, and in solutions of alkali carbonates; slightly soluble in cold water, in alcohol, and in acetic acid; insoluble in acetone, in chloroform, in ether, in benzene, and in dilute mineral acids; sparingly soluble in concentrated mineral acids.

Sodium Arsanilate *(BANM, rINNM)*

Arsanilate de Sodium; Arsanilato sódico; Natrii Arsanilas; Sodium Aminarsonate; Sodium Anilarsonate; Натрий Арсанилат.

Sodium 4-aminophenylarsonate.

$C_6H_7AsNNaO_3$=239.0

CAS — 127-85-5.

UNII — UC2409302Q.

Pharmacopoeias. *Fr.* includes the anhydrous substance and the trihydrate.

Profile

Arsanilic acid and sodium arsanilate are used in veterinary medicine for the prophylaxis and treatment of enteric infections in pigs and also as growth-promoting agents.

Aspoxicillin *(rINN)*

Aspoxicilina; Aspoxicilline; Aspoxicillinum; TA-058; Аспоксициллин.

(2*S*,5*R*,6*R*)-6-{[(2*R*)-2-[(2*R*)-2-Amino-3-(methylcarbamoyl)propionamido]-2-(*p*-hydroxyphenyl)acetamido}-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]-heptane-2-carboxylic acid.

$C_{21}H_{27}N_5O_7S$=493.5

CAS — 63358-49-6.

UNII — 0745KNO26J.

Pharmacopoeias. *Jpn* includes the trihydrate.

Profile

Aspoxicillin is a ureidopenicillin that has been given intravenously in the treatment of susceptible infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Doyle.

Astromicin Sulfate *(USAN, pINNM)*

Abbott-44747; Astromicin Sulphate; Astromicina, sulfato de; Astromicine, Sulfate d'; Astromicini Sulfas; Fortimicin A Sulphate; KW-1070; Sulfato de astromicina; Астромицина Сульфат.

4-Amino-1-(2-amino-*N*-methylacetamido)-1,4-dideoxy-3-*O*-(2,6-diamino-2,3,4,6,7-pentadeoxy-β-L-*lyxo*-heptopyranosyl)-6-*O*-methyl-L-*chiro*-inositol sulphate.

$C_{17}H_{35}N_5O_6.2H_2SO_4$=601.6

CAS — 55779-06-1 (astromicin); 72275-67-3 (astromicin sulfate); 66768-12-5 (xH_2SO_4).

UNII — POY3S0T3BD.

Pharmacopoeias. In *Jpn*.

Profile

Astromicin is an aminoglycoside antibacterial produced by *Micromonospora* spp. and with actions and uses similar to those of gentamicin (p. 306.2). Astromicin sulfate has been given by intramuscular injection or intravenous infusion. Dosage should be adjusted based on serum-astromicin concentration monitoring.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Fortimicin†.

Avilamycin *(BAN, USAN, rINN)*

Avilamicina; Avilamycine; Avilamycinum; LY-048740 (avilamycin or avilamycin A); Авиламицин.

$C_{61}H_{88}Cl_2O_{32}$ (avilamycin A)=1404.2

CAS — 11051-71-1 (avilamycin); 69787-79-7 (avilamycin A); 69787-80-0 (avilamycin C).

UNII — 720WDX56D3.

Profile

Avilamycin is an antibacterial that has been used in veterinary medicine as a growth promotor.

Avoparcin *(BAN, USAN, rINN)*

Avoparcina; Avoparcine; Avoparcinum; Compound 254; Авопарцин.

CAS — 37332-99-3.

Profile

Avoparcin is a glycopeptide antibacterial usually produced by *Amycolatopsis coloradensis* (*Streptomyces candidus*). It has been incorporated into animal feedstuffs to promote growth.

Cross-resistance. There is evidence of cross-resistance between avoparcin and vancomycin.[1] Suggestions that vancomycin-resistant organisms could enter the human population from the food chain as a result of the use of avoparcin as a growth promotor in animals[2,3] were disputed by the manufacturers of avoparcin,[4,5] but such use has now been banned in many countries. After a ban in the EU on the use of avoparcin as a growth promotor in animals there has been some evidence[6,7] of a decrease in the prevalence of vancomycin-resistant enterococci in animal and human flora, but other studies in various countries[8-10] have indicated considerable persistence of such organisms.

1. Klare I, *et al.* vanA-mediated high-level glycopeptide resistance in Enterococcus faecium from animal husbandry. *FEMS Microbiol Lett* 1995; 125: 165–72.
2. Howarth P, Poulter D. Vancomycin resistance: time to ban avoparcin? *Lancet* 1996; 347: 1047.
3. Wise R. Avoparcin and animal feedstuff. *Lancet* 1996; 347: 1835.
4. Mudd A. Vancomycin resistance and avoparcin. *Lancet* 1996; 347: 1412.
5. Mudd AJ. Is it time to ban all antibiotics as animal growth-promoting agents? *Lancet* 1996; 348: 1454–5.
6. Pantosti A, *et al.* Decrease of vancomycin-resistant enterococci in poultry meat after avoparcin ban. *Lancet* 1999; 354: 741–2.
7. van den Bogaard AE, *et al.* The effect of banning avoparcin on VRE carriage in The Netherlands. *J Antimicrob Chemother* 2000; 46: 146–7.
8. Manson JM, *et al.* Persistence of vancomycin-resistant enterococci in New Zealand broilers after discontinuation of avoparcin use. *Appl Environ Microbiol* 2004; 70: 5764–8.
9. Sørum M, *et al.* Prevalence, persistence, and molecular characterization of glycopeptide-resistant enterococci in Norwegian poultry and poultry farmers 3 to 8 years after the ban on avoparcin. *Appl Environ Microbiol* 2006; 72: 516–21.
10. Lim SK, *et al.* Persistence of vanA-type Enterococcus faecium in Korean livestock after ban on avoparcin. *Microb Drug Resist* 2006; 12: 136–9.

Azidamfenicol *(BAN, rINN)*

Azidamfénicol; Azidamfenicolum; Azidamphenicol; Azidanfenicol; Azidoamphenicol; Bayer-52910; Азидамфеникол.

2-Azido-*N*-[(α*R*,β*R*)-β-hydroxy-α-hydroxymethyl-4-nitrophenethyl]acetamide.

$C_{11}H_{13}N_5O_5$=295.3

CAS — 13838-08-9.

ATC — S01AA25.

ATC Vet — QS01AA25.

UNII — 40257685LM.

Profile

Azidamfenicol is an antibacterial that is related structurally to chloramphenicol (p. 259.1). It has been used as 1% eye drops in the treatment of bacterial eye infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Thilocof.

Azidocillin Sodium *(BANM, rINNM)*

Azidobenzylpenicillin Sodium; Azidocilina sódica; Azidocilline Sodique; Natrii Azidocillinum; Натрий Азидоциллин.

Sodium (6*R*)-6-(D-2-azido-2-phenylacetamido)penicillanate.

$C_{16}H_{16}N_5NaO_4S$=397.4

CAS — 17243-38-8 (azidocillin); 35334-12-4 (azidocillin sodium).

ATC — J01CE04.

ATC Vet — QJ01CE04.

UNII — 0XPT6W6670.

Profile

Azidocillin is a semisynthetic penicillin with actions and uses similar to those of phenoxymethylpenicillin (p. 340.3). It has been given orally as the sodium salt in the treatment of susceptible infections. The potassium salt has also been used.

Azithromycin *(BAN, USAN, rINN)*

Atsitromysiini; Azithromycine; Azithromycinum; Azitromicina; Azitromicinas; Azitromisin; Azitromycin; Azytromycyna; CP-62993; XZ-450; Азитромицин.

(2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-(2,6-Dideoxy-3-C-3-*O*-dimethyl-α-L-*ribo*-hexopyranosyloxy)-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-(3,4,6-trideoxy-3-dimethylamino-β-D-*xylo*-hexopyranosyloxy)-1-oxa-6-azacyclopentadecan-15-one dihydrate; 9-Deoxo-9a-aza-9a-methyl-9a-homoerythromycin A dihydrate.

$C_{38}H_{72}N_2O_{12}.2H_2O$=785.0

CAS — 83905-01-5 (anhydrous azithromycin); 121470-24-4 (azithromycin monohydrate); 117772-70-0 (azithromycin dihydrate).

ATC — J01FA10; S01AA26.

ATC Vet — QJ01FA10; QS01AA26.

UNII — F94OWS8Y8V (azithromycin); J2KLZ20U1M (anhydrous azithromycin); JTE4MNN1MD (azithromycin monohydrate); 5FD1131I7S (azithromycin dihydrate).

Pharmacopoeias. In *Chin.* and *Jpn.*

Eur. (see p. vii) and *US* include the monohydrate and the dihydrate.

Ph. Eur. 8: (Azithromycin). A white or almost white powder. Practically insoluble in water; freely soluble in dehydrated alcohol and in dichloromethane. A 0.2% solution in a mixture of methyl alcohol and water (1:1) has a pH of 9.0 to 11.0. Store in airtight containers.

USP 36: (Azithromycin). A white or almost white powder. Practically insoluble in water; freely soluble in anhydrous alcohol and in dichloromethane. It is anhydrous or contains one or two molecules of water of hydration. pH of a 0.2% solution in a mixture of methyl alcohol and water (1:1) is between 9.0 and 11.0. Store in airtight containers.

Uses and Administration

Azithromycin is a nitrogen-containing macrolide (azalide) with actions and uses similar to those of erythromycin (p. 294.1). It is given in the treatment of respiratory-tract infections (including otitis media), in skin and soft-tissue infections, and in uncomplicated genital infections. Azithromycin may also be used for the prophylaxis, and as a component of regimens in the treatment, of *Mycobacterium avium* complex (MAC) infections. It is used in some countries for the prophylaxis of endocarditis in at-risk patients unable to take penicillin. It is also used in the management of trachoma and typhoid.

For details of all these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Azithromycin has been tried in protozoal infections such as babesiosis (p. 223.3), cryptosporidiosis (p. 923.1), and toxoplasmosis (p. 926.1).

It is given orally or by intravenous infusion usually as the dihydrate; doses are expressed in terms of the anhydrous substance. Azithromycin dihydrate 524 mg is equivalent to about 500 mg of anhydrous azithromycin. The capsule formulation should be given at least 1 hour before, or 2 hours after, meals.

The usual oral dose of azithromycin is 500 mg as a single dose daily for 3 days. Alternatively, an initial dose of 500 mg may be followed by 250 mg daily for a further 4 days.

For uncomplicated genital infections caused by *Chlamydia trachomatis* and for chancroid, 1 g of azithromycin is given as a single dose. For uncomplicated gonococcal infections a single oral 1-g dose of azithromycin with a single dose of a cephalosporin such as ceftriaxone is generally recommended. For the treatment of granuloma inguinale, an initial dose of 1 g followed by 500 mg daily may be given, or 1 g may be given once a week for at least 3 weeks, until all lesions have completely healed.

In the USA, a modified-release preparation given as an oral suspension is available. The product delivers a single 2-g dose and should also be taken on an empty stomach. It is licensed for the treatment of acute bacterial sinusitis or community-acquired pneumonia in adults.

For prophylaxis of disseminated MAC infections, azithromycin 1.2 g may be given once weekly. For treatment or secondary prophylaxis, 500 to 600 mg (depending on the formulation used) should be given once daily, with other antimycobacterials.

For mild or moderate typhoid caused by multidrug-resistant strains, 500 mg once daily may be given for 7 days.

For details of doses in children, see p. 223.3.

Azithromycin dihydrate may also be given initially by intravenous infusion to adults in doses equivalent to 500 mg of azithromycin as a single daily dose in the treatment of community-acquired pneumonia and pelvic inflammatory disease; treatment should be changed to the oral route after at least 2 days in pneumonia and after 1 or 2 days in pelvic inflammatory disease. It may be given either in a solution containing 1 mg/mL over 3 hours or in a solution containing 2 mg/mL over 1 hour.

Azithromycin is also available as 1% (as the base) or 1.5% (as the dihydrate) eye drops for the topical treatment of conjunctivitis caused by susceptible strains of bacteria; the 1.5% solution may also be used for the treatment of trachomatous conjunctivitis (see p. 224.1).

Reviews.

1. Peters DH, *et al.* Azithromycin: a review of its antimicrobial activity, pharmacokinetic properties and clinical efficacy. *Drugs* 1992; 44: 750–99.
2. Langtry HD, Balfour JA. Azithromycin: a review of its use in paediatric infectious disease. *Drugs* 1998; 56: 273–97.
3. Garey KW, Amsden GW. Intravenous azithromycin. *Ann Pharmacother* 1999; 33: 218–28.
4. Ioannidis JPA, *et al.* Meta-analysis of randomized controlled trials on the comparative efficacy and safety of azithromycin against other antibiotics for upper respiratory tract infections. *J Antimicrob Chemother* 2001; 48: 677–89.
5. Contopoulos-Ioannidis DG, *et al.* Meta-analysis of randomized controlled trials on the comparative efficacy and safety of azithromycin against other antibiotics for lower respiratory tract infections. *J Antimicrob Chemother* 2001; 48: 691–703.
6. Law C, Amsden GW. Single-dose azithromycin for respiratory tract infections. *Ann Pharmacother* 2004; 38: 433–9.
7. Blumer JL. Evolution of a new drug formulation: the rationale for high-dose, short-course therapy with azithromycin. *Int J Antimicrob Agents* 2005; 26 (suppl 3): S143–S147.
8. Swainston Harrison T, Keam SJ. Azithromycin extended release: a review of its use in the treatment of acute bacterial sinusitis and community-acquired pneumonia in the US. *Drugs* 2007; 67: 773–92.
9. Panpanich R, *et al.* Azithromycin for acute lower respiratory tract infections. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 18/06/08).
10. Effa EE, Bukirwa H. Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever). Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 26/08/09).
11. Zuckerman JM, *et al.* Macrolides, ketolides, and glycylcyclines: azithromycin, clarithromycin, telithromycin, tigecycline. *Infect Dis Clin North Am* 2009; 23: 997–1026.

Administration in children. Azithromycin is licensed for use in infants and children for the treatment of infections caused by susceptible organisms. The usual oral dose in those over 6 months of age is 10 mg/kg once daily for 3 days, or an initial dose of 10 mg/kg may be followed by 5 mg/kg daily for a further 4 days; those who weigh over 45 kg may be given the usual adult dose (see Uses and Administration, above). A single dose of 30 mg/kg may also be given for acute otitis media. For pharyngitis or tonsillitis in children aged over 2 years, 12 mg/kg once daily for 5 days may be given. In the USA, a modified-release preparation is available as an oral suspension; and may be used in a single dose of 60 mg/kg (maximum 2 g) for the treatment of community-acquired pneumonia among children 6 months of age and older.

In the UK, the *BNFC* suggests that azithromycin may be used in penicillin allergic children for the prevention of secondary cases of group A streptococcal infection; those 6 months and older may be given an oral dose of 12 mg/kg (to a maximum of 500 mg) once daily for 5 days.

For chronic *Pseudomonas aeruginosa* infection in cystic fibrosis, the *BNFC* suggests that azithromycin may be given orally, 3 times a week, to children from 6 years of age. Those weighing 25 to 40 kg may be given 250 mg, while those weighing more than 40 kg may be given a dose of 500 mg.

The *BNFC* also suggests giving azithromycin 10 mg/kg (to a maximum of 500 mg) once daily for 7 days in the treatment of mild to moderate typhoid caused by multidrug-resistant strains in those aged 6 months and over.

US guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children suggest that for prophylaxis of disseminated *Mycobacterium avium* complex infections, azithromycin 20 mg/kg (to a maximum of 1.2 g) once weekly or 5 mg/kg (to a maximum of 250 mg) once daily may be given.[1] For treatment, 10 to 12 mg/kg (to a maximum of 500 mg) once daily should be given with other antimycobacterials.[1]

1. Panel on Opportunistic Infections in HIV-Exposed and HIV-Infected Children. *Guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and HIV-infected children: recommendations from the National Institutes of Health, CDC, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics* (issued 6th November, 2013). Available at: http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/oi_guidelines_pediatrics.pdf (accessed 09/12/13)

Babesiosis. In a prospective, randomised study[1] involving 58 patients with babesiosis (p. 922.2), azithromycin with atovaquone was found to be as effective as, and associated with fewer adverse effects than, standard therapy with quinine and clindamycin. Azithromycin 500 to 1000 mg on day 1 followed by 250 mg once daily thereafter, with atovaquone 750 mg twice daily, both orally for 7 to 10 days, has been recommended by some experts[2] in the USA for the treatment of babesiosis. Immunocompromised patients should be given higher doses of azithromycin (600 to 1000 mg daily). Children may be given azithromycin 10 mg/kg (maximum 500 mg) on day 1 followed by 5 mg/kg (maximum 250 mg) once daily thereafter, with atovaquone 20 mg/kg (maximum 750 mg) twice daily, both orally for 7 to 10 days.[2,3] Azithromycin with quinine

was reported to be effective in 2 patients who had not responded to quinine plus clindamycin.[4,5]

1. Krause PJ, *et al.* Atovaquone and azithromycin for the treatment of babesiosis. *N Engl J Med* 2000; **343:** 1454–8.
2. Wormser GP, *et al.* The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2006; **43:** 1089–1134. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/508667 (accessed 12/08/08)
3. Abramowicz M, ed. *Drugs for parasitic infections.* 3rd ed. New Rochelle NY: The Medical Letter, 2013.
4. Shaio MF, Yang KD. Response of babesiosis to a combined regimen of quinine and azithromycin. *Trans R Soc Trop Med Hyg* 1997; **91:** 214–15.
5. Shih C-M, Wang C-C. Ability of azithromycin in combination with quinine for the elimination of babesial infection in humans. *Am J Trop Med Hyg* 1998; **59:** 509–12.

Cholera. Azithromycin has been tried[1-3] in the treatment of cholera (p. 184.2). A single dose of 10 or 20 mg/kg was found to be effective in children[1,2] and 1 g in adults.[3]

1. Khan WA, *et al.* Comparison of single-dose azithromycin and 12-dose, 3-day erythromycin for childhood cholera: a randomised, double-blind trial. *Lancet* 2002; **360:** 1722–7.
2. Bhattacharya MK, *et al.* Azithromycin in the treatment of cholera in children. *Acta Paediatr* 2003; **92:** 676–8.
3. Saha D, *et al.* Single-dose azithromycin for the treatment of cholera in adults. *N Engl J Med* 2006; **354:** 2452–62.

Eye infections. Azithromycin 1 or 1.5% ophthalmic solution is effective[1-3] in the treatment of bacterial conjunctivitis, blepharitis, and dry eye, including contact lens-related dry eye. The 1.5% ophthalmic solution may also be used for the treatment of trachoma[3] including mass treatment programmes.[4] For further information on the management of trachoma, see p. 210.1.

1. Utine CA. Update and critical appraisal of the use of topical azithromycin ophthalmic 1% (AzaSite) solution in the treatment of ocular infections. *Clin Ophthalmol* 2011; **5:** 801–9.
2. Nichols JJ, *et al.* Safety and efficacy of topical azithromycin ophthalmic solution 1.0% in the treatment of contact lens-related dry eye. *Eye Contact Lens* 2012; **38:** 73–9.
3. Garnock-Jones KP. Azithromycin 1.5% ophthalmic solution: in purulent bacterial or trachomatous conjunctivitis. *Drugs* 2012; **72:** 361–73.
4. Amza A, *et al.* Elimination of active trachoma after two topical mass treatments with azithromycin 1.5% eye drops. *PLoS Negl Trop Dis* 2010; **4:** e895.

Hyperplasia. For reference to the use of azithromycin to control ciclosporin-induced gingival hyperplasia, see p. 1954.3.

Ischaemic heart disease. Macrolide antibacterials, including azithromycin,[1-4] clarithromycin,[5-9] and roxithromycin,[10-14] have been investigated in the prevention of ischaemic heart disease, based on a suggested link between atherosclerosis and infection with *Chlamydophila pneumoniae* (*Chlamydia pneumoniae*) (see p. 177.1). Although preliminary results from some pilot studies were promising, longer-term studies in large numbers of patients were disappointing and none of the three macrolides decreased ischaemic events or provided clinical benefit; indeed, in one study[9] an unexpected increase in cardiovascular mortality was seen in those taking clarithromycin.

1. Anderson JL, *et al.* Randomized secondary prevention trial of azithromycin in patients with coronary artery disease and serological evidence for Chlamydia pneumoniae infection: the Azithromycin in Coronary Artery Disease: Elimination of Myocardial Infection with Chlamydia (ACADEMIC) study. *Circulation* 1999; **99:** 1540–7.
2. Cercek B, *et al.* Effect of short-term treatment with azithromycin on recurrent ischaemic events in patients with acute coronary syndrome in the Azithromycin in Acute Coronary Syndrome (AZACS) trial: a randomised controlled trial. *Lancet* 2003; **361:** 809–13.
3. O'Connor CM, *et al.* Azithromycin for the secondary prevention of coronary heart disease events: the WIZARD study: a randomized controlled trial. *JAMA* 2003; **290:** 1459–66.
4. Grayston JT, *et al.* Azithromycin for the secondary prevention of coronary events. *N Engl J Med* 2005; **352:** 1637–45.
5. Sinisalo J, *et al.* Effect of 3 months of antimicrobial treatment with clarithromycin in acute non-Q-wave coronary syndrome. *Circulation* 2002; **105:** 1555–60.
6. Berg HF, *et al.* Effect of clarithromycin on inflammatory markers in patients with atherosclerosis. *Clin Diagn Lab Immunol* 2003; **10:** 525–8.
7. Berg HF, *et al.* Treatment with clarithromycin prior to coronary artery bypass graft surgery does not prevent subsequent cardiac events. *Clin Infect Dis* 2005; **40:** 358–65.
8. Berg HF, *et al.* Effect of clarithromycin treatment on Chlamydia pneumoniae in vascular tissue of patients with coronary artery disease: a randomized, double-blind, placebo-controlled trial. *J Clin Microbiol* 2005; **43:** 1325–9.
9. Jespersen CM, *et al.* Randomised placebo controlled multicentre trial to assess short term clarithromycin for patients with stable coronary heart disease: CLARICOR trial. *BMJ* 2006; **332:** 22–7. Correction. *ibid.*; 151.
10. Gurfinkel E, *et al.* Treatment with the antibiotic roxithromycin in patients with acute non-Q-wave coronary syndromes: the final report of the ROXIS Study. *Eur Heart J* 1999; **20:** 121–7.
11. Wiesli P, *et al.* Roxithromycin treatment prevents progression of peripheral arterial occlusive disease in Chlamydia pneumoniae seropositive men: a randomized, double-blind, placebo-controlled trial. *Circulation* 2002; **105:** 2646–52.
12. Zahn R, *et al.* Antibiotic therapy after acute myocardial infarction: a prospective randomized study. *Circulation* 2003; **107:** 1253–9.
13. Sander D, *et al.* Progression of early carotid atherosclerosis is only temporarily reduced after antibiotic treatment of Chlamydia pneumoniae seropositivity. *Circulation* 2004; **109:** 1010–15.
14. Kaehler J, *et al.* A randomized trial in patients undergoing percutaneous coronary angioplasty: roxithromycin does not reduce clinical restenosis but angioplasty increases antibody concentrations against Chlamydia pneumoniae. *Am Heart J* 2005; **150:** 987–93.

Malaria. Azithromycin has been studied[1-7] in the management of malaria. Studies[1,4] have shown that an initial loading dose of 750 mg of azithromycin on the first day followed by 250 mg daily thereafter for 20 weeks was effective in the prophylaxis of *Plasmodium vivax* malaria; the drug was well tolerated and the most frequently reported adverse effects were heartburn, paraesthesia, and itching.[3] A study[5] of the treatment of *P. vivax* malaria found that azithromycin 1 g daily for 3 days produced an 88% clinical response rate by day 7, but had a slower onset of action than chloroquine 600 mg daily for 2 days then 300 mg on day 3, which produced a response of 99%.

Azithromycin in various doses (typically 500 mg one to three times daily) with other antimalarials, such as artesunate 200 mg daily[2,7] or quinine 10 mg/kg 3 times daily,[6,7] given for 3 days was found to be effective in the treatment of uncomplicated multidrug-resistant *P. falciparum* malaria in Southeast Asia. However, a later study among Tanzanian children[8] did not support the use of azithromycin with artesunate to treat malaria or acute febrile illness in children in areas of Africa with high levels of antimalarial drug resistance. A systematic review[9] of studies over a period of 14 years suggested that azithromycin was a weak antimalarial. Furthermore, there was no evidence that azithromycin-containing regimens were better than or equivalent to other antimalarials or to current first-line antimalarial combinations for the treatment of *P. falciparum* or *P. vivax*.

Further studies are warranted, especially in children and pregnant women.

1. Taylor WR, *et al.* Malaria prophylaxis using azithromycin: a double-blind, placebo-controlled trial in Irian Jaya, Indonesia. *Clin Infect Dis* 1999; **28:** 74–81.
2. Krudsood S, *et al.* A randomized clinical trial of combinations of artesunate and azithromycin for treatment of uncomplicated Plasmodium falciparum malaria in Thailand. *Southeast Asian J Trop Med Public Health* 2000; **31:** 801–7.
3. Taylor WR, *et al.* Tolerability of azithromycin as malaria prophylaxis in adults in Northeast Papua, Indonesia. *Antimicrob Agents Chemother* 2003; **47:** 2199–2203.
4. Heppner DG, *et al.* Randomized, controlled, double-blind trial of daily oral azithromycin in adults for the prophylaxis of Plasmodium vivax malaria in Western Thailand. *Am J Trop Med Hyg* 2005; **73:** 842–9.
5. Dunne MW, *et al.* A double-blind, randomized study of azithromycin compared to chloroquine for the treatment of Plasmodium vivax malaria in India. *Am J Trop Med Hyg* 2005; **73:** 1108–11.
6. Miller RS, *et al.* Effective treatment of uncomplicated Plasmodium falciparum malaria with azithromycin-quinine combinations: a randomized, dose-ranging study. *Am J Trop Med Hyg* 2006; **74:** 401–6.
7. Noedl H, *et al.* Azithromycin combination therapy with artesunate or quinine for the treatment of uncomplicated Plasmodium falciparum malaria in adults: a randomized, phase 2 clinical trial in Thailand. *Clin Infect Dis* 2006; **43:** 1264–71.
8. Sykes A, *et al.* Azithromycin plus artesunate versus artemether-lumefantrine for treatment of uncomplicated malaria in Tanzanian children: a randomized, controlled trial. *Clin Infect Dis* 2009; **49:** 1195–1201.
9. van Eijk AM, Terlouw DJ. Azithromycin for treating uncomplicated malaria. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2011 (accessed 26/06/12).

Respiratory disorders. For reference to the use of azithromycin in the management of respiratory disorders, see under Erythromycin, p. 294.3.

Adverse Effects and Precautions

As for Erythromycin, p. 295.1.

Gastrointestinal disturbances are the most frequent adverse effect of azithromycin but are usually mild and less frequent than with erythromycin. Headache, somnolence, and taste disturbances may occur. Severe hypersensitivity reactions occur rarely but may be prolonged. Thrombocytopenia and mild transient neutropenia have been rarely reported in patients receiving azithromycin. Pain and inflammation may occur at the site of intravenous infusions particularly at high concentrations. Azithromycin may aggravate muscle weakness in patients with myasthenia gravis and new onset of myasthenic syndromes has been reported.

Licensed product information states that azithromycin should be used with caution in patients with hepatic or renal impairment. It should not be given to those with severe hepatic impairment as safety has not been established. Although plasma concentrations may be increased in renal impairment dosage adjustment is not usually required.

Incidence of adverse effects. In 39 patients given azithromycin daily long-term for mycobacterial infections,[1] gastrointestinal disorders occurred in 32 (82%), hearing impairment in 10 (26%), tinnitus in 18 (46%), and poor balance or dizziness in 11 (28%). In general, adverse effects were associated with higher serum-azithromycin concentrations.

1. Brown BA, *et al.* Relationship of adverse events to serum drug levels in patients receiving high-dose azithromycin for mycobacterial lung disease. *Clin Infect Dis* 1997; **24:** 958–64.

Effects on the ears. Reversible sensorineural hearing loss was reported in 3 patients given oral azithromycin 500 mg daily with clofazimine and ethambutol for the treatment of disseminated *Mycobacterium avium* complex infection.[1] Irreversible hearing loss has also been reported after low-dose exposure to oral azithromycin.[2,3] A patient who had had 8 days of treatment with intravenous azithromycin 500 mg daily for pneumonia reported complete deafness, which had resolved 20 days after stopping the drug.[4]

See also Incidence of Adverse Effects, above.

1. Wallace MR, *et al.* Ototoxicity with azithromycin. *Lancet* 1994; **343:** 241.
2. Ress BD, Gross EM. Irreversible sensorineural hearing loss as a result of azithromycin ototoxicity: a case report. *Ann Otol Rhinol Laryngol* 2000; **109:** 435–7.
3. Mick P, Westerberg BD. Sensorineural hearing loss as a probable serious adverse drug reaction associated with low-dose oral azithromycin. *J Otolaryngol* 2007; **36:** 257–63.
4. Bizjak ED, *et al.* Intravenous azithromycin-induced ototoxicity. *Pharmacotherapy* 1999; **19:** 245–8.

Effects on fluid and electrolyte homoeostasis. The syndrome of inappropriate antidiuretic hormone secretion was associated with azithromycin treatment in a patient.[1,2]

1. Cadle RM, *et al.* Symptomatic syndrome of inappropriate antidiuretic hormone secretion associated with azithromycin. *Ann Pharmacother* 1997; **31:** 1308–10.
2. Kintzel PE. Correction: symptomatic syndrome of inappropriate antidiuretic hormone secretion associated with azithromycin. *Ann Pharmacother* 1998; **32:** 388.

Effects on the kidneys. Acute interstitial nephritis leading to irreversible renal failure has been reported[1] in a patient who received azithromycin for 9 days. A later report[2] described a patient who developed recurrent acute interstitial nephritis after courses of azithromycin. Repeated exposure resulted in persistent renal damage; leucocytosis and eosinophilia were still present 1 year later.

1. Mansoor GA, *et al.* Azithromycin-induced acute interstitial nephritis. *Ann Intern Med* 1993; **119:** 636–7.
2. Soni N, *et al.* Recurrent acute interstitial nephritis induced by azithromycin. *Pediatr Infect Dis J* 2004; **23:** 965–6.

Effects on the liver. A case[1] of probable azithromycin-induced hepatotoxicity occurred in an elderly patient, with no history of liver disease, after receiving four days of high-dose oral azithromycin for the treatment of suspected bronchitis.

1. Lockwood AM, *et al.* Azithromycin-induced liver injury. *Am J Health-Syst Pharm* 2010; **67:** 810–14.

Hypersensitivity. A syndrome characterised by eosinophilia, arthralgia, fever, and rash was associated with azithromycin or roxithromycin treatment in a patient on separate occasions.[1] The authors believed the condition represented the Churg-Strauss syndrome, although this was disputed by others[2] and attributed to the eosinophilia-myalgia syndrome.

A fatal case of DRESS (drug rash with eosinophilia and systemic symptoms) syndrome and hypersensitivity myocarditis associated with azithromycin use has been reported.[3] There has also been a report[4] of vanishing bile duct syndrome associated with the use of azithromycin and developing a month after initial presentation of Stevens-Johnson syndrome; the patient eventually required liver transplantation.

1. Hübner C, *et al.* Macrolide-induced Churg-Strauss syndrome in a patient with atopy. *Lancet* 1997; **350:** 563.
2. Kränke B, Aberer W. Macrolide-induced Churg-Strauss syndrome in patient with atopy. *Lancet* 1997; **350:** 1551–2.
3. Pursnani A, *et al.* Hypersensitivity myocarditis associated with azithromycin exposure. *Ann Intern Med* 2009; **150:** 225–6.
4. Danica J, *et al.* Vanishing bile duct syndrome associated with azithromycin in a 62-year-old man. *Basic Clin Pharmacol Toxicol* 2010; **106:** 62–5.

Overdosage. Bradycardia with complete heart block was reported[1] in a 9-month-old infant who had been inadvertently given about 50 mg/kg of azithromycin intravenously.

1. Tilelli JA, *et al.* Life-threatening bradyarrhythmia after massive azithromycin overdose. *Pharmacotherapy* 2006; **26:** 147–50.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies azithromycin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

For a discussion of drug interactions of macrolide antibacterials, see Erythromycin, p. 296.2.

Giving azithromycin with antacids containing aluminium or magnesium salts can reduce the rate, but not the extent, of its absorption; azithromycin should be given at least 1 hour before or 2 hours after the antacid.

Antiretrovirals. Azithromycin serum concentrations are markedly increased when it is given with *nelfinavir*,[1] but

the clinical significance of this is uncertain. US licensed product information for azithromycin states that dosage adjustment is not required although the patient should be closely monitored for adverse effects.

1. Amsden GW, *et al.* A study of the pharmacokinetics of azithromycin and nelfinavir when coadministered in healthy volunteers. *J Clin Pharmacol* 2000; **40**: 1522–7.

Antimicrobial Action

As for Erythromycin, p. 297.1. Azithromycin is less active than erythromycin against streptococci and staphylococci, but has greater activity than erythromycin *in vitro* against some Gram-negative organisms such as *Haemophilus influenzae* and *Moraxella catarrhalis* (*Branhamella catarrhalis*), as well as having activity against some of the Enterobacteriaceae such as *Escherichia coli* and *Salmonella* and *Shigella* spp. Azithromycin is also more active than erythromycin against *Chlamydia trachomatis* and *Ureaplasma urealyticum*, and some opportunistic mycobacteria, including *Mycobacterium avium* complex. It has activity against the protozoa *Toxoplasma gondii* and *Plasmodium falciparum*.

Resistance. The pattern of resistance to azithromycin is similar to that seen with clarithromycin (p. 270.1).

Pharmacokinetics

Azithromycin given orally is rapidly absorbed and about 40% bioavailable. Absorption from capsules, but not tablets or suspension, is reduced by food. Peak plasma concentrations occur 2 to 3 hours after an oral dose and 1 to 2 hours after intravenous dosage. However, azithromycin is extensively distributed into the tissues, and tissue concentrations subsequently remain much higher than those in the blood; in contrast to most other antibacterials, plasma concentrations are therefore of little value as a guide to efficacy. High concentrations are taken up into white blood cells. There is little diffusion into the CSF when the meninges are not inflamed. Data from *animal* studies indicate that azithromycin crosses the placenta. Small amounts of azithromycin are demethylated in the liver, and it is excreted in bile mainly as unchanged drug and some inactive metabolites have also been detected. About 6% of an oral dose (representing about 20% of the amount in the systemic circulation) is excreted in the urine. The terminal elimination half-life is about 68 hours.

Reviews and references.

1. Lalak NJ, Morris DL. Azithromycin clinical pharmacokinetics. *Clin Pharmacokinet* 1993; **25**: 370–4.
2. Luke DR, *et al.* Safety, toleration, and pharmacokinetics of intravenous azithromycin. *Antimicrob Agents Chemother* 1996; **40**: 2577–81.
3. Rapp RP. Pharmacokinetics and pharmacodynamics of intravenous and oral azithromycin: enhanced tissue activity and minimal drug interactions. *Ann Pharmacother* 1998; **32**: 785–93.
4. Chandra R, *et al.* Clinical pharmacokinetics and gastrointestinal tolerability of a novel extended-release microsphere formulation of azithromycin. *Clin Pharmacokinet* 2007; **46**: 247–59.
5. Salman S, *et al.* Pharmacokinetic properties of azithromycin in pregnancy. *Antimicrob Agents Chemother* 2010; **54**: 360–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Arzomicin; Azibiotic; Azitral; Azitrogal; Azitrolabsa; Azitrolan; Azitrona; Azitrox; Cetaxim; Clearsing; Cronopen; Doyle; Fabodrox; Fabramicina; Macromax; Misultina; Naxocina; Neblic; Nifostin; Novozitron; Orobiotic; Sitrox; Talcilina; Tanezox; Triamid; Tritab; Tromiatlas; Vectocilina; Visag; Zitromax; *Austral.*: Azith; Zedd; Zithromax; Zitrocin; *Austria*: Azyter; Zithromax; *Belg.*: Zitromax; *Braz.*: Astro; Atromicin; Azalide†; Azatill†; Azi; Azimed; Azimix; Azinostil; Azitrin; Azitrogran; Azitrolab; Azitromicil; Azitron; Azitrophar; Azitrosol; Azitroxil†; Clindal; Ems-Max†; Mac Azi; Mazitrom; Novatrex; Selimax Pulso; Selimax; Tromix; Tromizir; Trozyman†; Zidimax; Zimicina; Zitril; Zitromax; Zitromil; Zitroneo; *Canad.*: Z-Pak; Zithromax; Zmax; *Chile*: Abacten; Atizor; Azimit; Azitrom; Ricilina; Trex; Zithromax; *China*: A Sai Qi (阿赛奇); Ai Mi Qi (爱米琦); Ao Li Ping (澳立平); Ba Qi (八奇); Bin Qi (宾奇); BinQi (滨齐); Chen Yu (辰羽); Feng Da Qi (锋达齐); Fu Qi-Hua Yuan (弗奇); Fuqixing (芙琦星); Jun Jie (君洁); Jun Wei Qing (君维清); Kai Qi (开奇); Kang Qi (康奇); Ke Lin Da (克琳达); Ke Yan Li (克严力); Kuai Di (快迪); Kuai Yu (快宇); Li Ke Si (利可思); Li Li Kai (利力凯); Li Li Xing (利力欣); Lin Bi (林比); Lipuqi (利普奇); Lipuxin (利普欣); Lizhu Qile (丽珠奇乐); Lu Jia Kang (露家康); Luo Bei Er (洛贝尔); Luo Qi (洛奇); Luoxin Shoukang (罗欣首抗); Ming Qi Xin (明齐欣); Pai Fen (派芬); Pai Fu (派扶); Paiqi (派奇); Pu He (普贺); Pu Le Qi (浦乐齐); Pu Yang (普阳); Qi Gu Mei (奇谷美); Qi Mai Xing (齐迈星); Qi Xian (其仙); QiLi (奇力); Qiyue (琦玥); Rui Qi (瑞奇); Rui Qi Lin (瑞琦霖); Sai Jin Sha (赛金沙); Sai Le Xin (赛乐欣); Sai Qi (赛奇); Sheng Nuo Ling (圣诺灵); Shepherd (欣匹特); Shu Luo Kang (抒罗康); Su Shuang (苏爽); Sumamed (舒美特); Tailite (泰力特); Te Li Xin (特立欣); Tong Tai Qi Li (通泰奇力); TuoQi (托琪); Wei Zong (维宗); Welhong (维宏); Xi Le Xin (西乐欣); Xi Mei (悉美); Xin Da Kang (信达康); Xin Pu Rui (欣普瑞); Ya Rui (雅瑞); Yan Sha (岩沙); Yi Nuo Da (依诺达); Yi Ou Qing (亦欧青); Yi Xin (益欣); Yin Pei Kang (因培康); Yong Qi (永齐); You Ni Ke (尤尼克); Zaiqi (再奇); Ze Qi (泽奇); Zithromax (希舒美); Cz.: Azibiot; Azitrox; Sumamed; Zetamac; Zitrocin; *Denm.*: Azyter; Zitromax; *Fin.*: Azyter; Zithromax; *Fr.*: Azadose; Azyter; Ordipha; Zithromax; *Ger.*: Azithro†; Azithrobeta; Azyter; Ultreon; Zithromax; *Gr.*: Azibacuron; Azifarm; Azirox; Azirutec; Azithral; Azithrin; Azitrolid; Azivirus; Azytan†; Bezanin; Binozyt; Disithrom; Figothrom; Flumax; Goldamycin; Gramokil; Novozithron; Razimax; Thoraxx; Throzimax; Zinfect; Zithro-Due; Zithrobest; Zithromax; Zithroned; Zithropan; Zithroplus; Zithrotel; Zithroxyn; Zitrax; Zyramycin; *Hong Kong*: Azee; Azicine; Clindal AZ; Zithromax; Zmax; Zotax; *Hung.*: Azi; Azibiot; Azicid†; Sumamed; Zitrocin; Zmax; *India*: A-OD; Acex; Actimycin; Alicin; Apocin; Arcin; Arizith; Arz; Atm; Avzeth; Az-1; Azard; Azauk; Azbir; Azee; Azegud; Azeloc; Azforin; Azi-Big; Azibact; Azibest; Azicip; Azicos; Azicure; Azid; Azidraw; Azifast; Azifem; Azifine; Azigram; Azikab; Azikare; Azikil; Azileb; Azilide; Azilife; Azilin; Azilup; Azim; Azimac; Azimax; Azin; Azina; Azinex; Azinix; Azinova; Azintra; Aziom; Azipar; Azipokyn; Azipos; Aziral; Azirid; Aziriv; Azirock; Azis; Azisafe; Azisara; Aziset; Azisia; Arison; Azistar; Azisym; Azitas; Aziter; Azith; Azithom; Azithral; Azithro; Azitone; Azitoz; Aziträc; Azitrin; Azitrop; Azitsa; Azitus; Azivar; Aziwin; Aziwok; Azix; Azla; Azmag; Azmic; Azobac; Azolid; Azolife; Azom; Azomax; Azone; Azopet; Azostar; Azras; Azrea; Azro; Aztin; Aztus; Azvig; Azy; Azylin; Azysafe; Azystate; Azyxin; Azza; Bezit; Bio-AZ; Cazita; Cumycin; Dazy; Elgram; Elzee; Ertycin; Eszit; Ezith; Flaag; Forit; Fydozith; G-Thro; Gitro; Hizy; I-Thro; Infurox; Itha; Jocin; Kanny; L-Thro; Laz; Lazith; Lethro; LG-Thral; Loromycin; Macrosafe; Macrotar; Maxazi; Myza; Nizithro; Nodycin; Zithrocin; Zycin; *Indon.*: Aztrin; Binozyt; Maxmor; Mezatrin; Trozin; Zarom; Zibramax; Zicho; Zifin; Zistic; Zithromax; Zycin; *Irl.*: Azromax; Azyter; Zithromax; *Israel*: Azenil; Zeto; Zithromax; Zmax; *Ital.*: Azitrocin; Batif; Ribotrex; Trozocina; Zindel; Zitrobiotic; Zitromax; *Jpn*: Zithromac; *Malaysia*: Binozyt; Zithromax; Zmax; *Mex.*: Amsati†; Atoxitom; Azibiot; Azidral; Aziphar; Aziteva†; Azitrocin; Azitrohexal†; Azo-Max; Charyn; Craztronin; Koptin; Macrozit; Marzivag; Medatz; Sicalan; Texis; Tromicina; Truxa; Zertalin; Zithran†; Zitroken; *Neth.*: Azacleus†; Azyter; Nucaza†; Zithromax; *Norw.*: Azitromax; Azyter; *NZ*: Zithromax; *Philipp.*: Azi; Azomycin; Azyth; Geozit; Macromax; Macrozyth; Trozin; Zenith; Zithromax; Zmax; *Pol.*: Azibiot; Azimycin; AziTeva; Azitrin; Azitro-Mepha; AzitroLEK; Azitrox; Azycyna; Azyter; Canbiox; Macromax; Nobaxin; Oranex; Sumamed; Zetamax; *Port.*: 3Z; Azimax†; Azimed; Aziton†; Azitrix; Azixratio†; Azyter; Biozitra†; Gigatrom†; Lazitrom†; Neofarmiz; Unizitro; Zithromax; Zitrina; Zitrozina; *Rus.*: Azicid (Азицид); Azimycin (Азимицин); Azithrox (Азитрокс); Azithrus (Азитрус); Azitral (Азитрал); Aziwok (Азивок); Hemomycin (Хемомицин); Sumaklid (Сумаклид); Sumamecin (Сумамецин); Sumamed (Сумамед); Sumamox (Сумамокс); Sumazid (Сумазид); Tremak (Тремак); Zetamax (Зетамакс); ZI-Factor (ЗИ-фактор); Zithrocin (Зитроцин); Zitrolid (Зитролид); *S.Afr.*: Azimax; Binozyt; Clamelle; Ultreon; Zeemide; Zithrogen; Zithromax; *Singapore*: AZmycin; Binozyt; Zithromax; Zmax; *Spain*: Altezym†; Aratro; Azydrop; Goxil†; Toraseptol†; Vinzam; Zentavion†; Zitromax; *Swed.*: Azitromax; Azyter; *Switz.*: Azitro; Zithromax; *Thai.*: Azith; Azithrin; Azithro; Azycin; Azyter; Binozyt; Floctil; Onzet; Zithromax; Zmax; *Turk.*: Azacid†; Azax; Azeltin; Azitro; Azitrotek; Azomax; Azro; Tremac; Zitromax; Zitrotek; *UAE*: Azomycin; *UK*: Azyter; Clamelle; Zedbac; Zithromax; *Ukr.*: Azax (Азакс); Azicin (Азицин); Azimed (Азимед); Azinort (Азинорт); Azithro (Азитро); Azithro (Азитроксал); Azitrox (Азитрокс); Aziwok (Азивок); Azo (Азо); Azro (Азро); Hemomicin (Хемомицин); Ormax (Ормакс); Sumamed (Сумамед); Zetamaks (Зетамакс); Zetamax (Зетамакс); Zithrocin (Зитроцин); Zithrolex (Зитролекс); Zomax (Зомакс); *USA*: AzaSite; Zithromax; Zmax; *Venez.*: Amizin; Amovin; Aruzilina; Arzomidol; Atromizin; Azigram; Azimakrol; Azitrom; Azitromin; Binozyt; Saver; Zitromax; Zival.

Multi-ingredient Preparations. *India*: AF-Kit; Azintra-3; Azintra-AX; Azithral Jun; Azithral XP; Azro AM; Azyxin Plus; Corzi; Eradikit; Eve Kit; Fas-3 Kit; FC-Kit; Fiscon Tab; Flunec Combikit; Fulkit; Fygek-AS; Gyn-3; Gynotrim Kit; Hif-AS; Kit-3D; Laz-AX; Myconor-4; Nuforce-3 Kit; Od-Kit; Orflaz Kit; Saf Kit; *Mex.*: Zitroflam; *Rus.*: Safocid (Сафоцид); *Ukr.*: Ginekit (Гинекит).

Pharmacopoeial Preparations

USP 36: Azithromycin Capsules; Azithromycin for Injection; Azithromycin Tablets.

Azlocillin *(BAN, USAN, rINN)*

Atsloslllin; Azlocilina; Azlocilline; Azlocillinum; Азлоциллин.

6-[*N*-(2-Oxoimidazolidin-1-ylcarbonyl)-D-phenylglycylamino]penicillanic acid.

$C_{20}H_{23}N_5O_6S$=461.5

CAS — 37091-66-0.

ATC — J01CA09.

ATC Vet — QJ01CA09.

UNII — HUM6H389W0.

Azlocillin Sodium *(BANM, rINNM)*

Azlocilina sódica; Azlocilline Sodique; Azlocillinum Natricum; Azlocylina sodowa; Bay-e-6905; Natrii Azlocillinum; Натрий Азлоциллин.

Sodium (6*R*)-6-[D-2-(2-oxoimidazolidine-1-carboxamido)-2-phenylacetamido]penicillanate.

$C_{20}H_{22}N_5NaO_6S$=483.5

CAS — 37091-65-9.

ATC — J01CA09.

ATC Vet — QJ01CA09.

UNII — DWV1EFW947.

Pharmacopoeias. In *Pol.*

Incompatibility. Azlocillin sodium has been reported to be incompatible with aminoglycosides, ciprofloxacin, metronidazole, and tetracyclines.

Uses and Administration

Azlocillin is a ureidopenicillin and, like piperacillin (p. 342.1), has been used mainly for the treatment of infections caused by *Pseudomonas aeruginosa*. It has been used particularly for septicaemia, and infections of the respiratory and urinary tracts, and also for peritonitis; for details of these infections, see under Choice of Antibacterial, p. 172.2.

Azlocillin has generally been used with an aminoglycoside; however, they should be given separately as they have been shown to be incompatible (see Incompatibility, above).

Azlocillin has been given intravenously as the sodium salt. Doses are expressed in terms of the equivalent amount of azlocillin; 1.05 g of azlocillin sodium is equivalent to about 1 g of azlocillin. A 10% solution in a suitable diluent may be given by slow injection for doses of 2 g or less; higher doses should be infused over 20 to 30 minutes.

A typical dose is 5 g every 8 hours for life-threatening infections, or 2 g every 8 hours for less severe infections and urinary-tract infections.

For details of doses in children, see p. 225.3.

Dosage of azlocillin may need to be adjusted in patients with hepatic or renal impairment (see p. 225.3).

Administration in children. Azlocillin has been used in neonates and children for the treatment of infections caused by susceptible organisms, given intravenously in the following doses:

- premature infants: 50 mg/kg twice daily
- neonates less than 7 days old: 100 mg/kg twice daily
- infants between 7 days and 1 year of age: 100 mg/kg 3 times daily
- children up to 14 years of age: 75 mg/kg 3 times daily

Administration in hepatic or renal impairment. The interval between doses of intravenous azlocillin may need to be increased to every 12 hours in moderate to severe renal impairment (creatinine clearance less than 30 mL/minute); additional dosage reductions may be needed in patients with both severe renal and hepatic impairment.

Adverse Effects and Precautions

As for Carbenicillin Sodium, p. 234.1.

Prolongation of bleeding time has been less frequent and less severe with azlocillin than with carbenicillin.

Hypouricaemia. Reports of transient asymptomatic decreases in serum-uric acid concentrations during treatment with azlocillin.[1,2]

1. Faris RM, Potts DW. Azlocillin and serum uric acid. *Ann Intern Med* 1983; **98**: 414.
2. Ernst JA, Sy ER. Effect of azlocillin on uric acid levels in serum. *Antimicrob Agents Chemother* 1983; **24**: 609–10.

Sodium content. Each g of azlocillin sodium contains about 2.1 mmol of sodium. As azlocillin sodium has a lower sodium content than carbenicillin sodium, hypernatraemia and hypokalaemia are less likely to occur.

Interactions

As for Benzylpenicillin, p. 232.1.

Antibacterials. For the effect of azlocillin on the clearance of *cefotaxime*, and a report of neurotoxicity, see p. 246.3. For reference to azlocillin affecting the disposition of *ciprofloxacin*, see p. 267.1.

Neuromuscular blockers. Azlocillin and other ureidopenicillins are reported to prolong the action of competitive muscle relaxants such as *vecuronium* (see Atracurium, p. 2032.1).

Antimicrobial Action

Azlocillin has an antimicrobial action similar to that of piperacillin (p. 343.1). Its activity *in vitro* against Enterobacteriaceae is generally less than that of mezlocillin or piperacillin, but it has comparable activity to piperacillin against *Pseudomonas aeruginosa*.

Pharmacokinetics

Azlocillin is not absorbed from the gastrointestinal tract to any significant extent. It has nonlinear dose-dependent pharmacokinetics. Doubling an intravenous dose results in more than double the plasma concentration. Between 20 and 46% of azlocillin in the circulation is bound to plasma proteins. The plasma half-life is usually about 1 hour, but is longer in neonates; in patients with renal impairment half-lives of 2 to 6 hours have been reported.

Azlocillin is widely distributed in body tissues and fluids. It crosses the placenta into the fetal circulation and small amounts are distributed into breast milk. There is little diffusion into the CSF except when the meninges are inflamed.

Azlocillin is metabolised to a limited extent. About 50 to 70% of a dose is excreted unchanged in the urine by glomerular filtration and tubular secretion within 24 hours of a dose, resulting in high urinary concentrations. Azlocillin is partly excreted in the bile where it is also found in high concentrations.

Plasma concentrations are enhanced if probenecid is given.

Azlocillin is removed by haemodialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Alocin (阿乐欣); *Gr.*: Abrodil.

Aztreonam *(BAN, USAN, rINN)*

Atstreonaami; Azthreonam; Aztréonam; Aztreonamum; SQ-26776; Азтреонам.

(Z)-2-(2-Aminothiazol-4-yl-[(2*S*,3*S*)-2-methyl-4-oxo-1-sulphoazetidin-3-ylcarbamoyl]methyleneamino-oxy)-2-methylpropionic acid.

$C_{13}H_{17}N_5O_8S_2$=435.4.

CAS — 78110-38-0.

ATC — J01DF01.

ATC Vet — QJ01DF01.

UNII — G2B4VE5GH8.

Pharmacopoeias. In *Jpn* and *US*, which allows the anhydrous or hydrated forms.

USP 36: (Aztreonam). A white, odourless crystalline powder. Very slightly soluble in dehydrated alcohol; practically insoluble in chloroform, in ethyl acetate, and in toluene; soluble in dimethylformamide and in dimethyl sulfoxide; slightly soluble in methyl alcohol. Store in airtight containers.

Aztreonam Lysine *(BANM, USAN, rINNM)*

Aztreonam lisina; Aztréonam Lysine; Aztreonamum Lysinum; Corus-1020; Азтреонамк Лизин.

(Z)-2-(2-Aminothiazol-4-yl-[(2*S*,3*S*)-2-methyl-4-oxo-1-sulfoazetidin-3-ylcarbamoyl]methyleneamino-oxy)-2-methylpropionic acid L-lysine.

$C_{13}H_{17}N_5O_8S_2.C_6H_{14}N_2O_2$=581.6

CAS — 827611-49-4.

ATC — J01DF01.

ATC Vet — QJ01DF01.

UNII — XNM7LT65NP.

Incompatibility and stability. Aztreonam has been reported to be incompatible with cefradine, metronidazole, nafcillin, and vancomycin.

References.

1. Bell RG, *et al.* Stability of intravenous admixtures of aztreonam and cefoxitin, gentamicin, metronidazole, or tobramycin. *Am J Hosp Pharm* 1986; 43: 1444–53.
2. Riley CM, Lipford LC. Interaction of aztreonam with nafcillin in intravenous admixtures. *Am J Hosp Pharm* 1986; 43: 2221–4.
3. Belliveau PP, *et al.* Stability of aztreonam and ampicillin sodium-sulbactam sodium in 0.9% sodium chloride injection. *Am J Hosp Pharm* 1994; 51: 901–4.
4. Trissel LA, Martinez JF. Compatibility of aztreonam with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1995; 52: 1086–90.
5. Trissel LA, *et al.* Compatibility and stability of aztreonam and vancomycin hydrochloride. *Am J Health-Syst Pharm* 1995; 52: 2560–4.

Uses and Administration

Aztreonam is a monobactam or monocyclic beta-lactam antibacterial used for the treatment of infections caused by susceptible Gram-negative aerobic organisms. These have included bone and joint infections, gonorrhoea, intra-abdominal and pelvic infections, lower respiratory-tract infections (including pseudomonal infections in patients with cystic fibrosis), meningitis, septicaemia, skin and soft-tissue infections, and urinary-tract infections. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2. To broaden the spectrum of activity for empirical treatment of infections, aztreonam should be used with other antibacterials. Use with an aminoglycoside may be of benefit in serious *Pseudomonas aeruginosa* infections.

Aztreonam is usually given *parenterally* by deep intramuscular injection, by slow intravenous injection over 3 to 5 minutes, or by intravenous infusion over 20 to 60 minutes. Single doses over 1 g should be given by the intravenous route. It is given in doses ranging from 1 to 8 g daily (usually 3 to 4 g daily), in divided doses every 6 to 12 hours, according to the severity of the infection. For infections due to *Ps. aeruginosa*, 2 g every 6 or 8 hours may be given for initial treatment.

A single intramuscular dose of 1 g has been recommended for the treatment of gonorrhoea or cystitis.

The dose of aztreonam may need to be reduced in renal impairment, see p. 226.3.

For details of doses in children, see p. 226.2.

Aztreonam lysine may be given by *inhalation* for the suppression of chronic respiratory-tract infections due to *Ps. aeruginosa* in patients with cystic fibrosis. The usual dose, expressed in terms of aztreonam, is 75 mg given 3 times within a 24 hour period for 28 days; doses should be taken at least 4 hours apart. Patients should use a bronchodilator before each dose; short-acting bronchodilators should be given 15 minutes to 4 hours before inhaled aztreonam, whereas long-acting bronchodilators may be given 30 minutes to 12 hours before. If patients require a mucolytic this should also be given before aztreonam (but after the bronchodilator). If additional courses of aztreonam are required, a minimum of 28 days between courses is recommended.

General references.

1. Brogden RN, Heel RC. Aztreonam: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1986; 31: 96–130.
2. Neu HC, ed. Aztreonam's role in the treatment of Gram-negative infections. *Am J Med* 1990; 88 (suppl 3C): 1S–43S.
3. Hellinger WC, Brewer NS. Carbapenems and monobactams: imipenem, meropenem, and aztreonam. *Mayo Clin Proc* 1999; 74: 420–34.

Administration. References to the use of aztreonam (as aztreonam lysine) by inhalation in the treatment of airway infections in patients with cystic fibrosis.[1-8]

1. Gibson RL, *et al.* Microbiology, safety, and pharmacokinetics of aztreonam lysinate for inhalation in patients with cystic fibrosis. *Pediatr Pulmonol* 2006; 41: 656–65.
2. Retsch-Bogart GZ, *et al.* A phase 2 study of aztreonam lysine for inhalation to treat patients with cystic fibrosis and Pseudomonas aeruginosa infection. *Pediatr Pulmonol* 2008; 43: 47–58.
3. McCoy KS, *et al.* Inhaled aztreonam lysine for chronic airway Pseudomonas aeruginosa in cystic fibrosis. *Am J Respir Crit Care Med* 2008; 178: 921–8.
4. Retsch-Bogart GZ, *et al.* Efficacy and safety of inhaled aztreonam lysine for airway pseudomonas in cystic fibrosis. *Chest* 2009; 135: 1223–32.
5. Elborn JS, Henig NR. Optimal airway antimicrobial therapy for cystic fibrosis: the role of inhaled aztreonam lysine. *Expert Opin Pharmacother* 2010; 11: 1373–85.
6. O'Sullivan BP, *et al.* Inhaled aztreonam. *Nat Rev Drug Discov* 2010; 9: 357–8.
7. Plosker GL. Aztreonam lysine for inhalation solution: in cystic fibrosis. *Drugs* 2010; 70: 1843–55.
8. Zeitler K, *et al.* Aztreonam lysine for inhalation: new formulation of an old antibiotic. *Am J Health-Syst Pharm* 2012; 69: 107–15.

Administration in children. Aztreonam may be given to neonates and children for the treatment of infections caused by susceptible Gram-negative aerobic organisms including *Pseudomonas aeruginosa*, *Haemophilus influenzae*, and *Neisseria meningitidis*. It is usually given *parenterally* by deep intramuscular injection, by slow intravenous injection over 3 to 5 minutes, or by intravenous infusion over 20 to 60 minutes. Single doses over 1 g should be given by the intravenous route.

UK licensed product information recommends that aztreonam be given in the following doses:

- infants older than one week and children less than 2 years of age: 30 mg/kg every 6 or 8 hours
- children 2 to 12 years: 30 mg/kg every 6 or 8 hours which may be increased to 50 mg/kg every 6 or 8 hours in severe infection (to a maximum total daily dose of 8 g)

Although not licensed in the UK for neonates less than one week old, the *BNFC* suggests a dose of 30 mg/kg given intravenously every 12 hours.

In the USA, the American Academy of Pediatrics[1] suggests the following doses for aztreonam:

- neonates aged 7 days or less with a birth-weight of 2 kg or less: 30 mg/kg every 12 hours
- neonates aged 7 days or less with a birth-weight more than 2 kg: 30 mg/kg every 8 hours
- neonates aged 8 to 28 days with a birth-weight of 2 kg or less: 30 mg/kg every 8 to 12 hours; a dosing interval of 12 hours may be used until 2 weeks of life in extremely low birth-weight neonates (weighing less than 1 kg)
- neonates aged 8 to 28 days with a birth-weight of more than 2 kg: 30 mg/kg every 6 hours
- children 1 month and older: 90 mg/kg in 3 divided doses (to a maximum daily dose of 3 g) for mild to moderate infections, or 90 to 120 mg/kg in 3 or 4 divided doses (to a maximum daily dose of 8 g) in severe infections

Aztreonam lysine may be given by *inhalation* for the suppression of chronic respiratory-tract infections due to *Ps. aeruginosa* in children aged 6 years and older with cystic fibrosis; doses are as for adults (see above).

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Administration in renal impairment. Parenteral doses of aztreonam should be reduced in moderate to severe renal impairment. Patients with renal impairment may be given a usual initial dose followed by a maintenance dose adjusted according to creatinine clearance (CC):

- CC 10 to 30 mL/minute: half the initial dose
- CC less than 10 mL/minute: one-quarter of the initial dose
- haemodialysis patients: a supplementary dose of one-eighth of the initial dose should be given after each dialysis session

A review[1] of antimicrobial dosing in critically ill patients receiving renal replacement therapy recommends that patients undergoing continuous renal replacement therapy (CRRT) receive a loading dose of 2 g, with the following maintenance doses, depending on the type of CRRT:

- continuous venovenous haemofiltration (CVVH): 1 to 2 g every 12 hours
- continuous venovenous haemodialysis (CVVHD) or haemodiafiltration (CVVHDF): 1 g every 8 hours or 2 g every 12 hours

For critically ill patients undergoing intermittent haemodialysis, the authors suggest a dosing regimen of 500 mg every 12 hours.[1]

Inhaled aztreonam lysine should be used with caution in patients whose serum creatinine is more then 2 times the upper limit of normal.

1. Heintz BH, *et al.* Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy* 2009; 29: 562–77.

Adverse Effects

The adverse effects of aztreonam are similar to those of other beta lactams (see Benzylpenicillin, p. 231.2, and Cefalotin, p. 237.2). Hypersensitivity reactions, including rashes, urticaria, angioedema, exfoliative dermatitis, eosinophilia, bronchospasm, and rarely anaphylaxis and toxic epidermal necrolysis, may occur in patients receiving aztreonam, although it has been reported to be only weakly immunogenic. Gastrointestinal effects include diarrhoea, nausea, vomiting, mouth ulcer, and an abnormal taste.

Phlebitis or thrombophlebitis has been reported after the intravenous use of aztreonam, and pain or swelling after intramuscular injection.

Use of aztreonam may result in the overgrowth of non-susceptible organisms, including Gram-positive cocci. Pseudomembranous colitis or gastrointestinal bleeding may develop.

Other adverse effects that have been reported with aztreonam include jaundice and hepatitis, increases in liver enzymes, and prolongation of prothrombin and partial thromboplastin times.

Cough, wheezing, nasal congestion, fever, and occasional reports of bronchospasm have been associated with inhalation of aztreonam lysine.

Effects on the skin. References.

1. McDonald BJ, *et al.* Toxic epidermal necrolysis possibly linked to aztreonam in bone marrow transplant patients. *Ann Pharmacother* 1992; 26: 34–5.
2. Gonzalo-Garijo MA, de Argila D. Erythroderma due to aztreonam and clindamycin. *J Investig Allergol Clin Immunol* 2006; 16: 210–1.

Precautions

Aztreonam should not be given to patients who are hypersensitive to it and should be used with caution in those known to be hypersensitive to other beta lactams, although the incidence of cross-sensitivity appears to be low (but see p. 227.1).

Aztreonam should be used with caution in patients with renal or hepatic impairment.

Breast feeding. In a study in 12 healthy women given aztreonam, peak concentrations in breast milk were found to be less than 1% of those in serum and this was considered suggestive of a low risk of adverse effects in breast-fed infants.[1] The last available guidance from the American Academy of Pediatrics stated that no adverse effects had been seen in breast-fed infants whose mothers received aztreonam and considered it to be usually compatible with breast feeding,[2] although UK licensed product information recommends that mothers should refrain from breast feeding while receiving aztreonam.

1. Fleiss PM, *et al.* Aztreonam in human serum and breast milk. *Br J Clin Pharmacol* 1985; 19: 509–11.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May

2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)

Hypersensitivity. Aztreonam is said to show little cross-reactivity with most other beta lactams,[1,2] but there have been isolated reports of immediate hypersensitivity to aztreonam in patients with a history of hypersensitivity to penicillin.[3,4]

Ceftazidime (p. 252.2) and aztreonam share a common side-chain, and there are some data to suggest that cross-reactivity between the two may exist. Therefore, extra caution is required if aztreonam is to be used in ceftazidime-allergic patients.[2]

1. Patriarca G, *et al.* Tolerability of aztreonam in patients with IgE-mediated hypersensitivity to beta-lactams. *Int J Immunopathol Pharmacol* 2008; **21**: 375–9.
2. Frumin J, Gallagher JC. Allergic cross-sensitivity between penicillin, carbapenem, and monobactam antibiotics: what are the chances? *Ann Pharmacother* 2009; **43**: 304–15.
3. Alvarez JS, *et al.* Immediate hypersensitivity to aztreonam. *Lancet* 1990; **335**: 1094.
4. Hantson P, *et al.* Immediate hypersensitivity to aztreonam and imipenem. *BMJ* 1991; **302**: 294–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies aztreonam as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/09/11)

Interactions

Caution is recommended in patients receiving aztreonam and oral anticoagulants because of the possibility of increased prothrombin time.

Antimicrobial Action

Aztreonam is bactericidal and acts similarly to the penicillins by inhibiting synthesis of the bacterial cell wall; it has a high affinity for the penicillin-binding protein 3 (PBP-3) of Gram-negative bacteria. The activity of aztreonam is restricted to Gram-negative aerobic organisms, with poor or no activity against Gram-positive aerobes or anaerobic organisms. It has good activity against *Haemophilus influenzae* and *Neisseria*spp., including beta-lactamase-producing strains. Aztreonam is also active against most Enterobacteriaceae (including *Escherichia coli, Citrobacter, Enterobacter, Klebsiella, Proteus, Providencia, Salmonella, Serratia, Shigella, Yersinia* spp., and *Morganella morganii*) providing that they do not produce extended-spectrum beta-lactamases (ESBLs) or KPC-type beta-lactamases, or hyperproduce AmpC beta-lactamases. Although *Pseudomonas aeruginosa* has historically been considered aztreonam-susceptible, antipseudomonal beta-lactam antibacterials such as ceftazidime are more active and about one-third of contemporary *Ps. aeruginosa* strains are resistant to aztreonam.

Synergy has been reported *in vitro* between aztreonam and aminoglycosides against *Ps. aeruginosa* and some Enterobacteriaceae.

Resistance. Aztreonam is stable to hydrolysis by many narrow-spectrum beta-lactamases but many current beta-lactamases, in particular the ESBLs and carbapenemases (but not metallo-β-lactamases), are associated with resistance to aztreonam. Hyperproduction of AmpC beta-lactamase (typically in *Enterobacter cloacae, Serratia marcescens, Citrobacter freundii*, and other related bacteria) also leads to aztreonam resistance.

Pharmacokinetics

Aztreonam is poorly absorbed from the gastrointestinal tract and is therefore given parenterally. Peak serum concentrations of about 90 and 200 micrograms/mL occur after single, 30-minute intravenous infusions of 1 and 2 g, respectively; when these doses are given by intravenous injection over 3 minutes, slightly higher peak serum concentrations (125 and 242 micrograms/mL) occur. Absorption after intramuscular injection is good, and serum concentrations at 1 hour are comparable for identical single intramuscular and intravenous doses. Aztreonam has a plasma half-life of about 1.7 hours. The half-life may be prolonged in neonates, in the elderly, in patients with renal impairment, and to some extent in those with hepatic impairment. Aztreonam is about 56% bound to plasma proteins. It is widely distributed in body tissues and fluids, including bile. Diffusion into the CSF is poor unless the meninges are inflamed. It crosses the placenta and enters the fetal circulation; small amounts are distributed into breast milk.

Aztreonam is not extensively metabolised. The principal metabolite, SQ-26992, is inactive and is formed by opening of the beta-lactam ring; it has a much longer half-life than the parent compound. Aztreonam is excreted mainly in the urine, by renal tubular secretion and glomerular filtration; about 60 to 70% of a dose appears within 8 hours as unchanged drug with only small quantities of metabolites. Only small amounts of unchanged drug and metabolites are excreted in the faeces.

Aztreonam is removed by haemodialysis and to a lesser extent by peritoneal dialysis.

Small but variable amounts are absorbed after inhalation of nebulised aztreonam lysine; about 10% of the dose is reported to be excreted in urine, largely as unchanged drug.

Reviews.

1. Mattie H. Clinical pharmacokinetics of aztreonam: an update. *Clin Pharmacokinet* 1994; **26**: 99–106.
2. Vinks AA, *et al.* Pharmacokinetics of aztreonam in healthy subjects and patients with cystic fibrosis and evaluation of dose-exposure relationships using Monte Carlo simulation. *Antimicrob Agents Chemother* 2007; **51**: 3049–55.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Azactam; ***Austria***: Azactam; Cayston; ***Belg.***: Azactam; ***Braz.***: Azactam; Azanem; Uni Aztrenam; ***Canad.***: Cayston; ***Chile***: Azactam†; ***China***: Azactam (君刻单); ***Cz.***: Azactam†; Cayston; ***Denm.***: Azactam; Cayston; ***Fin.***: Azactam; ***Fr.***: Azactam; Cayston; ***Ger.***: Azactam†; Cayston; ***Gr.***: Azactam; Azenam; Aztreotic; Cayston; ***India***: Azactam; Azenam; Azom; Azotum; Aztreo; Trezam; ***Indon.***: Vebac; ***Irl.***: Azactam; Cayston; ***Ital.***: Azactam†; Primbactam; ***Jpn***: Azactam; ***Mex.***: Monobac; ***Neth.***: Cayston; ***Norw.***: Azactam; ***NZ***: Azactam; ***Philipp.***: Azactam†; Aztram; ***Pol.***: Azactam†; Cayston; ***Port.***: Azactam; Cayston; ***Rus.***: Azmam (Азмам); Aztreobol (Азтреабол); ***S.Afr.***: Azactam; ***Singapore***: Azactam; ***Spain***: Azactam; Cayston; ***Swed.***: Azactam; ***Switz.***: Azactam; ***UK***: Azactam; Cayston; ***USA***: Azactam; Cayston; ***Venez.***: Azactam.

Pharmacopoeial Preparations
USP 36: Aztreonam for Injection; Aztreonam Injection.

Bacampicillin Hydrochloride

(BANM, USAN, rINNM)

Ampicillin Ethoxycarbonyloxyethyl Hydrochloride; Bacampicilina, hidrocloruro de; Bacampicilline, chlorhydrate de; Bacampicillinhydrochlorid; Bacampicillini Hydrochloridum; Bakampicilin-hydroklorid; Bakampicilino hidrochloridas; Bakampicillin-hidroklorid; Bakampicillinhydroklorid; Bakampisilin Hidroklorür; Bakampisilliinlhydrokloridi; Carampicillin; EPC-272; Hidrocloruro de bacampicilina; Бакампициллина Гидрохлорид.

1-(Ethoxycarbonyloxy)ethyl (6*R*)-6-(α-D-phenylglycylamino) penicillanate hydrochloride.

$C_{21}H_{27}N_3O_7S,HCl=502.0$

CAS — 50972-17-3 (bacampicillin); 37661-08-8 (bacampicillin hydrochloride).

ATC — J01CA06.

ATC Vet — QJ01CA06.

UNII — PM034U953T.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.*

Ph. Eur. 8: (Bacampicillin Hydrochloride). A white or almost white hygroscopic powder or granules. Soluble in water and in dichloromethane; freely soluble in alcohol. A 2% solution in water has a pH of 3.0 to 4.5. Store in airtight containers.

Uses and Administration

Bacampicillin has actions and uses similar to those of ampicillin (p. 218.3) to which it is rapidly hydrolysed in the body. It is given orally as the hydrochloride for the treatment of infections caused by susceptible bacteria in doses of 0.8 to 2.4 g daily, in 2 divided doses. For details of doses in children, see p. 227.2.

In uncomplicated gonorrhoea a single dose of bacampicillin hydrochloride 1.6 g with probenecid 1 g may be given in areas where gonococci remain sensitive.

Administration in children. In children, bacampicillin has been used orally for the treatment of susceptible bacterial infections, similarly to ampicillin. In children over 5 years of age, doses of 25 to 50 mg/kg daily, in 2 divided doses, have been used.

Adverse Effects and Precautions

As for Ampicillin, p. 219.2. Diarrhoea has been reported to occur less frequently with bacampicillin.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies bacampicillin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Interactions

As for Benzylpenicillin, p. 232.1.

Antimicrobial Action

Bacampicillin has the antimicrobial action of ampicillin *in vivo* (p. 219.3). It possesses no intrinsic activity and needs to be hydrolysed to ampicillin.

Pharmacokinetics

Bacampicillin is more rapidly and completely absorbed from the gastrointestinal tract than ampicillin, to which it is hydrolysed in the intestinal wall and plasma. Peak plasma-ampicillin concentrations occur about 30 to 60 minutes after oral doses, and are about 2 to 3 times those after an equivalent dose of ampicillin. The absorption of bacampicillin from tablets does not appear to be affected by the presence of food in the stomach. About 75% of a dose is excreted in the urine as ampicillin within 8 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Albaxin; ***India***: Penglobe; ***Ital.***: Bacacil; Bacagen; Bacasint; Bacillin; Winnipeg; ***Malaysia***: Bacamcillin; ***Philipp.***: Penglobe†; ***Thai.***: Penglobe; ***Turk.***: Bakamsilin; Penbak.

Pharmacopoeial Preparations
USP 36: Bacampicillin Hydrochloride Tablets.

Bacitracin *(BAN, rINN)*

Bacitracina; Bacitracinas; Bacitracine; Bacitracinum; Bacytracyna; Basitrasiini; Basitrasin; Бацитрацин.

CAS — 1405-87-4.

ATC — D06AX05; J01XX10; R02AB04.

ATC Vet — QA07AA93; QD06AX05; QJ01XX10; QR02AB04.

UNII — 58H6RWO52I (bacitracin); DDA3RRX0P7 (bacitracin A); 3968434C0D (bacitracin B1); AM2V8LQG5X (bacitracin B2); 1RE2J07DT4 (bacitracin B3).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Bacitracin). Mixture of antimicrobial polypeptides produced by certain strains of *Bacillus licheniformis* or *B. subtilis*. The potency is not less than 60 units/mg, calculated with reference to the dried substance. A white or almost white hygroscopic powder. Freely soluble in water and in alcohol. A 1% solution in water has a pH of 6.0 to 7.0. Store at a temperature of 8 degrees to 15 degrees in airtight containers.

USP 36: (Bacitracin). A mixture of polypeptides produced by the growth of an organism of the *licheniformis* group of *Bacillus subtilis* (Bacillaceae). The main components are bacitracins A, B1, B2, and B3. It has a potency of not less than 65 units/mg, calculated with reference to the dried substance. It is a white to pale buff, hygroscopic powder, odourless or having a slight odour. Freely soluble in water; soluble in alcohol, in glacial acetic acid, and in methyl alcohol; the solution in the organic solvents usually showing some insoluble residue; insoluble in acetone, in chloroform, and in ether. Its solutions deteriorate rapidly at room temperature. It is precipitated from its solutions and is inactivated by salts of many of the heavy metals. pH of a solution in water containing 10 000 units/mL is between 5.5 and 7.5. Store in airtight containers at a temperature of 8 degrees to 15 degrees.

Bacitracin Zinc *(BANM, rINNM)*

Bacitracin zinečnatý komplex; Bacitracin-Zink; Bacitracina zinc; Bacitracin-cink; Bacitracine Zincique; Bacitracine-zinc; Bacitracino cinko kompleksas; Bacitracins Zinc Complex; Bacitracinum Zincicum; Bacitracinum zincum; Bacytracyna cynkowa; Sinkkibasitrasiini; Zinc Bacitracin; Zinci Bacitracinum; Zinkbacitracin; Цинка Бацитрацин.

CAS — 1405-89-6.

ATC — D06AX05; J01XX10; R02AB04.

ATC Vet — QA07AA93; QD06AX05; QJ01XX10; QR02AB04.

UNII — 89Y4M234ES.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *US*.

Ph. Eur. 8: (Bacitracin Zinc). The zinc complex of bacitracin. The potency is not less than 60 units/mg, calculated with reference to the dried substance. A white or light-yellowish-grey hygroscopic powder. Slightly soluble in water and in alcohol. The filtrate of a saturated solution has a pH of 6.0 to 7.5. Store in airtight containers.

USP 36: (Bacitracin Zinc). The zinc complex of bacitracin, which consists of a mixture of antimicrobial polypeptides, the main components being bacitracins A, B1, B2, and B3. It has a potency of not less than 65 units/mg, calculated with reference to the dried substance. It contains not less than

4% and not more than 6% of zinc, calculated with reference to the dried substance. A white or pale tan, hygroscopic powder, odourless or having a slight odour. Sparingly soluble in water. pH of a saturated solution in water is between 6.0 and 7.5. Store in airtight containers at a temperature of 8 degrees to 15 degrees.

Incompatibility. Bacitracin was slowly inactivated in bases containing stearyl alcohol, cholesterol, polyoxyethylene derivatives, and sodium laurilsulfate, and was rapidly inactivated in bases containing water, macrogols, propylene glycol, glycerol, cetylpyridinium chloride, benzalkonium chloride, ichthammol, phenol, and tannic acid.[1]

1. Plaxco JM, Husa WJ. The effect of various substances on the antibacterial activity of bacitracin in ointments. *J Am Pharm Assoc (Sci)* 1956; **45**: 141–5.

Stability. Bacitracin zinc was more stable than bacitracin and could be stored for 18 months at temperatures up to 40 degrees without appreciable loss of activity. Lozenges of bacitracin zinc and ointments and tablets containing bacitracin zinc with neomycin were more stable than the corresponding bacitracin preparations. Bacitracin zinc was less bitter than bacitracin and the taste was more readily disguised.[1]

1. Gross HM, *et al.* Zinc bacitracin in pharmaceutical preparations. *Drug Cosmet Ind* 1954; **75**: 612–13.

Units

The second International Standard Preparation (1964) of bacitracin zinc contains 74 units/mg.

Uses and Administration

Bacitracin and bacitracin zinc are applied **topically** (as a cream, ointment, dusting powder, or ophthalmic ointment), often with other antibacterials such as neomycin and polymyxin B, and sometimes with corticosteroids, in the treatment of local infections due to susceptible organisms. Typical concentrations of bacitracin or bacitracin zinc in such products are 400 to 500 units/g. Absorption from open wounds and from the bladder or peritoneal cavity may lead to adverse effects, although the dose-limiting toxicity of combined preparations is considered to be due to neomycin.

Parenteral use of bacitracin is usually avoided because of nephrotoxicity but it may be given intramuscularly for the treatment of infants with staphylococcal pneumonia and empyema due to susceptible organisms. For details of doses in children, see p. 228.1.

Bacitracin has been given **orally** in the treatment of antibiotic-associated colitis due to *Clostridium difficile*.

Administration in children. In the USA, bacitracin may be given intramuscularly for the treatment of infants with staphylococcal pneumonia and empyema due to susceptible organisms. Infants weighing less than 2.5 kg may be given a dose of 900 units/kg daily in 2 or 3 divided doses; those weighing more than 2.5 kg may be given 1000 units/kg daily in 2 or 3 divided doses.

Adverse Effects and Precautions

Systemic bacitracin may produce severe nephrotoxicity, resulting in renal failure due to tubular and glomerular necrosis. Renal function should be determined before, and daily during, therapy. Fluid intake and urinary output should be maintained to avoid kidney toxicity. If renal toxicity occurs, bacitracin should be stopped. Use with other nephrotoxic drugs should be avoided (see Interactions, p. 228.1).

Nausea and vomiting may occur, as well as pain at the site of injection. Hypersensitivity reactions, including rashes and anaphylaxis, have occurred with systemic, and more rarely with topical, use.

Hypersensitivity. References[1-6] to hypersensitivity reactions to bacitracin, including anaphylaxis.

1. Sood A, Taylor JS. Bacitracin: allergen of the year. *Am J Contact Dermat* 2003; **14**: 3–4.
2. Jacob SE, James WD. From road rash to top allergen in a flash: bacitracin. *Dermatol Surg* 2004; **30**: 521–4.
3. Preiler JP, *et al.* Intraoperative anaphylaxis to bacitracin during pacemaker change and laser lead extraction. *Ann Allergy Asthma Immunol* 2005; **95**: 389–93.
4. Greenberg K, *et al.* Anaphylaxis to topical bacitracin ointment. *Am J Emerg Med* 2007; **25**: 95–6.
5. Greenberg SB, *et al.* Successful resuscitation of a patient who developed cardiac arrest from pulsed saline bacitracin lavage during thoracic laminectomy and fusion. *J Clin Anesth* 2008; **20**: 294–6.
6. Cronin H, Mowad C. Anaphylactic reaction to bacitracin ointment. *Cutis* 2009; **83**: 127–9.

Interactions

Additive nephrotoxicity would be anticipated if bacitracin were given systemically with other nephrotoxic drugs, particularly colistin, kanamycin, neomycin, polymyxin B, and streptomycin; such use should be avoided. Bacitracin is reported to enhance the neuromuscular blocking action of certain drugs, such as neuromuscular blockers and anaesthetics, if given during surgery or postoperatively.

Antimicrobial Action

Bacitracin interferes with bacterial cell wall synthesis by blocking the function of the lipid carrier molecule that transfers cell wall subunits across the cell membrane. It is active against many Gram-positive bacteria including staphylococci, streptococci (particularly group A streptococci), corynebacteria, and clostridia. It is also active against *Actinomyces, Treponema pallidum,* and some Gram-negative species such as *Neisseria* and *Haemophilus influenzae,* although most Gram-negative organisms are resistant.

Acquired bacterial resistance to bacitracin rarely occurs, but resistant strains of staphylococci have been detected.

Pharmacokinetics

Bacitracin is not appreciably absorbed from the gastrointestinal tract or from intact or denuded skin, wounds, or mucous membranes; however, systemic absorption has been reported after peritoneal lavage. It is rapidly absorbed when given by intramuscular injection. Bacitracin readily diffuses into pleural and ascitic fluids but little passes into the CSF. About 10 to 40% of a single injected dose is excreted slowly by glomerular filtration and appears in the urine within 24 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Baciject; Bacitin; *USA*: Baci-IM; *Venez.*: Baciderm.

Multi-ingredient Preparations. *Arg.*: Biotaer an Caramelos; Biotaer Nebulizable; Butimerin; Carnot Colutorio; Cicatrex Biotic; *Austral.*: Cicatrin†; Nemdyn; Neosporin†; *Austria*: Baneocin; Eucillin; Nebacetin; *Belg.*: Neobacitracine; Neobacitracine; *Braz.*: Anaseptil; Bacidermina; Bacigen; Bacina; Bactoderm; Cicatrene; Cutiderm†; Dermase; Epicitrin; Ferid; Kindcetin†; Nebacetin; Nebaciderme; Nebacimed; Neobacipan; Neocetrin; Neotop†; Neotricin; Polysporin†; Teutomicin; *Canad.*: Antibiotic Ointment; Antibiotique Onguent†; Bacimyxin; Band-Aid Antibiotic Adhesive Bandages plus Antibiotic; Bioderm; Cicatrin†; Complete Antibiotic Ointment; Cortimyxin; Cortisporin; Diosporin; Neosporin; Optimyxin; Ozonol Antibiotic Plus; Polyderm; Polysporin Complete; Polysporin Triple Antibiotic; Polysporin; Polytopic; Triple Antibiotic Ointment; *Chile*: Anbiotop; Bacitopic Compuesto†; Banedif Oftalmico con Prednisolona†; Banedif Oftalmico†; Banedif ZN; Banedif†; Dermabiotico; Monticina; Nasomin; Oftabiotico; Pensulan; Rinobanedif; Unguento Dermico Antibiotico†; *Cz.*: Framykoin; Ophthalmo-Framykoin Compositum; Ophthalmo-Framykoin; Pamycon; *Fin.*: Bacibact; *Fr.*: Baciconle; *Ger.*: Nebacetin†; Neobac†; Polyspectran HC; Polyspectran; *Gr.*: Apobacyn; Lysopaine; Nebacetin; Sopain-Plus; Vioplex-T; *Hong Kong*: Bacimyxin†; Polycin†; Polyspectran†; *Hung.*: Baneocin; Bivacyn†; *India*: Derbec-N; Nebasulf; Neosporin-H; Neosporin; Neotop; *Indon.*: Liposin; N B; Nebacetin; Netracin†; Scanderma Plus; Tigalin; Tracetin; *Irl.*: Cicatrin†; Polyfax; *Israel*: Bamyxin; *Ital.*: Bimixin; Cicatrene; Cicatrene; Enterostop; Orobicin; *Malaysia*: Bacitracin-N; Baneocin; *Mex.*: Nebacetina; Neosporin; Polixin; Soxaron; Tribiot; *Neth.*: Bacicoline-B; *Norw.*: Bacimycin; *Philipp.*: BNP Ointment; Terramycin Plus; Trimycin-H; Trimycin; *Pol.*: Baneocin; Bivacyn†; Maxibiotic; Multibiotic; Neotopic†; Scaldex; Tribiotic; *Port.*: Baciderma: Bacitracina Zimaia; Cicatrin; Dimicina; Distop†; Polisulfade; *Rus.*: Baneocin (Банеоцин); *S.Afr.*: Cicatrin†; Polysporin†; *Singapore*: Baneocin; Batramycin; Fast Powder†; Polybamycin; *Spain*: Bacisporin†; Banedif†; Dermisone Tri Antibiotic; Dermo Hubber; Edifaringen†; Lizipaina; Neo Bacitrin†; Phonal; Pomada Antibiotica; Rinobanedif; Tulgrasum Antibiotico; *Switz.*: Baneopol†; Batramycin†; Cicatrex; Lysopaine†; Neotracin; *Thai.*: Bacal; Banocin; Banocin; Basina; Citacin; Genquin; Izac; Lobacin; Medcin†; My-B; Mybacin Dermic; Mybacin; Novacin; Thrody; *Turk.*: Thiodilline; *UK*: Polyfax; *Ukr.*: Baneocin (Банеоцин); *USA*: Ak-Poly-Bac; Ak-Spore†; Bacitraycin Plus; Cortimycin; Neocin; Neosporin + Pain Relief; Neotricin HC†; Ocu-Spor-B; Ocutricin; Polycin-B; Polymycin; Polysporin; Polytracin; ProCoMycin; Tri-Biozene; *Venez.*: Dermabiotic.

Pharmacopoeial Preparations

BP 2014: Polymyxin and Bacitracin Eye Ointment; Polymyxin and Bacitracin Ointment;

USP 36: Bacitracin and Polymyxin B Sulfate Topical Aerosol; Bacitracin for Injection; Bacitracin Ointment; Bacitracin Ophthalmic Ointment; Bacitracin Zinc and Polymyxin B Sulfate Ointment; Bacitracin Zinc and Polymyxin B Sulfate Ophthalmic Ointment; Bacitracin Zinc Ointment; Neomycin and Polymyxin B Sulfates and Bacitracin Ointment; Neomycin and Polymyxin B Sulfates and Bacitracin Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates and Bacitracin Zinc Ointment; Neomycin and Polymyxin B Sulfates and Bacitracin Zinc Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Acetate Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Lidocaine Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin, and Hydrocortisone Acetate Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin, and Hydrocortisone Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin, and Lidocaine Ointment; Neomycin Sulfate and Bacitracin Ointment; Neomycin Sulfate and Bacitracin Zinc Ointment; Polymyxin B Sulfate and Bacitracin Zinc Topical Aerosol; Polymyxin B Sulfate and Bacitracin Zinc Topical Powder.

Balofloxacin *(rINN)*

Balofloxacine; Balofloxacino; Balofloxacinum; Q-35; Балофлоксацин.

(±)-1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[3-(methylamino)piperidino]-4-oxo-3-quinolinecarboxylic acid.

$C_{20}H_{24}FN_3O_4$=389.4

CAS — 127294-70-6.

UNII — Q022B63JPM.

Profile

Balofloxacin is a fluoroquinolone antibacterial used in the treatment of urinary-tract infections.

Reviews.

1. Alksne L. Balofloxacin Choongwae. *Curr Opin Investig Drugs* 2003; **4**: 224–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Heng Jie (恒诺); Tiantong (天统); *Kor.*: Q-Roxin.

Bambermycin *(BAN, pINN)*

Bambermicina; Bambermycine; Bambermycins (USAN); Bambermycinum; Flavophospholipol; Бамбермицин.

$C_{69}H_{108}N_3O_{34}P$ = 1582.6 (moenomycin A)

CAS — 11015-37-5 (bambermycin); 76095-39-1 (moenomycin A).

UNII — PP922A42V2.

Profile

Bambermycin is an antibacterial complex containing mainly moenomycin A and moenomycin C and which may be obtained from cultures of *Streptomyces bambergiensis* or by other means. It is used as a growth promotor in veterinary practice.

Baquiloprim *(BAN, rINN)*

138OU; Bakiloprimi; Bakiloprim; Baquiloprima; Baquiloprime; Baquiloprimum; Бахилоприм.

5-(8-Dimethylamino-7-methyl-5-quinolylmethyl)pyrimidin-2,4-diyldiamine.

$C_{17}H_{20}N_6$=308.4

CAS — 102280-35-3.

UNII — 3DE766VIG6.

Profile

Baquiloprim is a diaminopyrimidine antibacterial used similarly to trimethoprim (p. 383.2) as a sulfonamide potentiator, in veterinary medicine. Preparations usually contain 1 part of baquiloprim to 5 parts of sulfonamide.

Bedaquiline *(USAN, rINN)*

Bedaquilina; Bédaquiline; Bedaquilinum; R-207910; TMC-207; Бедаквилин; Бедахилин.

(1*R*, 2*S*)-1-(6-Bromo-2-methoxyquinolin-3-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol.

$C_{32}H_{31}BrN_2O_2$=555.5

CAS — 843663-66-1.

UNII — 78846I289Y.

Bedaquiline Fumarate *(USAN, rINNM)*

Bédaquiline, Fumarate de; Bedaquilini Fumaras; Fumarato de bedaquilina; R-403323; Бедаквилин Фумарат; Бедахилин Фумарат.

$C_{32}H_{31}BrN_2O_2.C_4H_4O_4$=671.6

CAS — 845533-86-0.

UNII — P04QX2C1A5.

Profile

Bedaquiline is a diarylquinoline antimycobacterial that is used as part of combination therapy, with at least 3 other antituberculous drugs, in the treatment of multidrug-

resistant pulmonary tuberculosis (p. 210.2) when an effective treatment regimen cannot otherwise be provided.

It is given as the fumarate although doses are expressed in terms of the base; 120.89 mg of bedaquiline fumarate is equivalent to about 100 mg of bedaquiline. It is given orally with food for a total treatment course of 24 weeks according to the following regimen:

- weeks 1 and 2: 400 mg once daily
- weeks 3 to 24: 200 mg 3 times a week (with at least 48 hours between doses)

Bedaquiline has a terminal half-life of about 4 to 5 months which results in extended periods of exposure to low levels of bedaquiline. Consequently, to avoid acquired resistance developing, treatment with bedaquiline should be stopped 4 to 5 months before the other antituberculous drugs are scheduled to be stopped. It is metabolised by the cytochrome P450 isoenzyme CYP3A4 and use with other drugs that induce or suppress this isoenzyme should be avoided. The concurrent use of drugs known to cause QT prolongation could increase the risk of cardiotoxicity in patients taking bedaquiline.

References.
1. Chahine EB, *et al.* Bedaquiline: a novel diarylquinoline for multidrug-resistant tuberculosis. *Ann Pharmacother* 2013. Available at: doi:10.1177/1060028013504087.
2. Chan B, *et al.* A review of tuberculosis: focus on bedaquiline. *Am J Health-Syst Pharm* 2013; 70: 1984–94.
3. CDC. Division of Tuberculosis Elimination, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, CDC. Provisional CDC guidelines for the use and safety monitoring of bedaquiline fumarate (Sirturo) for the treatment of multidrug-resistant tuberculosis. *MMWR* 2013; 62 (RR-9): 1–12. Also available at: http://www.cdc.gov/mmwr/pdf/rr/rr6209.pdf (accessed 02/12/13) Correction. *ibid.*: 906.
4. WHO. *The use of bedaquiline in the treatment of multidrug-resistant tuberculosis: interim policy guidance.* Geneva: WHO, 2013. Available at: http://apps.who.int/iris/bitstream/10665/84879/1/9789241505482_eng.pdf (accessed 02/12/13)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Sirturo.

Bekanamycin Sulfate *(rINNM)*

Aminodeoxykanamycin Sulphate; Bekanamicina, sulfato de; Bekanamycin Sulphate; Békanamycine, Sulfate de; Bekanamycini Sulfas; Kanamycin B Sulphate; KDM; NK-1006; Sulfato de bekanamicina; Беканамицина Сульфат.

6-O-(3-Amino-3-deoxy-α-D-glucopyranosyl)-2-deoxy-4-O-(2,6-diamino-2,6-dideoxy-α-D-glucopyranosyl)-D-streptamine sulphate.

$C_{18}H_{37}N_5O_{10}.2½H_2SO_4$=728.7

CAS — 4696-76-8 (bekanamycin); 70550-99-1 (bekanamycin sulfate).

UNII — KB71EA86HM.

Pharmacopoeias. In *Jpn*.

Profile

Bekanamycin is an aminoglycoside antibacterial and is a congener of kanamycin. It has properties similar to those of gentamicin (p. 306.2). It is given topically as the sulfate for the treatment of eye infections. It has also been given intramuscularly and orally. It is reported to be more toxic than kanamycin.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Ital.*: Visucloben Antibiotico; Visumetazone Antibiotico.

Benethamine Penicillin *(BAN, rINN)*

Bénéthamine Pénicilline; Benethaminum Penicillinum; Penicilina-benetamina; Бенетамин Пенициллин.

Benzyl(phenethyl)ammonium (6*R*)-6-(2-phenylacetamido) penicillanate.

$C_{15}H_{17}N.C_{16}H_{18}N_2O_4S$=545.7

CAS — 751-84-8.

ATC Vet — QJ01CE91.

UNII — O3S7RWT8R5.

Profile

Benethamine penicillin is a poorly soluble derivative of benzylpenicillin (p. 230.1) with similar actions and uses, although it is not recommended for chronic, severe, or deep-seated infections. After deep intramuscular injection it forms a depot from which it is slowly absorbed and hydrolysed to benzylpenicillin. Benethamine penicillin is usually given with benzylpenicillin sodium and also sometimes procaine benzylpenicillin to produce both an immediate and a prolonged effect; overall, the effect lasts for 2 to 3 days.

Benzathine Benzylpenicillin

(BAN, rINN)

Bensylpenicillinbensatin; Bensylpenicillinbenzatin; Bentsyylipenisilliinibentsatiini; Benzathin-benzylpenicilin; Benzathine benzylpénicilline; Benzathine Penicillin; Benzathini Benzylpenicillinum; Benzatin Penisilin; Benzatina bencilpenicilina; Benzethacil; Benzilpenicilinas benzatinas; Benzilpenicillina Benzatinica; Benzilpenicillin-benzantin; Benzylopenicylina benzatynowa; Benzylpenicillinum Benzanthinum; Benzylpenicillinum Benzathinum; Penicillin G Benzathine; Penisilin G Benzatin; Penzaethinum G; Бензатина Бензилпенициллин.

NN'-Dibenzylethylenediammonium bis[(6*R*)-6-(2-phenylacetamido)penicillanate].

$C_{16}H_{20}N_2(C_{16}H_{18}N_2O_4S)_2$=909.1

CAS — 1538-09-6 (anhydrous benzathine benzylpenicillin); 5928-83-6 (benzathine benzylpenicillin monohydrate); 41372-02-5 (benzathine benzylpenicillin tetrahydrate).

ATC — J01CE08.

ATC Vet — QJ01CE08.

UNII — RIT82F58GK.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Int.* *Jpn* and *US* include the tetrahydrate.

Ph. Eur. 8: (Benzylpenicillin, Benzathine). It contains a variable quantity of water. A white or almost white powder. Very slightly soluble in water; slightly soluble in alcohol; freely soluble in dimethylformamide and in formamide. Store in airtight containers.

USP 36: (Penicillin G Benzathine). The tetrahydrate is a white, odourless, crystalline powder. Soluble 1 in 5000 of water and 1 in 65 of alcohol. pH in a solution prepared by dissolving 50 mg in 50 mL of dehydrated alcohol, and adding 50 mL of water is between 4.0 and 6.5. Store in airtight containers.

Uses and Administration

Benzathine benzylpenicillin has the same antimicrobial action as benzylpenicillin (p. 232.1), to which it is hydrolysed gradually after deep intramuscular injection. This results in a prolonged effect, but because of the relatively low blood concentrations of benzylpenicillin produced, its use should be restricted to micro-organisms that are highly susceptible to benzylpenicillin. In acute infections, and when bacteraemia is present, the initial treatment should be with benzylpenicillin by injection.

Infections treated with benzathine benzylpenicillin include diphtheria (asymptomatic carriers), pharyngitis (*Streptococcus pyogenes; Arcanobacterium haemolyticum* (*Corynebacterium haemolyticum*)), and syphilis (including non-venereal treponematoses). It is also used for primary and secondary prophylaxis of rheumatic fever. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Benzathine benzylpenicillin is given by deep intramuscular injection, sometimes with procaine benzylpenicillin and benzylpenicillin itself. It has been given orally for mild infections, although phenoxymethylpenicillin is usually preferred. Benzathine benzylpenicillin 900 mg is equivalent to about 720 mg of benzylpenicillin (1.2 million units).

For early syphilis, a single dose of benzathine benzylpenicillin 1.8 g by deep intramuscular injection is given, usually as 2 injections at separate sites. In late syphilis, 1.8 g is given at weekly intervals for 3 consecutive weeks. Benzathine benzylpenicillin is not usually recommended for the treatment of neurosyphilis because of reports of inadequate penetration into the CSF.

For the treatment of other treponemal infections, such as yaws, pinta, and endemic syphilis (bejel), a single intramuscular dose of benzathine benzylpenicillin 900 mg is given.

For streptococcal pharyngitis and the primary prevention of rheumatic fever, the adult dose is a single intramuscular injection of 900 mg. To prevent recurrences of acute rheumatic fever, 900 mg is given intramuscularly every 3 or 4 weeks.

For details of doses in children see p. 229.2.

Administration in children. Benzathine benzylpenicillin may be given by deep intramuscular injection to infants and children for the treatment of susceptible bacterial infections, including congenital syphilis and streptococcal pharyngitis, and for the prevention of rheumatic fever.

In the USA, the following doses have been recommended for treatment of **streptococcal pharyngitis** and **primary prevention of rheumatic fever** by the American Academy of Pediatrics (AAP):[1]

- newborns and infants: 37.5 mg/kg (50 000 units/kg) as a single dose
- children weighing less than 27 kg: 225 to 450 mg (300 000 to 600 000 units) as a single dose
- children weighing 27 kg or more: 675 mg (900 000 units) as a single dose

The American Heart Association (AHA)[2] suggests doses of:

- infants and children weighing 27 kg or less: 450 mg (600 000 units) as a single dose
- children weighing more than 27 kg: 900 mg (1 200 000 units) as a single dose

Alternatively, WHO recommend:

- children weighing less than 30 kg: 450 to 675 mg as a single dose
- children weighing 30 kg or more: 900 mg as a single dose

To **prevent recurrence of acute rheumatic fever**, the AAP and AHA recommend the following doses given once every 4 weeks or once every 3 weeks in high-risk areas:

- children weighing less than 27 kg: 450 mg (600 000 units)
- children weighing more than 27 kg: 900 mg (1 200 000 units)

Similar dose recommendations are made by WHO.

For treatment of **yaws, pinta, and bejel (endemic syphilis)** in children, 450 mg as a single dose is recommended by WHO.

For doses used to treat **congenital syphilis** in infants, see p. 205.2.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases.* 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.
2. Gerber MA, *et al.* Prevention of rheumatic fever and diagnosis and treatment of acute Streptococcal pharyngitis: a scientific statement from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, the Interdisciplinary Council on Functional Genomics and Translational Biology, and the Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. *Circulation* 2009; 119: 1541–51. Also available at: http://circ.ahajournals.org/cgi/reprint/119/11/1541 (accessed 13/08/09)

Adverse Effects and Precautions

As for Benzylpenicillin, p. 231.2.

Non-allergic (embolic-toxic) reactions similar to those associated with procaine benzylpenicillin, p. 346.3, have been reported rarely with benzathine benzylpenicillin.

Benzathine benzylpenicillin should not be injected intravascularly since ischaemic reactions may occur.

Interactions

As for Benzylpenicillin, p. 232.1.

Pharmacokinetics

When benzathine benzylpenicillin is given by intramuscular injection, it forms a depot from which it is slowly released and hydrolysed to benzylpenicillin. Peak plasma concentrations are produced in about 24 hours and are lower than those after an equivalent dose of benzylpenicillin potassium or sodium. However, depending on the dose, benzylpenicillin is usually detectable in plasma for up to 4 weeks (but see p. 229.3).

Distribution into the CSF is reported to be poor.

Due to the slow absorption from the site of injection, benzylpenicillin has been detected in the urine for up to 12 weeks after a single dose.

Benzathine benzylpenicillin is relatively stable in the presence of gastric juice, but absorption from the gastrointestinal tract is variable. Plasma concentrations of benzylpenicillin after an oral dose are lower than those from the same dose of a soluble penicillin; peak concentrations are also produced less rapidly, but may persist for longer.

Plasma concentrations. Benzathine benzylpenicillin has been given every 4 weeks for secondary prophylaxis against rheumatic fever, although some advocate giving it every 3 weeks to ensure adequate plasma concentrations of benzylpenicillin. Typical concentrations achieved after a single intramuscular injection of benzathine benzylpenicillin 900 mg have been cited as about 100, 20, and 2 nanograms/mL on days 1, 14, and 32 respectively. In one study[1] adequate concentrations (defined as 20 nanograms or more per mL) were seen in more than 80% of serum samples at 3 weeks, but in only 36% at 4 weeks. In a further study,[2] in which single doses of 900 mg, 1.35 g and 1.8 g were compared, it appeared that doses higher than the 900-mg dose of benzathine benzylpenicillin usually recommended might prolong the duration of protective plasma concentrations of benzylpenicillin (defined as above 25 nanograms/mL) and improve the efficacy of dosing every 4 weeks for prophylaxis against rheumatic fever.

1. Kaplan EL, *et al.* Pharmacokinetics of benzathine penicillin G: serum levels during the 28 days after intramuscular injection of 1 200 000 units. *J Pediatr* 1989; 115: 146–50.
2. Currie BJ, *et al.* Penicillin concentrations after increased doses of benzathine penicillin G for prevention of secondary rheumatic fever. *Antimicrob Agents Chemother* 1994; 38: 1203–4.

Pregnancy. The pharmacokinetics of benzathine benzylpenicillin appear to be altered in late pregnancy. Of 10 healthy pregnant women given benzathine benzylpenicillin 1.8 g intramuscularly before caesarean section, only 4 achieved adequate serum concentrations of benzylpenicillin (for syphilis, at least 18 nanograms/mL) for 7 days.[1]

1. Nathan L, *et al.* Penicillin levels following the administration of benzathine penicillin G in pregnancy. *Obstet Gynecol* 1993; **82**: 338–42.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Benzetacil; Galtamicina; Pen di Ben; Retarpen; *Austral.*: Bicillin L-A; *Austria*: Retarpen; *Belg.*: Penadur; *Braz.*: Bactopen; Benzatron; Benzetacil; Bepeben; Longacilin; Pencil B†; *Canad.*: Bicillin L-A; *Cz.*: Pendepon Compositum; Retarpen†; *Fr.*: Extencilline; *Ger.*: Pendysin; *Gr.*: Penadur; *Hong Kong*: Pan-Benzathine G; *India*: Longacillin; Pencom; Penidure; *Israel*: Durabiotic; *Ital.*: Diaminocillina†; *Malaysia*: Retarpen; *Mex.*: Benacilina†; Bencelin; Benzafur†; Benzanil Simple†; Benzetacil; Ipenxin; Lentopenil; Unicil 6:3:3; Unicil L-A; *Neth.*: Penidural; *NZ*: Bicillin L-A; *Philipp.*: Penadur†; Zalpen; *Pol.*: Debecylina; *Port.*: Lentocilin S; *Rus.*: Benzycillin 1 (Бензициллин 1); Bicillin-1 (Бициллин-1); Extencilline (Экстенциллин); Retarpen (Ретарпен); *S.Afr.*: Bicillin L-A†; Penilente LA; *Singapore*: Retarpen; *Spain*: Benzetacil; Cepacilina†; *Turk.*: Benzapen 6.3.3; Benzapen; Deposilin 6.3.3; Deposilin; Penadur 6.3.3; Penadur; Pentin; *Ukr.*: Retarpen (Ретарпен); *USA*: Bicillin L-A; Permapen; *Venez.*: Benzetacil L-A.

Multi-ingredient Preparations. *Austria*: Retarpen compositum; *Ger.*: Retacillin compositum; Tardocillin; *Mex.*: Bencelin Combinado; Benzanil Compuesto†; Benzetacil Combinado; Pecivax; Pendiben Compuesto†; *Port.*: Lentocilin; *Rus.*: Benzycillin 3 (Бензициллин 3); Benzycillin 5 (Бензициллин 5); Bicillin-3 (Бициллин-3); Bicillin-5 (Бициллин-5); *S.Afr.*: Ultracillin†; *Spain*: Benzetacil Compuesta; Cepacilina 633†; Penilevel Retard; *Ukr.*: Bicillin-3 (Бициллин-3); Bicillin-5 (Бициллин-5); *USA*: Bicillin C-R; *Venez.*: Benzetacil 3-3; Benzetacil 6-3-3.

Pharmacopoeial Preparations
USP 36: Penicillin G Benzathine and Penicillin G Procaine Injectable Suspension; Penicillin G Benzathine Injectable Suspension; Penicillin G Benzathine Oral Suspension; Penicillin G Benzathine Tablets.

Benzathine Phenoxymethylpenicillin

Benzatin Fenoksimetil Penisilin; Benzatina fenoximetilpenicilina; Penicillin V Benzathine (USAN); Phenoxymethylpenicillini Dibenzylaethylendiaminum; Бензатинфеноксиметилпенициллин.

N,N'-Dibenzylethylenediammonium bis[(6*R*)-6-(2-phenoxyacetamido)penicillanate].

$(C_{16}H_{18}N_2O_5S)_2C_{16}H_{20}N_2$=941.1

CAS — 5928-84-7 (anhydrous benzathine phenoxymethylpenicillin); 63690-57-3 (benzathine phenoxymethylpenicillin tetrahydrate).

ATC — J01CE10.

ATC Vet — QJ01CE10.

UNII — 3T4EMH59ZU.

Pharmacopoeias. In *US.*

USP 36: (Penicillin V Benzathine). A practically white powder having a characteristic odour. Soluble 1 in 3200 of water, 1 in 330 of alcohol, 1 in 37 of acetone, 1 in 42 of chloroform, and 1 in 910 of ether. pH of a 3% suspension in water is between 4.0 and 6.5. Store in airtight containers.

Profile

Benzathine phenoxymethylpenicillin has actions and uses similar to those of phenoxymethylpenicillin (p. 340.3) and is given orally in the treatment of susceptible mild to moderate infections. Doses are expressed in terms of phenoxymethylpenicillin.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Abbocillin-V; Cilicaine V; *Austria*: Ospen; *Canad.*: Pen-Vee†; *Cz.*: Ospen; *Fr.*: Oracilline; *Ger.*: InfectoBicillin; *Gr.*: Ospen; *Hung.*: Ospen; *Pol.*: Ospen; *Rus.*: Ospen (Оспен); *Spain*: Benoral; *Switz.*: Ospen; *Turk.*: Pen-Os; *Ukr.*: Ospen (Оспен)†; *Venez.*: Ospen.

Pharmacopoeial Preparations
USP 36: Penicillin V Benzathine Oral Suspension.

Benzylpenicillin *(BAN, rINN)*

Bencilpenicilina; Bensylpenicillin; Bentsyylipenisilliini; Benzil Penisilliin; Benzylpénicilline; Benzylpenicillinum; Crystalline Penicillin G; Penicilina G; Penicillin; Penicillin G; Penisilin G; Бензилпенициллин.

(2*S*,5*R*,6*R*)-3,3-Dimethyl-7-oxo-6-(2-phenylacetamido)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid; (6*R*)-6-(2-Phenylacetamido)penicillanic acid.

$C_{16}H_{18}N_2O_4S$=334.4

CAS — 61-33-6.

ATC — J01CE01; S01AA14.

ATC Vet — QJ01CE01; QJ51CE01; QS01AA14.

UNII — Q42T66VG0C.

Description. The name benzylpenicillin is commonly used to describe either benzylpenicillin potassium or benzylpenicillin sodium as these are the forms in which benzylpenicillin is used.

In *Martindale*, benzylpenicillin means either the potassium or sodium salt.

Benzylpenicillin Potassium *(BANM, rINNM)*

Bencilpenicilina potásica; Bensylpenicillinkalium; Bentsyylipenisilliinikalium; Benzilpenicilino kalio druska; Benzilpenicillin-kálium; Benzylopenicylina potasowa; Benzylpenicilin draselná sůl; Benzylpenicillin-Kalium; Benzylpénicilline potassique; Benzylpenicillinum Kalicum; Kalii Benzylpenicillinum; Penicilina G potásica; Penicillin G Potassium; Penisilin G Potasyum; Калия бензилпенициллин.

$C_{16}H_{17}KN_2O_4S$=372.5

CAS — 113-98-4.

ATC — J01CE01; S01AA14.

ATC Vet — QJ01CE01; QS01AA14.

UNII — VL775ZTH4C.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Benzylpenicillin Potassium). The potassium salt of a substance produced by growing certain strains of *Penicillium notatum* or related organisms or obtained by any other means. A white or almost white crystalline powder. Very soluble in water; practically insoluble in fatty oils and in liquid paraffin. A 10% solution in water has a pH of 5.5 to 7.5. Store in airtight containers.

USP 36: (Penicillin G Potassium). Colourless or white crystals, or white crystalline powder. It is odourless or practically so, and is moderately hygroscopic. Very soluble in water, in sodium chloride 0.9%, and in glucose solutions; sparingly soluble in alcohol. Its solutions retain substantially full potency for several days at temperatures below 15 degrees, but are rapidly inactivated by acids, by alkali hydroxides, by glycerol, and by oxidising agents. pH of a 6% solution in water is between 5.0 and 7.5. Store in airtight containers.

Incompatibility and stability. See Benzylpenicillin Sodium, p. 230.2.

Benzylpenicillin Sodium *(BANM, rINNM)*

Bencilpenicilina sódica; Bensylpenicillinnatrium; Bentsyylipenisilliininatrium; Benzilpenicilino natrio druska; Benzilpenicillin-nátrium; Benzylopenicylina sodowa; Benzylpenicilin sodná sůl; Benzylpenicillin-Natrium; Benzylpénicilline Sodique; Benzylpenicillinum Natricum; Natrii Benzylpenicillinum; Penicilina G sódica; Penicillin G Sodium; Sodyum Penisilin G; Натрий бензилпенициллин.

$C_{16}H_{17}N_2NaO_4S$=356.4

CAS — 69-57-8.

ATC — J01CE01; S01AA14.

ATC Vet — QJ01CE01; QS01AA14.

UNII — YS5LY7JF4N.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 8: (Benzylpenicillin Sodium). The sodium salt of a substance produced by growing certain strains of *Penicillium notatum* or related organisms or obtained by any other means. A white or almost white crystalline powder. Very soluble in water; practically insoluble in fatty oils and in liquid paraffin. A 10% solution in water has a pH of 5.5 to 7.5. Store in airtight containers.

USP 36: (Penicillin G Sodium). Colourless or white crystals, or white to slightly yellow crystalline powder. It is odourless or practically so, and is moderately hygroscopic. Its solutions lose potency fairly rapidly at room temperature, but retain substantially full potency for several days at temperatures below 15 degrees. Its solutions are rapidly inactivated by acids, by alkali hydroxides, by oxidising agents, and by penicillinase. pH of a 6% solution in water is between 5.0 and 7.5. Store in airtight containers.

Incompatibility. Benzylpenicillin has been reported to be incompatible with metal ions and some rubber products. Its stability may be affected by ionic and nonionic surfactants, oxidising and reducing agents, alcohols, glycerol, glycols, macrogols and other hydroxy compounds, some paraffins and bases, some preservatives such as chlorocresol or thiomersal, carbohydrate solutions in an alkaline pH, fat emulsions, blood and blood products, and viscosity modifiers. Benzylpenicillin is incompatible with many acidic and basic drugs (see Stability, p. 230.3) and several other antimicrobials, including amphotericin B, some cephalosporins, and vancomycin. Benzylpenicillin and aminoglycosides are mutually incompatible and injections should be given at separate sites.

Stability. Benzylpenicillin is hydrolysed in aqueous solutions by degradation of the beta-lactam ring and hydrolysis is accelerated by increased temperature or alkaline conditions; inactivation also occurs under acid conditions. Degradation products include penillic, penicillenic, and penicilloic acids which lower the pH and cause a progressive increase in the rate of deterioration; *N*-formylpenicillamine and very small amounts of penicillamine have also been detected. Degradation is minimal at about pH 6.8 and deterioration of benzylpenicillin in solution may be retarded by using a citrate buffer. Dilute solutions are more stable than concentrated ones.

References.
1. Lynn B. The stability and administration of intravenous penicillins. *Br J Intraven Ther* 1981; **2** (Mar): 22–39.
2. Bird AE, *et al.* N-Formylpenicillamine and penicillamine as degradation products of penicillins in solution. *J Pharm Pharmacol* 1986; **38**: 913–17.

Units

The second International Standard Preparation (1952) of benzylpenicillin sodium contained 1670 units of penicillin per mg but was withdrawn in 1968 since penicillin can now be characterised completely by chemical tests. Despite this, doses of benzylpenicillin are still expressed in units in some countries.

Benzylpenicillin potassium 600 mg or benzylpenicillin sodium 600 mg have generally been considered to be equivalent to about 1 million units (1 mega unit).

Uses and Administration

Benzylpenicillin is used in the treatment of infections due to susceptible organisms (see Antimicrobial Action, p. 232.1). They include abscess, actinomycosis, anthrax, bites and stings, diphtheria, endocarditis, gas gangrene, leptospirosis, Lyme disease, meningitis, meningococcal infections, necrotising enterocolitis, necrotising fasciitis, neonatal conjunctivitis (if gonococci are sensitive), perinatal streptococcal infections (intrapartum prophylaxis against group B streptococci), pharyngitis (or tonsillitis), pneumonia, skin infections, syphilis (neurosyphilis and congenital syphilis), tetanus, toxic shock syndrome, and Whipple's disease. It is also used for surgical infection prophylaxis in first trimester abortion in women at high risk of pelvic infection. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Benzylpenicillin is usually given intramuscularly or intravenously. Where a prolonged effect is needed benzathine benzylpenicillin (p. 227.2) or procaine benzylpenicillin (p. 346.2) are preferred; they are given intramuscularly. Benzylpenicillin is sometimes given orally for infections of moderate severity, but one of the acid-resistant penicillins such as phenoxymethylpenicillin (p. 340.3) is preferable.

Benzylpenicillin is available as the potassium or sodium salt. The dose of benzylpenicillin should be sufficient to achieve an optimum bactericidal concentration in the blood as rapidly as possible; concentrations may be increased by giving it with probenecid (p. 608.1). In some countries, doses are still expressed in units. Benzylpenicillin potassium 600 mg or benzylpenicillin sodium 600 mg have generally been considered to be equivalent to about 1 million units (1 mega unit).

For some infections, doses of 0.6 to 4.8 g of benzylpenicillin daily in 4 to 6 divided doses by intramuscular or slow intravenous injection or intravenous infusion may be adequate, but higher doses given intravenously, often by infusion, are more usual for severe infections. For example, in endocarditis, benzylpenicillin 7.2 g daily (1.2 g every 4 hours) intravenously, usually with an aminoglycoside, is recommended; doses of up to 18 g daily are not unusual for less sensitive streptococci and enterococci. In meningococcal and pneumococcal meningitis, benzylpenicillin 14.4 g daily (2.4 g every 4 hours) intravenously is recommended; up to 18 g daily has been recommended for meningococcal meningitis. High doses should be given slowly to avoid irritation of the CNS and electrolyte imbalance, and a rate of not more than 300 mg/minute is recommended for intravenous doses above 1.2 g. High doses may need to be reduced in patients with renal impairment (see p. 231.1).

In patients with suspected meningococcal infection, benzylpenicillin 1.2 g by intravenous or intramuscular injection should be given before transfer to hospital.

A dose for intrapartum prophylaxis against group B streptococcal infection is benzylpenicillin 3 g intravenously initially, then 1.5 g every 4 hours until delivery.

For details of doses in children, see p. 231.1.

Other routes. Benzylpenicillin eye drops and eye ointment are used in the treatment of susceptible eye infections. For subconjunctival injection, 300 or 600 mg of benzylpenicillin has been dissolved in 0.5 to 1.0 mL of water, or another suitable solvent such as lidocaine 2% with or without adrenaline 1 in 200 000 or similar.

Benzylpenicillin has also been given orally on an empty stomach in adult doses of 125 to 312 mg every 4 to 6 hours.

Intrathecal injections are no longer recommended.

Administration in children. Benzylpenicillin may be given to neonates and children for the treatment of infections caused by susceptible organisms by intramuscular injection, or by slow intravenous injection or infusion; the intravenous route is recommended for neonates and infants and in the treatment of endocarditis or meningitis.

In the UK, the *BNFC* recommends the following doses:

For **mild to moderate susceptible infections**, including throat infections, otitis media, pneumonia, cellulitis, and neonatal sepsis:

- neonates under 7 days of age: 25 mg/kg every 8 to 12 hours
- neonates 7 to 28 days of age: 25 mg/kg every 8 hours; dose doubled for severe infection
- children from 1 month of age: 25 mg/kg every 6 hours; increased to 50 mg/kg every 4 to 6 hours (maximum 2.4 g every 4 hours) for severe infection

For **endocarditis**:

- children from 1 month of age: 25 mg/kg every 4 hours; dose may be doubled (maximum 2.4 g every 4 hours) if necessary

For **meningitis and meningococcal disease**:

- neonates: 50 mg/kg every 12 hours for those less than 7 days of age and every 8 hours for those 7 to 28 days of age
- children from 1 month of age: 50 mg/kg every 4 to 6 hours (maximum 2.4 g every 4 hours)

Where meningitis, and especially meningococcal disease are suspected, a single injection of benzylpenicillin is advised urgently before transfer to hospital in the following doses:

- infants under one year of age: 300 mg
- children 1 to 9 years of age: 600 mg
- children from 10 years of age: 1.2 g

In the USA, the American Academy of Pediatrics[1] suggests the following doses given intramuscularly or intravenously, although higher doses may be needed for the treatment of meningitis in neonates:

- for neonates aged 7 days or less (irrespective of body weight): 15 to 30 mg/kg (25 000 to 50 000 units/kg) every 12 hours
- for neonates aged 8 to 28 days (irrespective of body weight): 15 to 30 mg/kg (25 000 to 50 000 units/kg) every 8 hours; a dosing interval of 12 hours may be used until 2 weeks of life in extremely low birth-weight neonates (weighing less than 1 kg)
- children 1 month and older: in mild to moderate infections 60 to 90 mg/kg (100 000 to 150 000 units/kg) daily in 4 divided doses, to a maximum of 4.8 g (8 million units) daily; in severe infection, doses of 120 to 180 mg/kg daily (200 000 to 300 000 units/kg) in 6 divided doses, to a maximum of 14.4 g (24 million units) daily may be used

Dosing recommendations in some neonatal populations have been suggested based on pharmacokinetic models. A study in 20 preterm neonates (less than 32 weeks gestational age)[2] confirmed that a regimen of 30 mg/kg (50 000 units/kg) every 12 hours is adequate for empirical treatment of common infections on the third day of life; but for infections due to highly susceptible organisms, a 24-hour dosing interval is likely sufficient. A study in very low birth-weight neonates (less than 1.2 kg) with gestational age less than 28 weeks[3] suggested that, for that population, 15 mg/kg (25 000 units/kg) every 12 hours was sufficient to achieve effective drug concentrations in the serum and CSF for the treatment of group B streptococcal infections.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.
2. Muller AE, *et al.* Pharmacokinetics of penicillin G in infants with a gestational age of less than 32 weeks. *Antimicrob Agents Chemother* 2007; 51: 3720–5.
3. Metsvaht T, *et al.* Pharmacokinetics of penicillin G in very-low-birth-weight neonates. *Antimicrob Agents Chemother* 2007; 51: 1995–2000.

Administration in renal impairment. Doses of parenteral benzylpenicillin should be reduced in patients with renal impairment, particularly when high-dose regimens are being used. For doses of 0.6 to 1.2 g, UK licensed product information suggests dosing intervals no more frequent than every 8 hours. For high-dose regimens used in the treatment of serious infections, it recommends the following doses based on creatinine clearance (CC):

- CC 60 mL/minute: 1.2 g every 4 hours
- CC 40 mL/minute: 900 mg every 4 hours
- CC 20 mL/minute: 600 mg every 4 hours
- CC 10 mL/minute: 600 mg every 6 hours
- anuric: 300 mg every 6 hours or 600 mg every 8 hours

Where advanced liver disease is associated with severe renal failure, the recommended dose is 300 mg every 8 hours. Haemodialysis patients should be given an additional 300 mg every 6 hours during the dialysis run.

Alternatively, some US experts recommend the following:

- CC 10 to 50 mL/minute: 75% of the total recommended dose
- CC less than 10 mL/minute: 20 to 50% of the total recommended dose (where haemodialysis is required, doses should be timed to be given after the dialysis run)

A review[1] of antimicrobial dosing in critically ill patients receiving renal replacement therapy has suggested that those on intermittent haemodialysis may be given the usual recommended dose (see Uses and Administration, p. 228.3) for one dose, after which 25 to 50% of the usual dose should be given every 4 to 6 hours, or 50 to 100% of the dose may be given every 8 to 12 hours. For those on continuous renal replacement therapy (CRRT) a loading dose of 4 million-units (2.4 g) is recommended, with the following maintenance doses, depending on the type of CRRT, given every 4 to 6 hours:

- continuous venovenous haemofiltration (CVVH): 2 million units (1.2 g)
- continuous venovenous haemodialysis (CVVHD): 2 to 3 million units (1.2 to 1.8 g)
- continuous venovenous haemodiafiltration (CVVHDF): 2 to 4 million units (1.2 to 2.4 g)

1. Heintz BH, *et al.* Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy* 2009; 29: 562–77.

Adverse Effects

The most common adverse effects of benzylpenicillin are hypersensitivity reactions, especially skin rashes; anaphylaxis occasionally occurs and has sometimes been fatal.

Gastrointestinal effects such as diarrhoea and nausea are the most common adverse effects after oral use of benzylpenicillin; a sore mouth or tongue or a black hairy tongue have occasionally been reported. Pseudomembranous colitis has been associated with the use of most antibacterials; ampicillin or amoxicillin are the most frequently implicated penicillins (see Antibiotic-associated Colitis, p. 183.1).

Other adverse effects have generally been associated with large intravenous doses of benzylpenicillin; patients with renal impairment are also at increased risk. These adverse effects include haemolytic anaemia and neutropenia, both of which might have some immunological basis; prolongation of bleeding time and defective platelet function; convulsions and other signs of CNS toxicity (encephalopathy has followed intrathecal dosage and can be fatal); and electrolyte disturbances because of the large amounts of potassium or sodium given when benzylpenicillin potassium or sodium, respectively, are used.

Hepatitis and cholestatic jaundice have been reported rarely with many penicillins, notably penicillinase-resistant penicillins such as flucloxacillin and oxacillin, and also combinations of amoxicillin or ticarcillin with clavulanic acid.

Nephropathy and interstitial nephritis, which may have some immunological basis, have been especially associated with meticillin, but may be produced by other penicillins.

Some patients with syphilis and other spirochaete infections may have a Jarisch-Herxheimer reaction shortly after starting treatment with penicillin, which is probably due to the release of endotoxins from the killed treponemes and should not be mistaken for a hypersensitivity reaction. Symptoms include fever, chills, headache, and reactions at the site of the lesions. The reaction can be dangerous in cardiovascular syphilis, or where there is a serious risk of increased local damage, such as with optic atrophy.

Hypersensitivity. The overall incidence of allergic reactions to penicillin has been reported to vary from about 1 to 10% although some patients may have been incorrectly labelled 'allergic to penicillin'. Anaphylactic reactions occur in about 0.05% of patients, usually after parenteral use, but they have also been reported after taking oral penicillin.

Hypersensitivity to penicillin gives rise to immediate reactions including anaphylaxis, angioedema, urticaria, and some maculopapular rashes. Late reactions may include serum sickness-like reactions and haemolytic anaemia. Reactions are considered to be due mainly to breakdown products produced *in vitro* before use or to metabolites of penicillin, and possibly penicillin itself. These act as haptens which, when combined with proteins and other macromolecules, produce potential antigens. As the hypersensitivity is related to the basic penicillin structure, patients who are genuinely allergic to benzylpenicillin must be assumed to be allergic to all penicillins; sensitised patients may also react to the cephalosporins and other beta-lactam antibacterials.

Tests for hypersensitivity may be used to determine those patients most likely to develop serious allergic reactions to penicillins. Skin tests are used to evaluate the current risk of immediate or accelerated IgE-mediated reactions, the most serious being anaphylaxis. Both the major and minor determinants of penicillin hypersensitivity should be used; the major determinant is available as penicilloyl-polylysine (p. 2585.3) and a minor-determinant mixture consisting of benzylpenicillin and its derivatives, including penicilloic acid and benzylpenicilloylamine, can be used, although if this is not available a solution of benzylpenicillin may be substituted. Adrenaline should be available in case an anaphylactic reaction develops. The results of skin tests are unreliable if a significant time has elapsed before beginning therapy. Several *in-vitro* tests including the radioallergosorbent test (RAST) have been developed.

Desensitisation may be attempted in patients allergic to penicillin when treatment with penicillin is considered essential. It involves very small doses of penicillin given at relatively short intervals of 15 minutes or more, and gradually increased to therapeutic concentrations. However, desensitisation may be hazardous and should only be carried out if the patient can be monitored continuously and adrenaline and resuscitation equipment are immediately available. Desensitisation should be regarded as temporary, and allergic reactions may recur during the next exposure to penicillin.

Neutropenia. Neutropenia has been widely reported in patients given high doses of beta lactams and an incidence of 5 to more than 15% has been reported in patients treated for 10 days or more. Warning signs include fever, rash, and eosinophilia. Monitoring of the leucocyte count is recommended during long-term treatment with high doses. Some have proposed a direct toxic effect whereas others have postulated an immune mechanism.

Electrolyte disturbances. Many penicillins have been associated with electrolyte disturbances, particularly of sodium and potassium. Benzylpenicillin potassium in high doses may lead to hyperkalaemia, particularly in those with renal impairment. While hypernatraemia can result from the high sodium loads associated with the sodium salts of benzylpenicillin, carbenicillin, flucloxacillin, and ticarcillin; hypokalaemia may also result from sodium-induced solute diuresis. In addition, many semisynthetic penicillins (including carbenicillin, cloxacillin, mezlocillin, nafcillin, piperacillin, and ticarcillin) can act as non-absorbable anions in the distal tubule, resulting in urinary potassium loss and hypokalaemia. This effect may be mediated by volume depletion, and has been seen mainly in severely ill patients.

Effects on the blood. References to neutropenia associated with penicillins.

1. Anonymous. Antibiotic-induced neutropenia. *Lancet* 1985; ii: 814.
2. Neftel KA, *et al.* Inhibition of granulopoiesis in vivo and in vitro by β-lactam antibiotics. *J Infect Dis* 1985; 152: 90–8.
3. Olaison L, Alestig K. A prospective study of neutropenia induced by high doses of β-lactam antibiotics. *J Antimicrob Chemother* 1990; 25: 449–53.
4. Peralta FG, *et al.* Incidence of neutropenia during treatment of bone-related infections with piperacillin-tazobactam. *Clin Infect Dis* 2003; 37: 1568–72.
5. Scheetz MH, *et al.* Systematic review of piperacillin-induced neutropenia. *Drug Safety* 2007; 30: 295–306.

Effects on the nervous system. References to CNS effects associated with penicillins.

1. Schliamser SE, *et al.* Neurotoxicity of β-lactam antibiotics: predisposing factors and pathogenesis. *J Antimicrob Chemother* 1991; 27: 405–25.

Hypersensitivity. References to hypersensitivity reactions associated with penicillins.

1. Sullivan TJ, *et al.* Skin testing to detect penicillin allergy. *J Allergy Clin Immunol* 1981; 68: 171–80.
2. Beeley L. Allergy to penicillin. *BMJ* 1984; 288: 511–12.
3. Holgate ST. Penicillin allergy: how to diagnose and when to treat. *BMJ* 1988; 296: 1213–14.
4. Anonymous. Penicillin allergy in childhood. *Lancet* 1989; i: 420.
5. Surtees SJ, *et al.* Allergy to penicillin: fable or fact? *BMJ* 1991; 302: 1051–2. Correspondence. *ibid.*: 1462–3.
6. Anonymous. Penicillin allergy. *Drug Ther Bull* 1996; 34: 87–8.
7. Salkind AR, *et al.* Is this patient allergic to penicillin? An evidence-based analysis of the likelihood of penicillin allergy. *JAMA* 2001; 285: 2498–2505.
8. Park MA, Li JT. Diagnosis and management of penicillin allergy. *Mayo Clin Proc* 2005; 80: 405–10.
9. Yates AB. Management of patients with a history of allergy to beta-lactam antibiotics. *Am J Med* 2008; 121: 572–6.

Precautions

Patients known to be hypersensitive to penicillins should be given an antibacterial of another class; sensitised patients may also react to the cephalosporins and other beta lactams (but see also Hypersensitivity, under Cefalotin, p. 237.3). Desensitisation may be attempted if treatment with a penicillin is considered essential (see Adverse Effects, above). Penicillins should be given with caution to patients with a history of allergy, especially to drugs.

Care is necessary if very high doses of penicillins are given, especially if renal function is poor, because of the risk

of neurotoxicity. The intrathecal route should be avoided. Renal, hepatic, and haematological status should be monitored during prolonged and high-dose therapy. Because of the Jarisch-Herxheimer reaction, care is also necessary when treating patients with spirochaete infections, particularly syphilis.

Skin contact with penicillins should be avoided since sensitisation may occur.

Penicillin therapy changes the normal bacterial flora and can lead to superinfection with penicillin-resistant organisms including *Clostridium difficile* or *Candida*, particularly with prolonged use.

Penicillins may interfere with some diagnostic tests such as those for urinary glucose using copper sulfate, direct antiglobulin (Coombs') tests, and some tests for urinary or serum proteins. Penicillins may interfere with tests that use bacteria, for example the Guthrie test for phenylketonuria using *Bacillus subtilis* organisms.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies benzylpenicillin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Potassium and sodium content. Each g of benzylpenicillin potassium contains about 2.7 mmol of potassium and each g of benzylpenicillin sodium contains about 2.8 mmol of sodium. Care is necessary if large doses of the potassium or sodium salts are given to patients with renal impairment or heart failure. High doses of benzylpenicillin potassium should also be used with caution in patients receiving potassium-containing drugs or potassium-sparing diuretics.

Interactions

Probenecid prolongs the half-life of benzylpenicillin by competing with it for renal tubular secretion and may be used therapeutically for this purpose. Clinically significant reductions in renal clearance have also been noted for amoxicillin, nafcillin, and ticarcillin. Benzylpenicillin may also interact with bacteriostatic antibacterials such as chloramphenicol and tetracyclines (see Antimicrobial Action, p. 232.1), and may be incompatible *in vitro* with other drugs, including some other antibacterials (see p. 228.2).

The possibility of a prolonged bleeding time after oral treatment with a broad-spectrum drug like ampicillin should be borne in mind in patients receiving anticoagulants. For further details, and for the effect of other penicillins on the activity of warfarin, see p. 1531.1.

Hormonal contraceptives. For the effect of penicillins on oral contraceptives, see p. 2243.1.

Methotrexate. For the effect of penicillins on methotrexate, see p. 827.3.

Antimicrobial Action

Benzylpenicillin is a beta-lactam antibacterial and has a bactericidal action against Gram-positive bacteria, Gram-negative cocci, some other Gram-negative bacteria, spirochaetes, and actinomycetes.

It exerts its killing action on growing and dividing bacteria by inhibiting bacterial cell-wall synthesis, although the mechanisms involved are still not precisely understood. Bacterial cell walls are held rigid and protected against osmotic rupture by peptidoglycan. Benzylpenicillin inhibits the final cross-linking stage of peptidoglycan production by binding to and inactivating transpeptidases, penicillin-binding proteins on the inner surface of the bacterial cell membrane. However, it is now realised that other earlier stages in cell-wall synthesis can also be inhibited. Other mechanisms involved include bacterial lysis by the inactivation of endogenous inhibitors of bacterial autolysins.

Its action is inhibited by penicillinase and other beta-lactamases that are produced during the growth of certain micro-organisms.

Many Gram-negative organisms are intrinsically resistant by virtue of the inability of benzylpenicillin to penetrate their outer membranes. Intrinsic resistance can also be due to structural differences in the target penicillin-binding proteins. See under Resistance, below, for reference to acquired resistance.

The following pathogenic organisms are usually sensitive to benzylpenicillin:

- Gram-positive aerobes and anaerobes including *Bacillus anthracis, Clostridium perfringens, Cl. tetani, Corynebacterium diphtheriae, Erysipelothrix rhusiopathiae, Listeria monocytogenes, Peptostreptococcus* spp., non-beta-lactamase-producing staphylococci, and streptococci including *Streptococcus agalactiae* (group B), *Str. pneumoniae* (pneumococci), *Str. pyogenes* (group A), and some viridans streptococci; enterococci are relatively insensitive.
- Gram-negative cocci including *Neisseria meningitidis* (meningococci) and *Neisseria gonorrhoeae* (gonococci), although beta-lactamase-producing strains are common.
- Gram-negative bacilli including *Pasteurella multocida, Streptobacillus moniliformis*, and *Spirillum minus* (or *minor*); most Gram-negative bacilli, including *Pseudomonas* spp. and Enterobacteriaceae, are insensitive although some strains of *Proteus mirabilis* and *Escherichia coli* may be inhibited by high concentrations of benzylpenicillin.
- Gram-negative anaerobes including *Prevotella* (non-fragilis *Bacteroides*) and *Fusobacterium* spp.
- Other organisms including *Actinomyces* and the spirochaetes, *Borrelia, Leptospira*, and *Treponema* spp.
- Mycobacteria, fungi, mycoplasmas, and rickettsias are not sensitive.

Activity with other antimicrobials. Benzylpenicillin may exhibit synergy with other antimicrobials, particularly the aminoglycosides, and such combinations have been used against enterococci and other relatively insensitive bacteria. Its activity may be enhanced by clavulanic acid and other beta-lactamase inhibitors, and both enhancement and antagonism have been shown for beta-lactam combinations. Antagonism has been reported to occur with some bacteriostatic drugs, such as chloramphenicol or tetracyclines, that interfere with active bacterial growth necessary for benzylpenicillin to achieve its effect.

Resistance. Susceptible Gram-positive bacteria acquire resistance to beta lactams mainly through the induction of beta-lactamases, including penicillinases. These enzymes are liberated extracellularly and hydrolyse the beta-lactam ring. This resistance is usually plasmid-mediated and can be transferred from one bacterium to another. Gram-negative bacteria produce beta-lactamases within their cell membranes which may be chromosomally or plasmid-mediated; all Gram-negative species probably contain small amounts of beta-lactamases. Resistance in Gram-negative species may also be due to changes in their outer membrane resulting in the failure of beta lactams to reach their target penicillin-binding proteins. Changes in the binding characteristics of penicillin-binding proteins may also result in resistance in Gram-positive and Gram-negative bacteria.

Most strains of *Staphylococcus aureus* are now resistant to benzylpenicillin. *Streptococcus pneumoniae* with reduced susceptibility or complete resistance to benzylpenicillin have increasingly been reported. Strains of *Neisseria meningitidis* with reduced sensitivity to benzylpenicillin have been identified. Penicillinase-producing *Neisseria gonorrhoeae* are widespread; reduced sensitivity of gonococci to benzylpenicillin may also result from alterations in penicillin-binding proteins. Most strains of *Haemophilus influenzae* and *Moraxella catarrhalis* (*Branhamella catarrhalis*) are now resistant.

Some organisms, usually Gram-positive cocci such as staphylococci or streptococci, may develop tolerance and are inhibited but not killed by benzylpenicillin; in such cases the minimum bactericidal concentration is much greater than the minimum inhibitory concentration.

Pharmacokinetics

Benzylpenicillin rapidly appears in the blood after intramuscular injection of water-soluble salts, and maximum concentrations are usually reached in 15 to 30 minutes; peak plasma concentrations of about 12 micrograms/mL have been reported after single doses of 600 mg.

When given orally, benzylpenicillin is inactivated fairly rapidly by gastric acid and only up to about 30% is absorbed, mainly from the duodenum; maximum plasma-penicillin concentrations usually occur in about 1 hour. In order to attain plasma-penicillin concentrations after oral use similar to those after intramuscular injection, up to 5 times as much benzylpenicillin may be necessary. Absorption varies greatly in different individuals and is better in patients with reduced gastric acid production, including neonates and the elderly. Food decreases the absorption of benzylpenicillin and oral doses are best given at least half an hour before or 2 to 3 hours after a meal.

Benzylpenicillin is widely distributed. It appears in pleural, pericardial, peritoneal, and synovial fluids, but in the absence of inflammation diffuses only to a small extent into abscess cavities, avascular areas, the eye, the middle ear, and the CSF. Inflamed tissue is, however, more readily penetrated and, for example, in meningitis higher concentrations of benzylpenicillin occur in the CSF. Active transport out of the CSF is reduced by probenecid. In patients with uraemia, other organic acids may accumulate in the CSF and compete with benzylpenicillin for active transport; toxic concentrations of benzylpenicillin sufficient to cause convulsions can result.

Benzylpenicillin diffuses across the placenta into the fetal circulation, and small amounts appear in breast milk.

The plasma half-life is about 30 minutes, although it may be longer in neonates and the elderly because of reduced renal function. In renal impairment the half-life may be increased to about 10 hours. About 60% is reported to be bound to plasma protein.

Benzylpenicillin is metabolised to a limited extent and the penicilloic acid derivative has been recovered in the urine. Benzylpenicillin is rapidly excreted in the urine, principally by tubular secretion, and about 20% of an oral dose appears unchanged in the urine; about 60 to 90% of a dose of aqueous benzylpenicillin given intramuscularly appears in the urine, mainly within the first hour. Significant concentrations occur in bile, but in patients with normal renal function only small amounts are excreted via the bile. Benzylpenicillin is removed by haemodialysis.

Renal tubular secretion is inhibited by probenecid (p. 607.3), which is sometimes given to increase plasma-penicillin concentrations and prolong half-life.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Penilfedrin P†; *Austral.*: Benpen; *Braz.*: Aricilina; Benzecilin; Cristalpen; Pencil P†; *Canad.*: Crystapen; *Fin.*: Geepenil; *Ger.*: Infectocillin; *India*: Pencip; Pentids; *Irl.*: Crystapen; *Mex.*: Declin; Farmabep; Pendiben L-A†; Pengesod†; Penisol†; Procasol; Prosodina; Sodipen; Unicil 3/1; Unicil 6:3:3; Unicil Mega; *NZ*: Benpen; *Philipp.*: Bentapen; Crystacin; Harbipen; Pencarv; *S.Afr.*: Benzatec†; Bio-Pen; *Spain*: Penibiot; Penilevel; Sodiopen; *Thai.*: Pen-G; *Turk.*: Benzapen 6.3.3; Deposilin 6.3.3; Devapen; Iecilline; Kristapen; Kristasil; Penadur 6.3.3; Pencrist†; Penkain-K†; Pensilina†; Procillin†; *UK*: Crystapen; *USA*: Pfizerpen.

Multi-ingredient Preparations. *Austria*: Retarpen compositum; *Braz.*: Benapen; Benzapen G; Despacilina; Pencil 400†; Penkaron; Wycillin; *Chile*: Prevepen Forte; *Ger.*: Retacillin compositum; *Hong Kong*: Pan-Fort Procaine†; Penicillin G Procaine Fortified†; *Hung.*: Promptcillin Forte; *India*: Bistrepen; Fortified PP; Fortified Procaine Peni; FPP; *Malaysia*: Procaine Penicillin; *Mex.*: Aguipental; Anapenil; Bencelin Combinado; Benzanil Compuesto†; Benzetacil Combinado; Hidrocilina; Lugaxil; Megapenil Forte†; Pecivax; Pendiben Compuesto†; Penicil; Penipot; Penisodina; Penprocilina†; Procilin†; Robencaxil; Suipen; *Port.*: Atralcilina†; Lentocilin; *Rus.*: Benzycillin 3 (Бензициллин 3); Bicillin-3 (Бициллин-3); *S.Afr.*: Ultracillin†; *Spain*: Benzetacil Compuesta; Cepacilina 633†; Penilevel Retard; *Turk.*: Pencain K; Pronapen; *Ukr.*: Bicillin-3 (Бициллин-3); *Venez.*: Benzetacil 3-3; Benzetacil 6-3-3; Pronapen.

Pharmacopoeial Preparations

BP 2014: Benzylpenicillin Injection;

USP 36: Penicillin G Potassium Capsules; Penicillin G Potassium for Injection; Penicillin G Potassium for Oral Solution; Penicillin G Potassium Injection; Penicillin G Potassium Tablets; Penicillin G Sodium for Injection.

Besifloxacin *(rINN)*

Bésfloxacine; Besifloxacino; Besifloxacinum; Безифлоксацин.

7-[(3*R*)-3-Aminoazepan-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

$C_{19}H_{21}ClFN_3O_3$=393.8

CAS — 141388-76-3.

ATC — S01AE08.

ATC Vet — QS01AE08.

UNII — BFE2NBZ7NX.

Besifloxacin Hydrochloride *(USAN, rINNM)*

Bésifloxacine, Chlorhydrate de; Besifloxacini Hydrochloridum; BOL-303224-A; Hidrocloruro de besifloxacino; SS-734; Безифлоксацин Гидрохлорид.

(+)-7-[(3*R*)-3-Aminohexahydro-1*H*-azepin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid hydrochloride.

$C_{19}H_{21}ClFN_3O_3$,HCl=430.3

CAS — 405165-61-9.

ATC — S01AE08.

ATC Vet — QS01AE08.

UNII — 7506A6J57T.

Profile

Besifloxacin is a fluoroquinolone antibacterial with properties similar to those of ciprofloxacin. It is used topically as the hydrochloride in eye drops containing the equivalent of 0.6% besifloxacin for the treatment of conjunctivitis caused by susceptible bacteria.

References.

1. Tepedino ME, *et al.* Phase III efficacy and safety study of besifloxacin ophthalmic suspension 0.6% in the treatment of bacterial conjunctivitis. *Curr Med Res Opin* 2009; **25**: 1159–69.
2. Karpecki P, *et al.* Besifloxacin ophthalmic suspension 0.6% in patients with bacterial conjunctivitis: a multicenter, prospective, randomized, double-masked, vehicle-controlled, 5-day efficacy and safety study. *Clin Ther* 2009; **31**: 514–26.

3. McDonald MB, *et al.* Efficacy and safety of besifloxacin ophthalmic suspension 0.6% compared with moxifloxacin ophthalmic solution 0.5% for treating bacterial conjunctivitis. *Ophthalmology* 2009; 116: 1615–1623.e1.
4. Haas W, *et al.* Besifloxacin, a novel fluoroquinolone, has broad-spectrum in vitro activity against aerobic and anaerobic bacteria. *Antimicrob Agents Chemother* 2009; 53: 3552–60.
5. Carter NJ, Scott LJ. Besifloxacin ophthalmic suspension 0.6%. *Drugs* 2010; 70: 83–97.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Besivance; *Singapore*: Besivance; *USA*: Besivance.

Betamipron *(rINN)*

N-Benzoyl-β-alanine; Bétamipron; Betamipronum; CS-443; Бетамипрон.
3-Benzamidopropionic acid.
$C_{10}H_{11}NO_3$=193.2
CAS — 3440-28-6.
UNII — 3W0M245736.

Profile

Betamipron is a renal protectant used with the carbapenem antibacterial panipenem to reduce its adverse renal effects.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *China*: Carbenin (克倍宁); *Jpn*: Carbenin.

Biapenem *(USAN, rINN)*

Biapénem; Biapenemum; CL-186815; L-627; LJC-10627; Биапенем.
6-[[(4*R*,5*S*,6*S*)-2-Carboxy-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-en-3-yl]thio]-6,7-dihydro-5*H*-pyrazolo[1,2-*a*]-*s*-triazol-4-ium hydroxide, inner salt.
$C_{15}H_{18}N_4O_4S$=350.4
CAS — 120410-24-4.
ATC — J01DH05.
ATC Vet — QJ01DH05.
UNII — YR5U3L9ZH1.

Profile

Biapenem is a carbapenem beta-lactam antibacterial similar to imipenem (p. 311.2), although it is reported to be more stable to renal dehydropeptidase I than imipenem. It has been given in usual doses of 300 mg twice daily by intravenous infusion over 30 to 60 minutes.

Reviews.
1. Perry CM, Ibbotson T. Biapenem. *Drugs* 2002; 62: 2221–34.
2. Ikawa K, *et al.* Population pharmacokinetics and pharmacodynamics of biapenem in paediatric patients. *J Clin Pharm Ther* 2008; 33: 203–10.
3. Ikawa K, *et al.* Pharmacokinetic-pharmacodynamic target attainment analysis of biapenem in adult patients: a dosing strategy. *Chemotherapy* 2008; 54: 386–94.
4. Isobe Y, *et al.* Clinical and microbiological effects of biapenem in febrile neutropenic patients with hematologic malignancies. *Scand J Infect Dis* 2009; 41: 237–9.
5. Nakagawa Y, *et al.* Clinical efficacy and safety of biapenem for febrile neutropenia in patients with underlying hematopoietic diseases: a multi-institutional study. *J Infect Chemother* 2011; 17: 58–67. Correction. *ibid.*: 68–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Hua Jin (华劲); Newanti (安信); Nuo Jia Nan (诺加南); Tiance (天册); *Jpn*: Omegacin.

Brodimoprim *(rINN)*

Brodimoprima; Brodimoprime; Brodimoprimum; Ro-10-5970; Бродимоприм.
2,4-Diamino-5-(4-bromo-3,5-dimethoxybenzyl)pyrimidine.
$C_{13}H_{15}BrN_4O_2$=339.2
CAS — 56518-41-3.
ATC — J01EA02.
ATC Vet — QJ01EA02.
UNII — V1YC7T6LLI.

Profile

Brodimoprim is a diaminopyrimidine antibacterial closely related structurally to trimethoprim (p. 383.2) and has been used in the treatment of infections of the respiratory tract and ear.

References.
1. Braunsteiner AR, Finsinger F. Brodimoprim: therapeutic efficacy and safety in the treatment of bacterial infections. *J Chemother* 1993; 5: 507–11.

Capreomycin Sulfate

(BANM, USAN, rINNM)

34977; Capreomicina, sulfato de; Capreomycin Sulphate; Capréomycine; Sulfate de; Capreomycini Sulfas; Capromycin Sulphate; Sulfato de capreomicina; Капреомицина Сульфат.
CAS — 11003-38-6 (capreomycin); 1405-37-4 (capreomycin sulfate).
ATC — J04AB30.
ATC Vet — QJ04AB30.
UNII — 9H8D3J7V21.

Description. Capreomycin I consists of capreomycin IA ($C_{25}H_{44}N_{14}O_8$=668.7) and capreomycin IB ($C_{25}H_{44}N_{14}O_7$=652.7), which predominates. Capreomycin II, which makes up about 10% of the mixture, consists of capreomycin IIA and capreomycin IIB.

Pharmacopoeias. In *Chin.* and *US.*

USP 36: (Capreomycin Sulfate). The disulfate of capreomycin, a polypeptide mixture produced by the growth of *Streptomyces capreolus*. It contains not less than 90% of capreomycin I. A white to practically white amorphous powder. Freely soluble in water; practically insoluble in most organic solvents. pH of a 3% solution in water is between 4.5 and 7.5. Store in airtight containers.

Uses and Administration

Capreomycin is a second-line antimycobacterial that may be used in the treatment of tuberculosis (p. 210.2) as part of a multidrug regimen when resistance to primary drugs has developed.

Capreomycin is given as the sulfate by deep intramuscular injection or by intravenous infusion. The usual dose is the equivalent of 1 g of capreomycin base (maximum 20 mg/kg) given daily for 2 to 4 months, then 2 or 3 times weekly for the remainder of therapy.

For details of doses in children, the elderly, and those with renal impairment, see p. 233.2.

References.
1. Anonymous. Capreomycin. *Tuberculosis (Edinb)* 2008; 88: 89–91.

Administration in children. For the treatment of drug-resistant tuberculosis in infants, children, and adolescents the American Academy of Pediatrics[1] suggests an intramuscular dose of capreomycin 15 to 30 mg/kg daily, to a maximum dose of 1 g daily.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Administration in the elderly. While licensed product information recommends that elderly patients (without renal impairment) may be given the same parenteral capreomycin dose as other adults, US tuberculosis treatment guidelines[1] advise that for those older than 59 years of age, the dose should be reduced to 10 mg/kg (maximum 750 mg) daily.

1. American Thoracic Society, CDC, and the Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; 52 (RR-11): 1–77. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf (accessed 30/11/10) Correction. *ibid.* 2005: 53: 1203. [dose]

Administration in renal impairment. As with aminoglycosides, the parenteral dose of capreomycin in patients with renal impairment must be reduced based on creatinine clearance (CC); licensed product information recommends adjusted doses to maintain a desired mean steady-state serum-capreomycin concentration of 10 micrograms/mL.

Alternatively, for patients with a CC < 30 mL/minute or those receiving haemodialysis, US[1] and WHO[2] tuberculosis treatment guidelines recommend a capreomycin dose of 12 to 15 mg/kg 2 or 3 times weekly (for those requiring haemodialysis, doses should be timed for after the dialysis run).

1. American Thoracic Society, CDC, and the Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; 52 (RR-11): 1–77. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf (accessed 30/11/10) Correction. *ibid.* 2005: 53: 1203. [dose]
2. WHO. *Guidelines for the programmatic management of drug-resistant tuberculosis: emergency update 2008*. Geneva: WHO, 2008. Available at: http://whqlibdoc.who.int/publications/2008/9789241547581_eng.pdf (accessed 05/01/11)

Adverse Effects and Treatment

The effects of capreomycin on the kidney and eighth cranial nerve are similar to those of aminoglycosides such as gentamicin (p. 308.2). Nitrogen retention, renal tubular dysfunction, and progressive renal damage may occur. Hypokalaemia and other electrolyte abnormalities have been reported. Vertigo, tinnitus, and hearing loss may also occur and are sometimes irreversible. Abnormalities in liver function have been reported when capreomycin has been used with other antituberculous drugs. Hypersensitivity reactions including urticaria, maculopapular rashes, and sometimes fever have been reported. Leucocytosis and leucopenia have also occurred. Thrombocytopenia has been reported rarely. Eosinophilia is common with capreomycin. Capreomycin also has a neuromuscular blocking action. There may be pain, induration, and excessive bleeding at the site of intramuscular injection; sterile abscesses may also form.

Teratogenicity has been seen after high doses in *rodents*.

Treatment of overdose is generally supportive. Patients with normal renal function should be hydrated to maintain adequate urine output. Capreomycin may be removed by haemodialysis in patients with significant renal impairment.

Effects on the eyes. Report of a patient who developed optic neuritis 3 months after starting antimycobacterial therapy containing capreomycin.[1] His vision returned to normal within 10 weeks of withdrawal of capreomycin.

1. Magazine R, *et al.* Capreomycin-induced optic neuritis in a case of multidrug resistant pulmonary tuberculosis. *Indian J Pharmacol* 2010; 42: 247–8.

Impurities. The manufacturer of a highly-purified capreomycin product (*Capacin; Cheiljedang, Kor.*) has claimed that such purification reduces the toxicity and alters the pharmacokinetics in *animal* studies, suggesting that some of the toxicity of capreomycin is due to such impurities.[1]

1. Lee SH, *et al.* The impurities of capreomycin make a difference in the safety and pharmacokinetic profiles. *Int J Antimicrob Agents* 2003; 22: 81–3.

Precautions

Capreomycin should be given with care and in reduced dosage to patients with renal impairment. Care is also essential in patients with signs of eighth cranial nerve damage. It is advisable to monitor renal and auditory function and serum-potassium concentrations in patients before and during therapy. Periodic assessment of hepatic function is also recommended.

Interactions

Care should be taken when capreomycin is used with other drugs that have neuromuscular blocking activity. It should not be given with other drugs that are ototoxic or nephrotoxic.

Antimicrobial Action

Capreomycin has activity against various mycobacteria. Resistance develops readily if capreomycin is used alone. It shows cross-resistance with kanamycin and neomycin.

References.
1. Ho YH, *et al.* In-vitro activities of aminoglycoside-aminocyclitols against mycobacteria. *J Antimicrob Chemother* 1997; 40: 27–32.
2. Maus CE, *et al.* Molecular analysis of cross-resistance to capreomycin, kanamycin, amikacin, and viomycin in Mycobacterium tuberculosis. *Antimicrob Agents Chemother* 2005; 49: 3192–7.

Pharmacokinetics

Capreomycin is poorly absorbed from the gastrointestinal tract. An intramuscular dose of 1 g has been reported to give a peak serum concentration of about 30 micrograms/mL after 1 or 2 hours. About 50% of a dose is excreted unchanged in the urine by glomerular filtration within 12 hours. Capreomycin is removed by haemodialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Capastat†; *China*: Hai Pu Mei Xin (海普美欣); *Gr.*: Capastat; *Rus.*: Capastat (Капастат); Capremabol (Капремабол); Capreostat (Капреостат); Capricyn (Каприцин); Kapocin (Капоцин); Lykocin (Лайкоцин); *Spain*: Capastat; *UK*: Capastat; *USA*: Capastat.

Pharmacopoeial Preparations
USP 36: Capreomycin for Injection.

Carbadox *(BAN, USAN, pINN)*

Carbadoxum; GS-6244; Карбадокс.
Methyl 3-quinoxalin-2-ylmethylenecarbazate 1,4-dioxide.
$C_{11}H_{10}N_4O_4$=262.2
CAS — 6804-07-5.
UNII — M2X04R2E2Y.

Profile

Carbadox is an antibacterial that has been used in veterinary practice for treating swine dysentery and enteritis and for promoting growth. However, its use has been prohibited in

the EU and some other countries after reports of carcinogenicity.

Carbenicillin Sodium *(BANM, rINNM)*

BRL-2064; Carbenicilina sódica; Carbenicillin Disodium (USAN); Carbénicilline Sodique; Carbenicillinum natricum; α-Carboxybenzylpenicillin Sodium; CP-15-639-2; GS-3159 (carbenicillin potassium); Karbenicillin-nátrium; Karbenicylina sodowa; Natrii Carbenicillinum; NSC-111071; Натрий Карбенициллин.

The disodium salt of (6*R*)-6-(2-carboxy-2-phenylacetamido) penicillanic acid.

$C_{17}H_{16}N_2Na_2O_6S$=422.4

CAS — 4697-36-3 (carbenicillin); 4800-94-6 (carbenicillin disodium); 17230-86-3 (carbenicillin potassium).

ATC — J01CA03.

ATC Vet — QJ01CA03.

UNII — 9TS483H261.

Pharmacopoeias. In *Pol.* and *US.*

USP 36: (Carbenicillin Disodium). A white to off-white crystalline powder. Freely soluble in water; soluble in alcohol; practically insoluble in chloroform and in ether. pH of a solution in water containing the equivalent of carbenicillin 1% is between 6.5 and 8.0. Store in airtight containers.

Incompatibility. Carbenicillin sodium has been reported to be incompatible with aminoglycosides, tetracyclines, and many other drugs including other antimicrobials and these drugs should therefore be given separately.

Uses and Administration

Carbenicillin is a carboxypenicillin that has been given by injection as the disodium salt, often with gentamicin, in the treatment of infections due to *Pseudomonas aeruginosa*; however, other antipseudomonal penicillins such as ticarcillin (p. 380.2) or piperacillin (p. 342.1) are now preferred. It has also been given to treat serious infections due to non-penicillinase-producing strains of *Proteus* spp.

Esters of carbenicillin, such as carindacillin (p. 234.2), have been given orally in the treatment of urinary-tract infections.

Adverse Effects

As for Benzylpenicillin, p. 229.2.

Hypersensitivity reactions have been reported to be less frequent and less severe with carbenicillin than with benzylpenicillin.

Pain at the injection site and phlebitis may occur. Electrolyte disturbances, particularly hypokalaemia or hypernatraemia, may follow large doses of carbenicillin sodium.

A dose-dependent coagulation defect has been reported, especially in patients with renal impairment. Carbenicillin appears to interfere with platelet function thereby prolonging bleeding time; purpura and haemorrhage from mucous membranes and elsewhere may result.

Precautions

As for Benzylpenicillin, p. 229.3.

Sodium content. Each g of carbenicillin sodium contains about 4.7 mmol of sodium. Carbenicillin sodium should therefore be given with caution to patients on a restricted sodium diet.

Interactions

As for Benzylpenicillin, p. 230.1.

Antimicrobial Action

Carbenicillin has a bactericidal mode of action similar to that of benzylpenicillin, but with an extended spectrum of activity against Gram-negative bacteria.

- It has activity against *Pseudomonas aeruginosa*, although high concentrations are generally necessary. Activity against *Ps. aeruginosa* and some other organisms can be enhanced by gentamicin and other aminoglycosides.
- *Proteus*, including indole-positive spp. such as *Pr. vulgaris* are also sensitive.
- Against other Gram-negative bacteria activity is similar to ampicillin. Sensitive organisms include some Enterobacteriaceae, for example *Escherichia coli* and *Enterobacter* spp.; *Haemophilus influenzae*; and *Neisseria* spp. *Klebsiella* spp. are usually not susceptible.
- It has less activity against Gram-positive bacteria than benzylpenicillin.
- Anaerobic organisms are generally susceptible but high concentrations are required for *Bacteroides fragilis*.

Resistance. Carbenicillin is inactivated by penicillinases and some other beta-lactamases, although it is more stable to the chromosomally mediated beta-lactamases produced by some Gram-negative organisms, including *Ps. aeruginosa* and some *Proteus* spp. Resistance to carbenicillin may develop in *Ps. aeruginosa* during treatment with carbenicillin or other beta lactams. This resistance may be intrinsic where there are changes in cell wall permeability or penicillin-binding proteins, or it may be due to plasmid-mediated beta-lactamase production that may be transferred to and from certain strains of Enterobacteriaceae.

There may be cross-resistance between carbenicillin and other antipseudomonal penicillins.

Outbreaks of pseudomonal resistance to carbenicillin have been associated with extensive use in, for example, hospital burns units.

Pharmacokinetics

Carbenicillin is not absorbed from the gastrointestinal tract and has therefore been given either intramuscularly or intravenously.

The half-life of carbenicillin is reported to be about 1 to 1.5 hours; it is increased in patients with renal impairment, especially if there is also hepatic impairment, and also in neonates. Half-lives of 10 to 18 hours have been reported in renal impairment. Clearance is enhanced in patients with cystic fibrosis. Carbenicillin is about 50% bound to plasma proteins. Distribution of carbenicillin in the body is similar to that of other penicillins. Small amounts have been detected in breast milk. There is little diffusion into the CSF except when the meninges are inflamed.

Relatively high concentrations have been reported in bile, but carbenicillin is excreted principally by renal tubular secretion and glomerular filtration.

Probenecid increases and prolongs plasma concentrations of carbenicillin.

Carbenicillin is removed by haemodialysis and, to some extent, by peritoneal dialysis.

Preparations

Pharmacopoeial Preparations

USP 36: Carbenicillin for Injection.

Carindacillin Sodium *(BANM, pINNM)*

Carbenicillin Indanyl Sodium (USAN); Carindacilina sódica; Carindacilline Sodique; CP-15464-2; Natrii Carindacillinum; Натрий Кариндациллин.

Sodium (6*R*)-6-[2-(indan-5-yloxycarbonyl)-2-phenylacetamido]penicillanate.

$C_{26}H_{25}N_2NaO_6S$=516.5

CAS — 35531-88-5 (carindacillin); 26605-69-6 (carindacillin sodium).

ATC — J01CA05.

ATC Vet — QJ01CA05.

UNII — 4OUL81K2RT.

Pharmacopoeias. In *US.*

USP 36: (Carbenicillin Indanyl Sodium). A white to off-white powder. Soluble in water and in alcohol. pH of a 10% solution in water is between 5.0 and 8.0. Store in airtight containers.

Profile

Carindacillin is the indanyl ester of carbenicillin (above) to which it is hydrolysed after absorption from the gastrointestinal tract. Its use has been restricted to the treatment of urinary-tract infections due to *Pseudomonas* spp. and other sensitive bacteria including *Proteus* spp.

Carindacillin may be given orally as the sodium salt; 535 mg of carindacillin sodium is equivalent to about 382 mg of carbenicillin. Usual doses, expressed in terms of carbenicillin, have been 382 to 764 mg four times daily.

Sodium content. Each g of carindacillin sodium contains about 1.9 mmol of sodium.

Preparations

Pharmacopoeial Preparations

USP 36: Carbenicillin Indanyl Sodium Tablets.

Carumonam Sodium *(BANM, USAN, rINNM)*

AMA-1080 (carumonam); Carumonam sódico; Carumonam Sodique; CRMN; Natrii Carumonamum; Ro-17-2301 (carumonam); Ro-17-2301/006 (carumonam sodium); Натрий Карумонам.

(*Z*)-(2-Aminothiazol-4-yl)[[(2*S*,3*S*)-2-carbamoyloxymethyl-4-oxo-1-sulphoazetidin-3-yl]carbamoyl]methyleneamino-oxyacetic acid, disodium salt.

$C_{12}H_{12}N_6Na_2O_{10}S_2$=510.4

CAS — 87638-04-8 (carumonam); 86832-68-0 (carumonam sodium).

UNII — B4J4M4939D.

Pharmacopoeias. In *Jpn.*

Profile

Carumonam is a monobactam antibacterial with a spectrum of antimicrobial action *in vitro* similar to that of aztreonam (p. 225.1). It is given by intramuscular or intravenous injection as the sodium salt and doses are expressed in terms of carumonam; 1.09 g of carumonam sodium is equivalent to about 1 g of carumonam. The usual dose is 1 to 2 g daily in two divided doses.

Sodium content. Each g of carumonam sodium contains about 3.92 mmol of sodium.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Amasulin.

Cefaclor *(BAN, USAN, pINN)*

Céfaclor; Cefaclor-Monohydrat; Cefaclorum; Cefaclorum Monohydricum; Cefaklor; Cefaklór; Cefaklor monohydrát; Cefakloras; Compound 99638; Kefakloori; Sefaklor; Цефаклор.

(7*R*)-3-Chloro-7-(α-D-phenylglycylamino)-3-cephem-4-carboxylic acid monohydrate.

$C_{15}H_{14}ClN_3O_4S.H_2O$=385.8

CAS — 53994-73-3 (anhydrous cefaclor); 70356-03-5 (cefaclor monohydrate).

ATC — J01DC04.

ATC Vet — QJ01DC04.

UNII — 69K7K19H4L (cefaclor); 3Z6F53IK0K (anhydrous cefaclor).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.* *Jpn* includes the anhydrous substance.

Ph. Eur. 8: (Cefaclor). A white or slightly yellow powder. Slightly soluble in water; practically insoluble in dichloromethane and in methyl alcohol. A 2.5% suspension in water has a pH of 3.0 to 4.5.

USP 36: (Cefaclor). A white to off-white crystalline powder. Slightly soluble in water; practically insoluble in chloroform, in methyl alcohol, and in benzene. pH of a 2.5% suspension in water is between 3.0 and 4.5. Store in airtight containers.

Uses and Administration

Cefaclor is a cephalosporin antibacterial given orally in the treatment of susceptible Gram-positive and Gram-negative bacterial infections including upper and lower respiratory-tract infections, skin infections, and urinary-tract infections. Some classify cefaclor as a second-generation cephalosporin and its greater activity against *Haemophilus influenzae* makes it more suitable than cefalexin for the treatment of infections such as otitis media. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Cefaclor is given as the monohydrate. Doses are expressed in terms of the equivalent amount of anhydrous cefaclor; 1.05 g of cefaclor monohydrate is equivalent to about 1 g of anhydrous cefaclor. The usual adult dose is 250 to 500 mg every 8 hours; up to 4 g daily has been given.

For details of doses in children, see p. 234.3.

Modified-release formulations of cefaclor are available in some countries.

Administration in children. Cefaclor may be given orally to children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria, including *Haemophilus influenzae*. For mild to moderate infections in children over 1 month of age, the American Academy of Pediatrics[1] suggests a dose of 20 to 40 mg/kg daily in 2 or 3 divided doses, to a maximum total daily dose of 750 mg to 1.5 g. The following alternative dose regimen is also recommended by the *BNFC*; doses may be doubled if necessary.

- children 1 month to 1 year of age: 62.5 mg 3 times daily
- children 1 to 5 years of age: 125 mg 3 times daily
- children over 5 years of age: 250 mg 3 times daily

For asymptomatic carriage of *H. influenzae* or mild exacerbations in cystic fibrosis the *BNFC* recommends the following oral doses:

- children 1 month to 1 year of age: 125 mg every 8 hours

- those aged 1 to 7 years: 250 mg 3 times daily
- those more than 7 years of age: 500 mg 3 times daily

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases.* 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Adverse Effects and Precautions

As for Cefalexin, p. 236.2.

Hypersensitivity. Serum-sickness-like reactions may be more common with cefaclor than several other oral antibacterials[1] especially in young children,[2,3] and typically after several courses of cefaclor;[2] features include skin reactions and arthralgia. A relatively high incidence of anaphylactic reactions has been reported from Japan.[4]

There has been a report of myocarditis that developed as a hypersensitivity reaction to cefaclor in a 12-year-old child.[5]

1. McCue JD. Delayed detection of serum sickness caused by oral antimicrobials. *Adv Therapy* 1990; 7: 22–7.
2. Vial T, *et al.* Cefaclor-associated serum sickness-like disease: eight cases and review of the literature. *Ann Pharmacother* 1992; 26: 910–14.
3. King BA, Geelhoed GC. Adverse skin and joint reactions associated with oral antibiotics in children: the role of cefaclor in serum sickness-like reactions. *J Paediatr Child Health* 2003; 39: 677–81.
4. Hama R, Mori K. High incidence of anaphylactic reactions to cefaclor. *Lancet* 1988; i: 1331.
5. Beghetti M, *et al.* Hypersensitivity myocarditis caused by an allergic reaction to cefaclor. *J Pediatr* 1998; 132: 172–3.

Interactions

As for Cefalexin, p. 236.2.

Anticoagulants. UK licensed product information recommends that monitoring of prothrombin time should be considered in patients receiving cefaclor and *warfarin* after rare reports of increased prothrombin times. It is not known whether this interaction is related to the vitamin K-related hypoprothrombinaemia seen with some cephalosporins (see Adverse Effects of Cefamandole, p. 238.3), but cefaclor does not contain the side-chain usually implicated in this reaction.

Antimicrobial Action

Cefaclor is bactericidal and has antimicrobial activity similar to that of cefalexin (p. 236.2) but is reported to be more active against Gram-negative bacteria including *Escherichia coli, Klebsiella pneumoniae, Neisseria gonorrhoeae,* and *Proteus mirabilis,* and especially against *Haemophilus influenzae.* It is active against some beta-lactamase-producing strains of *H. influenzae.* It may be less resistant to staphylococcal penicillinase than cefalexin or cefradine and a marked inoculum effect has been reported *in vitro.*

Pharmacokinetics

Cefaclor is well absorbed from the gastrointestinal tract. Oral doses of 250 mg, 500 mg, and 1 g produce peak plasma concentrations of about 7, 13, and 23 micrograms/mL respectively after 0.5 to 1 hour. The presence of food may delay the absorption of cefaclor, but the total amount absorbed is unchanged. A plasma half-life of 0.5 to 1 hour has been reported; it may be slightly prolonged in patients with renal impairment. About 25% is bound to plasma proteins.

Cefaclor appears to be widely distributed in the body; it crosses the placenta and low concentrations have been detected in breast milk. It is rapidly excreted by the kidneys; up to 85% of a dose appears unchanged in the urine within 8 hours, the greater part within 2 hours. High concentrations of cefaclor occur in the urine within 8 hours of a dose; peak concentrations of 600, 900, and 1900 micrograms/mL have been reported after doses of 0.25, 0.5, and 1 g respectively. Probenecid delays excretion. Some cefaclor is removed by haemodialysis.

References.

1. Wise R. The pharmacokinetics of the oral cephalosporins—a review. *J Antimicrob Chemother* 1990; 26 (suppl E): 13–20.
2. Sourgens H, *et al.* Pharmacokinetic profile of cefaclor. *Int J Clin Pharmacol Ther* 1997; 35: 374–80.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Aclor; Ceclor; Cefkor†; Karlor; Keflor; Ozcef; *Austria*: Cec; Ceclor; Cefastad; Cefax†; *Belg.*: Doccefaclo†; *Braz.*: Ceclor; Cefacloren; Clorcin-Ped; *Canad.*: Ceclor; *China*: Beinuoke (贝诺克); Ceclor (希刻劳); Di Suo (迪素); Heng Di Ke (恒迪克); Hengyun (恒运); Keflor (可福乐); Long Wei Xin (龙威欣); Ou Jia (欧佳); Shen Luo (申洛); Sheng Han (胜寒); Shi Hua Luo (施华洛); Shuai Xian (帅先); Su Ke Le (苏刻乐); Wan Min Xin (万敏新); Xi Nuo (希诺); Xi You Luo (希优洛); Xifulai (喜福来); Xin Ke Nuo (欣可诺); Xincatlor (新达罗); You Ke Nuo (优克诺); Zaike (再克); *Cz.*: Ceclor†; Serviclor; Vercef; *Fin.*: Kefolor; *Fr.*: Alfatil; Haxifal; *Ger.*: Cec†; Ceclorbeta†; Cef-Diolan†; InfectoCef; Panoral; *Gr.*: Afecton; Camirox; Ceclor; Cefacloril; Fredyren; Hetaclox; Katinol; Makovan; Medelox; Panclor; Phacotrex; Streptocol-R; Ufoxillin; *Hong Kong*: Ceclor; Clortrin†; Medoclor; Phaclor†; Qualicecior; Qualiphor; Soficlor; Synfaclor†; Vercef; Vickclor; *Hung.*: Ceclor; Cecloretta; Vercef†; *India*: Acticlor; Articlor; Cecel; Ceflorr; Cloriv; Distaclor; Eclor; Halclor; Halocef; Keflor; Nayaclor; *Indon.*: Capabiotic†; Ceclor†; Cloracef; Especlor†; Forifek; Medikoncef†; Soclor; *Irl.*: Cefager†; Distaclor; Keftid; Pinaclor; *Israel*: Cefalor; *Ital.*: Altaclor; Bacticef; Bactigram; Cefulton; Clorad†; Clorazer†; Geniclor; Kliacef; Lafarclor; Macovan; Necloral; Oralcef; Panacef; Performer; Selviclor; Takecef; Tibifor; Valeclor; *Malaysia*: Distaclor; Efaclor; Sifaclor; Soficlor; Vercef; *Mex.*: Arcefal; Cec; Ceclor; Cefalan; Ceflacid†; Fasiclor; Fermed; Ranclor; Serviclor; Tecnoclor; Teraclox; *Neth.*: Ceclor; *NZ*: Clorotir†; *Philipp.*: Aczebri†; Brelox†; Ceclobid; Ceclor; Cefmed; CFC; Clorcef; Clorotir†; Ephron; Lorcef; Remedlor; Solril; Surecef; Vefarol; Versef†; Verzat; Xelent; Xeztron†; Yucro; Zeclor; Zynolex; Zyrcef; *Pol.*: Ceclor; Cek†; Panclor†; Serviclor†; Vercef; *Port.*: Ceclor; *Rus.*: Ceclor (Цеклор); Vercef (Верцеф)†; *S.Afr.*: Cec†; Vercef; *Singapore*: Cleancef; Distaclor†; Soficlor; Vercef; *Spain*: Ceclor; *Switz.*: Ceclor; *Thai.*: Cefclor; Celco†; Clorotir; Distaclor; Sifaclor; Tefaclor; Vercef; *Turk.*: Cec; Ceclor; Cekloteva; Kefsid; Losefar; Sanocef; *UAE*: Recocef; *UK*: Bacticlor; Distaclor; Keftid; *USA*: Ceclor; Raniclor†; *Venez.*: Ceclor.

Multi-ingredient Preparations. *China*: An Bu (安卜); Bi Li (毕利); Pu Kuai (浦快); Xi Meng (熙蒙); Zheng Da Su Ke (正大素克); *Mex.*: Ceclordox.

Pharmacopoeial Preparations

BP 2014: Cefaclor Capsules; Cefaclor Oral Suspension; Prolonged-release Cefaclor Tablets;

USP 36: Cefaclor Capsules; Cefaclor Chewable Tablets; Cefaclor Extended-Release Tablets; Cefaclor for Oral Suspension.

Cefadroxil *(BAN, USAN, pINN)*

BL-S578; Cefadroksilis monohidratas; Cefadroksyl jednowodny; Céfadroxil; Cefadroxil monohydrát; Cefadroxil-Monohydrat; Cefadroxil monohydraté; Cefadroxilmonohydrat; Cefadroxilo; Cefadroxilum; Cefadroxilum Monohydricum; Cephadroxil; Kefadroksiili; Kefadroksiilimonohydraatti; MJF-11567-3; Sefadroksil; Цефадроксил.

(7*R*)-7-(α-D-4-Hydroxyphenylglycylamino)-3-methyl-3-cephem-4-carboxylic acid monohydrate.

$C_{16}H_{17}N_3O_5S,H_2O$=381.4

CAS — 50370-12-2 (anhydrous cefadroxil); 119922-85-9 (cefadroxil hemihydrate); 66592-87-8 (cefadroxil monohydrate).

ATC — J01DB05.

ATC Vet — QJ01DB05.

UNII — Q525PA8JJB (anhydrous cefadroxil); 280111G160 (cefadroxil monohydrate); J9CMF6461M (cefadroxil hemihydrate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US. Jpn* includes the anhydrous substance.

Ph. Eur. 8: (Cefadroxil Monohydrate). A white or almost white powder. Slightly soluble in water; very slightly soluble in alcohol. A 5% suspension in water has a pH of 4.0 to 6.0. Protect from light.

USP 36: (Cefadroxil). A white to off-white crystalline powder. Slightly soluble in water; practically insoluble in alcohol, in chloroform, and in ether. pH of a 5% suspension in water is between 4.0 and 6.0. Store in airtight containers.

Uses and Administration

Cefadroxil is a first-generation cephalosporin antibacterial that is the para-hydroxy derivative of cefalexin (p. 236.1), and is used similarly in the treatment of mild to moderate susceptible Gram-positive and Gram-negative bacterial infections. It is given orally, and doses are expressed in terms of the anhydrous substance; 1.04 g of cefadroxil monohydrate is equivalent to about 1 g of anhydrous cefadroxil. The usual dose is 1 to 2 g daily as a single dose or in two divided doses.

The dose of cefadroxil may need to be reduced in renal impairment, see p. 235.2. See also p. 235.2 for details of doses in children.

Cefadroxil has also been used as the lysine derivative.

Administration in children. Cefadroxil may be given orally to children for the treatment of mild to moderate infections caused by susceptible Gram-positive and Gram-negative bacteria. The American Academy of Pediatrics[1] suggests that children aged 1 month and older may be given a usual daily dose of 30 mg/kg in 2 divided doses. Other authorities, including the UK licensed product holder, suggest doses up to 50 mg/kg daily may be given. The usual adult dose of 1 to 2 g daily should not be exceeded.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases.* 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Administration in renal impairment. Following an initial loading dose of 1 g, oral doses of cefadroxil should be adjusted in patients with renal impairment according to creatinine clearance (CC):

- CC 26 to 50 mL/minute per 1.73 m^2: 500 mg to 1 g every 12 hours
- CC 11 to 25 mL/minute per 1.73 m^2: 500 mg to 1 g every 24 hours
- CC 10 mL/minute per 1.73 m^2 or less: 500 mg to 1 g every 36 hours
- haemodialysis patients: an additional 500 mg to 1 g should be given at the end of each dialysis run

Adverse Effects and Precautions

As for Cefalexin, p. 236.2.

Breast feeding. Although higher concentrations of cefadroxil were reported in breast milk compared with cefalexin, cefalotin, cefapirin, and cefotaxime,[1] no detectable cefadroxil would be expected in breast-fed infants and no adverse effects have been seen in infants whose mothers were receiving cefadroxil. Accordingly, the American Academy of Pediatrics considers[2] that cefadroxil is usually compatible with breast feeding.

1. Kafetzis DA, *et al.* Passage of cephalosporins and amoxicillin into the breast milk. *Acta Paediatr Scand* 1981; 70: 285–8.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cefadroxil as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Interactions

As for Cefalexin, p. 236.2.

Antimicrobial Action

As for Cefalexin, p. 236.2.

Pharmacokinetics

Cefadroxil is almost completely absorbed from the gastrointestinal tract. After oral doses of 500 mg and 1 g, peak plasma concentrations of about 16 and 30 micrograms/mL respectively occur after 1.5 to 2 hours. Although peak concentrations are similar to those of cefalexin, plasma concentrations are more sustained. Dosage with food does not appear to affect the absorption of cefadroxil. About 20% of cefadroxil is reported to be bound to plasma proteins. The plasma half-life of cefadroxil is about 1.5 hours and is prolonged in patients with renal impairment.

Cefadroxil is widely distributed to body tissues and fluids. It crosses the placenta and appears in breast milk.

More than 90% of a dose of cefadroxil may be excreted unchanged in the urine within 24 hours by glomerular filtration and tubular secretion; peak urinary concentrations of 1.8 mg/mL have been reported after a dose of 500 mg. Cefadroxil is removed by haemodialysis.

References.

1. Tanrisever B, Santella PJ. Cefadroxil: a review of its antibacterial, pharmacokinetic and therapeutic properties in comparison with cephalexin and cephradine. *Drugs* 1986; 32 (suppl 3): 1–16.
2. Wise R. The pharmacokinetics of the oral cephalosporins—a review. *J Antimicrob Chemother* 1990; 26 (suppl E): 13–20.
3. Garrigues TM, *et al.* Dose-dependent absorption and elimination of cefadroxil in man. *Eur J Clin Pharmacol* 1991; 41: 179–83.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Cefacar; Cefacilina; Cefadrox; Cefamar; Cefasin†; Cefatenk; Droxil†; Kandicin; Klondroxil; Versatic; *Austria*: Duracef; *Belg.*: Duracef; *Braz.*: Cedroxil; Cefadroxon; Cefamox; Cefanaxil; Celocortin†; Neo Cefadril; *Canad.*: Duricef†; *Chile*: Adroxef; Cefamox; Sedafex†; Sefadex; *China*: Lai Si (来斯); Li Xin Qi (力欣奇); Ouyi (欧意); Sai Feng (赛锋); Sai Fu Xi (赛复喜); Xianfengjiu (仙逢久); Yangyi (洋意); Yi Da (毅达); *Cz.*: Biodroxil; Duracef; *Fin.*: Duracef†; *Fr.*: Oracefal; *Ger.*: Gruncef; *Gr.*: Biodroxil; Bitroxetan; Cefalom; Cyclomycine-K; Kleotrat; Med-Loral; Moxacef; Nefalox; Ultracef; *Hong Kong*: Amben; Duracef†; Qualidrox; *Hung.*: Duracef†; *India*: Actidrox; Acudrox; Adriz; Apdil; Bicef; Bid; Biodrox; Bless; Bludrox; Brotzu; C-Drox; Caredrox; Cedil; Cedrox; Cedroxin; Cefadrox; Cefadur; Cefastar; Cefataur; Cefdox; Cefmac; Cefoxid; Cefoxid; Cefoxil; Ceftic; Cefwin; Cetron; Cexil; Codroxil; Cosdrox; Cudrox; Dax; Droma; Droxbit; Droxibid; Droxycad; Droxyceph; Droxyl; Edoxil; Eliminate; Enacxil; Eudrox; Gigacef; Hindrox; Kefloxin; Kefzen; Kidrox; Lactocef; LB-Drox DPS; Lydroxil; Mapradrox; Modcef; Monodrox; Mydrox; Neodrox; Odoxil; Omidrox; Pendrox; Vepan; Vistadrox; *Indon.*: Alxil; Ancefa; Bidicef†; Biodroxil; Cefat; Dexacef; Doxef; Drovax; Droxal; Droxefa; Duricef†; Erphadrox; Ethicef; Grafacef; Kelfex; Lapicef; Librocef†; Longcef; Lostacef; Opicef; Osadrox; Pyricef; Q Cef; Qidrox; Renasistin; Roksicap; Sedro-

fen; Staforin; Tisacef; Vocefa; Vroxil; Widrox; Yaricef; ***Irl.***: Ultracef†; ***Israel***: Biodroxil; ***Ital.***: Cefadril; Oradroxil; ***Malaysia***: Androxyl; Cefadur; Kefloxin; Sofidrox; ***Mex.***: Cefamox; Cepotec; Duracef; Inedit; Kefloxin; Teroxina; ***Philipp.***: Drolex; Droxil; Drozid; Lexipad; Wincocef; ***Pol.***: Biodroxil; Duracef; Tadroxil; ***Port.***: Cefacile†; Ceforal; ***S.Afr.***: Cipadur; Dacef; Duracef†; ***Singapore***: Androxyl; Dexacef; Sofidrox; ***Spain***: Duracef; ***Swed.***: Cefamox; ***Turk.***: Cefradur; Duricef; ***UK***: Baxan†; ***Ukr.***: Cedrohexal (Цедрохексал)†; Cefangin (Цефангин); ***Venez.***: Bidroxyl; Cedroxim; Cefaval; Cefonax; Drocef; Droxifan; Grunicef; Sanodril.

Multi-ingredient Preparations. *Arg.*: Cefacilina Bronquial; ***India***: Bidroxil; Biopro; Caredroxyl-LB; CDCV; Cedbrox; Cefastar; Dax-LA; Drofa; Droxflora; Droxyl Clav; Drozil LB; Kefdil-AX; Lactodrox-DT; LB-Drox; ***Mex.***: Duracef Expec; Fasinat.

Pharmacopoeial Preparations
BP 2014: Cefadroxil Capsules; Cefadroxil Oral Suspension;
USP 36: Cefadroxil Capsules; Cefadroxil for Oral Suspension; Cefadroxil Tablets.

Cefalexin *(BAN, pINN)*

66873; Cefaleksinas monohidratas; Cefaleksyna; Cefalexin monohydrát; Cefalexina; Céfalexine; Céfalexine monohydratée; Cefalexinmonohydrat; Cefalexinum; Cefalexinum Monohydricum; Cephalexin (USAN); Cephalexin; Kefaleksiini; Kefaleksiinimonohydraatti; Sefaleksin; Цефалексин.

(7*R*)-3-Methyl-7-(α-D-phenylglycylamino)-3-cephem-4-carboxylic acid monohydrate.

$C_{16}H_{17}N_3O_4S,H_2O$=365.4

CAS — 15686-71-2 (anhydrous cefalexin); 23325-78-2 (cefalexin monohydrate).

ATC — J01DB01.

ATC Vet — QJ01DB01; QJ51DA01.

UNII — OBN7UDS42Y (cefalexin); 5SFF1W6677 (anhydrous cefalexin).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Cefalexin Monohydrate). A white or almost white crystalline powder. Sparingly soluble in water; practically insoluble in alcohol. A 0.5% solution in water has a pH of 4.0 to 5.5. Protect from light.

USP 36: (Cephalexin). A white to off-white crystalline powder. Slightly soluble in water; practically insoluble in alcohol, in chloroform, and in ether. pH of a 5% suspension in water is between 3.0 and 5.5. Store in airtight containers.

Cefalexin Hydrochloride *(BANM, pINNM)*

Cefalexina, hidrocloruro de; Céfalexine, Chlorhydrate de; Cefalexini Hydrochloridum; Cephalexin Hydrochloride (USAN); Hidrocloruro de cefalexina; LY-061188; Цефалексина Гидрохлорид.

$C_{16}H_{17}N_3O_4S,HCl,H_2O$=401.9

CAS — 105879-42-3.

ATC — J01DB01.

ATC Vet — QJ01DB01.

UNII — 6VJE5G3D98.

Pharmacopoeias. In *US*.

USP 36: (Cephalexin Hydrochloride). A white to off-white crystalline powder. Soluble 1 in 100 in water, in acetone, in acetonitrile, in alcohol, in dimethylformamide, and in methyl alcohol; practically insoluble in chloroform, in ether, in ethyl acetate, and in isopropyl alcohol. pH of a 1% solution in water is between 1.5 and 3.0. Store in airtight containers.

Uses and Administration

Cefalexin is a first-generation oral cephalosporin antibacterial for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria including infections of the respiratory and genito-urinary tracts, bones, and skin. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Cefalexin is usually given as the monohydrate although the hydrochloride is sometimes used. Doses are expressed in terms of the equivalent amount of anhydrous cefalexin; 1.05 g of cefalexin monohydrate and 1.16 g of cefalexin hydrochloride are each equivalent to about 1 g of anhydrous cefalexin.

It is given in doses ranging from 1 to 4 g daily in divided doses; 250 to 500 mg every 6 to 8 hours is typical. For skin and soft tissue infections, streptococcal pharyngitis, and uncomplicated urinary-tract infections a dose of 250 mg every 6 hours or 500 mg every 12 hours may be given. If daily doses greater than 4 g are needed, parenteral cephalosporins should be considered.

For the prophylaxis of recurrent urinary-tract infection, cefalexin may be given in a dose of 125 mg at night.

For details of doses in children, see p. 236.2.

The dose of cefalexin may need to be reduced in renal impairment, see p. 236.2.

Cefalexin sodium or cefalexin lysine have been used parenterally.

Administration in children. Cefalexin may be given orally to children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria. The usual recommended dose is 25 to 50 mg/kg daily in 2 or 3 divided doses. In severe infections the dose may be doubled and for otitis media a dose of 75 to 100 mg/kg daily in 4 divided doses is recommended.

Alternative doses recommended by the *BNFC* are:

- children over 1 month of age: 12.5 mg/kg twice daily; dose should be doubled in severe infection (to a maximum dose of 1 g 4 times daily) *or*
- children 1 month to 1 year of age: 125 mg twice daily
- children 1 to 5 years of age: 125 mg 3 times daily
- children more than 5 years of age: 250 mg 3 times daily

Although not licensed in the UK for neonates, the *BNFC* suggests a dose of 25 mg/kg (to a maximum of 125 mg) may be given twice daily for neonates less than 7 days old, 3 times daily for those aged 7 to 21 days, and 4 times daily for those aged 21 to 28 days.

For the prophylaxis of recurrent urinary-tract infection the *BNFC* recommends that children over 1 month of age be given 12.5 mg/kg orally at night (to a maximum dose of 125 mg).

Administration in renal impairment. Oral doses of cefalexin may need to be reduced in patients with renal impairment. The *BNF* recommends the following maximum daily doses according to creatinine clearance (CC):

- CC 40 to 50 mL/minute per 1.73 m^2: maximum 3 g daily
- CC 10 to 40 mL/minute per 1.73 m^2: maximum 1.5 g daily
- CC less than 10 mL/minute per 1.73 m^2: maximum 750 mg daily

Adverse Effects and Precautions

As for Cefalotin Sodium, p. 237.2.

The most common adverse effects of cefalexin and other oral cephalosporins are generally gastrointestinal disturbances and hypersensitivity reactions. Pseudomembranous colitis has been reported.

References.

1. Dave J, *et al.* Cephalexin induced toxic epidermal necrolysis. *J Antimicrob Chemother* 1991; **28**: 477–8.
2. Baran R, Perrin C. Fixed-drug eruption presenting as an acute paronychia. *Br J Dermatol* 1991; **125**: 592–5.
3. Clark RF. Crystalluria following cephalexin overdose. *Pediatrics* 1992; **89**: 672–4.
4. Murray KM, Camp MS. Cephalexin-induced Stevens-Johnson syndrome. *Ann Pharmacother* 1992; **26**: 1230–3.
5. Czechowicz RT, *et al.* Bullous pemphigoid induced by cephalexin. *Australas J Dermatol* 2001; **42**: 132–5.
6. Longstreth KL, *et al.* Cephalexin-induced acute tubular necrosis. *Pharmacotherapy* 2004; **24**: 808–11.
7. Skoog SM, *et al.* Cephalexin-induced cholestatic hepatitis. *J Clin Gastroenterol* 2004; **38**: 833.
8. Chan AL, *et al.* Fatal anaphylactic reaction to intravenous cephalexin. *Clin Drug Invest* 2005; **25**: 675–8.
9. Penttilä J, *et al.* Delirium in an adolescent patient during treatment with cephalexin. *J Adolesc Health* 2006; **39**: 782–3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cefalexin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Interactions

The renal excretion of cefalexin, and many other cephalosporins, is delayed by probenecid.

Hormonal contraceptives. There have been isolated reports of cefalexin decreasing the efficacy of oestrogen-containing oral contraceptives.[1] However, evidence does not generally support an interaction between broad-spectrum antibacterials and hormonal contraceptives (see p. 2243.1).

1. Friedman M, *et al.* Cephalexin and Microgynon-30 do not go well together. *J Obstet Gynaecol* 1982; **2**: 195–6.

Antimicrobial Action

As for Cefalotin Sodium, p. 238.1, although cefalexin is generally less potent. Some strains of Gram-negative bacteria may be inhibited only by the high concentrations achievable in the urinary tract. *Haemophilus influenzae* is moderately resistant to cefalexin.

Pharmacokinetics

Cefalexin is almost completely absorbed from the gastrointestinal tract and a peak plasma concentration of about 18 micrograms/mL occurs 1 hour after a 500-mg oral dose. If cefalexin is taken with food, absorption may be delayed, but the total amount absorbed is not appreciably altered. Up to 15% of a dose is bound to plasma proteins. The plasma half-life is about 1 hour; it increases with reduced renal function.

Cefalexin is widely distributed in the body but does not enter the CSF in significant quantities. It crosses the placenta and small quantities are found in breast milk. Cefalexin is not metabolised. About 80% or more of a dose is excreted unchanged in the urine in the first 6 hours by glomerular filtration and tubular secretion; urinary concentrations greater than 1 mg/mL have been achieved after a dose of 500 mg. Probenecid delays urinary excretion. Therapeutically effective concentrations may be found in the bile and some may be excreted by this route.

Cefalexin is removed by haemodialysis and peritoneal dialysis.

References.

1. Wise R. The pharmacokinetics of the oral cephalosporins—a review. *J Antimicrob Chemother* 1990; **26** (suppl E): 13–20.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Beliam; Butefina†; Cefagrand; Cefapoten†; Cefarinol†; Cefasporina; Cefosporen; Ceporexin Duo; Ceporexin; Fabotop; Keforal; Lafexina; Lars; Lexin; Lorbicefax; Novalexin†; Ospexin; Permvastat; Sanibiotic; Septilisin Duo; Septilisin; Trexina; Triblix; Velexina; ***Austral.***: Cephatrust; Cilex; Ialex; Ibilex; Keflex; Rancef; Sporahexal†; ***Austria***: Cephalobene; Keflex; Ospexin; Sanaxin; ***Belg.***: Keforal; ***Braz.***: Cefaben; Cefacimed; Cefagel; Cefagran; Cefalexol; Cefanal; Cefanid; Cefaxon; Cefexina; Celen†; Celexin†; Keflaxina; Keflex; Keforal†; Lexin; Neo Ceflex; Neoceflex; Primacef; Profalexina†; Valflex; ***Canad.***: Apo-Cephalex; Keflex; Novo-Lexin; Nu-Cephalex; ***China***: Bei Dun (贝盾); Fulin (福林); Meifeng (美丰); Shen Jia (申嘉); Sporidex (斯宝力克); ***Cz.***: Cefaclen†, Ospexin†; Sporidex†; ***Denm.***: Keflex; ***Fin.***: Kefalex; Kefexin; ***Fr.***: Cefacet; Ceporexine†; Keforal; ***Ger.***: Cephalex†; ***Gr.***: Kefalospes; Kefaxin; Keflex; Keflogen; Kekrinal; Medalexine; Neptolin; Nylichlor; Sinthecillin; Tricylamil; Zabyrex; ***Hong Kong***: Apo-Cephalex†; Cefacapxin†; Cefacin; Cephalexyl†; Cephin†; Felexin; Medolexin; Ora-C†; Ospexin; Sofilex; Solulexin†; Syntolexin†; ***Hung.***: Pyassan; ***India***: Alcephin; Alexin; Allsafe; Anphexin; Axin-LA; Bactocep; Betaspore; Biolex; Blucef; C-Lex; Cefacin; Cefact; Cefacure; Cefalex; Cefalin; Cefamax; Cefax; Cefbact; Cefcidal; Cefel; Ceff; Cefmix; Ceftop RM; Celexin; Cephadex; Cephal; Cephalex; Cephalkem; Cephalpet; Cephamax; Cepharil; Cephaxin; Cephaxtar; Cexin; Ciphlenat; Citaceph; Cucef; Culexin; DT LX-Kid; E Cef-OD; Emceph; Equitrol; Faxe; Fex; Gencef; Gexin; Halexin; Hycef; Keflex; Lecef; Lexa; Lexillin; Lexipil; LX; Mepycep; Mexef; Monacef; Neocef; Niphex; Nufex; Oralex; Oriphex; Phexin; Rofex; Sepexin; Sporidex; ***Indon.***: Cefabiotic; Madlexin; Ospexin; Pralexin†; Sofaxin; Tepaxin; Theralexin†; ***Irl.***: Keflex; ***Israel***: Ceforal; Cefovit; ***Ital.***: Ceporex; Keforal; Lafarin†; ***Jpn***: Larixin; ***Malaysia***: Celexin†; Cephanmycin; Felexin; Medolexin; Ospexin; Sofilex; Solulexin; Sporidex; Uphalexin; ***Mex.***: Acacin†; Ancetevt†; Arlexen; Capxin; Cefalver; Ceporex; Facelit†; Fleximin†; Flextinol; Keflex; Nafacil; Naxifelar; Nixelaf-C; Optocef; Paferxin; Quimosporina; Servicef; Sporicef; ***Neth.***: Keforal; ***Norw.***: Keflex; ***Philipp.***: Airex; Bacilexin; Bandax; Benlexin; Bloflex; Canelin; Cefalin; Cendalex; Ceporex; CFA; Civalex; Clephin†; Difalex; Edexin; Eliphorin; Exel; Fablex; Palex; Falteria; Forexine; Halcepin†; Infexin; Ivynall; Keflex†; Lewimycin; Lexum; Lonarel†; Lyceplix; Madexin; Medilexin; Medoxine; Mefolex; Mexin; Montralex†; Nefadon; Neolecsin; Nerfalex; Oneflex; Pediaflex; Respinal; Selzef; Servispor†; Sorlex; Sporidex†; Xeface; Xinflex; Zepharyl; Zeporin; Zepotex; Zexanta†; Zinace; Zucoflaxin†; ***Pol.***: Keflex; ***S.Afr.***: Belex; Keflex; Lenocef†; Ranceph; ***Singapore***: Apo-Cephalex; Celexin; Cephalen†; Cephanmycin; Ceporex; Felexin; Ospexin; Sofilex; Solulexin; Sporidex; Uphalexin; ***Spain***: Cefalexgobens†; Kefloridina; Lexincef†; Sulquipen†; Torlasporin†; ***Swed.***: Keflex; ***Thal.***: Celexin†; Cefute; Celex; Celexin†; Cephalexyl; Cephin; Farmalex; Felexin; Ibilex; Keflex; Mycef; Neolexin†; Pondnacef†; Sefasin†; Sialexin; Sporicef; Sporidex†; Sporidin; Suphalex; Teplexin; Toflex; Ulflex; Vataceph†; Zeplex; ***Turk.***: Maksipor; Sef; ***UAE***: Cefrin; ***UK***: Ceporex; Keflex; ***Ukr.***: Lexin (Лексин); Ospexin (Оспексин)†; ***USA***: Cefanex; Keflex; ***Venez.***: Bidocef; Keforal; Stricef.

Multi-ingredient Preparations. ***China***: Pixian (彼先); Xindabao (新达宝); ***India***: Alcephin-LA; Caceff; Carbicef; Cecarb; Cefalong-DS; Cefel-B; Ceff-LA; Cep-Bro; Cephadex LB; ***Mex.***: Arlexen B; Cefabroxil; Cepobrom; Mucocef; Rombox.

Pharmacopoeial Preparations
BP 2014: Cefalexin Capsules; Cefalexin Oral Suspension; Cefalexin Tablets;
USP 36: Cephalexin Capsules; Cephalexin for Oral Suspension; Cephalexin Tablets for Oral Suspension; Cephalexin Tablets.

Cefalonium *(BAN, pINN)*

41071; Carbamoylcefaloridine; Cefalonio; Céfalonium; Cephalonium; Цефалоний.

(7*R*)-3-(4-Carbamoyl-1-pyridiniomethyl)-7-[2-(2-thienyl)acetamido]-3-cephem-4-carboxylate.

$C_{20}H_{18}N_4O_5S_2$=458.5

CAS — 5575-21-3.

ATC Vet — QJ51DA90.
UNII — K2P920217W.

Pharmacopoeias. *BP(Vet)* includes the dihydrate.

BP(Vet) 2014: (Cefalonium). The dihydrate is a white or almost white crystalline powder. Very slightly soluble in water and in methyl alcohol; insoluble in alcohol, in dichloromethane, and in ether; soluble in dimethyl sulfoxide. It dissolves in dilute acids and in alkaline solutions. Store at temperature not exceeding 30 degrees. Protect from light.

Profile

Cefalonium is a cephalosporin antibacterial used in veterinary practice.

Cefaloridine *(BAN, pINN)*

40602; Cefaloridin; Cefaloridina; Céfaloridine; Cefaloridinum; Cephaloridine (USAN); Kefaloridiini; Цефалоридин.
(7*R*)-3-(1-Pyridiniomethyl)-7-[(2-thienyl)acetamido]-3-cephem-4-carboxylate.
$C_{19}H_{17}N_3O_4S_2$=415.5
CAS — 50-59-9.
ATC — J01DB02.
ATC Vet — QJ01DB02.
UNII — LVZ1VC61HB.

Profile

Cefaloridine was one of the first cephalosporin antibacterials to be available clinically. It has properties similar to those of cefalotin (p. 237.1), but is more nephrotoxic. It has been given by injection but is seldom used now.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Ceporan.

Cefalotin Sodium *(BANM, pINNM)*

38253; Cefalotin-Natrium; Cefalotin sodná sůl; Cefalotina sódica; Céfalotine sodique; Cefalotinnatrium; Cefalotin-nátrium; Cefalotino natrio druska; Cefalotinum natricum; Cefalotyna sodowa; Cephalothin Sodium (USAN); Kefalotiininatrium; Natrii Cefalotinum; Sodium Cephalothin; Натрий Цефалотин.
Sodium (7*R*)-7-[2-(2-thienyl)acetamido]cephalosporanate; Sodium (7*R*)-3-acetoxymethyl-7-[2-(2-thienyl)acetamido]-3-cephem-4-carboxylate.
$C_{16}H_{15}N_2NaO_6S_2$=418.4
CAS — 153-61-7 *(cefalotin)*; 58-71-9 *(cefalotin sodium)*.
ATC — J01DB03.
ATC Vet — QJ01DB03.
UNII — C22G6EYP8B.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Cefalotin Sodium). A white or almost white powder. Freely soluble in water; slightly soluble in dehydrated alcohol. A 10% solution in water has a pH of 4.5 to 7.0. Protect from light.

USP 36: (Cephalothin Sodium). A white to off-white, practically odourless, crystalline powder. Freely soluble in water, in sodium chloride 0.9%, and in glucose solutions; insoluble in most organic solvents. pH of a 25% solution in water is between 4.5 and 7.0. Store in airtight containers.

Incompatibility and stability. Cefalotin sodium has been reported to be incompatible with aminoglycosides and with many other drugs. Precipitation may occur in solutions with a pH of less than 5.

Uses and Administration

Cefalotin is a first-generation parenteral cephalosporin antibacterial that has been used in the treatment of infections due to susceptible bacteria, and for surgical infection prophylaxis, but has generally been replaced by newer cephalosporins. It has higher activity against Gram-positive than Gram-negative bacteria.

Cefalotin is given as the sodium salt by slow intravenous injection over 3 to 5 minutes or by intermittent or continuous infusion. It may be given intramuscularly but this route is painful. Doses are expressed in terms of the equivalent amount of cefalotin; 1.06 g of cefalotin sodium is equivalent to about 1 g of cefalotin. The usual dose is 0.5 to 1 g of cefalotin every 4 to 6 hours; up to 12 g daily has been given in severe infections.

For surgical infection prophylaxis, a dose of 2 g is given intravenously 30 to 60 minutes before the operation, followed by 2 g during surgery; 2 g is given every 6 hours postoperatively for 24 hours. For patients undergoing heart valve replacement or arthroplasty, cefalotin should be continued for up to 72 hours.

The dose of cefalotin may need to be reduced in renal impairment, see p. 237.2.

For details of doses in children, see p. 237.2.

Cefalotin sodium may be added to dialysis solutions or saline and given intraperitoneally.

Administration in children. Cefalotin may be given to children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria. It is given parenterally by deep intramuscular injection, by slow intravenous injection, or by intermittent or continuous intravenous infusion. The usual recommended dose is 80 to 160 mg/kg daily in divided doses.

For surgical infection prophylaxis, children may be given 20 to 30 mg/kg in the same dosing schedule as for adults (see Uses and Administration, above).

Administration in renal impairment. Reduced doses are recommended if cefalotin is given to patients with renal impairment. After an intravenous loading dose of 1 to 2 g patients may be given the following maximum doses according to their creatinine clearance (CC):

- CC 50 to 80 mL/minute: 2 g every 6 hours
- CC 25 to 50 mL/minute: 1.5 g every 6 hours
- CC 10 to 25 mL/minute: 1 g every 6 hours
- CC 2 to 10 mL/minute: 500 mg every 6 hours
- CC less than 2 mL/minute: 500 mg every 8 hours

Adverse Effects

The adverse effects associated with cefalotin and other cephalosporins are broadly similar to those described for penicillins (see Benzylpenicillin, p. 229.2). The most common are hypersensitivity reactions, including skin rashes, urticaria, eosinophilia, fever, reactions resembling serum sickness, and anaphylaxis.

There may be a positive response to the Coombs' test although haemolytic anaemia rarely occurs. Neutropenia and thrombocytopenia have occasionally been reported. Agranulocytosis has been associated rarely with some cephalosporins. Bleeding complications related to hypoprothrombinaemia and/or platelet dysfunction have occurred especially with cephalosporins and cephamycins having an *N-methylthiotetrazole* side-chain, including

- cefamandole
- cefbuperazone
- cefmenoxime
- cefmetazole
- cefonicid
- cefoperazone
- ceforanide
- cefotetan
- cefpiramide
- latamoxef.

The presence of a *methylthiadiazolethiol* side-chain, as in cefazolin, or an *N-methylthiotriazine* ring, as in ceftriaxone, has also been associated with such bleeding disorders. Hypoprothrombinaemia which is usually reversible with vitamin K, was once thought to be due to an alteration in intestinal flora but interference with prothrombin synthesis now seems more likely.

Nephrotoxicity has been reported with cefalotin although it is less toxic than cefaloridine. Acute renal tubular necrosis has followed excessive dosage and has also been associated with its use in older patients or those with pre-existing renal impairment, or when used with nephrotoxic drugs such as aminoglycosides. Acute interstitial nephritis is also a possibility as a manifestation of hypersensitivity.

Transient increases in liver enzyme values have been reported. Hepatitis and cholestatic jaundice have occurred rarely with some cephalosporins.

Convulsions and other signs of CNS toxicity have been associated with high doses, especially in patients with severe renal impairment.

Gastrointestinal adverse effects such as nausea, vomiting, and diarrhoea have been reported rarely. Prolonged use may result in overgrowth of non-susceptible organisms and, as with other broad-spectrum antibacterials, pseudomembranous colitis may develop (see also p. 237.2).

There may be pain at the injection site after intramuscular use, and thrombophlebitis has occurred on intravenous infusion of cephalosporins. Cefalotin appears to be more likely to cause such local reactions than other cephalosporins.

Antibiotic-associated colitis. Pseudomembranous colitis has occurred with many antibacterials, including broad-spectrum cephalosporins.[1-3] In 1991 the UK CSM warned[4] of the dangers of pseudomembranous colitis with the newer, as well as the older, oral cephalosporins. In addition to 33 reports of pseudomembranous colitis associated with cefalexin, cefradine, cefadroxil, and cefaclor, 6 of which proved fatal, they had received 12 reports of probable or confirmed cases with cefuroxime axetil and 15 with cefixime, one of them fatal. In clinical studies of cefuroxime axetil and cefixime, diarrhoea and pseudomembranous colitis appeared to be dose-related and therefore the CSM recommended that higher doses should be reserved for severe infections. In any event they advised that treatment should be stopped if symptoms suggestive of pseudomembranous colitis arose.

For further discussion of the management of this condition, see p. 183.1.

1. de Lalla F, *et al.* Third generation cephalosporins as a risk factor for Clostridium difficile-associated disease: a four-year survey in a general hospital. *J Antimicrob Chemother* 1989; 23: 623–31.
2. Golledge CL, *et al.* Extended spectrum cephalosporins and Clostridium difficile. *J Antimicrob Chemother* 1989; 23: 929–31.
3. Preiman JP, *et al.* Pseudomembranous colitis associated with single-dose cephalosporin prophylaxis. *JAMA* 1989; 262: 902.
4. CSM. Pseudomembranous (antibiotic-associated) colitis and diarrhoea with cephalosporins. *Current Problems* 32 1991. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024450&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)

Effects on the blood. References.

1. Lipsky JJ. Antibiotic-associated hypoprothrombinaemia. *J Antimicrob Chemother* 1988; 21: 281–300.
2. Shearer MJ, *et al.* Mechanism of cephalosporin-induced hypoprothrombinemia: relation to cephalosporin side chain, vitamin K metabolism, and vitamin K status. *J Clin Pharmacol* 1988; 28: 88–95.
3. Welage LS, *et al.* Comparative evaluation of the pharmacokinetics of N-methylthiotetrazole following administration of cefoperazone, cefotetan, and cefmetazole. *Antimicrob Agents Chemother* 1990; 34: 2369–74.

Effects on the kidneys. References.

1. Zhanel GG. Cephalosporin-induced nephrotoxicity: does it exist? *DICP Ann Pharmacother* 1990; 24: 262–5.
2. Tune BM. Nephrotoxicity of beta-lactam antibiotics: mechanisms and strategies for prevention. *Pediatr Nephrol* 1997; 11: 768–72.

Hypersensitivity. Hypersensitivity reactions, up to and including rare reports of anaphylaxis, are recognised adverse effects of cephalosporins. However, there is some debate about the risks of cross-sensitivity between cephalosporins and penicillins, and between cephalosporins of different classes.[1,2]

A study in patients with documented penicillin allergy found that 14 of 128 had positive skin-test results to one or more of cefalotin, cefamandole, cefuroxime, ceftazidime, ceftriaxone, or cefotaxime.[1] Of 101 patients with negative skin-test results to the latter 4 drugs, all tolerated subsequent test doses of cefuroxime axetil and ceftriaxone. However, the 11% cross-reactivity rate was considered to support the avoidance of cephalosporins in patients with positive results to penicillin skin tests.

In contrast, a review[2] questioned the evidence that cross-sensitivity rates between penicillins and cephalosporins are as high as the often-cited rates of 8 to 18%. It considered that the immune response to cephalosporins is highly dependent on their side-chain structure, which more closely resembles penicillins in some than in others. It was suggested that

- if a patient had a history consistent with a severe, IgE-mediated reaction to a penicillin then cephalosporins such as cefalotin and cefoxitin, with a similar 7-position side-chain on the beta-lactam ring, should be used with caution
- if the reaction followed use of ampicillin or amoxicillin the cephalosporins with a similar side-chain (cefalexin, cefradine, cefatrizine, cefadroxil, cefaclor, and cefprozil) should be used with caution
- patients who have had a non-IgE-mediated reaction to a penicillin, cephalosporins may be used (in uncertain cases, elective penicillin skin testing is advisable)

The incidence of cross-reactivity in penicillin-allergic patients appears to vary with the generation of the cephalosporin, being highest with the first-generation drugs (considered to be about 0.4%) and virtually absent for drugs such as cefuroxime, cefpodoxime, and cefdinir. Patients who have had a type-I reaction to a specific cephalosporin should probably never be given that drug again, but the risk of cross-sensitivity to another cephalosporin appears to be low if the side-chains of the drugs are not similar.

For mention of possible cross-reactivity between ceftazidime and aztreonam, see under Aztreonam, p. 225.1.

1. Romano A, *et al.* Cross-reactivity and tolerability of cephalosporins in patients with immediate hypersensitivity to penicillins. *Ann Intern Med* 2004; 141: 16–22.
2. Pichichero ME. A review of evidence supporting the American Academy of Pediatrics recommendation for prescribing cephalosporin antibiotics for penicillin-allergic patients. *Pediatrics* 2005; 115: 1048–57.

Precautions

Licensed product information states that cefalotin should not be given to patients who are hypersensitive to it or to other cephalosporins (but see also above). Immunological studies have suggested that up to 20% of penicillin-sensitive patients may also be allergic to cephalosporins although clinical studies indicate a lower frequency and the true

incidence is uncertain; great care should be taken if cefalotin is to be given to such patients. Care is also necessary in patients with a history of allergy.

Cefalotin should be given with caution to patients with renal impairment; dosage reduction may be necessary. Renal and haematological status should be monitored especially during prolonged and high-dose therapy. Cefalotin and some other cephalosporins and cephamycins (ceforanide, cefotetan, cefoxitin, and cefpirome) may interfere with the Jaffé method of measuring creatinine concentrations and may produce falsely high values; this should be borne in mind when measuring renal function. Positive results to the direct Coombs' test have been found during treatment with cefalotin and these can interfere with blood cross-matching. The urine of patients being treated with cefalotin may give false-positive reactions for glucose using copper-reduction reactions.

Sodium content. Each g of cefalotin sodium contains about 2.39 mmol of sodium.

Interactions

The use of nephrotoxic drugs such as the aminoglycosides gentamicin and tobramycin may increase the risk of kidney damage with cefalotin. There is also some evidence for enhanced nephrotoxicity with the loop diuretic furosemide, but this is less certain than for furosemide with cefaloridine. As with penicillins, the renal excretion of cefalotin and many other cephalosporins is inhibited by probenecid. There may be antagonism between cefalotin and bacteriostatic antibacterials.

Antimicrobial Action

Cefalotin is a beta-lactam antibacterial. It is bactericidal and acts similarly to benzylpenicillin (p. 230.1) by inhibiting synthesis of the bacterial cell wall. It is most active against Gram-positive cocci, and has moderate activity against some Gram-negative bacilli.

- Sensitive Gram-positive cocci include both penicillinase- and non-penicillinase-producing staphylococci, although meticillin-resistant staphylococci are resistant; most streptococci are also sensitive, but not penicillin-resistant *Streptococcus pneumoniae;* enterococci are usually resistant.
  Some Gram-positive anaerobes are also susceptible. Cefalotin is usually inactive against *Listeria monocytogenes.*
- Among Gram-negative bacteria cefalotin has activity against some Enterobacteriaceae including strains of *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Salmonella,* and *Shigella* spp., but not against *Enterobacter,* indole-positive *Proteus,* or *Serratia* spp.
  It is also active against *Moraxella catarrhalis* (*Branhamella catarrhalis*) and *Neisseria* spp., though *Haemophilus influenzae* is moderately resistant.
  Bacteroides fragilis and *Pseudomonas aeruginosa* are not sensitive. Mycobacteria, mycoplasma, and fungi are resistant.

Resistance of bacteria to cefalotin may be due to several mechanisms: the drug may be prevented from reaching its site of action, for example in some Gram-negative organisms the cell wall may be a potential barrier; the target penicillin-binding proteins may be altered so that cefalotin cannot bind with these proteins; or, most importantly, the organism may produce beta-lactamases (cephalosporinases). Cefalotin is relatively resistant to hydrolysis by staphylococcal beta-lactamase, but is inactivated by a variety of beta-lactamases produced by Gram-negative organisms; resistance of Gram-negative organisms often depends on more than one factor. Resistance can be chromosomally or plasmid-mediated and may sometimes be inducible by cephalosporins.

Certain strains of bacteria may be inhibited but not killed by cephalosporins or penicillins and in such cases the minimum bactericidal concentration is much greater than the minimum inhibitory concentration; this is known as tolerance.

As well as with other cephalosporins, some cross-resistance may occur between cefalotin and the penicillinase-resistant penicillins.

Pharmacokinetics

Cefalotin is poorly absorbed from the gastrointestinal tract. After intramuscular injection peak plasma concentrations of about 10 and 20 micrograms/mL occur within 30 minutes of doses of 500 mg and 1 g, respectively. A concentration of 30 micrograms/mL has been reported 15 minutes after the intravenous injection of a 1-g dose; a range of 14 to 20 micrograms/mL has been achieved by the continuous intravenous infusion of 500 mg/hour.

Cefalotin is widely distributed in body tissues and fluids except the brain and CSF where the concentrations achieved are low and unpredictable. It crosses the placenta and low concentrations have been detected in breast milk.

The plasma half-life varies from about 30 to 50 minutes, but may be longer in patients with renal impairment, especially that of the metabolite. About 70% of cefalotin is bound to plasma proteins.

About 20 to 30% of cefalotin is rapidly deacetylated in the liver and about 60 to 70% of a dose is excreted in the urine by the renal tubules within 6 hours as cefalotin and the less active metabolite, desacetylcefalotin. High urine concentrations of 800 micrograms/mL and 2.5 mg/mL have been seen after intramuscular doses of 500 mg and 1 g, respectively. Probenecid blocks the renal excretion of cefalotin. A very small amount is excreted in bile.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Arecamin; Cefade; Dasuglor; Keflin; *Austral.*: Keflin Neutral; *Braz.*: Cefalin; Cefalotil; Cefariston; Kefalomax; Keflin; *Canad.*: Ceporacin; *China*: Fengsaixing (锋赛星); *Gr.*: Practogen; *Indon.*: Cephation†; Exion; Moraxine†; *Mex.*: Cefelen†; Ceftina†; Falot; Famto; Keflin; Kefolit; Liroken I; Loriken; Lotin†; Tecphatil; *Neth.*: Keflin; *Norw.*: Keflin; *Philipp.*: Fezef†; *Singapore*: Cefadin; *Thai.*: Cefadin; *Venez.*: Ceflen.

Pharmacopoeial Preparations
USP 36: Cephalothin for Injection; Cephalothin Injection.

Cefamandole *(BAN, USAN, rINN)*

83405; Cefamandol; Céfamandole; Cefamandolum; Cephamandole; Compound 83405; Kefamandoli; Цефамандол.

(7*R*)-7-D-Mandelamido-3-(1-methyl-1*H*-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid;(6*R*-[6α,7β(*R**)]]-7-[(hydroxyphenylacetyl)amino]-3-[[(1-methyl-1*H*-tetrazol-5-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

$C_{18}H_{18}N_6O_5S_2$=462.5
CAS — 34444-01-4.
ATC — J01DC03.
ATC Vet — QJ01DC03.
UNII — 5CKP8C2LLI.

Cefamandole Nafate *(BAN, USAN, rINNM)*

106223; Cefamandol, nafato de; Cefamandole Formate Sodium; Céfamandole, Nafate de; Cefamandole Nafate Sodium; Cefamandoli nafas; Cefamandoli Nafatum; Cefamandolio nafatas; Cefamandolnafat; Cefamandol-nafát; Cefamandolu nafan; Cefmandoli Nafas; Cephamandole Nafate; Kefamandolinafaatti; Nafato de cefamandol; Цефамандола Нафат.

Sodium (7*R*)-7-[(2*R*)-2-formyloxy-2-phenylacetamido]-3-(1-methyl-1*H*-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylate.

$C_{19}H_{17}N_6NaO_6S_2$=512.5
CAS — 42540-40-9.
ATC — J01DC03.
ATC Vet — QJ01DC03.
UNII — 8HDO7941DO.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Cefamandole Nafate). A white, or almost white powder. Freely soluble in water; sparingly soluble in methyl alcohol. A 10% solution in water has a pH, measured after 30 minutes, of 6.0 to 8.0. Store in airtight containers. Protect from light.

USP 36: (Cefamandole Nafate). A white, odourless, crystalline solid. Soluble in water and in methyl alcohol; practically insoluble in chloroform, in cyclohexane, in ether, and in benzene. pH of a 10% solution in water is between 3.5 and 7.0. Store in airtight containers.

Incompatibility and stability. Cefamandole nafate has been reported to be incompatible with aminoglycosides and with metronidazole. Formulations of cefamandole nafate available for injection contain sodium carbonate and are incompatible with solutions containing calcium or magnesium salts. When reconstituted with water the sodium carbonate rapidly hydrolyses about 30% of the ester to cefamandole sodium; during storage of the reconstituted solution at room temperature carbon dioxide is produced.

References.
1. Frable RA, *et al.* Stability of cefamandole nafate injection with parenteral solutions and additives. *Am J Hosp Pharm* 1982; 39: 622–7. Correction. *ibid.*: 1479.

Cefamandole Sodium *(BANM, rINNM)*

Cefamandol sódico; Céfamandole Sodique; Cephamandole Sodium; Natrii Cefamandolum; Натрий Цефамандол.

$C_{18}H_{17}N_6NaO_5S_2$=484.5
CAS — 30034-03-8.
ATC — J01DC03.
ATC Vet — QJ01DC03.
UNII — IY6234ODVR.

Uses and Administration

Cefamandole is a second-generation cephalosporin antibacterial used in the treatment of infections due to susceptible Gram-positive and Gram-negative bacteria (including infections of the respiratory and genito-urinary tracts, bones and joints, and of the skin and skin structure) and for surgical infection prophylaxis. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Cefamandole is given principally as cefamandole nafate (the sodium salt of cefamandole formyl ester). Doses are expressed in terms of the equivalent amount of cefamandole; 1.05 g of cefamandole sodium and 1.11 g of cefamandole nafate are each equivalent to about 1 g of cefamandole. It is given by deep intramuscular injection, by slow intravenous injection over 3 to 5 minutes, or by intermittent or continuous infusion in doses of 0.5 to 2 g every 4 to 8 hours depending on the severity of the infection. If cefamandole is used with an aminoglycoside the drugs should be given separately.

For surgical infection prophylaxis, a dose of 1 or 2 g intravenously or intramuscularly 30 to 60 minutes before surgical incision, followed by 1 or 2 g every 6 hours for 24 to 48 hours, is recommended. For patients undergoing procedures involving implantation of prosthetic devices cefamandole should be continued for up to 72 hours.

The dose of cefamandole may need to be reduced in patients with renal impairment, see p. 238.3.

For details of doses in children, see p. 238.3.

Administration in children. Cefamandole may be given to children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria and for surgical infection prophylaxis. It is given parenterally by deep intramuscular injection, by slow intravenous injection over 3 to 5 minutes, or by intermittent or continuous infusion.

For treatment, children over 1 month of age may be given 50 to 100 mg/kg daily in divided doses every 4 to 8 hours; 150 mg/kg daily may be given in severe infections, but this dose should not exceed the maximum adult dose (see Uses and Administration, above).

For surgical infection prophylaxis, children over 3 months of age may be given cefamandole in a similar schedule to adults (see above); 50 to 100 mg/kg is given daily in equally divided doses.

Administration in renal impairment. Parenteral doses of cefamandole should be reduced for patients with renal impairment. After an initial dose of 1 to 2 g the following maintenance doses have been recommended based on creatinine clearance (CC):

- CC 50 to 80 mL/minute per 1.73 m^2: 0.75 to 2 g every 6 hours
- CC 25 to 50 mL/minute per 1.73 m^2: 0.75 to 2 g every 8 hours
- CC 10 to 25 mL/minute per 1.73 m^2: 0.5 to 1.25 g every 8 hours
- CC 2 to 10 mL/minute per 1.73 m^2: 0.5 to 1 g every 12 hours
- CC less than 2 mL/minute per 1.73 m^2: 250 to 750 mg every 12 hours

Adverse Effects and Precautions

As for Cefalotin Sodium, p. 235.2.

As mentioned under Cefalotin, cephalosporins with an *N*-methylthiotetrazole side-chain such as cefamandole (and possibly those with methylthiadiazolethiol or *N*-methylthiotriazine side-chains as well) may produce bleeding disorders associated with hypoprothrombinaemia and/or platelet disorders.

Sodium content. 1.05 g of cefamandole sodium and 1.11 g of cefamandole nafate each contain about 2.2 mmol of sodium.

Interactions

A disulfiram-like interaction with alcohol may occur and has been attributed to the *N*-methylthiotetrazole side-chain of cefamandole; patients should avoid alcohol during, and for at least several days after, cefamandole treatment. Interactions are also possible with preparations containing significant amounts of alcohol.

Cefamandole, and other cephalosporins with an *N*-methylthiotetrazole side-chain, may enhance the hypoprothrombinaemic response to anticoagulants as discussed under Warfarin (p. 1531.1).

Probenecid reduces the renal clearance of cefamandole and many other cephalosporins.

References.
1. Portier H, *et al.* Interaction between cephalosporins and alcohol. *Lancet* 1980; ii: 263.
2. Drummer S, *et al.* Antabuse-like effect of β -lactam antibiotics. *N Engl J Med* 1980; 303: 1417–18.

Antimicrobial Action

Cefamandole is bactericidal and acts similarly to cefalotin, but has a broader spectrum of activity. It generally has similar or less activity against Gram-positive staphylococci and streptococci, but is resistant to some beta-lactamases produced by Gram-negative bacteria. It is more active than cefalotin against many of the Enterobacteriaceae including some strains of *Enterobacter, Escherichia coli, Klebsiella, Salmonella,* and some *Proteus* spp. However, resistance to cefamandole and other beta lactams has emerged in some species, notably *Enterobacter,* during treatment with cefamandole. Cefamandole is very active *in vitro* against *Haemophilus influenzae* although an inoculum effect has been reported for beta-lactamase-producing strains. Like cefalotin, most strains of *Bacteroides fragilis* are resistant to cefamandole, as are *Pseudomonas* spp.

References.
1. Sabath LD. Reappraisal of the antistaphylococcal activities of first-generation (narrow-spectrum) and second-generation (expanded-spectrum) cephalosporins. *Antimicrob Agents Chemother* 1989; 33: 407–11.

Pharmacokinetics

Cefamandole is poorly absorbed from the gastrointestinal tract. It is given intramuscularly or intravenously, usually as the nafate which is rapidly hydrolysed to release cefamandole *in vivo*. Peak plasma concentrations for cefamandole of about 13 and 25 micrograms/mL have occurred 0.5 to 2 hours after intramuscular doses of 500 mg and 1 g respectively; concentrations are very low after 6 hours. About 70% is bound to plasma proteins. The plasma half-life varies from about 0.5 to 1.2 hours depending on the route of injection; it is prolonged in patients with renal impairment.

Cefamandole is widely distributed in body tissues and fluids including bone, joint fluid, and pleural fluid; it diffuses into the CSF when the meninges are inflamed, but concentrations are unpredictable. Cefamandole has also been detected in breast milk. It is rapidly excreted unchanged by glomerular filtration and renal tubular secretion; about 80% of a dose is excreted within 6 hours and high urinary concentrations are achieved. Probenecid competes for renal tubular secretion with cefamandole resulting in higher and prolonged plasma concentrations of cefamandole. Therapeutic concentrations of cefamandole are achieved in bile.

Cefamandole is removed by haemodialysis to some extent.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Mandol†; ***Austria***: Mandokef; ***Belg.***: Mandol†; ***China***: Mengdexin (孟得新); ***Gr.***: Acemycin; Cefadin; Kefabiotic; Mandocef†; Mandokef; ***Hung.***: Cefam†; ***Indon.***: Dardokef†; Dofacef; ***Ital.***: Cefam; Cemado†; Mancef; ***Neth.***: Mandol; ***NZ***: Mandol; ***Pol.***: Tarcefandol; ***Rus.***: Cefamabol (Цефамабол); Cefat (Цефат); Mandol (Мандол); ***S. Afr.***: Mandokef†; ***Switz.***: Mandokef; ***Thai.***: Cefadol†; Cefmandol.

Pharmacopoeial Preparations
USP 36: Cefamandole Nafate for Injection.

Cefapirin Sodium *(BANM, pINNM)*

BL-P-1322; Cefapirin-Natrium; Cefapirin sodná sůl; Cefapirina sódica; Céfapirine Sodique; Cefapirinnatrium; Cefapirinnátrium; Cefapirino natrio druska; Cefapirinum Natricum; Cephapirin Sodium (USAN); Kefapiriininatrium; Natrii Cefapirinum; Натрий Цефапирин.

Sodium (7*R*)-7-[2-(4-pyridylthio)acetamido]cephalosporanate; Sodium (7*R*)-3-acetoxymethyl-7-[2-(4-pyridylthio)acetamido]-3-cephem-4-carboxylate.

$C_{17}H_{16}N_3NaO_6S_2$=445.4

CAS — 21593-23-7 (cefapirin); 24356-60-3 (cefapirin sodium).
ATC — J01DB08.
ATC Vet — QJ01DB08.
UNII — 431LFF7I7I.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn,* and *US.*

US also includes Cephapirin Benzathine for veterinary use.

Ph. Eur. 8: (Cefapirin Sodium). A white or pale yellow powder. Soluble in water; practically insoluble in dichloromethane. A 1% solution in water has a pH of 6.5 to 8.5. Protect from light.

USP 36: (Cephapirin Sodium). A white to off-white crystalline powder, odourless or having a slight odour. Very soluble in water; insoluble in most organic solvents. pH of a solution in water containing the equivalent of cefapirin 1% is between 6.5 and 8.5. Store in airtight containers.

Profile

Cefapirin is a first-generation cephalosporin antibacterial with actions and uses very similar to those of cefalotin (p. 235.1). Doses have been expressed as either the sodium salt or as the base. 1.05 g of cefapirin sodium is equivalent to about 1 g of cefapirin. Usual doses of 0.5 to 1 g have been given every 4 to 6 hours by intramuscular injection or intravenously. In severe infections up to 12 g daily has been used.

Administration in renal impairment. Reduced parenteral doses of cefapirin sodium may be necessary in patients with renal impairment. One regimen, based on creatinine clearance (CC), that has been suggested is:

- CC 5 to 20 mL/minute: 1 g every 12 hours
- CC less than 5 mL/minute: 1 g every 24 hours

Patients undergoing haemodialysis may receive 7.5 to 15 mg/kg after each dialysis.

Sodium content. Each g of cefapirin sodium contains about 2.2 mmol of sodium.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Cefaloject†; ***Gr.***: Cefatrex.

Pharmacopoeial Preparations
USP 36: Cephapirin for Injection.

Cefatrizine *(BAN, USAN, pINN)*

BL-S640; Cefatrizina; Céfatrizine; Cefatrizinum; S-640P; SKF-60771; Цефатризин.

(7*R*)-7-(α-D-4-Hydroxyphenylglycylamino)-3-(1*H*-1,2,3-triazol-4-ylthiomethyl)-3-cephem-4-carboxylic acid.

$C_{18}H_{18}N_6O_5S_2$=462.5

CAS — 51627-14-6.
ATC — J01DB07.
ATC Vet — QJ01DB07.
UNII — 8P4W949T8K.

Cefatrizine Propylene Glycol *(BANM, pINNM)*

Cefatrizin-Propylenglycol; Cefatrizina propilenglicol; Cefatrizinas propilenglikolis; Céfatrizine Propylèneglycol; Cefatrizin-propilénglikol; Cefatrizin-propylenglykol; Cefatrizinpropylenglykol; Cefatrizinum propylen glycolum; Cefatrizinum Propylenglycolum; Kefatritsiinipropyleeniglykoli; Цефатризин Пропиленгликол.

(7*R*)-7-(α-D-4-Hydroxyphenylglycylamino)-3-(1*H*-1,2,3-triazol-4-ylthiomethyl)-3-cephem-4-carboxylate propylene glycol.

$C_{18}H_{18}N_6O_5S_2$, $(C_3H_8O_2)_n$

CAS — 64217-62-5.
ATC — J01DB07.
ATC Vet — QJ01DB07.
UNII — 3731IA5GI9.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.*

Ph. Eur. 8: (Cefatrizine Propylene Glycol). A white or almost white powder. Slightly soluble in water; practically insoluble in alcohol and in dichloromethane.

Profile

Cefatrizine is a first-generation cephalosporin antibacterial with actions and uses similar to those of cefalexin (p. 234.1), although it might be more active *in vitro*. It is given orally as the base or, more often, as a compound with propylene glycol, in usual doses equivalent to 500 mg twice daily of cefatrizine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Cefaperos†; ***Gr.***: Anfagladin; Axelorax; Banadroxin; Ceftazin; Cetrizin; Clomin; Fica-F; Gertemycin; Izerin; Kentacef; Klevasin; Liamycin; Liferost; Lingopen; Mekan; Nibocin; Northiron; Phacobiotic; Relyovix; Specicef-N; Tedosin; Trixilan; Vagotrosin; Zirenol; ***Ital.***: Faretrizin†; Ketrizin†; Trizina†; ***Port.***: Macropen; Supracefa†.

Cefazolin *(BAN, pINN)*

Cefazolina; Céfazoline; Cefazolinum; Cephazolin; Kefatsoliini; Sefazolin; Цефазолин.

3-[(5-Methyl-1,3,4-thiadiazol-2-yl)thiomethyl]-7-(tetrazol-1-ylacetamido)-3-cephem-4-carboxylic acid.

$C_{14}H_{14}N_8O_4S_3$=454.5

CAS — 25953-19-9.
ATC — J01DB04.
ATC Vet — QJ01DB04; QJ51DA04.
UNII — IH569L0Y4T.

Pharmacopoeias. In *US.*

USP 36: (Cefazolin). A white to slightly off-white, odourless crystalline powder. Slightly soluble in water, in alcohol, and in methyl alcohol; sparingly soluble in acetone; practically insoluble in chloroform, in dichloromethane, in ether, and in benzene; soluble in dimethylformamide and in pyridine; very slightly soluble in ethyl acetate, in isopropyl alcohol, and in methyl isobutyl ketone. Store in airtight containers.

Cefazolin Sodium *(BANM, USAN, pINNM)*

46083; Cefazolin-Natrium; Cefazolin sodná sůl; Cefazolina sódica; Céfazoline sodique; Cefazolinnatrium; Cefazolinnátrium; Cefazolino natrio druska; Cefazolinum natricum; Cephazolin Sodium; Kefatsolininatrium; Natrii Cefazolinum; Sefazolin Sodyum; SKF-41558; Натрий Цефазолин.

$C_{14}H_{13}N_8NaO_4S_3$=476.5

CAS — 27164-46-1.
ATC — J01DB04.
ATC Vet — QJ01DB04.
UNII — P380M0454Z.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Jpn,* and *US.*

Jpn also includes the pentahydrate.

Ph. Eur. 8: (Cefazolin Sodium). A white or almost white, very hygroscopic powder. It exhibits polymorphism. Freely soluble in water; very slightly soluble in alcohol. A 10% solution in water has a pH of 4.0 to 6.0. Store in airtight containers. Protect from light.

USP 36: (Cefazolin Sodium). A white to off-white, practically odourless, crystalline powder, or a white to off-white solid. Freely soluble in water, in sodium chloride 0.9%, and in glucose solutions; very slightly soluble in alcohol; practically insoluble in chloroform and in ether. pH of a solution in water containing the equivalent of cefazolin 10% is between 4.0 and 6.0. Store in airtight containers.

Incompatibility and stability. Cefazolin sodium has been reported to be incompatible with aminoglycosides and many other drugs. When the pH of a solution exceeds 8.5 there may be hydrolysis and when it is below 4.5 insoluble cefazolin may be precipitated.

References.
1. Nahata MC, Ahalt PA. Stability of cefazolin sodium in peritoneal dialysis solutions. *Am J Hosp Pharm* 1991; 48: 291–2.
2. Wu C-C, *et al.* Stability of cefazolin in heparinized and nonheparinized peritoneal dialysis solutions. *Am J Health-Syst Pharm* 2002; 59: 1537–8.
3. Lin Y-F, *et al.* Stability of cefazolin sodium in icodextrin-containing peritoneal dialysis solution. *Am J Health-Syst Pharm* 2002; 59: 2362, 2364.

Uses and Administration

Cefazolin is a first-generation cephalosporin antibacterial used to treat infections due to susceptible Gram-positive and Gram-negative bacteria (including infections of the biliary, respiratory, and genito-urinary tracts, bones and joints, and of the skin and skin structure) and for surgical infection prophylaxis. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Cefazolin is given as the sodium salt by deep intramuscular injection, by slow intravenous injection over 3 to 5 minutes, or by intermittent or continuous intravenous infusion. Doses are expressed in terms of the equivalent amount of cefazolin; 1.05 g of cefazolin sodium is equivalent to about 1 g of cefazolin. The usual dose is the equivalent of 0.25 to 1 g of cefazolin every 6, 8, or 12 hours. In severe, life-threatening infections 1 to 1.5 g every 6 hours may be given; up to 12 g daily has been used.

For the prophylaxis of infection during surgery, a 1-g dose is given half to one hour before the operation, followed by 0.5 to 1 g during surgery for lengthy procedures. A dose of 0.5 to 1 g is given every 6 to 8 hours postoperatively for 24 hours, or up to 5 days in certain cases.

The dose of cefazolin may need to be modified in patients with renal impairment, see p. 240.1. See also p. 240.1 for details of doses in children, including dose modification for those with renal impairment.

Other routes used for cefazolin sodium include intraperitoneal use in peritoneal dialysis solutions, and intra-ocular injection.

In some countries a modified-release intramuscular formulation of cefazolin sodium with the less soluble dibenzylamine salt of cefazolin, in the ratio of 1:4, has been used.

Administration in children. Cefazolin may be given to children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria. It is given parenterally by deep intramuscular injection, by slow intravenous injection over 3 to 5 minutes, or by intermittent or continuous intravenous infusion. Children over 1 month of age may be given 25 to 50 mg/kg daily in 3 or 4 divided doses, increased in severe infections to a maximum of 100 mg/kg daily.

The dose of cefazolin should be modified in children with renal impairment. After a loading dose the following doses based on creatinine clearance (CC) have been suggested:

- CC 40 to 70 mL/minute: 60% of the normal daily dose in 2 divided doses
- CC 20 to 40 mL/minute: 25% of the normal daily dose in 2 divided doses
- CC 5 to 20 mL/minute: 10% of the normal daily dose every 24 hours

In the USA, the American Academy of Pediatrics[1] suggests that the following doses of cefazolin may be given to neonates:

- for neonates aged ≤ 7 days (irrespective of weight): 25 mg/kg every 12 hours
- for neonates aged 8 to 28 days and weighing ≤ 2 kg: 25 mg/kg every 12 hours
- for neonates aged 8 to 28 days and weighing > 2 kg: 25 mg/kg every 8 hours

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Administration in renal impairment. Parenteral dosage of cefazolin should be reduced in patients with renal impairment and various modifications have been recommended. After a loading dose the licensed product information suggests the following doses based on creatinine clearance (CC):

- CC 55 mL or more per minute: usual doses
- CC 35 to 54 mL/minute: usual doses but at intervals of at least 8 hours
- CC 11 to 34 mL/minute: half the usual dose every 12 hours
- CC 10 mL or less per minute: half the usual dose every 18 to 24 hours

One report[1] indicated that, for patients on long-term haemodialysis, an intravenous dose of 20 mg/kg given 3 times weekly after dialysis maintained therapeutic cefazolin concentrations. Other authors[2] have suggested that critically ill patients receiving intermittent haemodialysis may be given doses of 500 mg to 1 g every 24 hours (after dialysis on dialysis days), or 1 to 2 g intravenously every 48 to 72 hours (after dialysis).

For critically ill patients undergoing continuous renal replacement therapy, an intravenous loading dose of 2 g has been recommended; maintenance doses are as follows:[2]

- continuous venovenous haemofiltration (CVVH): 1 to 2 g every 12 hours
- continuous venovenous haemodialysis (CVVHD) or haemodiafiltration (CVVHDF): 1 g every 8 hours or 2 g every 12 hours

1. Ahern JW, *et al.* Cefazolin dosing protocol for patients receiving long-term hemodialysis. *Am J Health-Syst Pharm* 2003; 60: 178–81.
2. Heintz BH, *et al.* Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy* 2009; 29: 562–77.

Adverse Effects and Precautions

As for Cefalotin Sodium, p. 235.2. Stevens-Johnson syndrome has occurred.

Like cephalosporins with an *N*-methylthiotetrazole side-chain, cefazolin has been associated with hypoprothrombinaemia.

Breast feeding. In a study[1] of 20 women receiving cefazolin, the amount of cefazolin in breast milk was found to be extremely small (equivalent to less than 0.075% of the dose). No adverse effects have been seen in breast-fed infants whose mothers were receiving cefazolin, and the American Academy of Pediatrics considers[2] that it is therefore usually compatible with breast feeding.

1. Yoshioka H, *et al.* Transfer of cefazolin into human milk. *J Pediatr* 1979; 94: 151–2.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)

Effects on the nervous system. References.

1. Manzella JP, *et al.* CNS toxicity associated with intraventricular injection of cefazolin: report of three cases. *J Neurosurg* 1988; 68: 970–1.
2. Martin ES, *et al.* Seizures after intraventricular cefazolin administration. *Clin Pharm* 1992; 11: 104–5.
3. Arkaravichien W, *et al.* Cefazolin induced seizures in hemodialysis patients. *J Med Assoc Thai* 2006; 89: 1981–3.

Sodium content. Each g of cefazolin sodium contains about 2.1 mmol of sodium.

Interactions

Cefazolin contains a methylthiadiazolethiol side-chain; like cephalosporins containing the related *N*-methylthiotetrazole side-chain (see Cefamandole, p. 236.3), it may have the potential to cause a disulfiram-like reaction with alcohol, and enhance the effects of warfarin.

The renal excretion of cefazolin and many other cephalosporins is delayed by probenecid.

Antimicrobial Action

As for Cefalotin Sodium, p. 236.1, although cefazolin is more sensitive to staphylococcal beta-lactamase.

Pharmacokinetics

Cefazolin is poorly absorbed from the gastrointestinal tract and is given by the intramuscular or intravenous routes. After a 500-mg dose given intramuscularly, peak plasma concentrations of 30 micrograms or more per mL occur after 1 hour. About 85% of cefazolin is bound to plasma proteins. The plasma half-life of cefazolin is about 1.8 hours, and is increased in patients with renal impairment. Cefazolin diffuses into bone and into ascitic, pleural, and synovial fluid but not appreciably into the CSF. It crosses the placenta; only low concentrations are detected in breast milk.

Cefazolin is excreted unchanged in the urine, mainly by glomerular filtration with some renal tubular secretion, at least 80% of a dose given intramuscularly being excreted within 24 hours. Peak urine concentrations of more than 2 and 4 mg/mL have been reported after intramuscular doses of 0.5 and 1 g respectively. Probenecid delays excretion. Cefazolin is removed to some extent by haemodialysis.

High biliary concentrations have been reported, although the amount excreted by this route is small.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cefalomicina; Cefamezin; ***Austral.***: Kefzol; ***Austria***: Kefzol; ***Belg.***: Kefzol; ***Braz.***: Ceftrat; Duocef†; Fazolon: Kefazol; ***China***: Saifuning (赛福宁); Xintailin (新泰林); ***Cz.***: Vulmizolin; ***Ger.***: Basocef; ***Gr.***: Biozolin; Kefarin; Kefzol; Tranclocin; Vifazolin; ***India***: Azolin; Cefadin; Cezolin; Ciprid; Orizolin; Ozolin; Reflin; ***Indon.***: Biozolin†; Cefazol; Evalin; ***Israel***: Cefamezin†; Kefazin; Pan-Cefazolin; ***Ital.***: Acef; Cefamezin; Cefazil; Cromezin; Nefazol; Recef; ***Jpn***: Cefamezin; Otsuka Cez†; ***Neth.***: Kefzol; Servazolin†; ***NZ***: Zepilen; ***Philipp.***: Biocef; Cefazole; Cefazovit; Cifoxim; Cizo; Cloviz; Fazol; Fazonil; Fonvicol; Hazolin; Ilozef; Leklin; Lozan; Lupex†; Maxcep†; Novazef; Oryan; Plezolin; Samarial; Stancef; Suporin; Tefazol; Zalulin; Zofadep; Zolival; ***Pol.***: Biofazolin; Tarfazolin; ***Port.***: Cefamezin†; Kurgan†; ***Rus.***: Cefamezin (Цефамезин); Cezolin (Цезолин); Ifizol (Ифизол)†; Intrazoline (Интразолин); Kefzol (Кефзол); Lyzolin (Лизолин); Nacef (Нацеф); Orizolin (Оризолин); Orpin (Орпин); Reflin (Рефлин)†; Totacef (Тотацеф); Zolfin (Золфин); Zolin (Золин); ***S.Afr.***: Cefacidal†; Izacef†; Kefzol; Ranzol; ***Singapore***: Cefarizon; Cezolin; ***Spain***: Areuzolin†; Intrazolina; Kurgan; Tasep; Teclazolina; Zolival; ***Switz.***: Kefzol; ***Thai.***: Cefalin†; Cefamezin; Cefazillin; Cefazol; Cefzolin; Fazolin; Zefa; Zolicef†; Zolimed†; ***Turk.***: Cefamezin; Cefozin; Cezol; Equizolin; Iespor; Maksiporin; Rebasin; Sefamax; Sefazol; ***Venez.***: Cefacidal; Cefarizon; Cellozina.

Pharmacopoeial Preparations
BP 2014: Cefazolin Injection;
USP 36: Cefazolin for Injection; Cefazolin Injection; Cefazolin Ophthalmic Solution.

Cefbuperazone *(USAN, rINN)*

BMY-25182; Cefbuperazona; Cefbupérazone; Cefbuperazonum; T-1982; Цефбуперазон.

7-[(2*R*,3*S*)-2-(4-ethyl-2,3-dioxopiperazin-1-ylcarboxamido)-3-hydroxybutyramido]-7-methoxy-3-(1-methyl-1*H*-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid.

$C_{22}H_{29}N_9O_9S_2$=627.6

CAS — 76610-84-9.

UNII — T0785J3X40.

Cefbuperazone Sodium *(rINNM)*

Cefbuperazona de sodio; Cefbupérazone Sodique; Natrii Cefbuperazonum; Натрий Цефбуперазон.

$C_{22}H_{28}N_9NaO_9S_2$=649.6

UNII — 1VX59V96BS.

Pharmacopoeias. In *Jpn*.

Profile

Cefbuperazone is a cephamycin antibacterial similar to cefoxitin (p. 248.2) but with an *N*-methylthiotetrazole side-chain like cefamandole (p. 236.2). It is given by injection as the sodium salt. Its spectrum of activity includes Enterobacteriaceae, but more especially anaerobic bacteria such as *Bacteroides fragilis*. Cefbuperazone does not appear to be active against cefoxitin-resistant strains of *B. fragilis*.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Tomiporan.

Cefcapene Pivoxil Hydrochloride *(rINNM)*

Cefcapène Pivoxil, Chlorhydrate de; Cefcapeni Pivoxilis Hydrochloridum; Cefcapeno pivoxilo, hidrocloruro de; Hidrocloruro de cefcapeno pivoxilo; S-1006 (cefcapene); S-1108; Цефкапена Пивоксила Гидрохлорид.

Pivaloyloxymethyl (+)-(6*R*,7*R*)-7-[(*Z*)-2-(2-amino-4-thiazolyl)-2-pentenamido]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid carbamate monohydrochloride monohydrate.

$C_{23}H_{29}N_5O_8S_2.HCl.H_2O$=622.1

CAS — 135889-00-8 (cefcapene); 105889-45-0 (cefcapen pivoxil); 147816-23-7 (anhydrous cefcapene pivoxil hydrochloride); 147816-24-8 (cefcapene pivoxil hydrochloride).

ATC — J01DD17.

ATC Vet — QJ01DD17.

UNII — 5J77167P9E.

Pharmacopoeias. In *Jpn*.

Profile

Cefcapene is an oral cephalosporin antibacterial given orally as the pivaloyloxymethyl ester, cefcapene pivoxil hydrochloride.

For reference to carnitine deficiency occurring with some pivaloyloxymethyl esters, see Pivampicillin, p. 344.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Flomox.

Cefdinir *(BAN, USAN, rINN)*

Cefdinirum; CI-983; FK-482; Kefdiniir; Цефдинир.

(-)-(6*R*,7*R*)-7-[2-(2-Amino-4-thiazolyl)glyoxylamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-(*Z*)-oxime; 7-[(2-Amino-1,3-thiazol-4-yl)-2-[(*Z*)-hydroxyimino]acetamido]-3-vinylcephem-4-carboxylic acid.

$C_{14}H_{13}N_5O_5S_2$=395.4

CAS — 91832-40-5.

ATC — J01DD15.

ATC Vet — QJ01DD15.

UNII — CI0FA063WC.

Pharmacopoeias. In *Chin.*, *Jpn*, and *US*.

USP 36: (Cefdinir). A white to light yellow crystalline powder. Practically insoluble in water, in alcohol, and in ether; sparingly soluble in 0.1M phosphate buffer (pH 7) solution. Store in airtight containers. Protect from light.

Uses and Administration

Cefdinir is a third-generation oral cephalosporin antibacterial used to treat infections due to susceptible Gram-positive and Gram-negative bacteria, including infections of the respiratory tract and of the skin and skin structures. For details of infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Cefdinir is given orally in a usual dose of 600 mg daily as a single dose or in two divided doses. Twice daily dosing should be used for pneumonia and skin infections.

The dose of cefdinir may need to be reduced in patients with renal impairment, see p. 241.1. See also p. 240.3 for details of doses in children.

Reviews.

1. Guay DRP. Cefdinir: an expanded-spectrum oral cephalosporin. *Ann Pharmacother* 2000; 34: 1469–77.
2. Guay DR, *et al.* Cefdinir: an advanced-generation, broad-spectrum oral cephalosporin. *Clin Ther* 2002; 24: 473–89.
3. Perry CM, Scott LJ. Cefdinir: a review of its use in the management of mild-to-moderate bacterial infections. *Drugs* 2004; 64: 1433–64.
4. Sader HS, Jones RN. Cefdinir: an oral cephalosporin for the treatment of respiratory tract infections and skin and skin structure infections. *Expert Rev Anti Infect Ther* 2007; 5: 29–43. Correction. *ibid.*: 754. [dose error]

Administration in children. Cefdinir may be given orally to children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria. Children from 6 months of age may be given 14 mg/kg daily as a single dose or in two divided doses (to a maximum daily dose of 600 mg).

For details of doses in children with renal impairment see p. 241.1.

Administration in renal impairment. Oral doses of cefdinir should be reduced to 300 mg once daily in patients with renal impairment whose creatinine clearance is less than 30 mL/minute.

The dose of oral cefdinir should be reduced in *children* with renal impairment (creatinine clearance less than 30 mL/minute) to 7 mg/kg given once daily, up to a maximum dose of 300 mg.

Cefdinir is removed by haemodialysis; therefore patients on chronic haemodialysis should initially be given a dose of 300 mg (or 7 mg/kg) every alternate day. A dose of 300 mg (or 7 mg/kg) should be given at the conclusion of each haemodialysis session. Subsequent doses are then given every alternate day.

Adverse Effects and Precautions

As for Cefalotin Sodium, p. 235.2. There have been reports of reddish stools in patients given cefdinir with iron supplements (see also Interactions, p. 241.1).

Interactions

Absorption of cefdinir is decreased by antacids or iron supplements and doses should be separated by an interval of at least 2 hours. Probenecid reduces the renal excretion of cefdinir.

Iron. A report[1] of red stools in an infant given cefdinir while being fed with an infant formula containing supplemental iron. It was considered important to be aware of the interaction because of the risk that it might be mistaken for a sign of gastrointestinal bleeding.

1. Lancaster J, *et al.* Nonbloody, red stools from coadministration of cefdinir and iron-supplemented infant formulas. *Pharmacotherapy* 2008; **28**: 678–81.

Antimicrobial Action

As for Cefixime, p. 243.1. However, cefdinir is reported to be much more active *in vitro* than cefixime against *Staphylococcus aureus*, but not meticillin-resistant strains, and it is less active against some Enterobacteriaceae.

Pharmacokinetics

Cefdinir is absorbed from the gastrointestinal tract and peak plasma concentrations occur 2 to 4 hours after an oral dose. Oral bioavailability has been estimated to range from 16 to 25%. It is widely distributed into tissues and is 60 to 70% bound to plasma proteins. Cefdinir is not appreciably metabolised and is excreted in the urine with an elimination half-life of 1.7 hours.

Cefdinir is removed by dialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Cefzon (全泽复); Xi Fu Ni (希福尼); *India*: Adcef; Adinir; Aldinir; Cednir; Cefcas; Cefdiel; Idinir; Kefdure; Kefnir; Maxicef-O; Oceph; Sefdin; *Indon.*: Omnicef; *Jpn*: Cefzon; *Malaysia*: Cefdiel; *Mex.*: Omnicef; *Philipp.*: Cefnaxl; Nirocef; Omicef; Onicef; *Thai.*: Omnicef; Samnir; *Turk.*: Ceftinex; Cempes; *USA*: Omnicef.

Multi-ingredient Preparations. *India*: Cefrine.

Pharmacopoeial Preparations
USP 36: Cefdinir Capsules.

Cefditoren Pivoxil *(rINNM)*

Cefditorène, Pivoxil de; Cefditoreni Pivoxil; Cefditoreno pivoxilo; ME-1206 (cefditoren); ME-1207; Цефдиторена Пивоксил.

Pivaloyloxymethyl (+)-(6*R*,7*R*)-7-[2-(2-Amino-4-thiazolyl)glyoxylamido]-3-[(*Z*)-2-(4-methyl-5-thiazolyl)vinyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid 7-(*Z*)-(*O*-methyloxime).

$C_{25}H_{28}N_6O_7S_3$=620.7

CAS — 104145-95-1 (cefditoren); 117467-28-4 (cefditoren pivoxil).

ATC — J01DD16.

ATC Vet — QJ01DD16.

UNII — 78THA212DH.

Pharmacopoeias. In *Jpn*.

Uses and Administration

Cefditoren is a third-generation oral cephalosporin antibacterial used to treat infections due to susceptible Gram-positive and Gram-negative bacteria, including infections of the respiratory tract and of the skin and skin structures. For details of infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Cefditoren is given orally as the pivaloyloxymethyl ester, cefditoren pivoxil, but doses are expressed in terms of cefditoren; 245 mg of cefditoren pivoxil is equivalent to about 200 mg of cefditoren. A usual dose is 200 to 400 mg given twice daily.

For details of reduced doses to be used in patients with moderate to severe renal impairment, see p. 241.2.

Reviews.

1. Wellington K, Curran MP. Cefditoren pivoxil: a review of its use in the treatment of bacterial infections. *Drugs* 2004; **64**: 2597–2618.
2. Hernández-Martín J, *et al.* Cefditoren pivoxilo: una nueva cefalosporina oral para infecciones de vías respiratorias y de piel y tejidos blandos. *Rev Esp Quimioter* 2006; **19**: 231–46.
3. Biedenbach DJ, Jones RN. Update of cefditoren activity tested against community-acquired pathogens associated with infections of the respiratory tract and skin and skin structures, including recent pharmacodynamic considerations. *Diagn Microbiol Infect Dis* 2009; **64**: 202–12.

Administration in renal impairment. Oral doses of cefditoren pivoxil should be reduced in patients with moderate to severe renal impairment according to creatinine clearance (CC):

- CC 30 to 49 mL/minute: the dose should not exceed 200 mg twice daily
- CC less than 30 mL/minute: the dose should be 200 mg once daily.

Adverse Effects and Precautions

As for Cefalotin, p. 235.2.

The most frequently reported adverse effects of cefditoren are gastrointestinal disturbances, especially diarrhoea.

For reference to carnitine deficiency with some pivaloyloxymethyl esters, see Pivampicillin, p. 344.1.

Interactions

Absorption of cefditoren after oral doses is decreased by antacids or histamine H_2-receptor antagonists. Probenecid reduces the renal excretion of cefditoren.

Antimicrobial Action

As for Cefixime, p. 243.1. Cefditoren also has activity against *Staphylococcus aureus*.

Pharmacokinetics

Cefditoren pivoxil is absorbed from the gastrointestinal tract and is hydrolysed to cefditoren by esterases to release active cefditoren in the bloodstream. Peak plasma concentrations average 1.8 micrograms/mL in fasting subjects 1.5 to 3 hours after a 200-mg dose. Bioavailability is about 14% in fasting subjects and is increased when cefditoren pivoxil is given with a high-fat meal. Plasma protein binding is reported to be 88%. The plasma half-life is about 1.6 hours and is prolonged in patients with renal impairment.

Cefditoren is not appreciably metabolised and is excreted mainly in the urine by glomerular filtration and tubular secretion. It is removed by haemodialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Meiact (美爱克); *Gr.*: Spectracef; *India*: Cefdicare; Cefditran; Ceftorin; *Indon.*: Meiact; *Ital.*: Giasion; *Jpn*: Meiact; *Mex.*: Spectracef; *Port.*: Meiact; Spectracef; *Spain*: Meiact; Spectracef; Telo; *Thai.*: Meiact; *Turk.*: Meiact; Spektracef; *USA*: Spectracef.

Cefepime Hydrochloride

(BANM, USAN, rINNM)

BMY-28142 (cefepime); Cefepima, hidrocloruro de; Céfépime, Chlorhydrate de; Céfépime, dichlorhydrate de; Cefepime Dihydrochloride; Cefepimi dihydrochloridum; Cefepimi Hydrochloridum; Hidrocloruro de cefepima; Sefepim Hidroklorür; Цефепима Гидрохлорид.

(6*R*-[6α,7β(*Z*)])-1-[(7-[[(2-Amino-4-thiazolyl)-(methoxyimino) acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methylpyrrolidinium chloride monohydrochloride monohydrate; 7-[(2-Amino-1,3-thiazol-4-yl)-2-[(*Z*)-methoxyimino]acetamido]-3-(1-methylpyrrolidiniomethyl)-3-cephem-4-carboxylate hydrochloride.

$C_{19}H_{25}ClN_6O_5S_2.HCl.H_2O$=571.5

CAS — 88040-23-7 (cefepime); 123171-59-5 (cefepime hydrochloride monohydrate).

ATC — J01DE01.

ATC Vet — QJ01DE01.

UNII — I8X1O0607P (cefepime hydrochloride monohydrate); 2A1O4FSN0C (anhydrous cefepime hydrochloride).

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Cefepime Dihydrochloride Monohydrate). A white or almost white, crystalline powder. Freely soluble in water and in methyl alcohol; practically insoluble in dichloromethane. Protect from light.

USP 36: (Cefepime Hydrochloride). A white to off-white, nonhygroscopic, crystalline powder. Freely soluble in water. Store in airtight containers. Protect from light.

Incompatibility and stability. References.

1. Stewart JT, *et al.* Stability of cefepime hydrochloride injection in polypropylene syringes at -20 degreesC, 4 degreesC, and 22-24 degreesC. *Am J Health-Syst Pharm* 1999; **56**: 457–9.
2. Stewart JT, *et al.* Stability of cefepime hydrochloride in polypropylene syringes. *Am J Health-Syst Pharm* 1999; **56**: 1134.
3. Williamson JC, *et al.* Stability of cefepime in peritoneal dialysis solution. *Ann Pharmacother* 1999; **33**: 906–9.
4. Baririan N, *et al.* Stability and compatibility study of cefepime in comparison with ceftazidime for potential administration by continuous infusion under conditions pertinent to ambulatory treatment of cystic fibrosis patients and to administration in intensive care units. *J Antimicrob Chemother* 2003; **51**: 651–8.
5. Trissel LA, Xu QA. Stability of cefepime hydrochloride in AutoDose infusion system bags. *Ann Pharmacother* 2003; **37**: 804–7.

Uses and Administration

Cefepime is a fourth-generation parenteral cephalosporin antibacterial used in the treatment of infections due to susceptible Gram-positive and Gram-negative bacteria, including those of the abdomen, urinary tract, respiratory tract, and skin and skin structures. It is effective against *Pseudomonas aeruginosa* and may be given empirically for febrile neutropenia. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Cefepime is given as the hydrochloride by deep intramuscular injection, or intravenously by infusion over at least 30 minutes. Doses are expressed in terms of the equivalent amount of cefepime; 1.19 g of cefepime hydrochloride is equivalent to about 1 g of cefepime. The usual dose is 1 to 2 g daily in 2 divided doses for mild to moderate infections, increased to 4 g daily in 2 divided doses in severe infections, although up to 6 g daily in 3 divided doses has been given for febrile neutropenia.

The dose of cefepime may need to be reduced in patients with renal impairment, see p. 241.3. See also p. 241.3 for details of doses in children, including dose recommendations for those with renal impairment.

Reviews.

1. Various. Cefepime: a β-lactamase-stable extended-spectrum cephalosporin. *J Antimicrob Chemother* 1993; **32** (suppl B): 1–214.
2. Barradell LB, Bryson HM. Cefepime: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1994; **47**: 471–505.
3. Okamoto MP, *et al.* Cefepime: a new fourth-generation cephalosporin. *Am J Hosp Pharm* 1994; **51**: 463–77.
4. Wynd MA, Paladino JA. Cefepime: a fourth-generation parenteral cephalosporin. *Ann Pharmacother* 1996; **30**: 1414–24.
5. Wong-Beringer A. Treating serious infections: focus on cefepime. *Pharmacotherapy* 2004; **24**: 2165–235.
6. Roberts JA, *et al.* Cefepime versus ceftazidime: considerations for empirical use in critically ill patients. *Int J Antimicrob Agents* 2007; **29**: 117–28.

Administration in children. Cefepime may be given to children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria. Cefepime is given by deep intramuscular injection, or intravenously by infusion over at least 30 minutes. In the USA, the American Academy of Pediatrics (AAP)[1] suggests a dose of 30 mg/kg every 12 hours may be given to neonates; the dose may be increased to 50 mg/kg for *Pseudomonas* infections. For those beyond the neonatal period, the AAP suggests a dose of 100 mg/kg daily in 2 divided doses for the treatment of mild to moderate infections; up to 150 mg/kg daily, in 2 or 3 divided doses, may be given for the treatment of severe infections. US licensed product information suggests similar doses for children aged 2 months and over. The total dose should not exceed the recommended adult dosage (see above).

US licensed product information recommends that for children with renal impairment these doses of cefepime should be reduced by similar proportions to reductions in adults (see p. 241.3).

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Administration in renal impairment. Parenteral dosage of cefepime should be modified in renal impairment. After a normal first dose the maintenance dosage should be adjusted according to the patient's creatinine clearance (CC) and the severity of the infection:

- CC 30 to 60 mL/minute: 0.5 to 2 g every 24 hours (2 g every 12 hours for febrile neutropenia)
- CC 11 to 29 mL/minute: 0.5 to 1 g every 24 hours (2 g every 24 hours for febrile neutropenia)
- CC 10 mL/minute or less: 250 to 500 mg every 24 hours (1 g every 24 hours for febrile neutropenia)

Patients undergoing haemodialysis should be given a dose of 1 g on the first day of treatment, followed by 500 mg daily; the dose should be given after haemodialysis on those days. A dose of 1 g daily should be used for febrile neutropenia. Patients undergoing continuous ambulatory peritoneal

dialysis should receive normal recommended doses at intervals of 48 hours. A dose of 2 g every 48 hours is used for febrile neutropenia.

For critically ill patients undergoing continuous renal replacement therapy, a loading dose of 2 g and the following maintenance doses have been recommended:[1]

- continuous venovenous haemofiltration (CVVH): 1 to 2 g every 12 hours
- continuous venovenous haemodialysis (CVVHD) and haemodiafiltration (CVVHDF): 1 g every 8 hours or 2 g every 12 hours

1. Heintz BH, *et al.* Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy* 2009; 29: 562–77.

Adverse Effects and Precautions

As for Cefalotin Sodium, p. 235.2.

The safety of cefepime has been reviewed.[1-3] A meta-analysis[2] of studies involving cefepime suggested that there might be an increased risk of all-cause mortality compared with other beta-lactams. The FDA subsequently announced that it would review safety data to further evaluate the risk of death associated with cefepime use.[4] In June 2009, after this analysis, the FDA issued a statement that no statistically significant increase in mortality for cefepime-treated patients compared to comparator-treated patients was noted and that cefepime remains an appropriate therapy for its approved indications.[5]

1. Neu HC. Safety of cefepime: a new extended-spectrum parenteral cephalosporin. *Am J Med* 1996; 100 (suppl 6A): 68S–75S.
2. Yahav D, *et al.* Efficacy and safety of cefepime: a systematic review and meta-analysis. *Lancet Infect Dis* 2007; 7: 338–48.
3. Drago L, De Vecchi E. The safety of cefepime in the treatment of infection. *Expert Opin Drug Safety* 2008; 7: 377–87.
4. FDA. Early communication about an ongoing safety review: cefepime (marketed as Maxipime) (issued 14th November 2007). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm070496.htm (accessed 20/07/10)
5. FDA. Information for healthcare professionals: cefepime (marketed as Maxipime): (issued 17th June 2009). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm167254.htm (accessed 19/06/09)

Effects on the nervous system. References to neurotoxicity,[1-10] sometimes manifesting as nonconvulsive status epilepticus, associated with use of cefepime (particularly but not exclusively in patients with impaired renal function).

1. Chow KM, *et al.* Retrospective review of neurotoxicity induced by cefepime and ceftazidime. *Pharmacotherapy* 2003; 23: 369–73.
2. Ferrara N, *et al.* Neurotoxicity induced by cefepime in a very old hemodialysis patient. *Clin Nephrol* 2003; 59: 388–90.
3. Dakdouki GK, Al-Awar GN. Cefepime-induced encephalopathy. *Int J Infect Dis* 2004; 8: 59–61.
4. Alpay H, *et al.* Cefepime-induced non-convulsive status epilepticus in a peritoneal dialysis patient. *Pediatr Nephrol* 2004; 19: 445–7.
5. Abanades S, *et al.* Reversible coma secondary to cefepime neurotoxicity. *Ann Pharmacother* 2004; 38: 606–8.
6. Capparelli FJ, *et al.* Cefepime- and cefixime-induced encephalopathy in a patient with normal renal function. *Neurology* 2005; 65: 1840.
7. Maganti R, *et al.* Nonconvulsive status epilepticus due to cefepime in a patient with normal renal function. *Epilepsy Behav* 2006; 8: 312–4.
8. Lam S, Gomolin IH. Cefepime neurotoxicity: case report, pharmacokinetic considerations, and literature review. *Pharmacotherapy* 2006; 26: 1169–74.
9. Sonck J, *et al.* The neurotoxicity and safety of treatment with cefepime in patients with renal failure. *Nephrol Dial Transplant* 2008; 23: 966–70.
10. Garces EO, *et al.* Renal failure is a risk factor for cefepime-induced encephalopathy. *J Nephrol* 2008; 21: 526–34.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cefepime as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Antimicrobial Action

Cefepime is a fourth-generation cephalosporin and is active against many Gram-positive and Gram-negative aerobic organisms. Against Gram-positive cocci, its activity is similar to that of cefotaxime (p. 246.3) and includes staphylococci (but not meticillin-resistant *Staphylococcus aureus*) and streptococci. Against Enterobacteriaceae, it has a broader spectrum of activity than other cephalosporins, including activity against organisms producing chromosomally mediated beta-lactamases such as *Enterobacter* spp. and *Proteus vulgaris*. Against *Pseudomonas aeruginosa*, it has similar or slightly less activity than ceftazidime (p. 253.3), although it may be active against some strains resistant to ceftazidime.

Pharmacokinetics

Cefepime is given by injection as the hydrochloride. It is rapidly and almost completely absorbed on intramuscular injection and mean peak plasma concentrations of about 14 and 30 micrograms/mL occur about 1.5 hours after doses of 500 mg and 1 g respectively. Within 30 minutes of similar intravenous doses, peak plasma concentrations are 40 and 80 micrograms/mL respectively. The plasma half-life of cefepime is about 2 hours and is prolonged in patients with renal impairment. About 20% of cefepime is bound to plasma proteins.

Cefepime is widely distributed in body tissues and fluids. High concentrations occur in bile. Low concentrations have been detected in breast milk.

Cefepime is eliminated principally by the kidneys and about 85% of a dose is recovered unchanged in the urine. Cefepime is substantially removed by haemodialysis.

References.
1. Okamoto MP, *et al.* Cefepime clinical pharmacokinetics. *Clin Pharmacokinet* 1993; 25: 88–102.
2. Rybak M. The pharmacokinetic profile of a new generation of parenteral cephalosporin. *Am J Med* 1996; 100 (suppl 6A): 39S–44S.
3. Reed MD, *et al.* Pharmacokinetics of intravenously and intramuscularly administered cefepime in infants and children. *Antimicrob Agents Chemother* 1997; 41: 1783–7.
4. Allaouchiche B, *et al.* Pharmacokinetics of cefepime during continuous venovenous hemodiafiltration. *Antimicrob Agents Chemother* 1997; 41: 2424–7.
5. Blumer JL, *et al.* Review of the pharmacokinetics of cefepime in children. *Pediatr Infect Dis J* 2001; 20: 337–42.
6. Capparelli E, *et al.* Population pharmacokinetics of cefepime in the neonate. *Antimicrob Agents Chemother* 2005; 49: 2760–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cefimen-K; Maxcef; Rivepime; ***Austral.***: Maxipime; ***Austria***: Maxipime; ***Belg.***: Maxipime; ***Braz.***: Clocef; Maxcef; Nepecef; Unifepim; ***Canad.***: Maxipime; ***Chile***: Maxipime; Pozineg; ***China***: Bo Shuai (博帅); Bo Zhi (博治); Da Li Neng (达力能); Heng Su (恒苏); Ka Luo Xin (卡洛欣); Kai Xin (凯欣); Laibixin (来比信); Li Si Ping (立斯平); Ling Di (灵迪); Luo Xin Wei (罗欣威); Maxipime (马斯平); Pai Nai Xin (派奈欣); Shi Rui Ping (士瑞平); Xian Ke Nuo (先可诺); XinLiWei (信力威); Ying Lan (英兰); ***Cz.***: Maxipime; ***Fin.***: Maxipime†; ***Fr.***: Axepim; ***Ger.***: Maxipime; ***Gr.***: Anticepim; Gencef; Maxinject; Maxipime; Verapime; Zefipime; ***Hong Kong***: Maxipime; ***Hung.***: Maxipime; ***India***: Adpime; Biopime; C-Pime; Cadpime; Calpime; Ceficad; Cefpime; Cefudix; Cepime; Chase; Effimax; Forpar; Inpime; Insipim; Ipacare; Ivipime; Kampi; Kefage; Kingcef; KPM; Leepime; Mapime; Maxicef; Maxipime; Megapime; Micropime; Neutrapime; Nitipime; Novapime; Orpime; ***Indon.***: Actacef; Biocepime; Caprifim; Ceforim; Emax; Exepime; Interpim; Macef; Maxicef; Maxilan; Maximer; Maxipime†; Procepim; Rapime; Rimax; Sandocef; Sopime; Vipime; ***Ital.***: Cepim; Cepimex; Maxipime; ***Malaysia***: Maxipime; Megapime; ***Mex.***: Imation; Maxef; Maxipime; ***NZ***: Maxipime; ***Philipp.***: Axera; Cepimax; Dimipra; Hapimax; Medipime; Pimcep; Pozineg; Sanpime; Vipefime; Zepim; Zepime; ***Pol.***: Maxipime; ***Port.***: Maxipime; ***Rus.***: Cepim (Цепим); Efepim (Эфипим); Maxipime (Максипим); Maxycef (Максицеф); Movizar (МОВИЗАР); ***S.Afr.***: Maxipime; ***Singapore***: Maxipime; ***Spain***: Maxipime; ***Swed.***: Maxipime†; ***Thai.***: Cefamax; Maxipime; Megapime; Orpime†; Pime; Sefpime; ***Turk.***: Ekipim; Maxipime; Unisef; ***UAE***: Qpime; ***Ukr.***: Cebopime (Цебопим); Efipime (Эфипим); Maxinort (Максинорт); Megapim (Мегапим); Pikcef (Пикцеф); Quadrocef (Квадроцеф); Quartacef (Кварташеф)†; ***USA***: Maxipime; ***Venez.***: Maxipime.

Multi-ingredient Preparations. ***India***: C-Pime-T; Magnova; Mikapime; Nicpime-AM.

Pharmacopoeial Preparations
USP 36: Cefepime for Injection.

Cefetamet (*USAN, rINN*)

Céfétamet; Cefetametum; LY-097964; Ro-15-8074; Цефетамет.

(*Z*)-7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methyl-3-cephem-4-carboxylic acid.

$C_{14}H_{15}N_5O_5S_2$=397.4

CAS — 65052-63-3 (cefetamet).
ATC — J01DD10.
ATC Vet — QJ01DD10.
UNII — 4R5TV783X3.

Cefetamet Pivoxil Hydrochloride (*rINNM*)

Céfétamet Pivoxil, Chlorhydrate de; Cefetamet pivoxilo, hidrocloruro de; Cefetameti Pivoxili Hydrochloridum; Cefetametpivoxilhydroklorid; Cefetametum Pivoxili Hydrochloridum; Hidrocloruro de cefetamet pivoxilo; Kefetameettipivoksiilihydrokloridi; Ro-15-8075 (cefetamet pivoxil); Цефетамета Пивоксила Гидрохлорид.

Cefetamet pivaloyloxymethyl hydrochloride.

$C_{20}H_{25}N_5O_7S_2$.HCl=548.0

CAS — 65243-33-6 (cefetamet pivoxil); 111696-23-2 (cefetamet pivoxil hydrochloride).
ATC — J01DD10.
ATC Vet — QJ01DD10.
UNII — 2YE9732GFU.

Profile

Cefetamet is a third-generation cephalosporin antibacterial similar to cefixime (p. 242.3). It has been given orally as the hydrochloride of the pivaloyloxymethyl ester, cefetamet pivoxil hydrochloride, which is hydrolysed to cefetamet *in vivo*. The usual dose is 500 mg twice daily.

For reference to carnitine deficiency occurring with some pivaloyloxymethyl esters, see Pivampicillin, p. 344.1.

Reviews.
1. Bryson HM, Brogden RN. Cefetamet pivoxil: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1993; 45: 589–621.
2. Blouin RA, Stoeckel K. Cefetamet pivoxil clinical pharmacokinetics. *Clin Pharmacokinet* 1993; 25: 172–88.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: An Su Mei (安素美); Ansaitamei (安塞他美); Hua Xian Mei (华仙美); Kang Di Xin (康迪欣); Kang Mai Xin (康迈欣); Li Xin Mei (力欣美); Sai Fu Mei (赛福美); Tepuxin (特普欣); Wei Rui (威锐); Zhen Liang (珍良); ***Gr.***: Globocef; ***India***: Altamet; Cepime-O.

Cefixime (*BAN, USAN, rINN*)

Cefiksimas; Cefixim; Cefixim trihydrát; Cefixima; Céfixime; Cefiximum; Cefiximum Trihydricum; CL-284635; FK-027; FR-17027; Kefiksiimi; Sefiksim; Цефиксим.

(*Z*)-7-[2-(2-Aminothiazol-4-yl)-2-(carboxymethoxyimino) acetamido]-3-vinyl-3-cephem-4-carboxylic acid trihydrate.

$C_{16}H_{15}N_5O_7S_2.3H_2O$=507.5

CAS — 79350-37-1.
ATC — J01DD08.
ATC Vet — QJ01DD08.
UNII — 97I1C92E55.

Pharmacopoeias. In *Eur.* (see p. vii) and *US. Jpn* includes the anhydrous substance.

Ph. Eur. 8: (Cefixime). A white or almost white, slightly hygroscopic, powder. Slightly soluble in water; sparingly soluble in dehydrated alcohol; practically insoluble in ethyl acetate; freely soluble in methyl alcohol. A 5% suspension in water has a pH of 2.6 to 4.1. Store in airtight containers. Protect from light.

USP 36: (Cefixime). A white to light yellow crystalline powder. Practically insoluble in water, in ether, in ethyl acetate, and in hexane; slightly soluble in alcohol, in acetone, and in glycerol; soluble in methyl alcohol and in propylene glycol; very slightly soluble in 70% sorbitol and in octanol. pH of a solution in water containing the equivalent of cefixime 0.07% is between 2.6 and 4.1. Store in airtight containers.

Uses and Administration

Cefixime is generally classified as a third-generation cephalosporin antibacterial and is given orally to treat infections due to susceptible Gram-positive and Gram-negative bacteria, including gonorrhoea and infections of the respiratory and urinary tracts. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Cefixime is available as the trihydrate and doses are expressed in terms of anhydrous cefixime; 1.12 g of cefixime trihydrate is equivalent to about 1 g of anhydrous cefixime. It is given orally in doses of 200 to 400 mg daily as a single dose or in two divided doses; the higher dose is recommended in the USA. A single 400-mg dose is given for uncomplicated gonorrhoea.

The dose of cefixime may need to be reduced in patients with renal impairment, see p. 242.3. See also p. 242.3 for doses in children.

General references.
1. Leggett NJ, *et al.* Cefixime. *DICP Ann Pharmacother* 1990; 24: 489–95.
2. Adam D, Wallace RJ, eds. Symposium on cefixime. *Drugs* 1991; 42 (suppl 4): 1–32.
3. Markham A, Brogden RN. Cefixime: a review of its therapeutic efficacy in lower respiratory tract infections. *Drugs* 1995; 49: 1007–22.
4. Hamilton-Miller JM. Overview of cefixime use in community-acquired infections. *Clin Microbiol Infect* 2000; 6 (suppl 3): 79–81.
5. Verhoef J, Gillissen A. Resistant Haemophilus influenzae in community-acquired respiratory tract infections: a role for cefixime. *Int J Antimicrob Agents* 2003; 21: 501–9.

Administration in children. Cefixime may be given orally to children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria. Children over 6 months and under 50 kg may be given 8 mg/kg daily as a single dose or in two divided doses.

Administration in renal impairment. Oral doses of cefixime should be reduced in patients with moderate to severe renal impairment according to creatinine clearance (CC). UK licensed product information recommends that a dose of 200 mg daily should not be exceeded in patients

with a CC less than 20 mL/minute, as well as those on continuous ambulatory peritoneal dialysis or haemodialysis. In the USA licensed product information recommends doses adjusted as follows:

- CC 60 mL/minute or more: the usual dose of 400 mg daily
- CC 21 to 59 mL/minute or those on haemodialysis: 300 mg daily
- CC less than 20 mL/minute or those on continuous ambulatory peritoneal dialysis: 200 mg daily

Adverse Effects and Precautions

As for Cefalotin Sodium, p. 235.2.

The most frequently reported adverse effects of cefixime are gastrointestinal disturbances, especially diarrhoea. Cefixime should be stopped if diarrhoea is severe.

Although cefixime does not have the *N*-methylthiotetrazole side-chain usually associated with hypoprothrombinaemia increases in prothrombin times have occurred in a few patients.

Antibiotic-associated colitis. For reports of diarrhoea and pseudomembranous colitis associated with cefixime, see Cefalotin, p. 235.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cefixime as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Interactions

Care should be exercised in patients receiving anticoagulants and cefixime due to the possibility that cefixime may increase prothrombin times (see above).

Antimicrobial Action

Cefixime is bactericidal and is stable to hydrolysis by many beta-lactamases. It has a mode of action and spectrum of activity similar to those of the third-generation cephalosporin cefotaxime (p. 246.3), but some Enterobacteriaceae are less susceptible to cefixime. *Haemophilus influenzae, Moraxella catarrhalis* (*Branhamella catarrhalis*), and *Neisseria gonorrhoeae* are sensitive, including penicillinase-producing strains. Of the Gram-positive bacteria, streptococci are sensitive to cefixime but most strains of staphylococci, enterococci, and *Listeria* spp. are not.

Enterobacter spp., *Pseudomonas aeruginosa*, and *Bacteroides* spp. are resistant to cefixime.

Pharmacokinetics

Only 40 to 50% of an oral dose of cefixime is absorbed from the gastrointestinal tract, whether taken before or after meals, although the rate of absorption may be decreased in the presence of food. Cefixime is better absorbed from oral suspension than from tablets. Absorption is fairly slow; peak plasma concentrations of 2 to 3 micrograms/mL and 3.7 to 4.6 micrograms/mL have been reported between 2 and 6 hours after single doses of 200 and 400 mg, respectively. The plasma half-life is usually about 3 to 4 hours and may be prolonged when there is renal impairment. About 65% of cefixime is bound to plasma proteins.

Information on the distribution of cefixime in body tissues and fluids is limited. It crosses the placenta. Relatively high concentrations may occur in bile and urine. About 20% of an oral dose (or 50% of an absorbed dose) is excreted unchanged in the urine within 24 hours. Up to 60% may be eliminated by nonrenal mechanisms; there is no evidence of metabolism but some is probably excreted into the faeces from bile. It is not substantially removed by dialysis.

References.

1. Brittain DC, *et al.* The pharmacokinetic and bactericidal characteristics of oral cefixime. *Clin Pharmacol Ther* 1985; 38: 590–4.
2. Guay DRP, *et al.* Pharmacokinetics of cefixime (CL-284,635; FK027) in healthy subjects and patients with renal insufficiency. *Antimicrob Agents Chemother* 1986; 30: 485–90.
3. Faulkner RD, *et al.* Pharmacokinetics of cefixime in the young and elderly. *J Antimicrob Chemother* 1988; 21: 787–94.
4. Stone JW, *et al.* Cefixime, in-vitro activity, pharmacokinetics and tissue penetration. *J Antimicrob Chemother* 1989; 23: 221–8.
5. Westphal JP, *et al.* Biliary excretion of cefixime: assessment in patients provided with T-tube drainage. *Antimicrob Agents Chemother* 1993; 37: 1488–91.
6. Somekh E, *et al.* Penetration and bactericidal activity of cefixime in synovial fluid. *Antimicrob Agents Chemother* 1996; 40: 1198–1200.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Novacef; Vixcef; *Austria*: Aerocef; Tricef; *Braz.*: Neo Cefix; *Canad.*: Suprax; *Chile*: Tricef; Urotricef; *China*: An Di Ke Tuo (安的克妥); An Di Ke Wei (安的克威); Ao De Ning (奥德宁); Cefspan (世福素); Dalifen (达力芬); Fu Xin Kang (扶欣抗); Han Guang Tuo (汉光妥); Hui Xin Sha (汇新沙); Ji Luo (基洛); Jin Chen (今辰); Jiu Bang (久邦); Jun Te (君特); Kang Pai (康啜); Ke Ao Sha (克沃莎); Ke Lin Dun (克林盾); Kui Ke (魁克); Li Jian Ke (立健克); Luo Wei Ke (洛伟克); Ou Jian (欧健); Qi An (琪安); Qin Ke Ao (勤克沃); Qing Ke Yi (青可奕); She Er (舍尔); Shi Rui Ke (士瑞克); Si Li Jie (司力捷); Suprax (速普乐); Te Pu Ning (特普宁); Xin Fu Su (新福素); Xindaxin (新达欣); Yan Ling (严灵); Yan Yi (严逸); Yu Shu (普舒); Zai Wo (再握); *Cz.*: Suprax; *Fr.*: Oroken; *Ger.*: Cephoral; InfectoOpticef; Suprax†; Uro-Cephoral; *Gr.*: Ceftoral; Covocef-N; *Hung.*: Suprax; *India*: AB-CEF; Aelxim; Afixim; Almocef; Arcef; Aricef; Aroxim; Asicef; Astute; Atocef; Avcif; Axim; Axiom-OR; Belfix; Bestocef; Biotax-O; Bixigard; Brufix; C-Fix; C-FX; C-Tax-O; Cadifix; Canbicef; Candycef; Carcef; Casxim; Cebay; Cefaden-O; Cefcem; Cefcon; Cefesym; Cefexy; Cefi; Cefia; Cefiact; Ceficacy; Cefiein; Cefigard; Cefigo; Cefigram; Cefikab; Cefime; Cefimed; Cefimo; Cefinar; Cefind; Cefine; Cefio; Cefisym; Cefit; Cefiwel; Cefix; Cefiza; Ceflim; Cefnil; Cefo; Cefocef-LB; Cefox; Cefrub; Celspan; Ceftas; Ceftiwin; Cefupop; Cefvel; Cefxi-O; Celitol; Cemax-O; Cemaxin; Ceme; Cevicim; Cexim; Cexime; Cifgen; Cifilac; Cifivar; Cifzone; Cinxim; Civic; Claferon-O; Clomid; Cocef; Daczim; Dotcef; E-Fix; Eden; Efoxim; Elce; Elcef; Elfi; Emtax; Esfix; Eurox; Evacef O; Excef; Extacef-P; Extacef; Femcef; Fevorit; Fexim; Fexitage; Fimi; Fixcef; Fixi; Fixsana; Fixsav; Fixtrim; Fixx; Focime-L; Formic-O; Gramocef-O; Halixim; Hifen-DS; Hifen; Hofim; I-M-Safe; Incef; Indcef; Jancef; Jidox; Kapdox CL; Kefix; Kxime; L-Cef; Labocef; Laximo; Laycef; LBCef; Letix; Lexime; Logcef; Magnexim; Mahacef; Medicip; Micfox; Milixim; Mintocef; Mytax-O; Nayafix; NBCef; Nitaxim-O; Nizocef; Novacef; Novafex; Nuclear; Nufix; O-Powercef; Oflomix; Omnapil; Omnatax-O; Orcef; Orfix; Oritaxim-O; Pancef-O; Si-Fixim; Xim; Ziprax; *Indon.*: Anfix; Cefacef; Cefarox; Cefika; Cefila; Cefspan; Ceptik; Comsporin; Ethifix; Fixacep; Fixam; Fixef; Fixiphar; Lanfix; Maxpro; Nucef; Opixime; Profim; Pyxime; Simcef; Sofix; Spancef†; Spaxim; Sporetik; Starcef; Taxime; Tocef; Trixim; Urticef; Yafix; *Irl.*: Suprax; *Israel*: Supran†; *Ital.*: Cefixoral; Stadium; Supracef; Suprax; Unixime; *Jpn*: Celspan; *Malaysia*: Cefix; Cefixycin; Ixime; Minixime; *Mex.*: Denvar; *Philipp.*: Actimax; Aeruxim; Axetef; C-Tax P; Cefixmycin; Cifacure; Ezcef; Fix-A; Fixcef; Fixxx; Refixime; Savecef†; Septipan; Synmex; Taxocef; Tergecef; Ultraxime; Zefral; *Pol.*: Suprax; *Port.*: Bonocef†; Cefimix; Cefiton; Cefizel; Neocef; Tricef; *Rus.*: Ceforal (Цефорал); Ixime (Иксим); Pancef (Панцеф); Suprax (Супракс); *S.Afr.*: Fixime†; *Spain*: Denvar; Necopen†; *Switz.*: Cephoral; *Thai.*: Celspan; Sixime; *Turk.*: Cephix; Fixef; Sancefix; Suprax; Zimaks; *UK*: Suprax; *Ukr.*: Cefix (Цефикс); Ceforal (Цефорал); Ixime (Иксим); Maxibat (Максибат)†; *USA*: Suprax; *Venez.*: Longacef.

Multi-ingredient Preparations. *India*: Aelxim-CL; Afixim Clav; Alfi-CV; Astute-CV; Belfix-CV; Bestocef-LB; Bilactam-XL; Bilactam; Bixigard-C; C-Fix-XT; C-Tax-O XL; Canbicef; Casclav; Casxim-DT; Cebay; Ceemi; Cefcal; Cefexy-CV; Cefglobe; Cefi XL; Cefic; Cefiped; Cefirap; Cefit-OZ; Cefit-XL; Cefix LB; Cefix-CV; Cefla; Cefline; Cefnet; Cefo-L; Cefo-LX; Cefocef-DXL; Cefocef-XL; Cefodav; Cefodin; Cefolac; Cefson; Ceftas AL; Ceftas-LB; Ceftobac; Cefupop-CV; Cefupop-XL; Ceme-CV; Cepoxit; Cexime-CL; Cifilac-CV; Cifivar-LB; Cifzone; Ciloxin; Clavtax-O; Clomid-CL; Clomid-LB; Cocef-LB; Comtrix-O; CX-Zim; Daczim-CL; E-Fix LB; Ecocef; Efelac; Elcef-LB; Elfi-XL; Emtax-CL; Extacef-LB; Extacef-P; Fevorit-LB; Fimi-CV; Fixcef-CL; Fixital; Fixsana-LB; Fixx Clav; Fixx LB; Formic-XL; Fydocef; Gefix; Glocef-CL; Glocef; Gramocef-CV; Hifen-CV; Hifen-LXX; HiFi-L; Hofim-C; Incef-CL; Incef-CV; Incef-LB; Jexime-LB; Jidox-C; L-Cef; Labocef-CV; Lafix; Laximo-XL; LBCef; Letlx-C; Lexime-CV; Logcef-CV; Magnexim LB; Mahacef-CV; Mahacef-OZ; Mahacef-XL; Mahacef; MDCef-CV; MDCef; Mefi; Milixim-CV; Milixim-LX; Mucomelt Forte; Nufex Beta; Omnapil-CV; Omnatax-CV; Omicef; Pancef-O LB.

Pharmacopoeial Preparations
USP 36: Cefixime for Oral Suspension; Cefixime Tablets.

Cefmenoxime Hydrochloride *(USAN, rINNM)*

Abbott-50192; Cefmenoxima, hidrocloruro de; Cefménoxime, Chlorhydrate de; Cefmenoxime Hemihydrochloride; Cefmenoximi Hydrochloridum; Hidrocloruro de cefmenoxima; SCE-1365 (cefmenoxime); Цефменоксима Гидрохлорид.

(*Z*)-(7*R*)-7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(1-methyl-1*H*-tetrazol-5-yl)thiomethyl]-3-cephem-4-carboxylic acid hydrochloride.

$(C_{16}H_{17}N_9O_5S_3)_2$,HCl=1059.6

CAS — 65085-01-0 (cefmenoxime); 75738-58-8 (cefmenoxime hydrochloride).

ATC — J01DD05.

ATC Vet — QJ01DD05.

UNII — NON736D32W.

Pharmacopoeias. In *Jpn* and *US*.

USP 36: (Cefmenoxime Hydrochloride). White to light orange-yellow crystals or crystalline powder. Very slightly soluble in water; practically insoluble in dehydrated alcohol and in ether; freely soluble in formamide; slightly soluble in methyl alcohol. Store in airtight containers.

Profile

Cefmenoxime is a third-generation cephalosporin antibacterial with actions and uses similar to those of cefotaxime (p. 246.1). It has been given as the hydrochloride by intramuscular injection, or intravenously by injection or infusion in the treatment of susceptible infections.

Like cefamandole (p. 236.2), cefmenoxime has an *N*-methylthiotetrazole side-chain and coagulopathy and a disulfiram-like interaction with alcohol have been reported rarely.

Cefmenoxime hydrochloride is also given as eye drops for the treatment of eye infections.

Reviews.

1. Campoll-Richards DM, Todd PA. Cefmenoxime: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1987; 34: 188–221.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: En Nuo Ni (恩诺尼); Lei Te Mai Xing (雷特迈星); *Gr.*: Tacef; *Jpn*: Bestcall; Bestron.

Pharmacopoeial Preparations
USP 36: Cefmenoxime for Injection.

Cefmetazole *(USAN, rINN)*

Cefmetazol; Cefmétazole; Cefmetazolum; U-72791; Цефметазол.

(6*R*,7*S*)-7-[2-[(Cyanomethyl)thio]acetamido]-7-methoxy-3-[[(1-methyl-1*H*-tetrazol-5-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylic acid.

$C_{15}H_{17}N_7O_5S_3$=471.5

CAS — 56796-20-4.

ATC — J01DC09.

ATC Vet — QJ01DC09.

UNII — 3J962UJT8H.

Pharmacopoeias. In *US*.

USP 36: (Cefmetazole). Store in airtight containers.

Cefmetazole Sodium *(USAN, rINNM)*

Cefmetazol sódico; Cefmétazole Sodique; Cefmetazolnatrium; Cefmetazolum Natricum; CS-1170; Kefmetatsolinatrium; Natrii Cefmetazolum; SKF-83088; U-72791A; Натрий Цефметазол.

$C_{15}H_{16}N_7NaO_5S_3$=493.5

CAS — 56796-39-5.

ATC — J01DC09.

ATC Vet — QJ01DC09.

UNII — 37Y9VR4W7A.

Pharmacopoeias. In *Jpn* and *US*.

USP 36: (Cefmetazole Sodium). A white solid. Very soluble in water and in methyl alcohol; soluble in acetone; practically insoluble in chloroform. pH of a 10% solution in water is between 4.2 and 6.2. Store in airtight containers.

Uses and Administration

Cefmetazole is a cephamycin antibacterial generally classified with the second-generation cephalosporins and used similarly to cefoxitin (p. 248.2) in the treatment and prophylaxis of anaerobic and mixed bacterial infections, especially intra-abdominal and pelvic infections. It may also be used in the treatment of gonorrhoea. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Cefmetazole is given intravenously as the sodium salt by infusion over 10 to 60 minutes or by slow injection over 3 to 5 minutes. Cefmetazole sodium is also used intramuscularly in some countries. Doses are expressed in terms of the equivalent amount of cefmetazole; 1.05 g of cefmetazole sodium is equivalent to about 1 g of cefmetazole.

The usual dose is 0.5 to 1 g intramuscularly or intravenously every 12 hours. For severe infections the dose may be increased to 3 to 4 g daily, given in divided doses every 6, 8, or 12 hours.

For details of reduced dosage of cefmetazole in patients with renal impairment, see p. 243.3.

References.

1. Finch R, *et al.* eds. Cefmetazole: a clinical appraisal. *J Antimicrob Chemother* 1989; 23 (suppl D): 1–142.

Administration in renal impairment. Parenteral doses of cefmetazole should be reduced in patients with renal impairment. It has been suggested that the interval between doses should be 12, 16, or 24 hours in patients with mild, moderate, or severe renal impairment, respectively; patients with virtually no renal function might be given cefmetazole every 48 hours, after haemodialysis.

Adverse Effects and Precautions

As for Cefalotin Sodium, p. 235.2.

Cefmetazole contains an *N*-methylthiotetrazole side-chain and has the potential to cause hypoprothrombinaemia and bleeding.

Effects on the blood. References.

1. Breen GA, St Peter WL. Hypoprothrombinemia associated with cefmetazole. *Ann Pharmacother* 1997; 31: 180–4.

Sodium content. Each g of cefmetazole sodium contains about 2 mmol of sodium.

Interactions

As for Cefamandole, p. 236.3.

Antimicrobial Action

Cefmetazole is a cephamycin antibacterial with a similar spectrum of antibacterial activity to that of cefoxitin (p. 249.1), including the anaerobe *Bacteroides fragilis*.

References.

1. Cornick NA, *et al.* Activity of cefmetazole against anaerobic bacteria. *Antimicrob Agents Chemother* 1987; 31: 2010–12.

Pharmacokinetics

After cefmetazole sodium 2 g intravenously every 6 hours, peak and trough plasma concentrations of 138 and 6 micrograms/mL have been achieved. Cefmetazole is 65 to 85% bound to plasma proteins, depending on the plasma concentration. A plasma half-life of about 1.1 to 1.5 hours has been reported; it is prolonged in patients with renal impairment. Small amounts have been detected in breast milk. Relatively high concentrations have been achieved in bile.

The majority of a dose is excreted unchanged in the urine resulting in high concentrations; up to 85% of a dose has been recovered within 12 hours. Cefmetazole is partly excreted by renal tubular secretion and probenecid prolongs elimination.

Cefmetazole is removed to some extent by haemodialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Bi Li Shu (毕立枢); Cefmetazon (先锋美他醇); Mei Zhi Quan (美之全); Xi Chang (悉畅); *Indon.*: Qizol; *Ital.*: Metafar; Metax; *Jpn*: Cefmetazon.

Pharmacopoeial Preparations

USP 36: Cefmetazole for Injection; Cefmetazole Injection.

Cefminox Sodium *(pINNM)*

Cefminox sódico; Cefminox Sodique; MT-141; Natrii Cefminoxum; Натрий Цефминокс.

Sodium 7-[2-[(*S*)-2-amino-2-carboxyethyl]thioacetamido]-7-methoxy-3-(1-methyl-1*H*-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylate.

$C_{16}H_{20}N_7NaO_7S_3$=541.5

CAS — 75481-73-1 (cefminox).

UNII — YNM4DBJ3N8.

Pharmacopoeias. *Jpn* includes the heptahydrate.

Profile

Cefminox sodium is a cephamycin antibacterial with properties similar to those of cefoxitin (p. 248.2) but with an *N*-methylthiotetrazole side-chain like cefamandole (p. 236.2). It is used in the treatment of anaerobic and mixed bacterial infections, especially intra-abdominal and pelvic infections. It is given intravenously as the sodium salt but doses are expressed in terms of cefminox; 1.04 g of cefminox sodium is equivalent to about 1 g of cefminox. A usual dose is 2 to 4 g daily given in divided doses.

References.

1. Watanabe S, Omoto S. Pharmacology of cefminox, a new bactericidal cephamycin. *Drugs Exp Clin Res* 1990; 16: 461–7.
2. Soriano F, *et al.* Comparative susceptibility of cefminox and cefoxitin to β-lactamases of Bacteroides spp. *J Antimicrob Chemother* 1991; 28: 55–60.
3. Aguilar L, *et al.* Cefminox: correlation between in-vitro susceptibility and pharmacokinetics and serum bactericidal activity in healthy volunteers. *J Antimicrob Chemother* 1994; 33: 91–101.
4. Mayama T, *et al.* Postmarketing surveillance on side-effects of cefminox sodium (Meicelin). *Int J Clin Pharmacol Ther* 1995; 33: 149–55.
5. Hoellman DB, *et al.* In vitro activities of cefminox against anaerobic bacteria compared with those of nine other compounds. *Antimicrob Agents Chemother* 1998; 42: 495–501.
6. Torres AJ, *et al.* Cefminox versus metronidazole plus gentamicin in intra-abdominal infections: a prospective randomized controlled clinical trial. *Infection* 2000; 28: 318–22.

Sodium content. Each g of cefminox sodium contains about 1.84 mmol of sodium.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Dalibang (达力邦); Han Guang Nuo (汉光诺); Meicelin (美士灵); Melnox; Qipu (奇朴); Xian Feng Mei Nuo (先锋美诺); *Jpn*: Meicelin; *Port.*: Tencef; *Spain*: Tencef; *Thai.*: Meicelin.

Cefodizime Sodium *(BANM, rINNM)*

Cefodizima sódica; Céfodizime Sodique; HR-221; Natrii Cefodizimum; S-771221B; Sefodizim Disodyum; THR-221; TRH-221; Натрий Цефодизим.

(*Z*)-7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(5-carboxymethyl-4-methylthiazol-2-ylthiomethyl)-3-cephem-4-carboxylic acid, disodium salt.

$C_{20}H_{18}N_6Na_2O_7S_4$=628.6

CAS — 69739-16-8 (cefodizime); 86329-79-5 (cefodizime sodium).

ATC — J01DD09.

ATC Vet — QJ01DD09.

UNII — HC1T51593A.

Pharmacopoeias. In *Jpn*.

Uses and Administration

Cefodizime is a third-generation cephalosporin antibacterial with uses similar to those of cefotaxime (p. 246.1).

Cefodizime is given as the disodium salt by intramuscular injection or intravenously by injection or infusion in the treatment of susceptible infections. Doses are expressed in terms of the equivalent amount of cefodizime; 1.08 g of cefodizime sodium is equivalent to about 1 g of cefodizime. Adults are usually given 1 g every 12 or 24 hours for lower respiratory-tract infections and 1 or 2 g every 24 hours for upper and lower urinary-tract infections. Total daily doses of up to 6 g may be given for severe infection. In women with uncomplicated lower urinary-tract infections a single dose of 1 to 2 g may be sufficient. For gonorrhoea a single dose of 250 to 500 mg may be given. Doses may need to be reduced in patients with renal impairment (see p. 244.2).

References.

1. Finch RG, *et al.*, eds. Cefodizime: a third generation cephalosporin with immunomodulating properties. *J Antimicrob Chemother* 1990; 26 (suppl C): 1–134.
2. Barradell LB, Brogden RN. Cefodizime: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1992; 44: 800–834.
3. Thalhammer F, *et al.* Single-dose cefodizime as infection prophylaxis in abdominal surgery: a prospective multicenter study. *Infection* 1998; 26: 136–8.
4. Matsumoto T, *et al.* Single dose of cefodizime completely eradicated multidrug-resistant strain of Neisseria gonorrhoeae in urethritis and uterine cervicitis. *J Infect Chemother* 2006; 12: 97–9.
5. Matsumoto T, *et al.* Multiple doses of cefodizime are necessary for the treatment of Neisseria gonorrhoeae pharyngeal infection. *J Infect Chemother* 2006; 12: 145–7.

Administration in renal impairment. Although the first dose is the same as for those with normal renal function (see above), subsequent parenteral doses of cefodizime should be adjusted in patients with renal impairment according to creatinine clearance (CC):

- CC 10 to 30 mL/minute: 1 to 2 g daily
- CC less than 10 mL/minute: 0.5 to 1 g daily

In patients undergoing dialysis, 0.5 to 1 g daily is given after dialysis.

Adverse Effects and Precautions

As for Cefotaxime, p. 246.3.

Sodium content. Each g of cefodizime sodium contains about 3.2 mmol of sodium.

Interactions

Probenecid reduces the renal clearance of cefodizime.

Antimicrobial Action

Cefodizime has similar antimicrobial activity to that of cefotaxime (p. 246.3) although cefodizime has no active metabolite. It has variable activity against *Citrobacter* spp., and *Pseudomonas aeruginosa* and *Bacteroides fragilis* are generally resistant.

Pharmacokinetics

Cefodizime is given by injection as the sodium salt. Intramuscular injection of 1 g cefodizime produces peak plasma concentrations of about 60 to 75 micrograms/mL at about 1 to 1.5 hours. Immediately after intravenous doses of 1 or 2 g cefodizime mean peak plasma concentrations of 215 and 394 micrograms/mL, respectively, have been achieved. Cefodizime is about 80% bound to plasma proteins and is widely distributed into body tissues and fluids. It crosses the placenta and small amounts have been detected in breast milk. Plasma elimination is reported to be triphasic with a terminal elimination half-life of about 4 hours. The half-life is prolonged by renal impairment.

The majority of a dose is excreted unchanged in the urine; up to 80% of a dose has been recovered within 24 hours. Cefodizime is mainly excreted by glomerular filtration with some tubular secretion. Probenecid delays excretion. Cefodizime is removed by dialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Timecef†; *China*: Ga De (高德); Jin Shan Qin (金汕秦); Kanglineng (康丽能); Li Mian (力勉); Modivid (莫敌); Newdizime; Zandixin (赞地新); *Ital.*: Diezime; Modivid; Timecef; *Jpn*: Kenicef; *NZ*: Timecef†; *Port.*: Modivid; *Turk.*: Modivid.

Cefonicid Sodium *(BANM, USAN, rINNM)*

Cefonicid sódico; Cefonicide sodique; Céfonicide Sodique Cefonicidum natricum; Natrii Cefonicidum; SKF-D-75073-Z (cefonicid monosodium); SKF-D-75073-Z_2; Натрий Цефоницид.

7-[(*R*)-Mandelamido]-3-(1-sulphomethyl-1*H*-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid, disodium salt.

$C_{18}H_{16}N_6Na_2O_8S_3$=586.5

CAS — 61270-58-4 (cefonicid); 61270-78-8 (cefonicic disodium); 71420-79-6 (cefonicid monosodium).

ATC — J01DC06.

ATC Vet — QJ01DC06.

UNII — F74MFL78A1 (cefonicid sodium); QD9G66C5UF (cefonicid monosodium).

Pharmacopoeias. In *US*.

USP 36: (Cefonicid Sodium). A white to off-white solid Freely soluble in water, in sodium chloride 0.9%, and in glucose 5%; very slightly soluble in dehydrated alcohol soluble in methyl alcohol. pH of a 5% solution in water i between 3.5 and 6.5. Store in airtight containers.

Uses and Administration

Cefonicid is a second-generation cephalosporin antibacteria used similarly to cefamandole (p. 236.3) in the treatment o susceptible infections and for surgical infection prophylaxis

It is given as the sodium salt by deep intramuscula injection, or intravenously by slow injection over 3 to 5 minutes or by infusion. Doses are expressed in terms of the equivalent amount of cefonicid; 1.08 g of cefonicid sodium is equivalent to about 1 g of cefonicid. The usual dose i cefonicid 1 g once daily. For uncomplicated urinary-trac infections, a dose of 500 mg once daily is recommended; up to 2 g once daily has been given in severe infections. More than 1 g should not be injected intramuscularly into a single site.

For surgical infection prophylaxis, a single dose of 1 g given 1 hour before surgical incision is usually sufficient, but may be given daily for a further 2 days in prosthetic arthroplasty or open-heart surgery.

References.

1. Saltiel E, Brogden RN. Cefonicid: a review of its antibacterial activity pharmacological properties and therapeutic use. *Drugs* 1986; 32: 222–59.

Administration in renal impairment. For patients with renal impairment a loading dose equivalent to cefonicid 7.5 mg/kg is recommended, followed by reduced maintenance doses according to the creatinine clearance and the severity of the infection. A dose supplement is not required after dialysis.

Adverse Effects and Precautions

As for Cefalotin Sodium, p. 235.2.

Cefonicid contains a substituted *N*-methylthiotetrazole side-chain, a structure associated with hypoprothrombinaemia.

Effects on the blood. References.

1. Riancho JA, *et al.* Life-threatening bleeding in a patient treated with cefonicid. *Ann Intern Med* 1995; 123: 472–3.

Effects on the liver. References.

1. Famularo G, *et al.* Eosinophilic hepatitis associated with cefonicid therapy. *Ann Pharmacother* 2001; 35: 1669–71.

Sodium content. Each g of cefonicid sodium contains about 3.4 mmol of sodium.

Interactions

As for Cefamandole, p. 236.3.

Antimicrobial Action

Cefonicid sodium has an antimicrobial action and pattern of resistance similar to those of cefamandole (p. 237.1), although it is generally less active against Gram-positive cocci.

Pharmacokinetics

Cefonicid is given parenterally as the sodium salt. Peak plasma concentrations ranging from 67 to 126 micrograms/mL have been achieved 1 to 2 hours after a 1-g intramuscular dose. Cefonicid is more than 90% bound to plasma proteins. It has a plasma half-life of about 4.5 hours, which is prolonged in patients with renal impairment.

Therapeutic concentrations of cefonicid have been reported in many body tissues and fluids.

Up to 99% of a dose of cefonicid is excreted unchanged in the urine within 24 hours. Probenecid reduces excretion of cefonicid.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Xirui (西锐); *Israel*: Monocef; *Ital.*: Bioticic†; Cefodie; Cefoplus; Cheflr; Daycef; Emidoxin; Fonicid; Kruceft; Lisa; Maxid†; Modiem; Monobiotic; Necid; Nokid; Praticef†; Raikocef; Sintocef; Sofarcid; Valecid†; *Port.*: Monocid; *Spain*: Monocid.

Pharmacopoeial Preparations
USP 36: Cefonicid for Injection.

Cefoperazone Sodium

(BANM, USAN, rINNM)

Cefoperazon-Natrium; Cefoperazon sodná sůl; Cefoperazon sodowy; Cefoperazona sódica; Céfopérazone Sodique; Cefoperazonnatrium; Cefoperazon-nátrium; Cefoperazono natrio druska; Cefoperazonum Natricum; CP-52640-2; CP-52640-3 (cefoperazone dihydrate); CP-52640 (anhydrous cefoperazone); Kefoperatsoninatrium; Natrii Cefoperazonum; Sefoperazon Sodyum; T-1551 (cefoperazone or cefoperazone sodium); Натрий Цефоперазон.

Sodium (7*R*)-7-[(*R*)-2-(4-ethyl-2,3-dioxopiperazin-1-ylcarboxamido)-2-(4-hydroxyphenyl)acetamido]-3-[(1-methyl-1*H*-tetrazol-5-yl)thiomethyl]-3-cephem-4-carboxylate.

$C_{25}H_{26}N_9NaO_8S_2$=667.6

CAS — 62893-19-0 (cefoperazone); 62893-20-3 (cefoperazone sodium).

ATC — J01DD12.

ATC Vet — QJ01DD12.

UNII — 5FQG9774WD.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Cefoperazone Sodium). A white or slightly yellow, hygroscopic, powder. If crystalline it exhibits polymorphism. Freely soluble in water; slightly soluble in alcohol; soluble in methyl alcohol. A 25% solution in water has a pH of 4.5 to 6.5. Store in airtight containers at a temperature of 2 degrees to 8 degrees. Protect from light.

USP 36: (Cefoperazone Sodium). A white to pale buff crystalline powder. Freely soluble in water; slightly soluble in dehydrated alcohol; soluble in methyl alcohol; insoluble in acetone, in ether, and in ethyl acetate. pH of a 25% solution in water is between 4.5 and 6.5. Store in airtight containers.

Incompatibility. As with most beta lactams, admixture of cefoperazone sodium with aminoglycosides is not recommended because of the potential for inactivation of either drug.

There have been reports of incompatibility with other drugs including diltiazem,[1] doxorubicin,[2] pentamidine,[3] perphenazine,[4] pethidine,[5] promethazine,[6] and remifentanil.[7]

1. Gayed AA, *et al.* Visual compatibility of diltiazem injection with various diluents and medications during simulated Y-site injection. *Am J Health-Syst Pharm* 1995; **52**: 516–20.
2. Trissel LA, *et al.* Compatibility of doxorubicin hydrochloride liposome injection with selected other drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; **54**: 2708–13.
3. Lewis JD, El-Gendy A. Cephalosporin-pentamidine isethionate incompatibilities. *Am J Health-Syst Pharm* 1996; **53**: 1461–2.
4. Gasca M, *et al.* Visual compatibility of perphenazine with various antimicrobials during simulated Y-site injection. *Am J Hosp Pharm* 1987; **44**: 574–5.
5. Nieves-Cordero AL, *et al.* Compatibility of narcotic analgesic solutions with various antibiotics during simulated Y-site injection. *Am J Hosp Pharm* 1985; **42**: 1108–9.
6. Scott SM. Incompatibility of cefoperazone and promethazine. *Am J Hosp Pharm* 1990; **47**: 519.
7. Trissel LA, *et al.* Compatibility of remifentanil hydrochloride with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; **54**: 2192–6.

Uses and Administration

Cefoperazone is a third-generation cephalosporin antibacterial used similarly to ceftazidime (p. 253.1) in the treatment of susceptible infections, especially those due to *Pseudomonas* spp. It is not recommended for the treatment of meningitis because of poor penetration into the CSF.

Cefoperazone is given as the sodium salt by deep intramuscular injection or intravenously by intermittent or continuous infusion. Doses are expressed in terms of the equivalent amount of cefoperazone; 1.03 g of cefoperazone sodium is equivalent to about 1 g of cefoperazone. The usual dose is 2 to 4 g daily in 2 divided doses. In severe infections, up to 12 g daily in 2 to 4 divided doses may be given.

For details of dosage in patients with hepatic and renal impairment, see p. 245.2.

If cefoperazone is used with an aminoglycoside, the drugs should be given separately.

Cefoperazone has also been given with the beta-lactamase inhibitor sulbactam.

Administration in hepatic and renal impairment. In general, the parenteral dose of cefoperazone should not exceed 4 g daily in patients with liver disease or biliary obstruction or 1 to 2 g daily in those with both hepatic and renal impairment; if higher doses are used plasma concentrations of cefoperazone should be monitored.

Adverse Effects and Precautions

As for Cefalotin Sodium, p. 235.2.

Like cefotaxime (p. 246.3), cefoperazone has the potential for promoting colonisation and superinfection with resistant organisms. Changes in bowel flora may be more marked than with cefotaxime because of the greater biliary excretion of cefoperazone; diarrhoea may occur more often.

Cefoperazone contains an *N*-methylthiotetrazole side-chain, a structure associated with hypoprothrombinaemia. Hypoprothrombinaemia has been reported in patients treated with cefoperazone and has rarely been associated with bleeding episodes. Prothrombin time should be monitored in patients at risk of hypoprothrombinaemia and vitamin K used if necessary.

Sodium content. Each g of cefoperazone sodium contains about 1.5 mmol of sodium.

Interactions

As for Cefamandole, p. 236.3.

Unlike many other cephalosporins, the renal clearance of cefoperazone is not affected by probenecid.

Antimicrobial Action

Cefoperazone has antimicrobial activity similar to that of ceftazidime (p. 253.3), although it is slightly less active against some Enterobacteriaceae. It has good activity against *Pseudomonas aeruginosa*, but is less active than ceftazidime.

Cefoperazone is more susceptible than cefotaxime to hydrolysis by certain beta-lactamases.

Activity, particularly against Enterobacteriaceae and *Bacteroides* spp. has been enhanced in the presence of the beta-lactamase inhibitor sulbactam; resistant *Ps. aeruginosa* are not sensitive to the combination.

References.

1. Fass RJ, *et al.* In vitro activities of cefoperazone and sulbactam singly and in combination against cefoperazone-resistant members of the family Enterobacteriaceae and nonfermenters. *Antimicrob Agents Chemother* 1990; **34**: 2256–9.
2. Clark RB, *et al.* Multicentre study on antibiotic susceptibilities of anaerobic bacteria to cefoperazone-sulbactam and other antimicrobial agents. *J Antimicrob Chemother* 1992; **29**: 57–67.

Pharmacokinetics

Cefoperazone is given parenterally as the sodium salt. With intramuscular doses equivalent to cefoperazone 1 or 2 g, peak plasma concentrations of 65 and 97 micrograms/mL have been reported after 1 to 2 hours. The plasma half-life of cefoperazone is about 2 hours, but may be prolonged in neonates and in patients with hepatic or biliary-tract disease. Cefoperazone is 82 to 93% bound to plasma proteins, depending on the concentration.

Cefoperazone is widely distributed in body tissues and fluids, although penetration into the CSF is generally poor. It crosses the placenta, and low concentrations have been detected in breast milk.

Cefoperazone is excreted mainly in the bile where it rapidly achieves high concentrations. Urinary excretion is primarily by glomerular filtration. Up to 30% of a dose is excreted unchanged in the urine within 12 to 24 hours; this proportion may be increased in patients with hepatic or biliary disease. Cefoperazone A, a degradation product less active than cefoperazone, has been found only rarely *in vivo*.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Cefobid; *Braz.*: Neoperazona; *Chile*: Cefobid†; *China*: Cefobid (先锋必); Da Nuo Xin (达诺欣 ???); Lijunpaitong (利君派同); Medocef (麦道必); Saifubi (赛福必); Shilexin (施乐欣); Xianbi (仙毕); Xianbixian (先必先); Xiankang (先抗); Yi Mei Xin (依美欣); *Cz.*: Cefobid; *Hong Kong*: Cefobid; *Hung.*: Cefobid; *India*: Cefaking; Cefina; Cefomycin; Cefpar; Ceprazo; Cizon; CT Spar; Dalcefa; Frone; Kephazon; Luckcare; Magnamycin; Megacef; Myticef; Negaplus; NKZone; Novacip; Nuperazone; Over; *Indon.*: Bifotik; Biorazon; Cefobid; Cefoject; Cefophar; Cepraz; Ceropid; Cerozon; Ferzobat; Logafox; Stabixin; Yazon; *Ital.*: Bioperazone; Dardum; Farecef†; *Jpn*: Cefobid; Cefoperazin; *Malaysia*: Bicafar; Cefobid; Medocef; Shinfomycin†; *Mex.*: Cefobid; *Philipp.*: Bactizon; *Pol.*: Biocefazon†; Cefobid; Dardum; *Rus.*: Cefobid (Цефобид); Cefoperabol (Цефоперабол); Cefoperus (Цефоперус); Cefpar (Цефпар); Dardum (Дардум); Medocef (Медоцеф); Movoperiz (Мовопериз); Operaz (Операз); *Singapore*: Cefobid; Cefozone; Dardum; *Thai.*: Cefobid; Cefozone; Medocef†; *Turk.*: Cefobid; *Ukr.*: Cefobid (Цефобид); Cefobocid (Цефобосид); Cerason (Церазон)†; Gepacef (Гепацеф).

Multi-ingredient Preparations. *Chile*: Sulperazon; *China*: Dalipaitan (达力哌坦); Dexiao (得消); Fanlin (凡林); Pengpaixin (锋派新); Kai Si (凯斯); Kaisheng (凯生); Kang Li Shu (康力舒); Lijunpaishu (利君派舒); Linglanxin (铃兰欣); Rulpuxin (瑞普欣); Sulperazon (舒普深); Xian Bi Ta (仙必他); Xian Qiang (先强); Xianjie (先捷); Xianpu (先普); Xianshu (先舒); Xinkuaixin (新快欣); Xinruipuxin (新瑞普欣); Zetong (祥同); *Cz.*: Sulperazon; *Hong Kong*: Sulperazon; *India*: Apozone-S; Arifzon-SB; Atozon-S; Bacticid-CS; Bactonis; Bactorus; Bahutcef-SL; Burnex; C-Bact; C-Bactum; C-Lactum; Cadcef-S; Cafazone-S; Cebac; Cebanex; Cebect; Cefac; Cefactam; Cefasul; Cefbect; Cefdinex-SB; Cefglobe-S; Cefina-SB; Cefmate; Cefobac; Cefobel-S; Cefobeta; Cefoden-SB; Cefogard-S; Cefom-S; Cefonet-S; Cefonex; Ceforex; Cefosal; Cefosul; Cefosun S; Cefozed-S; Cefpar SB; Cefrobactum; Cefrosan; Ceftocin; Ceftop; Cefum; Cefurax-D; Cefzon SB; Ceprazo-S; Ceprozone-S; Cerazone-S; Cesal; Cezon-S; Cis-SL; Cizon-SB; CT Spar SM; Cucef-S; Curemax; Dalcefa-SB; Decef; Duozone; Fofone-S; Fro-Cef; Frone-SL; Fuzosul; Fytobact; Hosizone; Imex; Inbac Kit; Indobact; Iszu; Kaircef-S; Kefbactam; Kefchek; Kefsurge; Kephazon-S; Krasule; L-Cef; Lactagard; Magnazone; Magnex; Magtam; Mecef-S; Medinex; Monoact; Nebect; Nefsul; Neftum-SB; Nosobac; Novacip-S; Nubact; Nuperazone Plus; Ocefa-SB; Odospi-S; Ofirex; Oramax; Orozone-SB; Osul-S; Over-SB; Parabact; Sulbacef; Zosul; *Indon.*: Bactazon; Ferotam; Fosular; Soperam; Stabactam; Sulbacef; Sulperazon; Zotam; *Malaysia*: Sulperazon; *Philipp.*: Sulperazone; *Pol.*: Sulperazon; *Rus.*: Bacperazone (Бакперазон); Cebanex (Цебанекс); Cephpar (Цефпар); Sulcef (Сульцеф); Sulcefazon (Сульцефазон); Sulmover (Сульмовер); Sulperacef (Сульперацеф); Sulperason (Сульперазон); Sulzoncef (Сульзонцеф); *Thai.*: Bacticep; Cebactam; Cefpar; Cefper; Prazone-S; Sulcef; Sulperazon; Sulpermed; Zonbactam; *Turk.*: Primasef†; Sefbaktam; Sulperazon; *Ukr.*: Cebanex (Цебанекс); Cefoperazone Plus (Цефоперазон плюс); Cefosulbin (Цефосульбин); Cesulpin (Цесульпин); Gepacef Combi (Гепацеф Комби); Prazone-S (Празон-С); Sulperasone (Сульперазон); *Venez.*: Sulperazon.

Pharmacopoeial Preparations
USP 36: Cefoperazone for Injection; Cefoperazone Injection.

Ceforanide *(BAN, USAN, rINN)*

BL-S786; Ceforanida; Céforanide; Ceforanidum; Цефоранид.

7-[2-(α-Amino-o-tolyl)acetamido]-3-(1-carboxymethyl-1*H*-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid.

$C_{20}H_{21}N_7O_6S_2$=519.6

CAS — 60925-61-3.

ATC — J01DC11.

ATC Vet — QJ01DC11.

UNII — 8M1YF8951V.

Pharmacopoeias. In *US*.

USP 36: (Ceforanide). A white to off-white powder. Practically insoluble in water, in chloroform, in ether, and in methyl alcohol; very soluble in 1N sodium hydroxide. pH of a 5% suspension in water is between 2.5 and 4.5. Store in airtight containers.

Profile

Ceforanide is a second-generation cephalosporin antibacterial with actions and uses similar to those of cefamandole (p. 236.2), although it is reported to be less active *in vitro* against some bacteria, including staphylococci and *Haemophilus influenzae*. It is used in the treatment of susceptible infections and for surgical infection prophylaxis.

It is given as the lysine salt ($C_{26}H_{33}N_9O_8S_2$ = 665.7) but doses are expressed in terms of the equivalent amount of ceforanide; 1.28 g of ceforanide lysine is equivalent to about 1 g of ceforanide. It is given by deep intramuscular injection, or intravenously by slow injection over 3 to 5 minutes or by infusion, in a usual dose of 1 to 2 g every 12 hours. For surgical infection prophylaxis, a dose of 1 to 2 g

intravenously 1 hour before surgical incision is used. For doses in children, see p. 246.1.

Ceforanide contains a substituted *N*-methylthiotetrazole side-chain, a structure associated with hypoprothrombinaemia and alcohol intolerance. Probenecid does not affect the renal excretion of ceforanide.

References.
1. Campoli-Richards DM, *et al.* Ceforanide: a review of its antibacterial activity, pharmacokinetic properties and clinical efficacy. *Drugs* 1987; 34: 411–37.

Administration in children. Children have been given ceforanide lysine by deep intramuscular injection, or intravenously by slow injection over 3 to 5 minutes or by infusion in doses equivalent to ceforanide 20 mg/kg daily, in 2 divided doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Radacef.

Pharmacopoeial Preparations
USP 36: Ceforanide for Injection.

Cefoselis Sulfate *(rINNM)*

Céfoselis, Sulfate de; Cefoselis, sulfato de; Cefoselis Sulphate; Cefoselisi Sulfas; FK-037; Sulfato de cefoselis; Цефозелиса Сульфат.

(-)-5-Amino-2-{[(6*R*,7*R*)-7-[2-(2-amino-4-thiazolyl)glyoxylamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl}-1-(2-hydroxyethyl)pyrazolium hydroxide, inner salt, 7²-(*Z*)-(*O*-methyloxime) sulfate.

$C_{19}H_{22}N_8O_6S_2$, H_2SO_4=620.6

CAS — 122841-10-5 (cefoselis); 122841-12-7 (cefoselis sulfate).

Profile

Cefoselis sulfate is a cephalosporin antibacterial that has been used in the treatment of susceptible bacterial infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Feng Di (丰迪).

Cefotaxime Sodium *(BANM, USAN, rINNM)*

Cefotaksimo natrio druska; Cefotaksym sodowy; Cefotaxim-Natrium; Cefotaxim sodná sůl; Cefotaxima sódica; Céfotaxime sodique; Cefotaximnatrium; Cefotaxim-nátrium; Cefotaximum Natricum; CTX; HR-756; Kefotaksiiminatrium; Natrii Cefotaximum; RU-24756; Sefotaksim Sodyum; Натрий Цефотаксим.

Sodium (7*R*)-7-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetamido]cephalosporanate; Sodium (7*R*)-3-acetoxymethyl-7-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetamido]-3-cephem-4-carboxylate.

$C_{16}H_{16}N_5NaO_7S_2$=477.4

CAS — 63527-52-6 (cefotaxime); 64485-93-4 (cefotaxime sodium).

ATC — J01DD01.

ATC Vet — QJ01DD01.

UNII — 258J72S7TZ.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Cefotaxime Sodium). A white or slightly yellow, hygroscopic, powder. Freely soluble in water; sparingly soluble in methyl alcohol. A 10% solution in water has a pH of between 4.5 and 6.5. Store in airtight containers. Protect from light.

USP 36: (Cefotaxime Sodium). An off-white to pale yellow crystalline powder. Freely soluble in water; practically insoluble in organic solvents. pH of a 10% solution in water is between 4.5 and 6.5. Store in airtight containers.

Incompatibility. Cefotaxime sodium has been reported to be incompatible with alkaline solutions such as sodium bicarbonate. Licensed product information recommends that it should be given separately from aminoglycosides.

Uses and Administration

Cefotaxime is a third-generation parenteral cephalosporin antibacterial used in the treatment of infections due to susceptible Gram-positive and Gram-negative bacteria, including infections of the abdomen, bones and joints, CNS, skin and skin structure, genito-urinary tract (including gonorrhoea) and respiratory tract, in gynaecological infections, and in early Lyme disease. It is also used for surgical infection prophylaxis. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Cefotaxime is given as the sodium salt by deep intramuscular injection or intravenously by slow injection over 3 to 5 minutes or by infusion over 20 to 60 minutes. Doses are expressed in terms of the equivalent amount of cefotaxime; 1.05 g of cefotaxime sodium is equivalent to about 1 g of cefotaxime. For mild to moderate infections cefotaxime is usually given in doses of 1 g 12-hourly and increased to 1 to 2 g every 8 hours for moderate to severe infections. For septicaemia up to 6 to 8 g daily may be given in 3 to 4 divided doses, while in the most severe infections up to 12 g may be given daily by the intravenous route in up to 6 divided doses. Pseudomonal infections usually require more than 6 g daily, but a cephalosporin with greater antipseudomonal activity, such as ceftazidime, is preferable.

In the treatment of gonorrhoea, a single dose of 0.5 or 1 g of cefotaxime is given.

For surgical infection prophylaxis, 1 g is given 30 to 90 minutes before surgery. At caesarean section, 1 g is given intravenously to the mother as soon as the umbilical cord is clamped and two further doses intramuscularly or intravenously 6 and 12 hours later.

The dose of cefotaxime may need to be reduced in patients with renal impairment, see p. 246.2.

For details of doses in children, see p. 246.2.

Cefotaxime may be used with an aminoglycoside as synergy may occur against some Gram-negative organisms, but the drugs should be given separately. It has sometimes been used with another beta lactam to broaden the spectrum of activity. Cefotaxime has also been used with metronidazole in the treatment of mixed aerobic-anaerobic infections.

General references to third-generation cephalosporins.

1. Neu HC, *et al.*, eds. Third-generation cephalosporins: a decade of progress in the treatment of severe infections. *Am J Med* 1990; 88 (suppl 4A): 1S–45S.

General references to cefotaxime.

1. Todd PA, Brogden RN. Cefotaxime: an update of its pharmacology and therapeutic use. *Drugs* 1990; 40: 608–51.
2. Gentry LO. Cefotaxime and prophylaxis: new approaches with a proven agent. *Am J Med* 1990; 88 (suppl 4A): 32S–37S.
3. Davies A, Speller DCE, eds. Cefotaxime—recent clinical investigations. *J Antimicrob Chemother* 1990; 26 (suppl A): 1–83.
4. Brogden RN, Spencer CM. Cefotaxime: a reappraisal of its antibacterial activity and pharmacokinetic properties, and a review of its therapeutic efficacy when administered twice daily for the treatment of mild to moderate infections. *Drugs* 1997; 53: 483–510.

Administration in children. Cefotaxime may be given to neonates and children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria and for surgical prophylaxis. It is given by intramuscular injection or intravenously by slow injection over 3 to 5 minutes or by infusion over 20 to 60 minutes.

In the UK, the *BNFC* recommends the following doses for cefotaxime; the dose may be doubled for neonates with severe infection or meningitis:

- neonates under 7 days of age: 25 mg/kg every 12 hours
- neonates 7 to 21 days of age: 25 mg/kg every 8 hours
- neonates 21 to 28 days of age: 25 mg/kg every 6 to 8 hours
- children 1 month of age and older: 50 mg/kg every 8 to 12 hours; the frequency should be increased to every 6 hours in very severe infections and meningitis (to a maximum dose of 12 g daily)

In the USA, the American Academy of Pediatrics[1] suggests the following doses for cefotaxime:

- for neonates aged ⩽ 7 days (irrespective of body weight): 50 mg/kg every 12 hours
- for neonates aged 8 to 28 days and weighing ⩽ 2 kg: 50 mg/kg every 8 to 12 hours; a dosing interval of 12 hours may be used until 2 weeks of life in extremely low birth-weight neonates (weighing less than 1 kg)
- for neonates aged 8 to 28 days and weighing > 2 kg: 50 mg/kg every 8 hours
- children 1 month and older: 50 to 180 mg/kg daily in 3 or 4 divided doses (to a maximum daily dose of 3 to 6 g) for mild to moderate infections, or 200 to 225 mg/kg daily in 4 or 6 divided doses (to a maximum daily dose of 8 to 12 g) in severe infections; up to 300 mg/kg daily in divided doses may be given for meningitis

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Administration in renal impairment. Parenteral doses of cefotaxime should be reduced in severe renal impairment; after an initial loading dose of 1 g, halving the dose while maintaining the usual frequency of dosing has been suggested.

For critically ill patients undergoing renal replacement therapy, the following cefotaxime doses have been recommended:[1]

- continuous venovenous haemofiltration (CVVH): 1 to 2 g every 8 to 12 hours
- continuous venovenous haemodialysis (CVVHD): 1 to 2 g every 8 hours
- continuous venovenous haemodiafiltration (CVVHDF) 1 to 2 g every 6 to 8 hours
- intermittent haemodialysis: 1 to 2 g every 24 hours (after the dialysis run)

1. Heintz BH, *et al.* Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy* 2009; 29: 562–77.

Adverse Effects and Precautions

As for Cefalotin Sodium, p. 235.2. Arrhythmias have been associated with rapid bolus dosage through a central venous catheter in a few cases.

The broad-spectrum third-generation cephalosporins have the potential for promoting colonisation and superinfection with resistant organisms such as *Pseudomonas aeruginosa*, *Enterobacter* spp., *Candida*, and enterococci, at various sites in the body, although the incidence has generally been low with cefotaxime. Changes in bowel flora are a predisposing factor and have been more marked with cefoperazone and ceftriaxone, possibly because of their greater biliary excretion. Pseudomembranous colitis, associated with *Clostridium difficile* infection, may occasionally be seen with any of the third-generation cephalosporins.

Reviews on adverse effects associated with third-generation cephalosporins.

1. Neu HC. Third generation cephalosporins: safety profiles after 10 years of clinical use. *J Clin Pharmacol* 1990; 30: 396–403.
2. Fekety FR. Safety of parenteral third-generation cephalosporins. *Am J Med* 1990; 88 (suppl 4A): 38S–44S.

Antibiotic-associated colitis. It has been suggested[1] that cefotaxime is associated with an increased risk of *Clostridium difficile* diarrhoea in elderly patients; however, the manufacturer[2] has disputed this, arguing that cefotaxime compares favourably with alternative third-generation cephalosporins.

1. Impallomeni M, *et al.* Increased risk of diarrhoea caused by Clostridium difficile in elderly patients receiving cefotaxime. *BMJ* 1995; 311: 1345–6.
2. Rothschild E, *et al.* Risk of diarrhoea due to Clostridium difficile during cefotaxime treatment. *BMJ* 1996; 312: 778.

Breast feeding. Although cefotaxime is excreted in breast milk in small amounts,[1] no adverse effects have been seen in breast-fed infants whose mothers were receiving cefotaxime, and the American Academy of Pediatrics considers[2] that it is therefore usually compatible with breast feeding.

1. Kafetzis DA, *et al.* Passage of cephalosporins and amoxicillin into the breast milk. *Acta Paediatr Scand* 1981; 70: 285–8.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cefotaxime as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Sodium content. Each g of cefotaxime sodium contains about 2.09 mmol of sodium.

Interactions

As for many cephalosporins, probenecid reduces the renal clearance of cefotaxime, resulting in higher and prolonged plasma concentrations of cefotaxime and its desacetyl metabolite.

Antibacterials. The total body clearance of cefotaxime has been reduced in patients with normal and reduced renal function by the ureidopenicillins *azlocillin*[1] or *mezlocillin*.[2] Doses of cefotaxime may need to be reduced if either of these penicillins is being given. Encephalopathy with focal motor status and generalised convulsions have been reported in a patient with renal failure given cefotaxime and high doses of azlocillin.[3]

1. Kampf D, *et al.* Kinetic interactions between azlocillin, cefotaxime, and cefotaxime metabolites in normal and impaired renal function. *Clin Pharmacol Ther* 1984; 35: 214–20.
2. Rodondi LC, *et al.* Influence of coadministration on the pharmacokinetics of mezlocillin and cefotaxime in healthy volunteers and in patients with renal failure. *Clin Pharmacol Ther* 1989; 45: 527–34.
3. Wroe SJ, *et al.* Focal motor status epilepticus following treatment with azlocillin and cefotaxime. *Med Toxicol* 1987; 2: 233–4.

Antimicrobial Action

Cefotaxime is a third-generation cephalosporin. It has a bactericidal action similar to cefamandole, but a broader spectrum of activity. It is highly stable to hydrolysis by most beta-lactamases and has greater activity than first- or second-generation cephalosporins against Gram-negative bacteria. Although cefotaxime is generally considered to

have slightly less activity than first-generation cephalosporins against Gram-positive bacteria, many streptococci are very sensitive.

Desacetylcefotaxime is an active metabolite of cefotaxime and there may be additive or synergistic effects against some species.

Spectrum of activity.

- Among Gram-negative bacteria, cefotaxime is active *in vitro* against many Enterobacteriaceae including *Citrobacter* and *Enterobacter* spp., *Escherichia coli, Klebsiella* spp., both indole-positive and indole-negative *Proteus, Providencia, Salmonella, Serratia, Shigella,* and *Yersinia* spp.
  Other susceptible Gram-negative bacteria, including penicillin-resistant strains, are *Haemophilus influenzae, Moraxella catarrhalis* (*Branhamella catarrhalis*), *Neisseria gonorrhoeae,* and *N. meningitidis. Brucella melitensis* is also reported to be moderately sensitive. Some strains of *Pseudomonas* spp. are moderately susceptible to cefotaxime, but most are resistant.
  Desacetylcefotaxime is active against many of these Gram-negative bacteria, but not against *Pseudomonas* spp.
- Among Gram-positive bacteria, cefotaxime is active against staphylococci and streptococci. *Staphylococcus aureus,* including penicillinase-producing strains but not meticillin-resistant *Staph. aureus,* is sensitive. *Staph. epidermidis* is also sensitive but penicillinase-producing strains are resistant. *Streptococcus agalactiae* (group B streptococci), *Str. pneumoniae,* and *Str. pyogenes* (group A streptococci) are all very sensitive although truly penicillin-resistant pneumococci are apparently not sensitive.
  Enterococci and *Listeria monocytogenes* are resistant.
- Cefotaxime is active against some anaerobic bacteria. *Bacteroides fragilis* may be moderately sensitive, but many strains are resistant; synergy has been shown with desacetylcefotaxime *in vitro. Clostridium perfringens* is sensitive, but most *Cl. difficile* are resistant.
- Other organisms sensitive to cefotaxime include the spirochaete *Borrelia burgdorferi* and *Haemophilus ducreyi.*

Activity with other antimicrobials. In addition to possible synergy or additive effects with desacetylcefotaxime, the activity of cefotaxime may be enhanced by aminoglycosides such as gentamicin; synergy has been shown *in vitro* against Gram-negative bacteria including *Pseudomonas aeruginosa.* There have also been reports of enhanced activity *in vitro* with other antibacterials including fosfomycin and ciprofloxacin and variable results with penicillins.

Resistance may develop during treatment with cefotaxime due to derepression of chromosomally mediated beta-lactamases, and has been reported particularly in *Enterobacter* spp., with multiresistant strains emerging during treatment. This type of resistance has also developed in other bacteria including *Citrobacter, Serratia,* and *Pseudomonas* spp. Another mechanism of cefotaxime resistance is the development of plasma-mediated, extended-spectrum beta-lactamases, and this has occurred in *Klebsiella* spp. and also other Enterobacteriaceae. Resistance in *Str. pneumoniae* is due to the production of altered penicillin-binding proteins.

References to the antimicrobial activity of cefotaxime and other third-generation cephalosporins, including the problem of bacterial resistance.

1. Neu HC. Pathophysiologic basis for the use of third-generation cephalosporins. *Am J Med* 1990; **88** (suppl 4A): 3S–11S.
2. Chow JW, *et al.* Enterobacter bacteremia: clinical features and emergence of antibiotic resistance during therapy. *Ann Intern Med* 1991; **115**: 585–90.
3. Sanders CC. New β -lactams: new problems for the internist. *Ann Intern Med* 1991; **115**: 650–1.
4. Thomson KS, *et al.* High-level resistance to cefotaxime and ceftazidime in Klebsiella pneumoniae isolates from Cleveland, Ohio. *Antimicrob Agents Chemother* 1991; **35**: 1001–3.
5. Piddock LJV, *et al.* Prevalence and mechanism of resistance to 'third-generation' cephalosporins in clinically relevant isolates of Enterobacteriaceae from 43 hospitals in the UK, 1990-1991. *J Antimicrob Chemother* 1997; **39**: 177–87.
6. Gums JG, *et al.* Differences between ceftriaxone and cefotaxime: microbiological inconsistencies. *Ann Pharmacother* 2008; **42**: 71–9.

Pharmacokinetics

Cefotaxime is given by injection as the sodium salt. It is rapidly absorbed after intramuscular injection and mean peak plasma concentrations of about 12 and 20 micrograms/mL have occurred 30 minutes after doses of 500 mg and 1 g of cefotaxime, respectively. Immediately after intravenous injection of 0.5, 1, or 2 g of cefotaxime, mean peak plasma concentrations of 38, 102, and 215 micrograms/mL, respectively, have occurred with concentrations ranging from about 1 to 3 micrograms/mL after 4 hours. The plasma half-life of cefotaxime is about 1 hour and that of the active metabolite desacetylcefotaxime about 1.5 hours; half-lives are increased in neonates and in patients with severe renal impairment, especially those of the metabolite, and a reduction in dosage may be necessary. The effects of liver disease on clearance of cefotaxime and its metabolite have been variable, but in general dosage adjustment has not been considered necessary. About 40% of cefotaxime is reported to be bound to plasma proteins.

Cefotaxime and desacetylcefotaxime are widely distributed in body tissues and fluids; therapeutic concentrations occur in the CSF particularly when the meninges are inflamed. Cefotaxime crosses the placenta and low concentrations have been detected in breast milk.

After partial metabolism in the liver to desacetylcefotaxime and inactive metabolites, elimination is mainly by the kidneys and about 40 to 60% of a dose has been recovered unchanged in the urine within 24 hours; a further 20% is excreted as the desacetyl metabolite. Relatively high concentrations of cefotaxime and desacetylcefotaxime occur in bile and about 20% of a dose has been recovered in the faeces.

Probenecid competes for renal tubular secretion with cefotaxime resulting in higher and prolonged plasma concentrations of cefotaxime and its desacetyl metabolite. Cefotaxime and its metabolites are removed by haemodialysis.

When microbiological assays have been used, reported pharmacokinetic values may relate to cefotaxime plus its active metabolite, desacetylcefotaxime.

Hepatic impairment. References.

1. Höffken G, *et al.* Pharmacokinetics of cefotaxime and desacetylcefotaxime in cirrhosis of the liver. *Chemotherapy* 1984; **30**: 7–17.
2. Graninger W, *et al.* Cefotaxime and desacetyl-cefotaxime blood levels in hepatic dysfunction. *J Antimicrob Chemother* 1984; **14** (suppl B): 143–6.
3. Hary L, *et al.* The pharmacokinetics of ceftriaxone and cefotaxime in cirrhotic patients with ascites. *Eur J Clin Pharmacol* 1989; **36**: 613–16.
4. Ko RJ, *et al.* Pharmacokinetics of cefotaxime and desacetylcefotaxime in patients with liver disease. *Antimicrob Agents Chemother* 1991; **35**: 1376–80.

Renal impairment. References.

1. Matzke GR, *et al.* Cefotaxime and desacetyl cefotaxime kinetics in renal impairment. *Clin Pharmacol Ther* 1985; **38**: 31–6.
2. Paap CM, *et al.* Pharmacokinetics of cefotaxime and its active metabolite in children with renal dysfunction. *Antimicrob Agents Chemother* 1991; **35**: 1879–83.
3. Paap CM, *et al.* Cefotaxime and metabolite disposition in two pediatric continuous ambulatory peritoneal dialysis patients. *Ann Pharmacother* 1992; **26**: 341–3.
4. Paap CM, Nahata MC. The relation between type of renal disease and renal drug clearance in children. *Eur J Clin Pharmacol* 1993; **44**: 195–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Cefacolin; Terasep; ***Austria***: Claforan; ***Belg.***: Claforan; ***Braz.***: Ceforan; Claforan; Clafordil; Fotax; Kefaxim†; Kefozil; Taxima†; ***Canad.***: Claforan; ***Chile***: Grifotaxima; ***China***: Claforan (凯福隆); Dalilong (达力隆); Haifuxun (海复迅); Kaidilong (凯帝龙); Raxim (诺西福); Saifulong (赛福隆); Taxim (泰可欣); Xiankai (先凯); ***Cz.***: Ceftax; Sefotak; Taxcef†; ***Denm.***: Claforan†; ***Fin.***: Claforan†; ***Fr.***: Claforan; ***Ger.***: Claforan; ***Gr.***: Ceramil; Ciltiren; Claforan; Doctistatin; Flemycin; Gloryfen; Golafen; Letynol; Mastovet; Molelant; Naspor; Phacocef; Solubilax; Spirosine; Stoparen; ***Hong Kong***: Claforan; Valoran; ***Hung.***: Cefalekol; Claforan; Tirotax; ***India***: Amtaxime; Avicef; Axiom; Bestax; Biotax; C-Tax; Cefaden; Cefantral; Cefatox; Ceflin; Cefokil; Cefotim; Ceftex; Claforan; Desatax; Efotax; Evacef; Faxim; Flamotax; Haltax; Ivitax; Lyforan; Mutax; Nepotax; Nitaxim; Novatax; Nutaxin; Ominax; Omnatax; Omnicef; Oritaxime; Osotax; Zetaxim†; ***Indon.***: Baxima; Biocef; Cefarin; Cefor; Cefovell; Cefoxal†; Clacef; Clafexim; Claforan; Clatax; Combicef; Efotax; Ethiclaf; Fobet; Foxim; Glocef; Goforan; Kalfoxim; Lancef; Lapixime; Procefa; Rycef; Siclaxim; Soclaf; Starclaf; Taxecap; Taxef; Taxegram; Taximax; Tirdicef; ***Irl.***: Claforan; ***Israel***: Claforan; Kefotam; ***Ital.***: Aximad; Batixim; Cefomit; Delius; Lirgosin; Refotax; Salocef; Spectrocef; Taxime; Zariviz; Zimanel; ***Malaysia***: Claforan; Claraxim; Rekaxime; ***Mex.***: Baxytax†; Benaxima; Biosint; Cefotex; Cefradil; Ceftomax†; Claforan; Defradil†; Fot-Amsa; Fotexina; Sefoxiram; Sepsilem†; Taporin; Tebruxim; Tecnoxima; Tirotax; Viken†; Xendin; ***Neth.***: Claforan; Tirotax; ***NZ***: Claforan†; ***Philipp.***: Axitof; Cefotax; Cefox; Ceptax; Cetaxima; Cladex; Clafetam; Clafojen; Claforan; Clafoxim; Clavocef†; Clinbaxef; Fotexin; Foximet; Haxim; Lac-xim; Losforexan; Ofetaxim; Pantaxin; Sefotak; Tafoxam†; Taxim; Zalor; Zefocent; ***Pol.***: Biotaksym; Rantaksym; Tarcefoksym; Tirotax†; ***Port.***: Antadar; Ralopar; Resibelacta; Totam†; ***Rus.***: Cefabol (Цефабол); Cefantral (Цефантрал); Cefosin (Цефосин); Cefotex (Кефотекс); Cetax (Цетакс); Clafobrin (Клафобрин); Claforan (Клафоран); Intrataxime (Интрataксим); Lyforan (Лифоран); Oritax (Оритакс); Oritaxim (Оритаксим); Talcef (Тальцеф); Tarcefoksym (Тарцефоксим); Tax-O-Bid (Такс-О-Бид); Tirotax (Тиротакс); ***S.Afr.***: Claforan†; Clatax; Kefotax; Klafotaxim; Oritaxim†; Reftax†; ***Singapore***: Clacef†; Claforan; ***Spain***: Claforan; ***Swed.***: Claforan; ***Switz.***: Claforan†; ***Thai.***: Cefomic; Ceforan; Cefotax†; Cefox; Ceftaxan†; Claforan; Claraxim; Fontax†; Fotax; Motaxim†; Necaxime; ***Turk.***: Betaksim; Claforan; Deforan†; Equitax; Sefagen; Sefoksim; Sefotak; Sefoxim; Taksidem; Taxocef; ***UAE***: Primocef; ***UK***: Claforan; ***Ukr.***: Sefotak (Сефотак)†; Tax-O-Bid (Такс-О-Бид); ***USA***: Claforan; ***Venez.***: Cefam; Cefatox; Claforan; Novatax; Tirotax.

Multi-ingredient Preparations. ***China***: Xinzhijun (新治君); ***India***: Augtax; Avicef-S; Cefalin-S; Cefantral-S; Cefup; Duotax; Effimax Plus; Evacef-S; Ivimax; Labicef-S; Magnatax; Maxitax; Montero; Mutax Plus; Nutaxin-S; Oritaximax; Osotax-S; Sultax; ***Ukr.***: Taxtam (Таксгам).

Pharmacopoeial Preparations
BP 2014: Cefotaxime Injection;
USP 36: Cefotaxime for Injection; Cefotaxime Injection.

Cefotetan *(BAN, USAN, rINN)*

Cefotetán; Céfotétan; Cefotetanum; ICI-156834 (cefotetan or cefotetan disodium); YM-09330 (cefotetan or cefotetan disodium); Цефотетан.

(7*S*)-7-[(4-Carbamoylcarboxymethylene-1,3-dithietan-2-yl) carboxamido]-7-methoxy-3-[(1-methyl-1*H*-tetrazol-5-yl)thiomethyl]-3-cephem-4-carboxylic acid.

$C_{17}H_{17}N_7O_8S_4$=575.6

CAS — 69712-56-7.

ATC — J01DC05.

ATC Vet — QJ01DC05.

UNII — 48SPP0PA9Q.

Pharmacopoeias. In *Jpn* and *US.*

USP 36: (Cefotetan). Store in airtight containers.

Cefotetan Disodium *(BANM, USAN, rINNM)*

Cefotetán disódico; Céfotétan Disodique; Cefotetan Sodium; Cefotetanum Dinatricum; ICI-156834 (cefotetan or cefotetan disodium); YM-09330 (cefotetan or cefotetan disodium); Динатрий Цефотетан.

(7*S*)-7-[(4-Carbamoylcarboxymethylene-1,3-dithietan-2-yl) carboxamido]-7-methoxy-3-[(1-methyl-1*H*-tetrazol-5-yl)thiomethyl]-3-cephem-4-carboxylic acid, disodium salt.

$C_{17}H_{15}N_7Na_2O_8S_4$=619.6

CAS — 74356-00-6.

ATC — J01DC05.

ATC Vet — QJ01DC05.

UNII — 0GXP746VXB.

Pharmacopoeias. In *US.*

USP 36: (Cefotetan Disodium). pH of a 10% solution in water is between 4.0 and 6.5. Store in airtight containers.

Incompatibility and stability. There may be incompatibility with aminoglycosides. Precipitation has been reported with promethazine hydrochloride.

References.

1. Das Gupta V, *et al.* Chemical stability of cefotetan disodium in 5% dextrose and 0.9% sodium chloride injections. *J Clin Pharm Ther* 1990; **15**: 109–14.
2. Erickson SH, Ulict D. Incompatibility of cefotetan disodium and promethazine hydrochloride. *Am J Health-Syst Pharm* 1995; **52**: 1347.

Uses and Administration

Cefotetan is a cephamycin antibacterial generally classified with the second-generation cephalosporins and used similarly to cefoxitin (p. 248.2) in the treatment and prophylaxis of anaerobic and mixed bacterial infections, especially intra-abdominal and pelvic infections.

It is given as the disodium salt by deep intramuscular injection or intravenously by slow injection over 3 to 5 minutes or by infusion. Doses are expressed in terms of the equivalent amount of cefotetan; 1.08 g of cefotetan disodium is equivalent to about 1 g of cefotetan. The usual dose is 1 or 2 g every 12 hours. For the treatment of life-threatening infections, 3 g every 12 hours may be given intravenously. Doses of cefotetan should be reduced in patients with moderate to severe renal impairment (see p. 247.3).

For infection prophylaxis during surgical procedures, an intravenous dose of 1 or 2 g is given 30 to 60 minutes before surgery or, in caesarean section, as soon as the umbilical cord is clamped.

Administration in renal impairment. Parenteral doses of cefotetan should be reduced in patients with moderate to severe renal impairment. US licensed product information gives the following dosing guidelines based on creatinine clearance (CC):

- CC 10 to 30 mL/minute: the usual dose every 24 hours or one-half the usual dose every 12 hours
- CC less than 10 mL/minute: the usual dose every 48 hours or one-quarter the usual dose every 12 hours

In patients undergoing haemodialysis, one-quarter the usual dose may be given every 24 hours on days between dialysis and one-half the usual dose on the day of dialysis.

Adverse Effects and Precautions

As for Cefalotin Sodium, p. 235.2.

Cefotetan contains an *N*-methylthiotetrazole side-chain and has the potential to cause hypoprothrombinaemia and bleeding.

Cefotetan, especially at high doses, may interfere with the Jaffé method of measuring creatinine concentrations to produce falsely elevated values; this should be borne in mind when measuring renal function.

Effects on the blood. Reviews[1,2] and a case report[3] of haemolytic anaemia associated with cefotetan.

1. Moes GS, MacPherson BR. Cefotetan-induced hemolytic anemia: a case report and review of the literature. *Arch Pathol Lab Med* 2000; 124: 1344–6.
2. Viraraghavan R, *et al.* Cefotetan-induced haemolytic anaemia: a review of 85 cases. *Adverse Drug React Toxicol Rev* 2002; 21: 101–7.
3. Robinson HE, *et al.* Cefotetan-induced life-threatening haemolysis. *Med J Aust* 2006; 184: 251.

Sodium content. Each g of cefotetan disodium contains about 3.2 mmol of sodium.

Interactions

As for Cefamandole, p. 236.3.

Antimicrobial Action

Cefotetan is a cephamycin antibacterial with a mode of action and spectrum of activity similar to those of cefoxitin (p. 249.1). It is generally much more active *in vitro* than cefoxitin against the Gram-negative Enterobacteriaceae, but has similar activity against *Bacteroides fragilis* and may be less active against some other *Bacteroides* spp.

Pharmacokinetics

On intramuscular injection of cefotetan, peak plasma concentrations of about 70 micrograms/mL at 1 hour and 90 micrograms/mL at 3 hours have occurred after doses of 1 and 2 g, respectively. The plasma half-life of cefotetan is usually in the range of 3.0 to 4.6 hours and is prolonged in patients with renal impairment. About 88% of cefotetan may be bound to plasma proteins, depending on the plasma concentration.

Cefotetan is widely distributed in body tissues and fluids. It crosses the placenta and low concentrations have been detected in breast milk. High concentrations occur in bile.

Cefotetan is excreted in the urine, primarily by glomerular filtration, as unchanged drug; 50 to 80% of a dose has been recovered in the urine in 24 hours and high concentrations are achieved. Small amounts of the tautomeric form of cefotetan have been detected in both plasma and urine.

Biliary excretion of cefotetan probably accounts for nonrenal clearance.

Some cefotetan is removed by dialysis.

References.
1. Martin C, *et al.* Clinical pharmacokinetics of cefotetan. *Clin Pharmacokinet* 1994; 26: 248–58.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Cefotan†.

Pharmacopoeial Preparations
USP 36: Cefotetan for Injection; Cefotetan Injection.

Cefotiam Hydrochloride *(BANM, USAN, rINNM)*

Abbott-48999; Cefotiam, Chlorhydrate de; Cefotiam, hidrocloruro de; Cefotiami Hydrochloridum; CGP-14221E (cefotiam or cefotiam hydrochloride); Hidrocloruro de cefotiam; SCE-963; Цефотиама Гидрохлорид.

7-[2-(2-Amino-1,3-thiazol-4-yl)acetamido]-3-[1-(2-dimethylaminoethyl)-1*H*-tetrazol-5-ylthiomethyl]-3-cephem-4-carboxylic acid dihydrochloride.

$C_{18}H_{23}N_9O_4S_3.2HCl$=598.5

CAS — 61622-34-2 (cefotiam); 66309-69-1 (cefotiam hydrochloride).

ATC — J01DC07.

ATC Vet — QJ01DC07.

UNII — H7V12WDZ93.

Pharmacopoeias. In *Jpn* and *US*. *Jpn* also includes cefotiam hexetil hydrochloride.

USP 36: (Cefotiam Hydrochloride). Store in airtight containers.

Profile

Cefotiam is a third-generation cephalosporin antibacterial with actions and uses similar to those of cefamandole (p. 236.2). It is given intravenously or intramuscularly as the hydrochloride but doses are expressed in terms of the base; 1.14 g of cefotiam hydrochloride is equivalent to about 1 g of cefotiam. The usual dose is the equivalent of up to 6 g of cefotiam daily in divided doses, according to the severity of the infection.

Cefotiam hexetil hydrochloride, a prodrug of cefotiam, is given orally in doses equivalent to 200 to 400 mg of cefotiam twice daily.

References.
1. Brogard JM, *et al.* Clinical pharmacokinetics of cefotiam. *Clin Pharmacokinet* 1989; 17: 163–74.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Spizef†; *China*: Fengtixin (锋替新); Fontien (复仙安); Haitishu (海替舒); Sa Lan Xin (萨兰欣); *Fr.*: Taketiam; Texodil; *Ger.*: Spizef†; *Gr.*: Takedrol; *Indon.*: Aspil; Cefradol; Ceradolan; Ethidol; Fodiclo; Fotaram; *Jpn*: Pansporin; *Philipp.*: Ceradolan; Ceratim; Fotaram; Harolan; *Singapore*: Ceradolan†; *Thai.*: Ceradolan†.

Pharmacopoeial Preparations
USP 36: Cefotiam for Injection.

Cefovecin Sodium *(USAN, rINNM)*

Cefovecina sódica; Céfovécine Sodique; Natrii Cefovecinum; UK-287074-02; Натрий Цефовецин.

Sodium (6*R*,7*R*)-7-{[(2*Z*)-(2-aminothiazol-4-yl)(methoxyimino) acetyl]amino}-8-oxo-3-{(2*S*)-tetrahydrofuran-2-yl}-5-thia-1-azabicyclo[4.4.0]oct-2-ene-2-carboxylate.

$C_{17}H_{18}N_5NaO_6S_2$=475.5

CAS — 234096-34-5 (cefovecin); 141195-77-9 (cefovecin sodium).

UNII — DL8Q24959P.

Profile

Cefovecin sodium is a third-generation cephalosporin antibacterial used in veterinary medicine.

Cefoxitin Sodium *(BANM, USAN, rINNM)*

Cefoksitino natrio druska; Cefoksytyna sodowa; Cefoxitin Natrium; Cefoxitin sodná sůl; Cefoxitina sódica; Céfoxitine sodique; Cefoxitinnatrium; Cefoxitin-nátrium; Cefoxitinum natricum; Kefoksitiininatrium; L-620388; MK-306; Natrii Cefoxitinum; Натрий Цефокситин.

Sodium 3-carbamoyloxymethyl-7-methoxy-7-[2-(2-thienyl) acetamido]-3-cephem-4-carboxylate.

$C_{16}H_{16}N_3NaO_7S_2$=449.4

CAS — 35607-66-0 (cefoxitin); 33564-30-6 (cefoxitin sodium).

ATC — J01DC01.

ATC Vet — QJ01DC01.

UNII — Q68050H03T.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Cefoxitin Sodium). A white or almost white, very hygroscopic, powder. Very soluble in water; sparingly soluble in alcohol. A 1% solution in water has a pH between 4.2 and 7.0. Store in airtight containers.

USP 36: (Cefoxitin Sodium). White to off-white, somewhat hygroscopic, granules or powder, having a slight characteristic odour. Very soluble in water; slightly soluble in acetone; insoluble in chloroform and in ether; sparingly soluble in dimethylformamide; soluble in methyl alcohol. pH of a 10% solution in water is between 4.2 and 7.0. Store in airtight containers at a temperature not exceeding 8 degrees.

Uses and Administration

Cefoxitin is a parenteral cephamycin antibacterial that differs structurally from the cephalosporins by the addition of a 7-α-methoxy group to the 7-β-aminocephalosporanic acid nucleus.

It is generally classified with the second-generation cephalosporins and can be used similarly to cefamandole (p. 236.3) for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria, including infections of the abdomen, bones and joints, skin and skin structure, genito-urinary and respiratory tracts, and gynaecological infections including pelvic inflammatory disease. However, because of its activity against *Bacteroides fragilis* and other anaerobic bacteria, it is used principally in the treatment and prophylaxis of anaerobic and mixed bacterial infections. For details of infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Administration and dosage. Cefoxitin is given as the sodium salt by deep intramuscular injection, by slow intravenous injection over 3 to 5 minutes, or by intermittent or continuous intravenous infusion.

Doses are expressed in terms of the equivalent amount of cefoxitin; 1.05 g of cefoxitin sodium is equivalent to about 1 g of cefoxitin. For mild, uncomplicated infections cefoxitin is usually given in doses of 1 g every 6 to 8 hours and increased to 2 g every 6 to 8 hours for moderate to severe infections. For more severe infections up to 12 g may be given daily in 4 to 6 divided doses.

For the treatment of uncomplicated urinary-tract infections, cefoxitin 1 g twice daily has been given intramuscularly. For the treatment of uncomplicated gonorrhoea, a single dose of 2 g intramuscularly has been given with probenecid 1 g orally.

For surgical infection prophylaxis, the usual dose is cefoxitin 2 g intramuscularly or intravenously 30 to 60 minutes before the procedure and then every 6 hours, not usually for more than 24 hours.

At caesarean section a single 2-g dose may be given intravenously to the mother as soon as the umbilical cord is clamped. If necessary, a 3-dose regimen, with further 2-g doses 4 and 8 hours after the initial dose, may be used.

The dose of cefoxitin may need to be reduced in patients with renal impairment, see p. 248.3.

For details of doses in children, including those with renal impairment, see p. 248.3.

Reviews.
1. DiPiro JT, May JR. Use of cephalosporins with enhanced antianaerobic activity for treatment and prevention of anaerobic and mixed infections. *Clin Pharm* 1988; 7: 285–302.
2. Goodwin CS. Cefoxitin 20 years on: is it still useful? *Rev Med Microbiol* 1995; 6: 146–53.

Administration in children. Cefoxitin may be given to neonates and children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria and for surgical infection prophylaxis. It is given intravenously by slow injection over 3 to 5 minutes or by intermittent or continuous infusion; it may also be given by intramuscular injection in children 3 months of age and older.

For treatment, neonates may be given 20 to 40 mg/kg, every 12 hours for premature infants (weighing more than 1.5 kg) and neonates up to 1 week old and every 8 hours for those aged 1 to 4 weeks. Infants and children may be given 20 to 40 mg/kg every 6 to 8 hours; in severe infections, up to 200 mg/kg daily may be given, to a maximum of 12 g daily.

Infants and children undergoing surgical procedures can be given doses of 30 to 40 mg/kg, at the same time intervals as adults (see Uses and Administration, above.); neonates may be given 30 to 40 mg/kg, but at intervals of 8 to 12 hours.

In children with renal impairment the dose of cefoxitin should be proportionally reduced, and the frequency of dosage modified, in accordance with the recommendation for adults, see p. 248.3.

Administration in renal impairment. In renal impairment, parenteral doses of cefoxitin should be reduced according to creatinine clearance (CC). After an initial loading dose of 1 to 2 g, maintenance doses are:

- CC 30 to 50 mL/minute: 1 to 2 g every 8 to 12 hours
- CC 10 to 29 mL/minute: 1 to 2 g every 12 to 24 hours
- CC 5 to 9 mL/minute: 0.5 to 1 g every 12 to 24 hours
- CC below 5 mL/minute: 0.5 to 1 g every 24 to 48 hours

In patients undergoing haemodialysis, the loading dose should be repeated after each dialysis session.

Adverse Effects and Precautions

As for Cefalotin Sodium, p. 235.2.

Cefoxitin may interfere with the Jaffé method of measuring creatinine concentrations to produce falsely high values; this should be borne in mind when measuring renal function.

Breast feeding. Cefoxitin is distributed into breast milk but is detectable only in low concentrations. In a study[1] in which cefoxitin was given prophylactically in doses of 2 to 4 g to 18 women undergoing caesarean section, only one sample of breast milk contained measurable concentrations of cefoxitin, 19 hours after the last dose. No adverse effects have been seen in breast-fed infants whose mothers were receiving cefoxitin, and the American Academy of Pediatrics considers[2] that it is therefore usually compatible with breast feeding.

1. Roex AJM, *et al.* Secretion of cefoxitin in breast milk following short-term prophylactic administration in caesarean section. *Eur J Obstet Gynecol Reprod Biol* 1987; 25: 299–302.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)

Effects on the gastrointestinal tract. Marked changes in anaerobic, facultative, and aerobic faecal flora have been noted with cefoxitin.[1]

1. Mulligan ME, *et al.* Alterations in human fecal flora, including ingrowth of Clostridium difficile, related to cefoxitin therapy. *Antimicrob Agents Chemother* 1984; 26: 343–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cefoxitin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 15/10/11)

Sodium content. Each g of cefoxitin sodium contains about 2.2 mmol of sodium.

Interactions

Probenecid reduces the renal clearance of cefoxitin.

Antimicrobial Action

Cefoxitin is a cephamycin antibacterial which, like the other beta lactams, is bactericidal and is considered to act through the inhibition of bacterial cell wall synthesis.

It has a similar spectrum of activity to cefamandole (p. 237.1) but is more active against anaerobic bacteria, especially *Bacteroides fragilis*.

Cefoxitin can induce the production of beta-lactamases by some bacteria, and use of cefoxitin with other beta lactams have been shown to be antagonistic *in vitro*.

Cefoxitin itself is considered to be resistant to many beta-lactamases, including those produced by *Bacteroides* spp. However, acquired resistance to cefoxitin has been reported in *B. fragilis* (see Anaerobic Bacterial Infections, p. 173.1) and has been attributed to beta-lactamase as well as to alterations in penicillin-binding proteins or to outer membrane proteins; there may be cross-resistance to other antibacterials.

References.
1. Cuchural GJ, *et al.* Transfer of β-lactamase-associated cefoxitin resistance in Bacteroides fragilis. *Antimicrob Agents Chemother* 1986; 29: 918–20.
2. Piddock LJV, Wise R. Cefoxitin resistance in Bacteroides species: evidence indicating two mechanisms causing decreased susceptibility. *J Antimicrob Chemother* 1987; 19: 161–70.
3. Brogan O, *et al.* Bacteroides fragilis resistant to metronidazole, clindamycin and cefoxitin. *J Antimicrob Chemother* 1989; 23: 660–2.
4. Wexler HM, Halebian S. Alterations to the penicillin-binding proteins in the Bacteroides fragilis group: a mechanism for non-β-lactamase mediated cefoxitin resistance. *J Antimicrob Chemother* 1990; 26: 7–20.
5. Cherubin CE, Appleman MD. Susceptibility of cefoxitin-resistant isolates of bacteroides to other agents including β-lactamase inhibitor/β-lactam combinations. *J Antimicrob Chemother* 1993; 32: 168–70.

Pharmacokinetics

Cefoxitin is not absorbed from the gastrointestinal tract; it is given parenterally as the sodium salt. After 1 g by intramuscular injection a peak plasma concentration of up to 30 micrograms/mL at 20 to 30 minutes has been reported whereas concentrations of 125, 72, and 25 micrograms/mL have been achieved after intravenous doses of 1 g over 3, 30, and 120 minutes respectively. Cefoxitin is about 70% bound to plasma proteins. It has a plasma half-life of 45 to 60 minutes which is prolonged in renal impairment. Cefoxitin is widely distributed in the body but there is normally little penetration into the CSF, even when the meninges are inflamed. It crosses the placenta and has been detected in breast milk. Relatively high concentrations occur in bile.

The majority of a dose is excreted unchanged by the kidneys, up to about 2% being metabolised to descarbamylcefoxitin which is virtually inactive. Cefoxitin is excreted in the urine by glomerular filtration and tubular secretion and about 85% of a dose is recovered within 6 hours; probenecid slows this excretion. After an intramuscular dose of 1 g, peak concentrations in the urine are usually greater than 3 mg/mL.

Cefoxitin is removed to some extent by haemodialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Mefoxin†; ***Austria***: Mefoxitin†; ***Braz.***: Cefoxan†; Cefoxin†; Cefton; Gamacef; Kefox; Mefoxin; ***China***: Daliding (达力叮); ***Fr.***: Mefoxin; ***Gr.***: Destrepen; Mefoxil; Metaptyl; ***Hong Kong***: Mefoxin†; ***Ital.***: Cefocidin; Mefoxin; ***NZ***: Mefoxin; ***Philipp.***: Cefoxivit; Dintaxin; Foxitin; Haxotin; Monowel; Pacetin; Panafox; Zepax; Zepotin; ***Port.***: Atralxitina; ***Rus.***: Anaerocef (Анаэроцеф); ***S.Afr.***: Mefoxin; ***Thai.***: Cefoxin; Cefxitin; Maxotin†; Zefin†; ***Turk.***: Mefoxim; ***USA***: Mefoxin.

Pharmacopoeial Preparations
BP 2014: Cefoxitin Injection;
USP 36: Cefoxitin for Injection; Cefoxitin Injection.

Cefozopran Hydrochloride *(rINNM)*

Cefozopran, Chlorhydrate de; Cefozoprán, hidrocloruro de; Cefozopranі Hydrochloridum; Hidrocloruro de cefozoprán; SCE-2787; Цефозопрана Гидрохлорид.

(-)-1-[[(6*R*,7*R*)-7-[2-(5-Amino-1,2,4-thiadiazol-3-yl)glyoxylamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1*H*-imidazo[1,2-*b*]pyridazin-4-ium hydroxide inner salt, 7²-(*Z*)-(*O*-methyloxime), hydrochloride.

$C_{19}H_{17}N_9O_5S_2,HCl$=552.0

CAS — 113359-04-9 (cefozopran); 113981-44-5 (cefozopran hydrochloride).
ATC — J01DE03.
ATC Vet — QJ01DE03.
UNII — 060I5C0GRC.

Pharmacopoeias. In *Jpn*.

Profile

Cefozopran is a cephalosporin antibacterial used parenterally as the hydrochloride.

References.
1. Iwahi T, *et al.* In vitro and in vivo activities of SCE-2787, a new parenteral cephalosporin with a broad antibacterial spectrum. *Antimicrob Agents Chemother* 1992; 36: 1358–66.
2. Paulfeuerborn W, *et al.* Comparative pharmacokinetics and serum bactericidal activities of SCE-2787 and ceftazidime. *Antimicrob Agents Chemother* 1993; 37: 1835–41.
3. Fujii R, *et al.* Pharmacokinetics and clinical effects of cefozopran in pediatric patients. *Jpn J Antibiot* 1996; 49: 17–33.
4. Toyokawa M, *et al.* In vitro combined effects of cefozopran/teicoplanin and cefozopran/vancomycin on methicillin-resistant Staphylococcus aureus. *J Chemother* 2003; 15: 31–6.
5. Nomura K, *et al.* Optimized dosage and frequency of cefozopran for patients with febrile neutropenia based on population pharmacokinetic and pharmacodynamic analysis. *J Antimicrob Chemother* 2008; 61: 892–900.
6. Sato T, *et al.* A prospective, randomized study comparing cefozopran with piperacillin-tazobactam plus ceftazidime as empirical therapy for febrile neutropenia in children with hematological disorders. *Pediatr Blood Cancer* 2008; 51: 774–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Firstcin.

Cefpiramide *(USAN, rINN)*

Cefpiramida; Cefpiramidum; SM-1652; Wy-44635; Цефпирамид.

(7*R*)-7-[(*R*)-2-(4-Hydroxy-6-methylnicotinamido)-2-(4-hydroxyphenyl)acetamido]-3-(1-methyl-1*H*-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid.

$C_{25}H_{24}N_8O_7S_2$=612.6

CAS — 70797-11-4.
ATC — J01DD11.
ATC Vet — QJ01DD11.
UNII — P936YA152N.

Pharmacopoeias. In *US*.

USP 36: (Cefpiramide). Store in airtight containers. pH of a 0.5% suspension in water is between 3.0 and 5.0.

Cefpiramide Sodium *(USAN, rINNM)*

Cefpiramida sódica; Cefpiramide Sodique; Natrii Cefpiramidum; Натрий Цефпирамид.

$C_{25}H_{23}N_8NaO_7S_2$=634.6

CAS — 74849-93-7.
ATC — J01DD11.
ATC Vet — QJ01DD11.
UNII — 137KB7GYKB.

Pharmacopoeias. In *Jpn*.

Profile

Cefpiramide is a third-generation cephalosporin antibacterial related to cefoperazone (p. 243.1) and with similar activity against *Pseudomonas aeruginosa*, but possibly less active against Enterobacteriaceae. Cefpiramide is also active against staphylococci and streptococci and marginal activity against enterococci *in vitro* has been reported. Like cefamandole (p. 236.2), cefpiramide contains an *N*-methylthiotetrazole side-chain, a structure associated with hypoprothrombinaemia, alcohol intolerance, and potentiation of anticoagulants.

Cefpiramide is given by intravenous injection or infusion as the sodium salt in the treatment of susceptible infections but doses are expressed in terms of cefpiramide; 1.04 g of cefpiramide sodium is equivalent to about 1 g of cefpiramide. The usual dose is 1 to 2 g daily in 2 divided doses.

References.
1. Wang H, *et al.* In-vitro antibacterial activities of cefpiramide and other broad-spectrum antibiotics against 440 clinical isolates in China. *J Infect Chemother* 2000; 6: 81–5.

Sodium content. Each g of cefpiramide sodium contains about 1.6 mmol of sodium.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Tailixin (泰力信); Tamicin (泰吡信); ***Jpn***: Sepatren†.

Pharmacopoeial Preparations
USP 36: Cefpiramide for Injection.

Cefpirome Sulfate *(BANM, USAN, rINNM)*

Cefpiroma, sulfato de; Cefpirome, Sulfate de; Cefpirome Sulphate; Cefpiromi Sulfas; Cefpiromsulfat; HR-810 (cefpirome or cefpirome sulfate); Kefpiromisulfaatti; Sulfato de cefpiroma; Цефпирома Сульфат.

(*Z*)-7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1-pyrindiniomethyl)-3-cephem-4-carboxylate sulphate.

$C_{22}H_{22}N_6O_5S_2,H_2SO_4$=612.6

CAS — 84957-29-9 (cefpirome); 98753-19-6 (cefpirome sulfate).
ATC — J01DE02.
ATC Vet — QJ01DE02.
UNII — BA5ALU2ZT9.

Pharmacopoeias. In *Jpn*.

Uses and Administration

Cefpirome is a fourth-generation cephalosporin antibacterial used in the treatment of infections due to susceptible organisms. They include infections of the urinary tract, respiratory tract, and skin, and also septicaemia. It is effective against *Pseudomonas aeruginosa* and may be given to treat infections in neutropenic patients. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Cefpirome is given by intravenous injection over 3 to 5 minutes or infusion over 20 to 30 minutes as the sulfate, but doses are expressed in terms of the base; 1.19 g of cefpirome sulfate is equivalent to about 1 g of cefpirome. The usual dose is the equivalent of 1 or 2 g of cefpirome every 12 hours. For details of reduced doses to be used in renal impairment, see p. 249.3.

References.
1. Brown EM, *et al.* eds. Cefpirome: a novel extended spectrum cephalosporin. *J Antimicrob Chemother* 1992; 29 (suppl A): 1–104.
2. Wiseman LR, Lamb HM. Cefpirome: a review of its antibacterial activity, pharmacokinetic properties and clinical efficacy in the treatment of severe nosocomial infections and febrile neutropenia. *Drugs* 1997; 54: 117–40.

Administration in renal impairment. Intravenous doses of cefpirome should be modified in renal impairment; after a loading dose of 1 or 2 g-depending on the severity of infection, the maintenance dosage should be adjusted according to creatinine clearance (CC) and the severity of infection:

- CC 20 to 50 mL/minute: 0.5 or 1 g twice daily
- CC 5 to 20 mL/minute: 0.5 or 1 g once daily
- CC 5 mL/minute or less (in haemodialysis patients): 0.5 or 1 g once daily plus a half-dose after each dialysis session.

Adverse Effects and Precautions

As for Cefalotin, p. 235.2.

Cefpirome is reported to interfere with the Jaffé method of measuring creatinine concentrations to determine renal function.

References.
1. Rubinstein E, *et al.* A review of the adverse events profile of cefpirome. *Drug Safety* 1993; 9: 340–5.

Interactions

Probenecid reduces the renal clearance of cefpirome.

Antimicrobial Action

Cefpirome is a fourth-generation cephalosporin that is stable to many beta-lactamases. It has a spectrum of activity similar to that of the third-generation cephalosporin cefotaxime (p. 244.3), but it appears to be more active *in vitro* against staphylococci, some enterococci, some Enterobacteriaceae, and *Pseudomonas aeruginosa*. Cefpirome may be less active than ceftazidime (p. 253.3) against *Ps. aeruginosa*.

Pharmacokinetics

Cefpirome is given by injection as the sulfate. Mean peak serum concentrations of 80 to 90 micrograms/mL are attained after a single intravenous 1-g dose. The elimination half-life is about 2 hours and is prolonged in patients with renal impairment. Cefpirome is less than 10% bound to plasma proteins.

Cefpirome is widely distributed into body tissues and fluids and appears in breast milk. It is mainly excreted by the kidneys and 80 to 90% of a dose is recovered unchanged in the urine. Significant amounts are removed by haemodialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Cefrom†; ***Austria***: Cefrom; ***China***: Cefrom (泷新); Luobang (罗邦); ***Fr.***: Cefrom; ***Gr.***: Cefrom; ***India***: Allard; Bacirom; C-Rome; Cef-4; Ceforth; Cefph; Cefrom; Cepirom; Forgen; Forom; Ivcef; Ivirome; Neopirome; Nispirome; Nitpirome; Omnirom; Opirom; Tafrom; ***Indon.***: Bactirom; Bioprom; Caprocef; Ceflr; Cefmer 1; Cefnos; Cefrin; Cefrom; Ethirom; Interome; Lanpirome; Lapirom; Mor-

cef; Nufirom; Rime; Romicef; Sopirom; Xenoprom; Yarox; *Mex.*: Cefrom; *Neth.*: Cefrom†; *Philipp.*: Cefrin; Sanprome†; Zeferom; *Port.*: Cipiram; Parmocefe; *Rus.*: Cefanorm (Цефанорм); *S.Afr.*: Cefrom; *Thai.*: Cefrom†; Perome.

Cefpodoxime Proxetil

(BANM, USAN, rINNM)

Cefpodoxima proxetilo; Cefpodoxime proxétil; Cefpodoxime, Proxétil de; Cefpodoximi Proxetilum; Cefpodoximum proxetili; CS-807; R-3763 (cefpodoxime); U-76252; U-76253 (cefpodoxime); Цефподоксима Проксетил.

The 1-[(isopropoxycarbonyl)oxy]ethyl ester of (*Z*)-7-[2-(2-amino-1,3-thiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid.

$C_{21}H_{27}N_5O_9S_2$=557.6

CAS — 80210-62-4 (cefpodoxime); 87239-81-4 (cefpodoxime proxetil).

ATC — J01DD13.

ATC Vet — QJ01DD13.

UNII — 2TB00A1Z7N.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Cefpodoxime Proxetil). A white or pale yellow or light brown, amorphous powder. Very slightly soluble or practically insoluble in water; freely soluble in anhydrous ethanol; very soluble in acetonitrile and in methyl alcohol. Protect from light.

USP 36: (Cefpodoxime Proxetil). A white to light brownish-white powder, odourless or having a faint odour. Very slightly soluble in water; freely soluble in dehydrated alcohol; soluble in acetonitrile and in methyl alcohol; slightly soluble in ether. Store in airtight containers at a temperature not exceeding 25 degrees.

Uses and Administration

Cefpodoxime is a third-generation cephalosporin antibacterial used in the treatment of infections due to susceptible Gram-positive and Gram-negative bacteria, including infections of the respiratory and urinary tracts, skin and skin structure, and gonorrhoea. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Cefpodoxime is given orally as the proxetil ester, which is hydrolysed on absorption to cefpodoxime. Doses are expressed in terms of the equivalent amount of cefpodoxime; 130 mg of cefpodoxime proxetil is equivalent to about 100 mg of cefpodoxime. Absorption may be enhanced if cefpodoxime proxetil is given with food. The usual dose for adults is 100 to 200 mg every 12 hours for respiratory-tract and urinary-tract infections. A dose of 200 or 400 mg every 12 hours may be used for skin and soft-tissue infections.

For uncomplicated gonorrhoea, a single dose of 200 mg may be given.

The interval between doses of cefpodoxime may need to be extended in patients with renal impairment (see p. 250.1).

For details of doses in children, see p. 250.1.

References.
1. Moore EP, *et al.*, eds. Cefpodoxime proxetil: a third-generation oral cephalosporin. *J Antimicrob Chemother* 1990; 26 (suppl E): 1–101.
2. Adam D, *et al.*, eds. Cefpodoxime proxetil: a new third generation oral cephalosporin. *Drugs* 1991; 42 (suppl 3): 1–66.
3. Frampton JE, *et al.* Cefpodoxime proxetil: a review of its antibacterial activity, pharmacokinetic properties and therapeutic potential. *Drugs* 1992; 44: 889–917.
4. Chocas EC, *et al.* Cefpodoxime proxetil: a new, broad-spectrum, oral cephalosporin. *Ann Pharmacother* 1993; 27: 1369–77.
5. Fulton B, Perry CM. Cefpodoxime proxetil: a review of its use in the management of bacterial infections in paediatric patients. *Paediatr Drugs* 2001; 3: 137–58.

Administration in children. Cefpodoxime may be given to children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria. In the UK, licensed product information recommends that children and infants aged 15 days and older may be given 4 mg/kg orally every 12 hours, up to a maximum of 200 mg daily. In the USA, children aged 2 months and older may be given oral doses of 5 mg/kg every 12 hours, up to a maximum of 200 mg daily for pharyngitis or tonsillitis or 400 mg daily for acute otitis media or maxillary sinusitis.

Administration in renal impairment. The interval between oral doses of cefpodoxime should be extended in patients with renal impairment to every 24 hours in those with creatinine clearance of 10 to 39 mL/minute, and to every 48 hours when the creatinine clearance is less than 10 mL/minute. In patients on haemodialysis the dose should be given after each dialysis session.

Adverse Effects and Precautions

As for Cefalotin Sodium, p. 235.2.

The most frequently reported adverse effects of cefpodoxime are gastrointestinal disturbances, especially diarrhoea.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cefpodoxime as probably not porphyrinogenic: it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Interactions

Absorption of cefpodoxime is decreased by antacids or histamine H_2-receptor antagonists. Probenecid reduces the renal excretion of cefpodoxime.

Antimicrobial Action

As for Cefixime, p. 241.1, but cefpodoxime has greater activity against *Staphylococcus aureus*.

References.
1. Valentini S, *et al.* In-vitro evaluation of cefpodoxime. *J Antimicrob Chemother* 1994; 33: 495–508.

Pharmacokinetics

Cefpodoxime proxetil is de-esterified in the intestinal epithelium after oral doses, to release active cefpodoxime in the bloodstream. Bioavailability is about 50% in fasting subjects and may be increased in the presence of food. Absorption is decreased in conditions of low gastric acidity. Peak plasma concentrations of about 1.5, 2.5, and 4.0 micrograms/mL have been achieved 2 to 3 hours after oral doses of 100, 200, and 400 mg cefpodoxime respectively. About 20 to 30% of cefpodoxime is bound to plasma proteins. The plasma half-life is about 2 to 3 hours and is prolonged in patients with renal impairment.

Cefpodoxime reaches therapeutic concentrations in the respiratory and genito-urinary tracts and bile. It has been detected in low concentrations in breast milk.

Cefpodoxime is excreted unchanged in the urine. Some is removed by dialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Biocef; Otreon; *Braz.*: Orelox; *Chile*: Baxemin; Cefirax; *China*: Banan (博拿); Bo Man Xin (博曼欣); Bo Wo Xin (博沃欣); Cepodem (施博); Chun Di (纯迪); Chun Xin (纯欣); Hai Ling Yi (海凌依); Heng Ze (恒泽); Jia Bo (加博); Kang Fei (抗菲); Liang Bo (亮博); Min Xin (敏新); Ou Shuang (欧爽); Shan Pu Lan (善普兰); Shi Rui Bo (士瑞泊); Shuai Pu (帅孚); Si Li Tai (司力泰); Tao Te (焰特); Wei-Jiexin (维洁信); Xi Bo Te Xin (西博特欣); Yan Zhi (延知); *Fr.*: Orelox; *Ger.*: Orelox; Podomexef; *Gr.*: Cefodox; Orelox; *Hong Kong*: Banan; *India*: Apodox; Aripdox; Arodox; Avicef-O; Bactogard; Banin; Baroxime; Belpro; Bioproxe; Bobcef; C-Prox; Cacef; Capadex; Capoten; Caspod; CCL; Cedon; Cedoxime; Cefakind-P; Cefdolife; Cefective; Cefetil; Cefmag; Cefoact; Cefobit; Cefolex; Cefoprox; Ceforiz; Cefpogard; Cefpolar; Ceftils; Ceftop-DT; Cefvig; Cefwar; Cepocef; Cepocor; Cepodem; Ceporiz; Cepotil; Cepotuf; Cepotus; Cepox; Codimol; CPod; Docsef; Doxinis; Doxiz; Edrigard; Epodox; Everpod; Expodox; Fixtan; GSProx; Hipodox; Ipod; Ipodex; Kefodime; Kefpod; Kinopox; Kudox; Kzidime; Maxipod; Metoxim; Microcef; Monocef-O; Monotax-O; Nayacef; Nolia; Nudoxim; Odop; Omnacefpo; Oripod; Pandox; Tambac; *Indon.*: Banadoz; Banan†; *Irl.*: Cefodox; *Ital.*: Cefodox; Orelox; Otreon; *Jpn*: Banan; *Mex.*: Orelox; *Neth.*: Otreon†; *Philipp.*: Banan†; Cefadox; Zudem; *Port.*: Orelox†; *S.Afr.*: Cepodem; Orelox; *Spain*: Instanan†; Otreon†; *Switz.*: Orelox; Podomexef; *Thai.*: Banan†; *Turk.*: Dokselin; Orelox; Sefpotec; Sefsidal; *UK*: Orelox; *Ukr.*: Cefodox (Цефодокс); Cepodem (Цеподем); Dokcef (Докцеф); *USA*: Vantin.

Multi-ingredient Preparations. *India*: C-Prox-LB; Cedon-LB; Cedon-P; Cedoxime-LB; Ceftop; Doxinis-CV; Gudcef; Infactum; Kinopox-CV; Novodoxim; Nupod-CV; Papcef-CV.

Pharmacopoeial Preparations

USP 36: Cefpodoxime Proxetil for Oral Suspension; Cefpodoxime Proxetil Tablets.

Cefprozil *(BAN, USAN, rINN)*

BMY-28100-03-800; BMY-28100 (*cis*-isomer); BMY-28167 (*trans*-isomer); Cefprozilo; Cefprozilum; Kefprotsilli; Sefprozil; Цефпрозил.

(6*R*,7*R*)-7-[(*R*)-2-Amino-2-(*p*-hydroxyphenyl)acetamido]-8-oxo-3-(1-propenyl)-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid monohydrate; 7-(D-4-Hydroxyphenylglycylamino)-3-[(*E*)prop-1-enyl]cephem-4-carboxylic acid monohydrate.

$C_{18}H_{19}N_3O_5S.H_2O$=407.4

CAS — 92665-29-7 (anhydrous cefprozil); 121123-17-9 (cefprozil monohydrate).

ATC — J01DC10.

ATC Vet — QJ01DC10.

UNII — 4W0459ZA4V (cefprozil monohydrate); 1M698F4H4E (anhydrous cefprozil); S1SDI2FJIY (anhydrous cefprozil, e-isomer); W5T767OA4G (anhydrous cefprozil, z-isomer); 3ADV90MJVU (cefprozil, e-isomer); 358K60B00H (cefprozil, z-isomer).

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Cefprozil Monohydrate). A mixture of the diastereoisomers of cefprozil monohydrate. A white or yellow, slightly hygroscopic, crystalline powder. Slightly soluble in water and in methyl alcohol; practically insoluble in acetone. Store in airtight containers.

USP 36: (Cefprozil). pH of a 0.5% solution in water is between 3.5 and 6.5. Store in airtight containers.

Uses and Administration

Cefprozil is a cephalosporin antibacterial consisting of *cis*- and *trans*- isomers in a ratio of about 90:10. It should probably be classified as a second-generation cephalosporin and is used in the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria, including infections of the urinary and respiratory tracts and skin and skin structure. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Cefprozil is given orally as the monohydrate. Doses are expressed in terms of the equivalent amount of anhydrous cefprozil; 523 mg of cefprozil monohydrate is equivalent to about 500 mg of anhydrous cefprozil. The usual adult dose is 500 mg daily (as a single dose or in two divided doses), increased to 500 mg twice daily if necessary.

The dose of cefprozil may need to be reduced in patients with renal impairment, see p. 250.3.

For details of doses in children, see p. 250.3.

Reviews.
1. Wiseman LR, Benfield P. Cefprozil: a review of its antibacterial activity, pharmacokinetic properties, and therapeutic potential. *Drugs* 1993; 45: 295–317.
2. Barriere SL. Review of in vitro activity, pharmacokinetic characteristics, safety, and clinical efficacy of cefprozil, a new oral cephalosporin. *Ann Pharmacother* 1993; 27: 1082–9.
3. Aronovitz G. Treatment of upper and lower respiratory tract infections: clinical trials with cefprozil. *Pediatr Infect Dis J* 1998; 17 (suppl): S83–S88.
4. Bhargava S, *et al.* Cefprozil: a review. *Indian J Pediatr* 2003; 70: 395–400.

Administration in children. Cefprozil may be given to children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria. Children from the age of 6 months may be given oral doses of 15 mg/kg every 12 hours for the treatment of otitis media, 7.5 or 15 mg/kg every 12 hours for acute sinusitis, and 7.5 mg/kg every 12 hours for pharyngitis or tonsillitis. Children from the age of 2 years may be given 20 mg/kg once daily for skin and skin structure infections. Total daily doses used in children should not exceed 1 g.

Administration in renal impairment. Oral doses of cefprozil should be reduced in patients with renal impairment; standard doses should be halved in patients with a creatinine clearance ≤30 mL/minute. In patients on haemodialysis the dose should be given after each dialysis session.

Adverse Effects and Precautions

As for Cefalexin, p. 234.2.

Breast feeding. A study[1] in 9 healthy women found that concentrations of cefprozil in breast milk corresponded to no more than 0.3% of a dose and concluded that cefprozil could be given safely during breast feeding. The American Academy of Pediatrics[2] states that there have been no reports of any clinical effect on the infant associated with the use of cefprozil in breast-feeding mothers, and that it may be considered to be usually compatible with breast feeding.

1. Shyu WC, *et al.* Excretion of cefprozil into human breast milk. *Antimicrob Agents Chemother* 1992; 36: 938–41.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)

Hypersensitivity. Serum sickness-like reactions were reported in 4 patients, 3 of them children, given cefprozil.[1] Such reactions have been associated with cefaclor (p. 233.1), but whether they represent a class-related hypersensitivity reaction is not clear. Hypersensitivity vasculitis[2] and hepatitis[3] have also been reported with cefprozil.

1. Lowery N, *et al.* Serum sickness-like reactions associated with cefprozil therapy. *J Pediatr* 1994; 125: 325–8.
2. Totan M, Islek I. Hypersensitivity vasculitis induced by cefprozil. *Ann Saudi Med* 2002; 22: 269–70.
3. Bilici A, *et al.* A rare case of hepatitis associated with cefprozil therapy. *Scand J Infect Dis* 2007; 39: 190–2.

Interactions

As for Cefalexin, p. 234.2.

Antimicrobial Action

Cefprozil is bactericidal and has a similar but wider range of antimicrobial activity than cefaclor (p. 233.1).

Pharmacokinetics

Cefprozil is well absorbed from the gastrointestinal tract with a reported bioavailability of 90 to 95%. Oral doses of 0.25, 0.5, and 1 g produce peak plasma concentrations of about 6, 10, and 18 micrograms/mL respectively at 1 to 2 hours. The presence of food is reported to have little or no effect on the absorption of cefprozil. A plasma half-life of 1 to 1.4 hours has been reported; it is increased in patients with renal impairment, up to about 6 hours in those with end-stage renal failure. About 35 to 45% of cefprozil is bound to plasma proteins.

Cefprozil is widely distributed in the body tissues. Concentrations of cefprozil in tonsillar and adenoidal tissue are reported to be about 40 to 50% of those in plasma, and less than 0.3% of a 1-g dose has been recovered in breast milk in 24 hours. About 60% of a dose is excreted unchanged in the urine in the first 8 hours by glomerular filtration and tubular secretion. Concentrations of cefprozil of 700, 1000, and 2900 micrograms/mL have occurred in the urine within 4 hours of doses of 0.25, 0.5, and 1 g respectively. Some cefprozil is removed by haemodialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ceprof†; ***Braz.***: Cefzil; ***Canad.***: Cefzil; ***China***: Cefzil (施复捷); Kai Ke Zhi (凯可之); Xi Neng (希能); Yinlishu (银力舒); Yuanrui (元锐); ***Cz.***: Cefzil; ***Gr.***: Cefgram; Cefipra; Cefium; Cefpro; Cefzil; Cepius; Gramium; Mycoterb; Natrofen; Pricefil; Procef; Prozidil; Sanocef; Teliomon; Top 1; Tricef; Zamalin; ***Hong Kong***: Procef†; ***Hung.***: Cefzil; ***India***: Orprozil; Refzil-O; ***Indon.***: Cefzil†; Lizor; ***Ital.***: Cronocef; Procef†; Rozicel†; ***Mex.***: Procef; ***Philipp.***: Procef†; ***Pol.***: Cefzil†; ***Port.***: Procef; Radacefe; ***S.Afr.***: Auroprozil; Prozef; ***Singapore***: Procef; ***Spain***: Brisoral†; ***Switz.***: Procef; ***Thai.***: Procef†; ***Turk.***: Erasef; Prefix; Serozil; ***Venez.***: Procef.

Pharmacopoeial Preparations

USP 36: Cefprozil for Oral Suspension; Cefprozil Tablets.

Cefquinome Sulfate *(BANM, USAN, rINNM)*

Cefquinoma, sulfato de; Cefquinome, Sulfate de; Cefquinome Sulphate; Cefquinomi Sulfas; HR-111V; Sulfato de cefquinoma; Цефхинома Сульфат.

(6*R*-[6α,7β(*Z*)]]-1-[(7-[[(2-amino-4-thiazolyl)-(methoxylmino) acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl)methyl]-5,6,7,8,-tetrahydroquinolinium sulfate (1:1).

$C_{23}H_{24}N_6O_5S_2.H_2SO_4$=626.7

CAS — 84957-30-2 (cefquinome); 118443-89-3 (cefquinome sulfate); 123766-80-3 (cefquinome sulfate).

UNII — 3858K104DQ.

Profile

Cefquinome is a fourth-generation cephalosporin antibacterial used as the sulfate in veterinary medicine.

Cefradine *(BAN, rINN)*

Cefradin; Cefradina; Cefradinas; Céfradine; Cefradinum; Cefradyna; Cephradine (USAN); Cephradiini; Sefradin; SKF-D-39304; SQ-11436; SQ-22022 (cefradine dihydrate); Цефрадин.

(7*R*)-7-(α-D-Cyclohexa-1,4-dienylglycylamino)-3-methyl-3-cephem-4-carboxylic acid.

$C_{16}H_{19}N_3O_4S$=349.4

CAS — 38821-53-3 (anhydrous cefradine); 31828-50-9 (non-stoichiometric cefradine hydrate); 58456-86-3 (cefradine dihydrate).

ATC — J01DB09.

ATC Vet — QJ01DB09.

UNII — F1BC02I72W (cefradine); 9YA6SX554D (anhydrous cefradine); FUC0D71IZN (cefradine monohydrate); 56PPJ9MMPE (cefradine dihydrate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US* (which allows the anhydrous form, the monohydrate, or the dihydrate).

Ph. Eur. 8: (Cefradine). A white or slightly yellow, hygroscopic powder. Sparingly soluble in water; practically insoluble in alcohol and in *n*-hexane. A 1% solution in water has a pH of 3.5 to 6.0. Store at 2 degrees to 8 degrees in airtight containers. Protect from light.

USP 36: (Cephradine). A white to off-white crystalline powder. Sparingly soluble in water; very slightly soluble in alcohol and in chloroform; practically insoluble in ether. pH of a 1% solution in water is between 3.5 and 6.0. Store in airtight containers.

Incompatibility and stability. Commercially available injections contain sodium carbonate or arginine as neutralisers. Injections containing sodium carbonate are incompatible with solutions such as compound sodium lactate injection that contain calcium salts.

References.
1. Wang Y-C J, Monkhouse DC. Solution stability of cephradine neutralized with arginine or sodium bicarbonate. *Am J Hosp Pharm* 1983; 40: 432.
2. Mehta AC, *et al.* Chemical stability of cephradine injection solutions. *Intensive Therapy Clin Monit* 1988; 9: 195–6.

Uses and Administration

Cefradine is a first-generation cephalosporin antibacterial given orally or by the parenteral route in the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria (including infections of the respiratory and urinary tracts, bones and joints, and of the skin and skin structure) and for surgical infection prophylaxis. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Cefradine is given orally in doses of 1 to 2 g daily in 2 to 4 divided doses; up to 4 g daily may be given by this route. It may be given parenterally, by deep intramuscular injection or intravenously by slow injection over 3 to 5 minutes or by intermittent or continuous infusion, in doses of 2 to 4 g daily in 4 divided doses; up to 8 g daily may be given parenterally.

For surgical infection prophylaxis, 1 to 2 g may be given pre-operatively by intramuscular or intravenous injection; subsequent parenteral or oral doses are given as appropriate.

The dose of cefradine may need to be reduced in patients with renal impairment, see also p. 251.2.

For details of doses in children, see also p. 251.2.

Administration in children. Cefradine may be given to children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria. It is given orally, by intramuscular injection, or intravenously by slow injection over 3 to 5 minutes or intermittent or continuous infusion. The usual oral dose is 25 to 50 mg/kg daily in 2 or 4 divided doses; for otitis media 75 to 100 mg/kg daily in divided doses every 6 to 12 hours (to a maximum of 4 g daily) may be given. Cefradine is given parenterally in a dose of 50 to 100 mg/kg daily in 4 divided doses, increasing to 200 to 300 mg/kg daily in severe infections.

Although not licensed in the UK, for the prevention of *Staphylococcus aureus* lung infection in children with cystic fibrosis the *BNFC* recommends that those aged 7 years and older may be given an oral dose of 2 g twice daily.

Administration in renal impairment. Doses of cefradine should be reduced in patients with severe renal impairment. The following oral and parenteral doses are recommended in UK licensed product information according to creatinine clearance (CC):

- CC more than 20 mL/minute: 500 mg every 6 hours
- CC 5 to 20 mL/minute: 250 mg every 6 hours
- CC less than 5 mL/minute: 250 mg every 12 hours

Patients undergoing chronic, intermittent haemodialysis may be given a 250-mg dose at the start of the session, repeated after 6 to 12 hours, then again 36 to 48 hours after the initial dose, and again at the start of the next haemodialysis if more than 30 hours have elapsed since the previous dose.

Further dosage modification may be required in children with renal impairment.

Adverse Effects and Precautions

As for Cefalexin, p. 234.2. Intramuscular injections of cefradine can be painful and thrombophlebitis has occurred on intravenous injection.

Interactions

As for Cefalexin, p. 234.2.

Antimicrobial Action

As for Cefalexin, p. 234.2.

Pharmacokinetics

Cefradine is rapidly and almost completely absorbed from the gastrointestinal tract after oral doses. Doses of 0.25, 0.5, and 1 g given orally have produced peak plasma concentrations of about 9, 17, and 24 micrograms/mL respectively at 1 hour and are similar to those achieved with cefalexin. Absorption is delayed by the presence of food although the total amount absorbed is not appreciably altered. After intramuscular injection peak plasma concentrations of about 6 and 14 micrograms/mL have occurred within 1 to 2 hours of doses of 500 mg and 1 g respectively.

Only about 8 to 12% is reported to be bound to plasma proteins. A plasma half-life of about 1 hour has been reported; this is prolonged in patients with renal impairment. Cefradine is widely distributed to body tissues and fluids, but does not enter the CSF in significant quantities. Therapeutic concentrations occur in the bile. It crosses the placenta into the fetal circulation and is distributed in small amounts into breast milk.

Cefradine is excreted unchanged in the urine by glomerular filtration and tubular secretion, over 90% of an oral dose or 60 to 80% of an intramuscular dose being recovered within 6 hours. Peak urinary concentrations of about 3 mg/mL have been achieved after a 500-mg oral dose. Probenecid delays excretion.

Cefradine is removed by haemodialysis and peritoneal dialysis.

References.
1. Wise R. The pharmacokinetics of the oral cephalosporins—a review. *J Antimicrob Chemother* 1990; 26 (suppl E): 13–20.
2. Schwinghammer TL, *et al.* Pharmacokinetics of cephradine administered intravenously and orally to young and elderly subjects. *J Clin Pharmacol* 1990; 30: 893–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Veloseft†; ***China***: Di La (迪拉); Kebili (克必力); Saifuding (赛福定); Shen You (申优); Taiding (泰迪定); Velosef (泛捷复); Xianyi (先宜); Xindadelei (新达德雷); ***Fr.***: Dexef; Kelsef†; Zeefra†; ***Gr.***: Ampisodex; Amritacid; Bionovium; Nipredin; Opebrin; Sporobiotic; Tracilarin; Veloset; Vethisel; ***Hong Kong***: Qualisef; Veloseft†; Zeefra†; ***Indon.***: Dynacef; Loveceft†; Velodine; Velodrom; Veloseft†; ***Irl.***: Veloseft†; ***Ital.***: Ecosporina; ***Mex.***: Veracef; ***Philipp.***: Altozef; Cefralon; Gramcep; Medrin; Racep; Sedinef; Senadex; Solphride; Tolzep†; Vamosef; Velodyne; Yudinef; Zefadin; Zepdril; Zolicef; ***Pol.***: Tafril; ***Port.***: Biocefra; Cefaimin; Cefradur; ***S.Afr.***: Cefril†; ***Spain***: Septaceft†; Veloceft†; ***UAE***: Eskacef†; Julphacef; ***UK***: Nicef; Veloseft†; ***Venez.***: Veracef.

Pharmacopoeial Preparations

BP 2014: Cefradine Capsules; Cefradine Injection; Cefradine Oral Suspension;

USP 36: Cephradine Capsules; Cephradine for Injection; Cephradine for Oral Suspension; Cephradine Tablets.

Cefsulodin Sodium *(BANM, USAN, rINNM)*

Abbott-46811; Cefsulodina sódica; Cefsulodine Sodique; Cefsulodinnatrium; Cefsulodinum Natricum; CGP-7174E; Kefsulodiininatrium; Natrii Cefsulodinum; SCE-129; Sulcephalosporin Sodium; Натрий Цефсулодин.

Sodium 3-(4-carbamoylpyridiniomethyl)-7-[(2*R*)-2-phenyl-2-sulphoacetamido]-3-cephem-4-carboxylate.

$C_{22}H_{19}N_4NaO_8S_2$=554.5

CAS — 62587-73-9 (cefsulodin); 52152-93-9 (cefsulodin sodium).

ATC — J01DD03.

ATC Vet — QJ01DD03.

UNII — 2D087186PY.

Pharmacopoeias. In *Jpn.*

Uses and Administration

Cefsulodin is a third-generation cephalosporin antibacterial with a narrow spectrum of activity that has been used similarly to ceftazidime (p. 253.1) for the treatment of infections caused by susceptible strains of *Pseudomonas aeruginosa*.

It is given as the sodium salt by intravenous injection. Doses are expressed in terms of the equivalent amount of cefsulodin; 1.04 g of cefsulodin sodium is equivalent to about 1 g of cefsulodin. The usual adult dose is 6 g daily in 4 divided doses; in less severe infections daily doses of 3 to 4 g may be given.

For details of doses in children and in those with renal impairment, see p. 251.3.

Administration in children. Cefsulodin may be given to children for the treatment of infections caused by susceptible organisms, in particular *Pseudomonas aeruginosa*. Children may be given an intravenous dose of 100 mg/kg daily; 50 mg/kg daily may be given in less severe infections.

Administration in renal impairment. The dosage of cefsulodin given intravenously should be adjusted in patients with renal impairment according to creatinine clearance (CC):

- CC 20 to 50 mL/minute: a loading dose of 1.5 g then 1 g every 8 hours

- CC 5 to 20 mL/minute: a loading dose of 1.5 g then 1 g every 12 hours
- CC less than 5 mL/minute: a loading dose of 1.5 g then 1 g every 24 hours; for those receiving haemodialysis, a 1-g dose is given before dialysis on dialysis days, followed by a second 1-g dose after the dialysis run

Adverse Effects and Precautions

As for Cefalotin Sodium, p. 235.2.

Sodium content. Each g of cefsulodin sodium contains about 1.8 mmol of sodium.

Antimicrobial Action

Cefsulodin is a bactericidal antibiotic with activity against *Pseudomonas aeruginosa* as great as that of ceftazidime (p. 253.3), but no significant activity against other Gram-negative bacteria. Gram-positive bacteria and anaerobes are not very susceptible. Its activity against *Ps. aeruginosa* may be enhanced by aminoglycosides.

Cefsulodin is stable to hydrolysis by many beta-lactamases, but emergence of resistant *Ps. aeruginosa* has been reported.

Pharmacokinetics

Cefsulodin is given parenterally as the sodium salt. It has a plasma half-life of about 1.6 hours, which is prolonged in renal impairment. Up to 30% of cefsulodin in the circulation is bound to plasma proteins. Therapeutic concentrations have been reported in many body tissues and fluids. The major route of excretion of cefsulodin is via the urine, mainly by glomerular filtration. Clearance may be enhanced in cystic fibrosis, although there have been conflicting reports.

References.
1. Granneman GR, *et al.* Cefsulodin kinetics in healthy subjects after intramuscular and intravenous injection. *Clin Pharmacol Ther* 1982; 31: 95–103.
2. Reed MD, *et al.* Single-dose pharmacokinetics of cefsulodin in patients with cystic fibrosis. *Antimicrob Agents Chemother* 1984; 25: 379–81.
3. Hedman A, *et al.* Increased renal clearance of cefsulodin due to higher glomerular filtration rate in cystic fibrosis. *Clin Pharmacokinet* 1990; 18: 168–75.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Ulfaret; *Jpn*: Takesulin†.

Ceftaroline Fosamil Acetate

(BANM, USAN, rINNM)

Acetato de ceftarolina fosamilo; Ceftaroline Fosamil, Acétate de; Ceftarolini Fosamili Acetas; PPI-0903 (ceftaroline fosamil or ceftaroline fosamil acetate); TAK-599 (ceftaroline fosamil or ceftaroline fosamil acetate); Цефаролина Фозамил Ацетат.

(6R,7R)-7-[((2Z)-(Ethoxyimino)[5-(phosphonoamino)-1,2,4-thiadiazol-3-yl]acetyl)amino]-3-[[4-(1-methylpyridinium-4-yl) thiazol-2-yl]sulfanyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-2-carboxylate monoacetate monohydrate.

$C_{22}H_{21}N_8O_8PS_4.C_2H_4O_2.H_2O$=762.7

CAS — 229016-73-3 (ceftaroline fosamil); 400827-46-5 (anhydrous ceftaroline fosamil acetate); 400827-55-6 (ceftaroline fosamil acetate monohydrate).

ATC — J01DI02.

ATC Vet — QJ01DI02.

UNII — EZ9W6O5S09 (anhydrous ceftaroline fosamil acetate); P9VXV1408Y (ceftaroline fosamil acetate monohydrate).

Uses and Administration

Ceftaroline fosamil is a broad-spectrum cephalosporin antibacterial, sometimes described as a 'fifth-generation' cephalosporin, that is used in the treatment of community-acquired pneumonia and acute skin and skin structure infections caused by susceptible organisms; it may be of particular use for skin infections caused by MRSA.

Ceftaroline fosamil is given as the acetate salt by intravenous infusion over 1 hour. Doses are expressed in terms of the equivalent amount of ceftaroline fosamil; 1.11 g of ceftaroline fosamil acetate is equivalent to about 1 g of ceftaroline fosamil. The usual dose is the equivalent of 600 mg ever 12 hours. Doses may need to be reduced in renal impairment (see p. 252.2).

References.
1. Parish D, Scheinfeld N. Ceftaroline fosamil, a cephalosporin derivative for the potential treatment of MRSA infection. *Curr Opin Investig Drugs* 2008; 9: 201–9.
2. Zhanel GG, *et al.* Ceftaroline: a novel broad-spectrum cephalosporin with activity against meticillin-resistant *Staphylococcus aureus*. *Drugs* 2009; 69: 809–31.
3. Steed ME, Rybak MJ. Ceftaroline: a new cephalosporin with activity against resistant gram-positive pathogens. *Pharmacotherapy* 2010; 30: 375–89.
4. Corey GR, *et al.* Integrated analysis of CANVAS 1 and 2: phase 3, multicenter, randomized, double-blind studies to evaluate the safety and efficacy of ceftaroline versus vancomycin plus aztreonam in complicated skin and skin-structure infection. *Clin Infect Dis* 2010; 51: 641–50.

Administration in renal impairment. In patients with renal impairment, the following intravenous doses of ceftaroline fosamil are recommended, according to creatinine clearance (CC):

- CC 31 to 50 mL/minute: 400 mg every 12 hours
- CC 15 to 30 mL/minute: 300 mg every 12 hours
- CC < 15 mL/minute: 200 mg every 12 hours (for patients on haemodialysis, doses should be given after the dialysis run)

Adverse Effects and Precautions

As for Cefalotin Sodium (p. 235.2). Like other broad-spectrum cephalosporins (see Cefotaxime, p. 244.3), ceftaroline has the potential for promoting colonisation and superinfection with resistant organisms.

Antimicrobial Action

Ceftaroline fosamil is a fifth-generation cephalosporin with broad-spectrum bactericidal activity against many Gram-positive and Gram-negative organisms. Its activity is similar to that of cefotaxime (p. 244.3); however, it has an expanded spectrum of activity against Gram-positive bacteria that includes MRSA and multidrug-resistant *Streptococcus pneumoniae*. Enterococci are generally resistant, but there may be some susceptibility shown by *Enterococcus faecalis*.

Although ceftaroline has good activity against many Gram-negative bacteria, *Pseudomonas aeruginosa*, *Acinetobacter* spp., *Alcaligenes* spp., and *Stenotrophomonas maltophilia* have decreased susceptibility.

Ceftaroline has poor activity against Gram-negative anaerobes such as *Bacteroides fragilis* and *Prevotella* spp., however, Gram-positive anaerobes such as *Propionibacterium* spp. and *Peptostreptococcus* spp. are highly susceptible.

Pharmacokinetics

After infusion, ceftaroline fosamil is rapidly converted in the plasma to ceftaroline, the bio-active form of the drug. Mean peak plasma concentrations of 19 micrograms/mL have been reported after a single 600 mg dose of ceftaroline fosamil given intravenously over 1 hour. Ceftaroline is about 20% bound to plasma proteins, and in healthy patients, has a mean steady-state volume of distribution of about 20.3 litres.

Ceftaroline is metabolised in small amounts to the microbiologically-inactive metabolite ceftaroline M-1 via hydrolysis of the β-lactam ring.

Ceftaroline and its metabolite are excreted mainly by the kidneys, with about 88% of a dose recovered in the urine within 48 hours (mainly as unchanged drug); a small amount of drug is excreted in faeces. The elimination half-life of ceftaroline is about 2.66 hours. Ceftaroline exposure and half-life are significantly increased in renal impairment.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Denm.*: Zinforo; *Norw.*: Zinforo; *UK*: Zinforo; *USA*: Teflaro.

Ceftazidime *(BAN, USAN, rINN)*

Ceftazidim; Ceftazidim pentahydrát; Ceftazidima; Ceftazidimas; Ceftazidimum; Ceftazidimum Pentahydricum; Ceftazydym; GR-20263; Keftatsidiimi; LY-139381; Seftazidim; Цефтазидим.

(Z)-*(7R)*-7-[2-(2-Aminothiazol-4-yl)-2-(1-carboxy-1-methylethoxyimino)acetamido]-3-(1-pyridiniomethyl)-3-cephem-4-carboxylate pentahydrate.

$C_{22}H_{22}N_6O_7S_2.5H_2O$=636.6

CAS — 72558-82-8 (anhydrous ceftazidime); 78439-06-2 (ceftazidime pentahydrate).

ATC — J01DD02.

ATC Vet — QJ01DD02.

UNII — 9M416Z9QNR (ceftazidime pentahydrate); DZR1ENT301 (anydrous ceftazidime).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Ceftazidime Pentahydrate). A semisynthetic product derived from a fermentation product. A white or almost white crystalline powder. Slightly soluble in water and in methyl alcohol; practically insoluble in alcohol and in acetone; it dissolves in acid and alkali solutions. A 0.5% solution in water has a pH of 3.0 to 4.0. Store in airtight containers.

Ph. Eur. 8: (Ceftazidime Pentahydrate with Sodium Carbonate for Injection). A sterile mixture of ceftazidime pentahydrate and anhydrous sodium carbonate. A white or pale yellow powder. Freely soluble in water and in methyl alcohol; practically insoluble in acetone. Store in airtight containers. Protect from light and humidity.

USP 36: (Ceftazidime). A white to cream-coloured crystalline powder. Slightly soluble in water, in dimethylformamide, and in methyl alcohol; insoluble in alcohol, in acetone, in chloroform, in dioxan, in ether, in ethyl acetate, and in toluene; soluble in alkali and in dimethyl sulfoxide. pH of a 0.5% solution in water is between 3.0 and 4.0. Store in airtight containers.

Formulation. Ceftazidime for injection is available as a dry powder containing ceftazidime with sodium carbonate. When reconstituted ceftazidime sodium is formed with the evolution of carbon dioxide. An alternative formulation, ceftazidime with arginine, appears to overcome the problems associated with effervescence.[1] In some countries a frozen injection containing ceftazidime sodium is also used.

1. Stiles ML, *et al.* Gas production of three brands of ceftazidime. *Am J Hosp Pharm* 1991; 48: 1727–9.

Incompatibility. It has been reported that ceftazidime does not cause decreased activity when incubated in solution with *gentamicin*[1] or *tobramycin*[2] at 37 degrees, or when mixed with tobramycin in serum.[3] Ceftazidime and tobramycin[4] were also stable for up to 16 hours at room temperature when combined in a glucose-containing dialysis solution, and for a further 8 hours at 37 degrees. However, licensed product information recommends that ceftazidime, like most other beta lactams, should not be mixed with an aminoglycoside in the same giving set or syringe because of the potential for inactivation of either drug.

Ceftazidime is generally considered to be compatible with *metronidazole*, but degradation of ceftazidime has been reported.[5] Precipitation has occurred with *vancomycin*[6] and therefore the product information considers it prudent to flush giving sets and intravenous lines between giving the two drugs. However, in one study[7] ceftazidime and/or vancomycin were stable in a glucose-containing peritoneal dialysis solution when kept for 6 days in a refrigerator or 48 to 72 hours at room temperature, and in a further study[8] the two drugs were stable when combined in similar solutions containing 1.5% or 4.25% glucose for up to 12 hours when stored at 37 degrees and for 24 hours when stored at 4 degrees and 24 degrees. Ceftazidime and *teicoplanin*[9] were stable in combination in a peritoneal dialysis solution at 37 degrees for 8 hours when it had been previously stored at 4 degrees, but not when previously stored at 25 degrees. Ceftazidime was not stable when mixed in solution with *aminophylline*.[10] There was some evidence of possible incompatibility with *pentamidine*.[11]

1. Elliott TSJ, *et al.* Stability of gentamicin in combination with selected new β-lactam antibiotics. *J Antimicrob Chemother* 1984; 14: 668–9.
2. Elliott TSJ, *et al.* Stability of tobramycin in combination with selected new β-lactam antibiotics. *J Antimicrob Chemother* 1986; 17: 680–1.
3. Pennell AT, *et al.* Effect of ceftazidime, cefotaxime, and cefoperazone on serum tobramycin concentrations. *Am J Hosp Pharm* 1991; 48: 520–2.
4. Mason NA, *et al.* Stability of ceftazidime and tobramycin sulfate in peritoneal dialysis solution. *Am J Hosp Pharm* 1992; 49: 1139–42.
5. Messerschmidt W. Pharmazeutische kompatibilität von ceftazidim und metronidazol. *Pharm Zig* 1990; 135: 36–8.
6. Cairns CJ, Robertson J. Incompatibility of cefuzidime and vancomycin. *Pharm J* 1987; 238: 577.
7. Vaughan LM, Poon CY. Stability of ceftazidime and vancomycin alone and in combination in heparinized and nonheparinized peritoneal dialysis solution. *Ann Pharmacother* 1994; 28: 572–6.
8. Stamatakis MK, *et al.* Stability of high-dose vancomycin and ceftazidime in peritoneal dialysis solutions. *Am J Health-Syst Pharm* 1999; 56: 246–8.
9. Manduru M, *et al.* Stability of ceftazidime sodium and teicoplanin sodium in a peritoneal dialysis solution. *Am J Health-Syst Pharm* 1996; 53: 2731–4.
10. Pleasants RA, *et al.* Compatibility of ceftazidime and aminophylline admixtures for different methods of intravenous infusion. *Ann Pharmacother* 1992; 26: 1221–6.
11. Lewis JD, El-Gendy A. Cephalosporin-pentamidine isethionate incompatibilities. *Am J Health-Syst Pharm* 1996; 53: 1462–3.

Stability. References.

1. Richardson BL, *et al.* The pharmacy of ceftazidime. *J Antimicrob Chemother* 1981; 8 (suppl B): 233–6.
2. Brown AF, *et al.* Freeze thaw stability of ceftazidime. *Br J Parenter Ther* 1985; 6: 43, 45, 50.
3. Walker SE, Dranitsaris G. Ceftazidime stability in normal saline and dextrose in water. *Can J Hosp Pharm* 1988; 41: 65–6, 69–71.
4. Wade CS, *et al.* Stability of ceftazidime and amino acids in parenteral nutrient solutions. *Am J Hosp Pharm* 1991; 48: 1515–19.
5. Stiles ML, *et al.* Stability of ceftazidime (with arginine) and of cefuroxime sodium in infusion-pump reservoirs. *Am J Hosp Pharm* 1992; 49: 2761–4.
6. Stewart JT, *et al.* Stability of ceftazidime in plastic syringes and glass vials under various storage conditions. *Am J Hosp Pharm* 1992; 49: 2765–8.
7. Nahata MC, *et al.* Stability of ceftazidime (with arginine) stored in plastic syringes at three temperatures. *Am J Hosp Pharm* 1992; 49: 2954–6.
8. Bednar DA, *et al.* Stability of ceftazidime (with arginine) in an elastomeric infusion device. *Am J Health-Syst Pharm* 1995; 52: 1912–14.

9. van Doorne H, *et al.* Ceftazidime degradation rates for predicting stability in a portable infusion-pump reservoir. *Am J Health-Syst Pharm* 1996; 53: 1302–5.
10. Stendal TL, *et al.* Drug stability and pyridine generation in ceftazidime injection stored in an elastomeric infusion device. *Am J Health-Syst Pharm* 1998; 55: 683–5.
11. Servais H, Tulkens PM. Stability and compatibility of ceftazidime administered by continuous infusion to intensive care patients. *Antimicrob Agents Chemother* 2001; 45: 2643–7.

Uses and Administration

Ceftazidime is a third-generation cephalosporin antibacterial with enhanced activity against *Pseudomonas aeruginosa*. It is used in the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria, especially infections due to *Pseudomonas* spp. They include biliary-tract infections, bone and joint infections, respiratory-tract infections, infections in immunocompromised patients (neutropenic patients), skin and skin structure infections, and urinary-tract infections. It is also used for surgical infection prophylaxis. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Ceftazidime is available as the pentahydrate but it is formulated with sodium carbonate, to form the sodium salt in solution, or with arginine. Doses are expressed in terms of anhydrous ceftazidime; ceftazidime pentahydrate 1.16 g is equivalent to about 1 g of anhydrous ceftazidime. It is given by deep intramuscular injection, slow intravenous injection over 3 to 5 minutes, or intravenous infusion over up to 30 minutes.

The usual dose for adults ranges from 1 to 6 g daily in divided doses every 8 or 12 hours. The higher doses are used in severe infections especially in immunocompromised patients. In adults with cystic fibrosis who have pseudomonal lung infections, high doses of 90 to 150 mg/kg daily in 3 divided doses are used; up to 9 g daily has been given to those with normal renal function. Single doses of more than 1 g should be given intravenously.

For surgical infection prophylaxis in patients undergoing prostatic surgery, a dose of 1 g may be given at induction of anaesthesia and repeated if necessary when the catheter is removed.

The dose of ceftazidime may need to be reduced in patients with renal impairment, see p. 253.2. For details of doses in children, see also p. 253.1.

Ceftazidime can be used with an aminoglycoside, another beta lactam such as piperacillin, or vancomycin in patients with severe neutropenia, or, if infection with *Bacteroides fragilis* is suspected, with an antimicrobial such as clindamycin or metronidazole. The drugs should generally be given separately (see also Incompatibility, p. 250.3).

References.
1. Rains CP, *et al.* Ceftazidime: an update of its antibacterial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1995; 49: 577–617.
2. Roberts JA, *et al.* Cefepime versus ceftazidime: considerations for empirical use in critically ill patients. *Int J Antimicrob Agents* 2007; 29: 117–28.
3. Hubert D, *et al.* Continuous versus intermittent infusions of ceftazidime for treating exacerbation of cystic fibrosis. *Antimicrob Agents Chemother* 2009; 53: 3650–6.

Administration in children. Ceftazidime may be given to children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria. It is given by deep intramuscular injection, slow intravenous injection over 3 to 5 minutes, or intravenous infusion.

In the UK, the *BNFC* recommends that neonates and children may be given a dose of 25 mg/kg every 24 hours in neonates less than 7 days old, every 12 hours in those aged 7 to 21 days, and every 8 hours in older neonates and children. The dose may be doubled in severe infection, febrile neutropenia, and meningitis (to a maximum daily dose of 6 g in children 1 month of age and older).

For pseudomonal lung infection in cystic fibrosis in patients aged 1 month and older a dose of 50 mg/kg every 8 hours (to a maximum daily dose of 9 g) may be given.

In the USA, the American Academy of Pediatrics[1] suggests the following doses for ceftazidime:

- for neonates aged ≤ 7 days (irrespective of body weight): 50 mg/kg every 12 hours
- for neonates aged 8 to 28 days and weighing ≤ 2 kg: 50 mg/kg every 8 to 12 hours; a dosing interval of 12 hours may be used until 2 weeks of life in extremely low birth-weight neonates (weighing less than 1 kg)
- for neonates aged 8 to 28 days and weighing > 2 kg: 50 mg/kg every 8 hours
- children 1 month and older: 90 to 150 mg/kg daily in 3 divided doses (to a maximum daily dose of 3 g) for mild to moderate infections, or 200 to 300 mg/kg daily in 3 divided doses (to a maximum daily dose of 6 g) in severe infections

Although not licensed for nebulisation in the UK, the *BNFC* suggests a dose of 1 g inhaled twice daily for the management of chronic *Burkholderia cepacia* infection in patients aged 1 month and older with cystic fibrosis.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Administration in renal impairment. In patients with renal impairment parenteral doses of ceftazidime may need to be reduced. After a loading dose of 1 g, maintenance doses are based on the creatinine clearance (CC):

- CC 31 to 50 mL/minute: 1 g every 12 hours
- CC 16 to 30 mL/minute: 1 g every 24 hours
- CC 6 to 15 mL/minute: 500 mg every 24 hours
- CC less than 5 mL/minute: 500 mg every 48 hours

In severe infections these doses may need to be increased by 50%. In these patients ceftazidime trough serum concentrations should not exceed 40 micrograms/mL. In patients undergoing peritoneal dialysis a loading dose of 1 g may be given followed by 500 mg every 24 hours; ceftazidime sodium may also be added to the dialysis fluid, usually 125 to 250 mg of ceftazidime for 2 litres of dialysis fluid. In patients undergoing haemodialysis a loading dose of 1 g is given and then 1 g after each dialysis period.

For critically ill patients undergoing continuous renal replacement therapy, a loading dose of 2 g and the following maintenance doses, given intravenously, have been recommended:[1]

- for continuous venovenous haemodialysis (CVVHD) or haemodialfiltration (CVVHDF): 1 g every 8 hours or 2 g every 12 hours; 2 g every 8 hours may be necessary for very resistant Gram-negative pathogens
- for continuous venovenous haemofiltration (CVVH): 1 to 2 g every 12 hours

Continuous infusion dosing regimens have also been suggested for use in patients undergoing CVVHDF[2] and CVVH.[3]

1. Heintz BH, *et al.* Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy* 2009; 29: 562–77.
2. Mariat C, *et al.* Continuous infusion of ceftazidime in critically ill patients undergoing continuous venovenous haemodiafiltration: pharmacokinetic evaluation and dose recommendation. *Crit Care* 2006; 10: R26. Available at: http://ccforum.com/content/pdf/cc3993.pdf (accessed 24/06/10)
3. Moriyama B, *et al.* Continuous-infusion beta-lactam antibiotics during continuous venovenous hemofiltration for the treatment of resistant gram-negative bacteria. *Ann Pharmacother* 2009; 43: 1324–37.

Adverse Effects and Precautions

As for Cefalotin Sodium, p. 235.2.

Like cefotaxime (p. 244.3), ceftazidime has the potential to promote colonisation and superinfection with resistant organisms. The risk of superinfection with, for example, *Staphylococcus aureus* may be higher than with cefotaxime, since ceftazidime is less active against staphylococci.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving ceftazidime, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)

Effects on the blood. References.
1. Hui CH, Chan LC. Agranulocytosis associated with cephalosporin. *BMJ* 1993; 307: 484.

Effects on the nervous system. References.
1. Al-Zahawi MF, *et al.* Hallucinations in association with ceftazidime. *BMJ* 1988; 297: 858.
2. Jackson GD, Berkovic SF. Ceftazidime encephalopathy: absence status and toxic hallucinations. *J Neurol Neurosurg Psychiatry* 1992; 55: 333–4.
3. Chow KM, *et al.* Retrospective review of neurotoxicity induced by cefepime and ceftazidime. *Pharmacotherapy* 2003; 23: 369–73.

Effects on the skin. References.
1. Vinks SATMM, *et al.* Photosensitivity due to ambulatory intravenous ceftazidime in cystic fibrosis patient. *Lancet* 1993; 341: 1221–2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ceftazidime as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Interactions

Unlike that of many other cephalosporins, the renal clearance of ceftazidime is not much affected by probenecid.

References.
1. Verhagen CA, *et al.* The renal clearance of cefuroxime and ceftazidime and the effect of probenecid on their tubular excretion. *Br J Clin Pharmacol* 1994; 37: 193–7.

Antimicrobial Action

Ceftazidime has a bactericidal action and broad spectrum of activity similar to that of cefotaxime (p. 244.3), but increased activity against *Pseudomonas* spp.; it is less active against staphylococci and streptococci. Unlike cefotaxime it has no active metabolite.

Ceftazidime is highly stable to hydrolysis by most beta-lactamases.

- It is active *in vitro* against many Gram-negative bacteria including *Pseudomonas aeruginosa*, *Burkholderia pseudomallei* (*Pseudomonas pseudomallei*), and Enterobacteriaceae including *Citrobacter* and *Enterobacter* spp., *Escherichia coli*, *Klebsiella* spp., both indole-positive and indole-negative *Proteus*, *Providencia*, *Salmonella*, *Serratia*, and *Shigella* spp. and *Yersinia enterocolitica*.
  Other susceptible Gram-negative bacteria include *Haemophilus influenzae*, *Moraxella catarrhalis* (*Branhamella catarrhalis*), and *Neisseria* spp.
- Among Gram-positive bacteria it is active against some staphylococci and streptococci, but meticillin-resistant staphylococci, enterococci, and *Listeria monocytogenes* are generally resistant.
- Ceftazidime is active against some anaerobes, although most strains of *Bacteroides fragilis* and *Clostridium difficile* are resistant.

The activity of ceftazidime against *Ps. aeruginosa* and some Enterobacteriaceae may be enhanced by aminoglycosides. Antagonism has been reported *in vitro* between ceftazidime and chloramphenicol.

Resistance. As with cefotaxime, resistance may develop during treatment due to the derepression of chromosomally mediated beta-lactamases. It has been noted particularly in *Pseudomonas* spp. and in Enterobacteriaceae including *Citrobacter*, *Enterobacter* spp. and *Proteus vulgaris*. Resistance may also occur due to the production of plasmid-mediated extended-spectrum beta-lactamases, particularly in *Klebsiella* spp. and *E. coli*.

Pharmacokinetics

Ceftazidime is given by injection as the sodium salt or in solution with arginine. Mean peak plasma concentrations of 17 and 39 micrograms/mL have been reported about 1 hour after intramuscular doses of 0.5 and 1 g of ceftazidime, respectively. Five minutes after intravenous bolus injections of 0.5, 1, and 2 g of ceftazidime, mean plasma concentrations of 45, 90, and 170 micrograms/mL, respectively, have been reported. The plasma half-life of ceftazidime is about 2 hours, but this is prolonged in patients with renal impairment and in neonates. Clearance may be enhanced in patients with cystic fibrosis. It is about 10% bound to plasma proteins.

Ceftazidime is widely distributed in body tissues and fluids; therapeutic concentrations occur in the CSF when the meninges are inflamed. It crosses the placenta and is distributed into breast milk.

Ceftazidime is passively excreted in bile, although only a small proportion is eliminated by this route. It is mainly excreted by the kidneys, almost exclusively by glomerular filtration; probenecid has little effect on the excretion. About 80 to 90% of a dose appears unchanged in the urine within 24 hours. It is removed by haemodialysis and peritoneal dialysis.

Critically ill patients. References.
1. Georges B, *et al.* Population pharmacokinetics of ceftazidime in intensive care unit patients: influence of glomerular filtration rate, mechanical ventilation, and reason for admission. *Antimicrob Agents Chemother* 2009; 53: 4483–9.

Cystic fibrosis. References.
1. Leeder JS, *et al.* Ceftazidime disposition in acute and stable cystic fibrosis. *Clin Pharmacol Ther* 1984; 36: 355–62.
2. Hedman A, *et al.* Influence of the glomerular filtration rate on renal clearance of ceftazidime in cystic fibrosis. *Clin Pharmacokinet* 1988; 15: 57–65.
3. Vinks AATMM, *et al.* Continuous infusion of ceftazidime in cystic fibrosis patients during home treatment: clinical outcome, microbiology and pharmacokinetics. *J Antimicrob Chemother* 1997; 40: 125–33.
4. Bulitta JB, *et al.* Population pharmacokinetic comparison and pharmacodynamic breakpoints of ceftazidime in cystic fibrosis patients and healthy volunteers. *Antimicrob Agents Chemother* 2010; 54: 1275–82.

The elderly. References.
1. LeBel M, *et al.* Pharmacokinetics of ceftazidime in elderly volunteers. *Antimicrob Agents Chemother* 1985; 28: 713–15.
2. Higbee MD, *et al.* Pharmacokinetics of ceftazidime in elderly patients. *Clin Pharm* 1989; 8: 59–62.
3. Sirgo MA, Norris S. Ceftazidime in the elderly: appropriateness of twice-daily dosing. *DICP Ann Pharmacother* 1991; 25: 284–8.

Hepatic impairment. References.
1. El Touny M, *et al.* Pharmacokinetics of ceftazidime in patients with liver cirrhosis and ascites. *J Antimicrob Chemother* 1991; 28: 95–100.

Neonates. References.
1. van den Anker JN, *et al.* Ceftazidime pharmacokinetics in preterm infants: effects of renal function and gestational age. *Clin Pharmacol Ther* 1995; 58: 650–9.

2. van den Anker JN, *et al.* Ceftazidime pharmacokinetics in preterm infants: effect of postnatal age and postnatal exposure to indomethacin. *Br J Clin Pharmacol* 1995; 40: 439–43.
3. van den Anker JN, *et al.* Once-daily versus twice-daily administration of ceftazidime in the preterm infant. *Antimicrob Agents Chemother* 1995; 39: 2048–50.

Renal impairment. References.

1. Welage LS, *et al.* Pharmacokinetics of ceftazidime in patients with renal insufficiency. *Antimicrob Agents Chemother* 1984; 25: 201–4.
2. Leroy A, *et al.* Pharmacokinetics of ceftazidime in normal and uremic subjects. *Antimicrob Agents Chemother* 1984; 25: 638–42.
3. Ackerman BH, *et al.* Effect of decreased renal function on the pharmacokinetics of ceftazidime. *Antimicrob Agents Chemother* 1984; 25: 785–6.
4. Lin N-S, *et al.* Single- and multiple-dose pharmacokinetics of ceftazidime in infected patients with varying degrees of renal function. *J Clin Pharmacol* 1989; 29: 331–7.
5. Kinowski J-M, *et al.* Multiple-dose pharmacokinetics of amikacin and ceftazidime in critically ill patients with septic multiple-organ failure during intermittent hemofiltration. *Antimicrob Agents Chemother* 1993; 37: 464–73.
6. Demotes-Mainard F, *et al.* Pharmacokinetics of intravenous and intraperitoneal ceftazidime in chronic ambulatory peritoneal dialysis. *J Clin Pharmacol* 1993; 33: 475–9.
7. Kim K, *et al.* Pharmacokinetic profiles of ceftazidime after intravenous administration in patients undergoing automated peritoneal dialysis. *Antimicrob Agents Chemother* 2011; 55: 2523–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Crima; Fortum; Pluseptic; Tinacef; Zidima†; ***Austral.***: Fortum; ***Austria***: Fortum; Kefazim; ***Belg.***: Glazidim; Kefadim; ***Braz.***: Ceftazidon; Ceften; Cetaz; Fortaz; Intracef†; Kefadim; ***Canad.***: Fortaz; ***Chile***: Ceftiol; Fortum; ***China***: Ansaiding (安塞定); Dalishu (达力舒); Deding (得定); Fengdaxin (锋达欣); Fortum (复达欣); Kangliding (康力啶); Kefadim (凯复定); Lizhu Ruixin (丽珠锐欣); Ruitading (瑞他定); Shuerxin (舒而欣); Tazime (泰得欣); Xianding (先定); Xintianxin (新天欣); Cz.: Fortum; ***Denm.***: Fortum; Solvetan; ***Fin.***: Glazidim; ***Fr.***: Fortum; Fortumset; ***Ger.***: Fortum; InfectoZidim†; ***Gr.***: Cefin; Ceftaridem; Ftazidime; Lemoxol; Limozidim; Malocef; Novocral; Septax; Sipiel; Solvetan; ***Hong Kong***: Fortum; ***Hung.***: Cetazime†; Fortum; ***India***: Afzid; Ailzid; Amcef; Aritaz; Azid; Bectozid; Betasys; Binzid; C-Zid; Cadzid; Cef-G; Cefazid; Cefcure; Cefdina; Cefid; Ceftabit; Ceftariz; Ceftavir; Ceftaz; Ceftidin; Cefzid; Cefzidime; Cefzy; Cuzid; Czidnate; Efta; Eutum; Fasst; Fectim; Fobidime; Fortacef; Fortum; Forzid; Fotaran; Glifest; Indozid; Izid; Kayzid; Laboceta; Larzid; Lazid; Magnazide; Manzid; Megazid; N-Ciz; Nanocef; Neceft; Nepocef; Nidim; NKCefta; Novazidim; Omnazide; Orzid; Oszid; Zytaz; ***Indon.***: Biozim; Caltum; Cefdime; Ceftamax; Ceftum; Cetazum; Eximon; Fortum; Lacedim; Pharodime; Sodime; Thidim; Veltadim; Yadim; Zefidim; Zibac; Zidifec; ***Irl.***: Fortum; ***Israel***: Fortum†; Septax; ***Ital.***: Ceftim†; Deltazime; Dizatec; Etazim; Fribat; Glazidim; Liotixil; Panzid; Spectrum; Starcef; Tazidif; Tottizim; ***Malaysia***: Cef-4; Cefatum; Fortum; Tazid; Vaxcel Ceftazidime; ***Mex.***: Fenit; Fortum; Izadima; Tagal; Taloken†; Taxifur†; Teczidima; Zadolina; Zidicef†; ***Neth.***: Fortum; Tazalux; ***Norw.***: Fortum; ***NZ***: Fortum; ***Philipp.***: Bactizef; Baxidyme; Ceftaz; Ceftazivit; Ceftibac; Clovizeme; Dimzef; Fivtum; Flazidem; Fortazep†; Fortum; Forzid; Hacef; Megacef; Onetazid; Romacef; Spexil; Tazicef; Tazid; Tazidan; Tazidem; Tazim; Uniranz; Vinsef; Zadim; Zeptrigen; Ziamid; ***Pol.***: Biotum; Fortum; Miroceft†; ***Port.***: Cefortam; Ceftazim; Ceftim; Zidimox; ***Rus.***: Bestum (Бестум); Ceftidin (Цефтидин); Cefzid (Цефзид); Fortoferin (Фортоферин); Fortum (Фортум); Lorazidime (Лоразидим); Orzid (Орзид); Tizime (Тизим); Vicef (Вицеф); ***S.Afr.***: Fortum; Keftaz; Orzid; Tazject; ***Singapore***: Cefazime; Cetazine; Fortum; Parzidim; Tazime; ***Spain***: Fortam; Kefamin†; ***Swed.***: Fortum; ***Switz.***: Fortam; ***Thai.***: Cef-4; Cef-Dime; Cefodime; Ceftime; Dimase†; Fortadim†; Fortum; Forzid†; Tazid†; Zedim; Zeftam; ***Turk.***: Fortum; Iesetum; Zidim; ***UAE***: Negacef; ***UK***: Fortum; Kefadim; ***Ukr.***: Biotum (Биоформ)†; Ceftadime (Цефтадим); Ceftum (Цефтум); Fortum (Фортум); Orzid (Орзид)†; Zacef (Зацеф); ***USA***: Ceptaz; Fortaz; Tazicef; Tazidime†; ***Venez.***: Betazidim; Biozidima; Cefgram; Fortum.

Multi-ingredient Preparations. ***India***: Combitaz; Fobidime-TZ.

Pharmacopoeial Preparations
BP 2014: Ceftazidime Injection;
USP 36: Ceftazidime for Injection; Ceftazidime Injection.

Cefteram Pivoxil *(rINNM)*

Cefteram, Pivoxil de; Cefteram pivoxilo; Cefterami Pivoxil; T-2588; Цефтерама Пивоксил.
Pivaloyloxymethyl (Z)-7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(5-methyl-2*H*-tetrazol-2-ylmethyl)-3-cephem-4-carboxylic acid.
$C_{22}H_{27}N_9O_7S_2$=593.6
CAS — 82547-58-8 (cefteram); 82547-81-7 (cefteram pivoxil).
UNII — 0OD86RT58C.

Pharmacopoeias. In *Jpn*.

Profile

Cefteram is a cephalosporin antibacterial used for the treatment of susceptible infections. It is given orally as the pivaloyloxymethyl ester, cefteram pivoxil, and doses are expressed in terms of cefteram; 186 mg of cefteram pivoxil is equivalent to about 150 mg of cefteram. The usual dose is 150 to 300 mg daily in 3 divided doses after meals. For severe infections, up to 600 mg daily may be given.

For reference to carnitine deficiency occurring after the administration of some pivaloyloxymethyl esters, see Pivampicillin, p. 344.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Tomiron (富山龙); ***Jpn***: Tomiron.

Ceftezole Sodium *(rINNM)*

Ceftezol sódico; Ceftézole Sodique; Natrii Ceftezolum; Натрий Цефтезол.
Sodium (7*R*)-7-[2-(1*H*-tetrazol-1-yl)acetamido]-3-(1,3,4-thiadiazol-2-ylthiomethyl)-3-cephem-4-carboxylate.
$C_{13}H_{11}N_8NaO_4S_3$=462.5
CAS — 26973-24-0 (ceftezole); 41136-22-5 (ceftezole sodium).
ATC — J01DB12.
ATC Vet — QJ01DB12.
UNII — 3NHZ4Y117H.

Pharmacopoeias. In *Chin*.

Profile

Ceftezole is a cephalosporin antibacterial with properties similar to those of cefalotin (p. 235.1). It is given as the sodium salt but doses are expressed in terms of the base; 1.05 g of ceftezole sodium is equivalent to about 1 g of ceftezole. The usual dose is 2 to 4 g daily by intramuscular injection in 2 or 3 divided doses.

Sodium content. Each g of ceftezole sodium contains about 2.16 mmol of sodium.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Bi An Lai (必安来); Luohao (罗昊); Tezacef (特于社复); Yi Ti Xin (益替欣).

Ceftibuten *(BAN, USAN, rINN)*

Ceftibutène; Ceftibuteno; Ceftibutenum; Keftibuteeni; 7432-S; Sch-39720; Цефтибутен.
7-[2-(2-Amino-1,3-thiazol-4-yl)-4-carboxyisocrotonamide]-3-cephem-4-carboxylic acid.
$C_{15}H_{14}N_4O_6S_2$=410.4
CAS — 97519-39-6.
ATC — J01DD14.
ATC Vet — QJ01DD14.
UNII — IW71N46B4Y (ceftibuten); 62F4443RWP (ceftibuten dihydrate).

Pharmacopoeias. *Jpn* includes the dihydrate.

Uses and Administration

Ceftibuten is a third-generation cephalosporin antibacterial used in the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria including urinary-tract and respiratory-tract infections. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Ceftibuten is given orally as the dihydrate, but doses are expressed in terms of anhydrous ceftibuten; 435 mg of ceftibuten dihydrate is equivalent to about 400 mg of anhydrous ceftibuten. The usual adult dose is 400 mg once daily on an empty stomach.

The dose of ceftibuten may need to be reduced in patients with renal impairment, see p. 254.3.

For details of doses in children, see p. 254.2.

Reviews.

1. Wiseman LR, Balfour JA. Ceftibuten: review of its antibacterial activity, pharmacokinetic properties and clinical efficacy. *Drugs* 1994; 47: 784–808.
2. Nelson JD, McCracken GH (eds). Ceftibuten: a new orally active cephalosporin for pediatric infections. *Pediatr Infect Dis J* 1995; 14 (suppl): S76–S133.
3. Guay DRP. Ceftibuten: a new expanded-spectrum oral cephalosporin. *Ann Pharmacother* 1997; 31: 1022–33.
4. Owens RC, *et al.* Ceftibuten: an overview. *Pharmacotherapy* 1997; 17: 707–20.

Administration in children. Ceftibuten may be given to children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria. Children over 6 months of age and weighing 45 kg or less may be given 9 mg/kg daily as a single oral dose.

In studies,[1] the same dose for 10 days has proved safe and effective for the management of urinary-tract infection in children from 1 month of age.

1. Mårild S, *et al.* Ceftibuten versus trimethoprim-sulfamethoxazole for oral treatment of febrile urinary tract infection in children. *Pediatr Nephrol* 2009; 24: 521–6.

Administration in renal impairment. Doses of ceftibuten should be reduced in patients with moderate to severe renal impairment. The following oral doses based on creatinine clearance (CC) may be used:
- CC 30 to 49 mL/minute: 200 mg once daily
- CC 5 to 29 mL/minute: 100 mg once daily

Patients undergoing haemodialysis 2 or 3 times weekly may be given a dose of 400 mg after each dialysis session.

Adverse Effects and Precautions

As for Cefalotin Sodium, p. 235.2.

The most frequently reported adverse effects of ceftibuten are gastrointestinal disturbances, especially diarrhoea, and headache.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ceftibuten as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Antimicrobial Action

As for Cefixime, p. 241.1. It is less active *in vitro* against *Streptococcus pneumoniae*.

References.

1. Shawar R, *et al.* Comparative in vitro activity of ceftibuten (Sch-39720) against bacterial enteropathogens. *Antimicrob Agents Chemother* 1989; 33: 781–4.
2. Bragman SGL, Casewell MW. The in-vitro activity of ceftibuten against 475 clinical isolates of Gram-negative bacilli, compared with cefuroxime and cefadroxil. *J Antimicrob Chemother* 1990; 25: 221–6.
3. Wise R, *et al.* Ceftibuten—in-vitro activity against respiratory pathogens, β-lactamase stability and mechanism of action. *J Antimicrob Chemother* 1990; 26: 209–13.
4. Maioli E, *et al.* In vitro activity of ceftibuten at sub-inhibitory concentrations in comparison with other antibiotics against respiratory and urinary tract pathogens. *J Chemother* 2007; 19: 152–60.

Pharmacokinetics

Ceftibuten is rapidly absorbed from the gastrointestinal tract, although the rate and extent of absorption are somewhat decreased by the presence of food. Peak plasma concentrations of about 17 micrograms/mL occur about 2 hours after a 400-mg dose. The plasma half-life of ceftibuten is about 2.0 to 2.3 hours and is prolonged in patients with renal impairment. Ceftibuten is 65 to 77% bound to plasma proteins.

Ceftibuten distributes into middle-ear fluid and bronchial secretions. About 10% of a dose is converted to the *trans*-isomer, which has about one-eighth of the activity of the *cis*-isomer. Ceftibuten is excreted mainly in the urine and also in the faeces. Significant amounts are removed by haemodialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Keimax; ***Gr.***: Caedax; ***Hong Kong***: Cedax; ***Hung.***: Cedax; ***India***: Procadax; ***Ital.***: Cedax; Isocef; ***Jpn***: Seftem; ***Malaysia***: Cedax; ***Mex.***: Cedax; ***Neth.***: Cedax; ***Philipp.***: Cedax†; ***Pol.***: Cedax; ***Port.***: Caedax; ***Rus.***: Cedax (Цедекс); ***Singapore***: Cedax; ***Spain***: Biocef†; Cedax; ***Swed.***: Cedax; ***Switz.***: Cedax; ***Thai.***: Cedax; ***Turk.***: Cedax; ***Ukr.***: Cedax (Цедекс); ***USA***: Cedax; ***Venez.***: Cedax.

Ceftiofur *(BAN, rINN)*

Ceftiofurum; Keftiofuuri; Цефтиофур.
CAS — 80370-57-6.
ATC Vet — QJ01DD90; QJ51DA91.
UNII — 83JL932I1C.

Ceftiofur Hydrochloride *(BANM, USAN, rINNM)*

Ceftiofur, Chlorhydrate de; Ceftiofuri Hydrochloridum; Hidrocloruro de ceftiofur; U-64279A; Цефтиофура Гидрохлорид.
(6*R*,7*R*)-7-[2-(2-Amino-4-thiazolyl)-glyoxylamido]-3-mercaptomethyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate, 7²-(*Z*)-(*O*-methyloxime), 2-furoate (ester), monohydrochloride.
$C_{19}H_{17}N_5O_7S_3.HCl$=560.0
CAS — 103980-44-5.
ATC Vet — QJ01DD90; QJ51DA91.
UNII — 6822A07436.

Ceftiofur Sodium *(BANM, USAN, rINNM)*

Ceftiofur sódico; Ceftiofur Sodique; Ceftiofurum natricum; CM-31-916; Natrii Ceftiofurum; U-64279E; Натрий Цефтиофур.

$C_{19}H_{16}N_5NaO_7S_3$=545.5

CAS — 104010-37-9.

ATC Vet — QJ01DD90; QJ51DA91.

UNII — NHI34IS56E.

Profile

Ceftiofur is a cephalosporin antibacterial used as the hydrochloride and sodium salts in veterinary practice.

Ceftizoxime Sodium *(BANM, USAN, rINNM)*

Ceftizoxima sódica; Ceftizoxime Sodique; Ceftizoximnatrium; Ceftizoximum Natricum; FK-749; FR-13749; Keftitsoksiiminatrium; Natrii Ceftizoximum; Seftizoksim Sodyum; SKF-88373-Z; Натрий Цефтизоксим.

Sodium (*Z*)-7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-cephem-4-carboxylate.

$C_{13}H_{12}N_5NaO_5S_2$=405.4

CAS — 68401-81-0 (ceftizoxime); 68401-82-1 (ceftizoxime sodium).

ATC — J01DD07.

ATC Vet — QJ01DD07.

UNII — 26337D5X88.

Pharmacopoeias. In *Jpn* and *US*.

USP 36: (Ceftizoxime Sodium). A white to pale yellow crystalline powder. Freely soluble in water. pH of a 10% solution in water is between 6.0 and 8.0. Store in airtight containers.

Stability. References.

1. Lesko AB, *et al.* Ceftizoxime stability in iv solutions. *DICP Ann Pharmacother* 1989; 23: 615–18.

Uses and Administration

Ceftizoxime is a third-generation parenteral cephalosporin antibacterial used for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria, including infections of the abdomen, bones and joints, CNS, skin and skin structures, genito-urinary and respiratory tracts, and gynaecological infections. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Ceftizoxime is given as the sodium salt by deep intramuscular injection, or intravenously as a slow injection over 3 to 5 minutes or as a continuous or intermittent infusion. If 2 g of ceftizoxime is injected intramuscularly the dose should be divided between sites.

Doses are expressed in terms of the equivalent amount of ceftizoxime; 1.06 g of ceftizoxime sodium is equivalent to about 1 g of ceftizoxime. It is usually given in an adult dose of 1 to 2 g every 8 to 12 hours. In severe infections 2 to 4 g may be given intravenously every 8 hours; doses up to 2 g every 4 hours have been given in life-threatening infections.

For the treatment of uncomplicated urinary-tract infections, a dose of 500 mg every 12 hours is used. A single intramuscular dose of 1 g has been given in uncomplicated gonorrhoea.

The dose of ceftizoxime may need to be reduced in patients with renal impairment, see p. 255.1. For details of doses in children, see also p. 255.1.

References.

1. Richards DM, Heel RC. Ceftizoxime: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1985; 29: 281–329.

Administration in children. Ceftizoxime may be given to children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria. It is given by deep intramuscular injection, or intravenously as a slow injection over 3 to 5 minutes or as a continuous or intermittent infusion. The American Academy of Pediatrics[1] recommends that children aged 1 month and older may be given 150 mg/kg daily in 3 divided doses (to a maximum daily dose of 3 to 4 g) for mild to moderate infections; the dose may be increased to 150 to 200 mg/kg daily in 3 or 4 divided doses (to a maximum daily dose of 6 to 12 g) in severe infections.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Administration in renal impairment. Parenteral doses of ceftizoxime should be modified in renal impairment; after a loading dose of 0.5 to 1 g, the maintenance dosage should be adjusted according to creatinine clearance (CC) and the severity of the infection:

- CC 50 to 79 mL/minute: 0.5 to 1.5 g every 8 hours
- CC 5 to 49 mL/minute: 0.25 to 1 g every 12 hours
- CC less than 5 mL/minute: 250 to 500 mg every 24 hours or 0.5 to 1 g every 48 hours, after dialysis.

Adverse Effects and Precautions

As for Cefotaxime Sodium, p. 244.3.

Sodium content. Each g of ceftizoxime sodium contains about 2.5 mmol of sodium.

Interactions

Probenecid reduces the renal clearance of ceftizoxime.

Antimicrobial Action

As for Cefotaxime Sodium, p. 244.3, although ceftizoxime has no active metabolite.

Pharmacokinetics

After intramuscular injection of 0.5 and 1 g of ceftizoxime, mean peak plasma concentrations of about 14 and 39 micrograms/mL respectively have been reported after 1 hour. The plasma half-life of ceftizoxime is about 1.7 hours and is prolonged in neonates and in renal impairment. Ceftizoxime is 30% bound to plasma proteins.

Ceftizoxime is widely distributed in body tissues and fluids; therapeutic concentrations occur in the CSF when the meninges are inflamed. It crosses the placenta and low concentrations have been detected in breast milk.

Nearly all of a dose is excreted unchanged in the urine within 24 hours of dosage, thus achieving high urinary concentrations. Ceftizoxime is excreted by tubular secretion as well as glomerular filtration and giving it with probenecid results in higher and more prolonged plasma concentrations. Some ceftizoxime is removed by haemodialysis.

Neonates. References.

1. Pujli R. Investigation of half-life and clinical effects of ceftizoxime in premature and newborn infants. *Drug Invest* 1990; 2: 143–9.
2. Reed MD, *et al.* Ceftizoxime disposition in neonates and infants during the first six months of life. *DICP Ann Pharmacother* 1991; 25: 344–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Dalijing (达力净); Daliqing (达力清); Epocelin (益保世灵); Zhuobisha (卓必沙); ***India***: Cefizox; Eldcef; Epocelin; ***Indon.***: Cefim; Ceftizox; Tizos; ***Ital.***: Eposerin; ***Jpn***: Epocelin; ***Philipp.***: Tergecin†; Unizox; Zoxim; ***Port.***: Cefizox; ***Turk.***: Cefizox; ***USA***: Cefizox†.

Pharmacopoeial Preparations

USP 36: Ceftizoxime for Injection; Ceftizoxime Injection.

Ceftobiprole Medocaril *(USAN, rINN)*

BAL-5788-001; BAL-5788; BAL-9141 (ceftobiprole); Ceftobiprol medocarilo; Ceftobiprole Médocaril; Ceftobiprolum Medocarilum; Ro-65-5788; Ro-63-9141 (ceftobiprole); Цефтобипрол Медокарил.

(6*R*,7*R*)-7-[(2*Z*)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-(hydroxyimino)acetamido]-3-{[(*E*)-[(3′*R*)-1′-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methoxycarbonyl]-2-oxo-(1,3′-bipyrrolidin)-3-ylidene]methyl}-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

$C_{26}H_{26}N_8O_{11}S_2$=690.7

CAS — 209467-52-7 (ceftobiprole); 376653-43-9 (ceftobiprole medocaril); 252188-71-9 (ceftobiprole medocaril sodium).

ATC — J01DI01.

ATC Vet — QJ01DI01.

UNII — N99027V28J.

NOTE. Ceftobiprole medocaril is normally formulated as ceftobiprole medocaril sodium ($C_{26}H_{25}N_8NaO_{11}S_2$=712.6).

Profile

Ceftobiprole is a broad-spectrum cephalosporin antibacterial used in the treatment of complicated skin and skin structure infections caused by susceptible organisms, including meticillin-resistant *Staphylococcus aureus*.

It is given by intravenous infusion over 1 to 2 hours as the prodrug, ceftobiprole medocaril (formulated as its sodium salt); doses are expressed in terms of ceftobiprole; 1.33 g of ceftobiprole medocaril sodium is equivalent to about 1 g of ceftobiprole. The usual dose is the equivalent of 500 mg every 8 or 12 hours. The dose of ceftobiprole may need to be reduced in patients with renal impairment, see p. 255.3.

References.

1. Noel GJ. Clinical profile of ceftobiprole, a novel beta-lactam antibiotic. *Clin Microbiol Infect* 2007; 13 (suppl 2): 25–9.
2. Murthy B, Schmitt-Hoffmann A. Pharmacokinetics and pharmacodynamics of ceftobiprole, an anti-MRSA cephalosporin with broad-spectrum activity. *Clin Pharmacokinet* 2008; 47: 21–33.
3. Zhanel GG, *et al.* Ceftobiprole: a review of a broad-spectrum and anti-MRSA cephalosporin. *Am J Clin Dermatol* 2008; 9: 245–54.
4. Deresinski SC. The efficacy and safety of ceftobiprole in the treatment of complicated skin and skin structure infections: evidence from 2 clinical trials. *Diagn Microbiol Infect Dis* 2008; 61: 103–9.
5. Anderson SD, Gums JG. Ceftobiprole: an extended-spectrum anti-methicillin-resistant Staphylococcus aureus cephalosporin. *Ann Pharmacother* 2008; 42: 806–16.
6. Vidaillac C, Rybak MJ. Ceftobiprole: first cephalosporin with activity against methicillin-resistant Staphylococcus aureus. *Pharmacotherapy* 2009; 29: 511–25.
7. Barbour A, *et al.* Ceftobiprole: a novel cephalosporin with activity against Gram-positive and Gram-negative pathogens, including methicillin-resistant Staphylococcus aureus (MRSA). *Int J Antimicrob Agents* 2009; 34: 1–7.

Administration in renal impairment. Reduced doses of ceftobiprole may be necessary in patients with moderate to severe renal impairment. Suggested intravenous doses should be given over 2 hours and are based on creatinine clearance (CC):

- CC 30 to 49 mL/minute: 500 mg every 12 hours
- CC less than 30 mL/min: 250 mg every 12 hours

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Zeftera†; ***Rus.***: Zeftera (Зефтера).

Ceftriaxone Sodium *(BANM, USAN, rINNM)*

Ceftriakson sodowy; Ceftriaksono natrio druska; Ceftriaxon-Dinatrium; Ceftriaxon sodná sůl trihemihydrát; Ceftriaxona sódica; Ceftriaxone sodique; Ceftriaxonnatrium; Ceftriaxonnátrium; Ceftriaxonum natricum; Ceftriaxonum Natricum Trihemihydricum; Keftriaksoniinatrium; Natrii Ceftriaxonum; Ro-13-9904; Ro-13-9904/000 (ceftriaxone); Seftriakson Sodyum; Натрий Цефтриаксон.

(*Z*)-7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl)thiomethyl]-3-cephem-4-carboxylic acid, disodium salt, sesquaterhydrate.

$C_{18}H_{16}N_8Na_2O_7S_3.3½H_2O$=661.6

CAS — 73384-59-5 (ceftriaxone); 74578-69-1 (anhydrous ceftriaxone sodium); 104376-79-6 (ceftriaxone sodium sesquaterhydrate).

ATC — J01DD04.

ATC Vet — QJ01DD04.

UNII — 023ZSBR09K.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Ceftriaxone Sodium). A semisynthetic product derived from a fermentation product. An almost white to yellowish, slightly hygroscopic, crystalline powder. Freely soluble in water; very slightly soluble in dehydrated alcohol; sparingly soluble in methyl alcohol. A 12% solution in water has a pH of 6.0 to 8.0. Store in airtight containers. Protect from light.

USP 36: (Ceftriaxone Sodium). A white to yellowish-orange crystalline powder. Freely soluble in water; very slightly soluble in alcohol; sparingly soluble in methyl alcohol. pH of a 10% solution in water is between 6.0 and 8.0. Store in airtight containers.

Incompatibility. UK licensed product information warns of incompatibility if ceftriaxone sodium is mixed with calcium-containing solutions or with aminoglycosides, amsacrine, fluconazole, labetalol, or vancomycin. Published reports of incompatibility have included that between ceftriaxone and vancomycin[1] or pentamidine.[2]

1. Pritts D, Hancock D. Incompatibility of ceftriaxone with vancomycin. *Am J Hosp Pharm* 1991; 48: 77.
2. Lewis JD, El-Gendy A. Cephalosporin-pentamidine isethionate incompatibilities. *Am J Health-Syst Pharm* 1996; 53: 1461–2.

Stability. References.

1. Nahata MC. Stability of ceftriaxone sodium in peritoneal dialysis solutions. *DICP Ann Pharmacother* 1991; 25: 741–2.
2. Canton E, Esteban MJ. Stability of ceftriaxone solution. *J Antimicrob Chemother* 1992; 30: 397–8.
3. Bailey LC, *et al.* Stability of ceftriaxone sodium in injectable solutions stored frozen in syringes. *Am J Hosp Pharm* 1994; 51: 2159–61.
4. Plumridge RJ, *et al.* Stability of ceftriaxone sodium in polypropylene syringes at -20, 4, and 20 degreesC. *Am J Health-Syst Pharm* 1996; 53: 2320–3.

Uses and Administration

Ceftriaxone is a third-generation cephalosporin antibacterial used for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria, including infections of the abdomen, bones and joints, CNS, skin and skin structures, genito-urinary tract (including gonorrhoea), respiratory tract, gynaecological infections, and early Lyme disease. It is also used for infections in

neutropenic patients and surgical infection prophylaxis. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Ceftriaxone is given as the sodium salt by slow intravenous injection over at least 2 to 4 minutes, by intermittent intravenous infusion over at least 30 minutes, or by deep intramuscular injection. If more than 1 g is to be injected intramuscularly then the dose should be divided between more than one site. Doses are expressed in terms of the equivalent amount of ceftriaxone; 1.19 g of ceftriaxone sodium is equivalent to about 1 g of ceftriaxone.

The usual dose is 1 to 2 g daily as a single dose or in two divided doses; in severe infections up to 4 g daily may be given. A single intramuscular dose of 250 mg is recommended for the treatment of uncomplicated gonorrhoea.

For surgical infection prophylaxis, a single dose of 1 g may be given 0.5 to 2 hours before surgery; a 2-g dose is suggested before colorectal surgery.

Although not licensed for the prevention of secondary cases of meningococcal meningitis, the *BNF* suggests a single intramuscular dose of 250 mg may be used.

The dose of ceftriaxone may need to be modified in patients with renal impairment, see p. 256.1. For details of doses in children, see also p. 256.1.

References.

1. Brogden RN, Ward A. Ceftriaxone: a reappraisal of its antibacterial activity and pharmacokinetic properties, and an update on its therapeutic use with particular reference to once-daily administration. *Drugs* 1988; 35: 604–45.
2. Lamb HM, *et al.* Ceftriaxone: an update of its use in the management of community-acquired and nosocomial infections. *Drugs* 2002; 62: 1041–89.
3. Bille H, *et al.* In vitro activity, pharmacokinetics, clinical efficacy, safety and pharmacoeconomics of ceftriaxone compared with third and fourth generation cephalosporins: review. *J Chemother* 2005; 17: 3–24.
4. Woodfield JC, *et al.* A meta-analysis of randomized, controlled trials assessing the prophylactic use of ceftriaxone; a study of wound, chest, and urinary infections. *World J Surg* 2009; 33: 2538–50.

Administration in children. Ceftriaxone may be given to children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria. It is given by deep intramuscular injection, or intravenously as a slow injection over 2 to 4 minutes, or by intermittent intravenous infusion over 30 to 60 minutes; intravenous doses in neonates should be given over 60 minutes.

The *BNFC* recommends the following doses:

- neonates: 20 to 50 mg/kg once daily
- children 1 month of age and older and weighing less than 50 kg: 50 mg/kg once daily, increased to up to 80 mg/kg daily in severe infections and meningitis
- older children and those weighing more than 50 kg: 1 g daily, increased to 2 to 4 g daily in severe infections and meningitis

In the USA, the American Academy of Pediatrics[1] suggests neonates may be given a dose of 50 mg/kg every 24 hours. Children 1 month and older may be given a dose of 50 to 75 mg/kg (maximum 1 g) once daily for mild to moderate infections, or 100 mg/kg daily in 1 or 2 divided doses (to a maximum daily dose of 2 to 4 g) in severe infections.

The *BNFC* also permits the use of ceftriaxone in the following unlicensed indications:

- for the prevention of secondary cases of meningococcal meningitis
- children from 1 month to 12 years of age may be given 125 mg as a single intramuscular dose
- those older than 12 years may be given 250 mg as a single intramuscular dose
  for the prevention of secondary cases of *Haemophilus influenzae* type b in children who cannot take rifampicin
- from 1 month to 12 years of age ceftriaxone may be given by intravenous infusion at a dose of 50 mg/kg (to a maximum of 1 g) once daily for 2 days
- those older than 12 years may be given 1 g once daily for 2 days either by intramuscular injection or intravenously

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Administration in hepatic and renal impairment. A reduction in dosage of ceftriaxone may be necessary in patients with severe renal impairment (creatinine clearance below 10 mL/minute), in whom the daily parenteral dose should not exceed 2 g. In patients undergoing dialysis, and in those with both renal and hepatic impairment, plasma concentrations of ceftriaxone should be monitored to determine whether dose adjustment is needed.

Meningitis. A meta-analysis[1] of randomised controlled studies to evaluate the effectiveness and safety of short-course antibacterial treatment for community-acquired bacterial meningitis in children reported no difference between short-course (4 to 7 days) and standard long-course (7 to 14 days) treatment with intravenous ceftriaxone in terms of clinical success, long-term neurological complications, long-term hearing impairment, total adverse events, or secondary nosocomial infections.

An international, placebo-controlled, study[2] of 5 or 10 days of treatment with intravenous ceftriaxone in 1004 children aged 2 months to 12 years (including those with HIV infection) with bacterial meningitis concluded that parenteral ceftriaxone could be safely discontinued in those children who are stable by day 5 of treatment. The authors considered that prompt treatment with antibacterials were probably more important in reducing morbidity and mortality than a long-course treatment regimen.

1. Karageorgopoulos DE, *et al.* Short versus long duration of antibiotic therapy for bacterial meningitis: a meta-analysis of randomised controlled trials in children. *Arch Dis Child* 2009; 94: 607–14.
2. Molyneux E, *et al.* CSF 5 Study Group. 5 versus 10 days of treatment with ceftriaxone for bacterial meningitis in children: a double-blind randomised equivalence study. *Lancet* 2011; 377: 1837–45.

Adverse Effects and Precautions

As for Cefotaxime Sodium, p. 244.3. Changes in bowel flora may be more marked than with cefotaxime because of the greater biliary excretion of ceftriaxone; diarrhoea may occur more often, especially in children.

Biliary sludge or pseudolithiasis due to a precipitate of calcium ceftriaxone has been seen occasionally in patients given ceftriaxone. Similarly, deposition of the calcium salt has occurred rarely in the urine. Isolated cases of death in term or premature neonates have been associated with precipitation of calcium ceftriaxone in lungs and kidneys, and in some of these cases a calcium-containing product has been given by a different route or line, or at a different time. The FDA therefore contra-indicates the use of ceftriaxone and intravenous calcium-containing products in neonates 28 days of age and younger. In older patients they consider the risk of precipitation to be low and ceftriaxone and calcium-containing products may be given sequentially, provided the infusion lines are thoroughly flushed between infusions. Ceftriaxone should not be given together with intravenous calcium-containing solutions via a Y-site in any age group.

Ceftriaxone is highly protein bound and is able to displace bilirubin from albumin binding sites, causing hyperbilirubinaemia; its use should be avoided in jaundiced neonates. Use is also contra-indicated in premature neonates (postmenstrual age less than 41 weeks).

Neutropenia has been reported with most cephalosporins; a complex mechanism has been attributed to that associated with ceftriaxone. There have been rare reports of fatal haemolysis associated with ceftriaxone.

Although ceftriaxone has an *N*-methylthiotriazine ring rather than an *N*-methylthiotetrazole side-chain, it might still have the potential to cause hypoprothrombinaemia.

Breast feeding. A study of drug distribution and protein binding between maternal blood and breast milk post partum in a 26-year-old woman given ceftriaxone 2 g daily by intravenous infusion for 10 days found that penetration of ceftriaxone into breast milk increased at these doses as protein binding capacity was saturated, although no adverse effects occurred in the infant.[1] The authors advised caution in breast-feeding mothers given acidic drugs which also have high protein binding such as ceftriaxone[1] although, on the basis that no adverse effects have been seen in breast-fed infants whose mothers were receiving ceftriaxone, the American Academy of Pediatrics considers[2] that it is therefore usually compatible with breast feeding.

1. Bourget P, *et al.* Ceftriaxone distribution and protein binding between maternal blood and milk postpartum. *Ann Pharmacother* 1993; 27: 294–7.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)

Effects on the biliary tract. Using abdominal ultrasonography, biliary sludge or pseudolithiasis was found in about 40% of severely ill children being treated with high doses of ceftriaxone[1] and was later reported in adults.[2,3] The sludge has been identified as a calcium salt of ceftriaxone.[4] Patients are often asymptomatic and the sludge usually dissolves once ceftriaxone is stopped. Gallstones with ceftriaxone as a major component have been identified in a patient given long-term high-dose treatment.[7] Similarly, a bile-duct stone composed of ceftriaxone occurred with high-dose ceftriaxone in a child.[8] In another report, intractable hiccups were associated with ceftriaxone-related pseudolithiasis in a 10-year-old boy.[9]

1. Schaad UB, *et al.* Reversible ceftriaxone-associated biliary pseudolithiasis in children. *Lancet* 1988; ii: 1411–13.
2. Pigrau C, *et al.* Ceftriaxone-associated biliary pseudolithiasis in adults. *Lancet* 1989; ii: 165.
3. Heim-Duthoy KL, *et al.* Apparent biliary pseudolithiasis during ceftriaxone therapy. *Antimicrob Agents Chemother* 1990; 34: 1146–9.
4. Bickford CL, Spencer AP. Biliary sludge and hyperbilirubinemia associated with ceftriaxone in an adult: case report and review of the literature. *Pharmacotherapy* 2005; 25: 1389–95.
5. Rienstra M, *et al.* Ceftriaxone-associated biliary pseudolithiasis. *Neth J Med* 2009; 67: 113–4.
6. Park HZ, *et al.* Ceftriaxone-associated gallbladder sludge: identification of calcium-ceftriaxone salt as a major component of gallbladder precipitate. *Gastroenterology* 1991; 100: 1665–70.
7. Lopez AJ, *et al.* Ceftriaxone-induced cholelithiasis. *Ann Intern Med* 1991 115: 712–14.
8. Robertson FM, *et al.* Ceftriaxone choledocholithiasis. *Pediatrics* 1996; 98 133–5.
9. Bonioli E, *et al.* Pseudolithiasis and intractable hiccups in a boy receiving ceftriaxone. *N Engl J Med* 1994; 331: 1532.

Effects on the blood. References.

1. Haubenstock A, *et al.* Hypoprothrombinaemic bleeding associated with ceftriaxone. *Lancet* 1983; i: 1215–16.
2. Rey D, *et al.* Ceftriaxone-induced granulopenia related to a peculiar mechanism of granulopoiesis inhibition. *Am J Med* 1989; 87: 591–2.
3. Bernini JC, *et al.* Fatal hemolysis induced by ceftriaxone in a child with sickle cell anemia. *J Pediatr* 1995; 126: 813–15.
4. Lascari AD, Amyot K. Fatal hemolysis caused by ceftriaxone. *J Pediatr* 1995; 126: 816–17.
5. Scimeca PG, *et al.* Hemolysis after treatment with ceftriaxone. *J Pediatr* 1996; 128: 163.
6. Moallem HJ, *et al.* Ceftriaxone-related fatal hemolysis in an adolescent with perinatally acquired human immunodeficiency virus infection. *J Pediatr* 1998; 133: 279–81.
7. Meyer O, *et al.* Fatal immune haemolysis due to a degradation product of ceftriaxone. *Br J Haematol* 1999; 105: 1084–5.
8. Viner Y, *et al.* Severe hemolysis induced by ceftriaxone in a child with sickle-cell anemia. *Pediatr Infect Dis J* 2000; 19: 83–5.
9. Seltsam A, Salama A. Ceftriaxone-induced immune haemolysis: two case reports and a concise review of the literature. *Intensive Care Med* 2000; 26: 1390–4.
10. Citak A, *et al.* Ceftriaxone-induced haemolytic anaemia in a child with no immune deficiency or haematological disease. *J Paediatr Child Health* 2002; 38: 209–10.

Effects on the pancreas. References.

1. Zimmermann AE, *et al.* Ceftriaxone-induced acute pancreatitis. *Ann Pharmacother* 1993; 27: 36–7.
2. Maranan MC, *et al.* Gallstone pancreatitis caused by ceftriaxone. *Pediatr Infect Dis J* 1998; 17: 662–3.

Neonates. References to the displacement of bilirubin by ceftriaxone in neonates.

1. Gulian J-M, *et al.* Bilirubin displacement by ceftriaxone in neonates: evaluation by determination of 'free' bilirubin and erythrocyte-bound bilirubin. *J Antimicrob Chemother* 1987; 19: 823–9.
2. Fink S, *et al.* Ceftriaxone effect on bilirubin-albumin binding. *Pediatrics* 1987; 80: 873–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ceftriaxone as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Sodium content. Each g of ceftriaxone sodium contains about 3.0 mmol of sodium.

Interactions

Ceftriaxone has an *N*-methylthiotriazine side-chain and may have the potential to increase the effects of anticoagulants and to cause a disulfiram-like reaction with alcohol. For contra-indications to the use of ceftriaxone with calcium-containing products see Adverse Effects and Precautions, above.

Unlike that of many cephalosporins, the renal excretion of ceftriaxone is not affected by probenecid.

Antimicrobial Action

As for Cefotaxime Sodium, p. 244.3, although ceftriaxone has no active metabolite.

References.

1. Goldstein FW, *et al.* Resistance to ceftriaxone and other β-lactams in bacteria isolated in the community. *Antimicrob Agents Chemother* 1995; 39: 2516–19.

Pharmacokinetics

Ceftriaxone has nonlinear dose-dependent pharmacokinetics because of its protein binding; about 85 to 95% is bound to plasma proteins depending on the concentration of ceftriaxone.

Mean peak plasma concentrations of about 40 and 80 micrograms/mL have been reported 2 hours after intramuscular injection of 500 mg and 1 g of ceftriaxone respectively. The plasma half-life of ceftriaxone is not dependent on the dose and varies between 6 and 9 hours; it may be prolonged in neonates. The half-life does not change appreciably in patients with moderate renal impairment, but it may be prolonged in severe impairment especially when there is also hepatic impairment.

Ceftriaxone is widely distributed in body tissues and fluids. It crosses both inflamed and non-inflamed meninges, generally achieving therapeutic concentrations in the CSF. It crosses the placenta and low concentrations have been detected in breast milk. High concentrations occur in bile.

About 40 to 65% of a dose of ceftriaxone is excreted unchanged in the urine, principally by glomerular filtration; the remainder is excreted in the bile and is ultimately found

in the faeces as unchanged drug and microbiologically inactive compounds.

Reviews.
1. Hayton WL, Stoeckel K. Age-associated changes in ceftriaxone pharmacokinetics. *Clin Pharmacokinet* 1986; 11: 76–86.
2. Yuk JH, *et al.* Clinical pharmacokinetics of ceftriaxone. *Clin Pharmacokinet* 1989; 17: 223–35.
3. Perry TR, Schentag JJ. Clinical use of ceftriaxone: a pharmacokinetic-pharmacodynamic perspective on the impact of minimum inhibitory concentration and serum protein binding. *Clin Pharmacokinet* 2001; 40: 685–94.
4. Garot D, *et al.* Population pharmacokinetics of ceftriaxone in critically ill septic patients: a reappraisal. *Br J Clin Pharmacol* 2011; 72: 758–67.

Hepatic impairment. References.

1. Stoeckel K, *et al.* Single-dose ceftriaxone kinetics in liver insufficiency. *Clin Pharmacol Ther* 1984; 36: 500–9.
2. Hary L, *et al.* The pharmacokinetics of ceftriaxone and cefotaxime in cirrhotic patients with ascites. *Eur J Clin Pharmacol* 1989; 36: 613–16.
3. Toth A, *et al.* Pharmacokinetics of ceftriaxone in liver-transplant recipients. *J Clin Pharmacol* 1991; 31: 722–8.

Pregnancy. References.

1. Bourget P, *et al.* Pharmacokinetics and protein binding of ceftriaxone during pregnancy. *Antimicrob Agents Chemother* 1993; 37: 54–9.

Renal impairment. The pharmacokinetics of ceftriaxone are not markedly altered in mild to moderate renal impairment,[1] but the half-life can be prolonged in severe or end-stage renal disease.[1-4] Ceftriaxone is generally not removed by peritoneal dialysis[4] or by haemodialysis[1-3] although a decrease in half-life has been reported during haemodialysis.[5] In many patients no alteration in dosage is necessary, but some individuals have reduced non-renal clearance despite apparently normal hepatic function.[2,3] It is advisable to monitor plasma ceftriaxone in patients with severe renal impairment and unknown non-renal clearance.

1. Patel IH, *et al.* Ceftriaxone pharmacokinetics in patients with various degrees of renal impairment. *Antimicrob Agents Chemother* 1984; 25: 438–42.
2. Stoeckel K, *et al.* Single-dose ceftriaxone kinetics in functionally anephric patients. *Clin Pharmacol Ther* 1983; 33: 633–41.
3. Cohen D, *et al.* Pharmacokinetics of ceftriaxone in patients with renal failure and in those undergoing hemodialysis. *Antimicrob Agents Chemother* 1983; 24: 529–32.
4. Ti T-Y, *et al.* Kinetic disposition of intravenous ceftriaxone in normal subjects and patients with renal failure on hemodialysis or peritoneal dialysis. *Antimicrob Agents Chemother* 1984; 25: 83–7.
5. Garcia RL, *et al.* Single-dose pharmacokinetics of ceftriaxone in patients with end-stage renal disease and hemodialysis. *Chemotherapy* 1988; 34: 261–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Acantex; Bioteral; Cefomax; Ceftriaz; Exempla; Rivacefin; Soltrimox: ***Austral.***: Rocephin; ***Austria***: Cefotrix; Rocephin; ***Belg.***: Rocephine; ***Braz.***: Ceftriax; Glicocef†; Keftron; Mesporan†; Neocefturiona; Prodoxin†; Rocefin; Triaxin; Triaxon; Triaxton; Trioxina; ***Canad.***: Rocephin†; ***Chile***: Acantex; Grifotriaxona; ***China***: Ansailong (安塞隆); Cefin (泛生舒复); Dezhi (得治); Likang Kesong (丽康可松); Livzonphin (丽珠芬); Locekin (罗塞泰); Oframax (果复每); Rocephin (罗氏芬); Xianqin (先噪); ***Cz.***: Lendacin; Megion†; Samixon; ***Denm.***: Cefotrix; Rocephalin; ***Fin.***: Rocephalin; ***Fr.***: Rocephine; Triacefan; ***Ger.***: Cefotrix; Rocephin; ***Gr.***: Antibacin; Azatyl; Bresec; Ceftrixon; Ceriaxon; Farcef; Fredofol; Gladius; Glorixone; Infeflox; Labilex; Medaxone; Riaxon; Rocephin; Rolisporin; Travilan; Ugotrex; Veracol; ***Hong Kong***: Medaxonum; Mesporin; Rocephin; Zoxon; ***Hung.***: Cefotrix†; Lendacin; Megion; Rocephin; ***India***: Acticef; Afzone; Alitax; Alkaceff; Alnacef; Amcef; Arixon; Avcef; Axocare; Axone; Axtrum; Becef; Bintrax; Broadcef; Brucef; C Tri; C-Tech; C-Tri; Cadizone; Cafage; Cafzone; Cameo; Cebay TRX; Cef; Cefa Kit; Cefaday; Cefamed; Cefast; Cefaxone; Cefcin; Cefera; Cefezone; Cefmac; Cefmol; Cefoat; Cefocef; Cefogram; Cefotec; Cefritz-S; Cefritz; Cefs; Cefset; Cefsine; Ceftraset; Ceftrax; Ceftrian; Ceftril; Ceftrisone; Ceftrol; Ceftron; Cefwon; Cefxi; Cefzox; Cepoxit-CX; Ceptradin; Cetazone; Cetriax; Cetzone; Cezone; Champione; Chuncif; Ciforion; Ciplacef; Comtrix; Contrax; Cosrex; Cotyx; Cruzone; CSI; CT Ceff; CT-Xone; CTX; Cucef; Cuxone; CX-One; D-Cef; Daltrix; Deczone; Dewcef; E-Cef; Efectal; Efoceft; Eftanu; Ekcef; Emtri; Emtriaxone; Eracef; Estxone; Extacef-I; Fexon; Finetriax; Fixi; Forone; Geminate; Glen; Glicef; Gloriax; Gramocef; Gutencef; Hicef; Hocef; I-Tone; Ifytrox; Incef; Indocef; Indoxone; Infoxon; Intax; Ivixone; Kafi; Keftra; Kexone; Labxone; Lezone; Lifecare; Lisel; Lyceft; Magtrax; Marcef; Mediceft; Mepcef; Mintrax; Mocef; Monocef; Monotax; Multi-Xone; Nefzon; Nexef-O; Nizotrax; NKCef; Nosocef; Novaceft; Novatrax; Nu Axiom; Nutracip; O-Cef; Oframax; Omisafe; Omna One; Oncef; Opticef; Ostri; Oxy; Pancef; Parcef; Powercef; Safelo; ***Indon.***: Betrix; Biotriax; Bioxon; Broadced; Brospec; Cefaxon; Cefriex; Cefsix; Ceftrox; Cefxon; Cephaflox; Cocefin; Criax; Ecotrixon; Elpicef; Erocef; Foricef; Gracef; Intricef; Intrix; Renxon; Rixone; Rocephin; Socef; Starxon; Terfacef; Termicef; Tricefin; Trijec; Trixon; Tyason; Zeftrix; ***Irl.***: Rocephin; ***Israel***: Keftriaxone; Pan-Ceftriaxone; Rocephin; Triax†; ***Ital.***: Axobat; Bixon; Cefrag; Davixon; Daytrix; Deixim; Diaxone; Eftry; Eraxitron; Fidato; Prineg; Kocefan; Monoxar; Nilson; Panatrix; Pantoxon; Ragex; Rocefin; Setriox; Sirtap; Valexirne; ***Jpn***: Rocephin; ***Malaysia***: Cefaxone; Ceftrex; Eftriax†; Mesporin; Rocephin; Trixone; Unocef; Vaxcel Ceftriaxone; ***Mex.***: Amcef; Asepzona; Aurofox; Axtar; Benaxona; Cefaxona; Cefraden; Ceftrex; Ceftrilem; Centrifal; Limiprol; Megion; Oframax; Primotox; Rocephin; Tacex; Terbac†; Tindortec; Triaken; Triox; Xonatil; ***Neth.***: Exogran; Lopratin†; Rocephin; ***Norw.***: Rocephalin†; ***NZ***: Rocephin†; Veracol; ***Philipp.***: Acrexon; Afrixon; Armak; Auroxone; Bactrias; Bettrix; CEF-3; Cefotrim; Ceftrialis; Ceftrox; Ceptrocin; Cikedrix; Clovizone; Cotenzo; Cryaxon; Dintri; Efekton; Eroxet; Euroset†; Fazactin; Fenadef; Forgram; Haxon; Hoftrex; Kenaxef; Keptrix; Maxeftin; Medzef; Megion; Monocrin; Norccphin; Novosef; Noxoram; Onizef; Panjecxone; Pantrixon; Pneumosolv; Recephin; Retrokor; Roceftin; Rocephin; Rolaphin; Roxifen; Roxon; Samjizon; Seltroz; Sergimax; Supraxone; Torocef; Triax; Triaxon; Tricexone; Trixophin; Tyoxone; Unixone; Xtenda; Zerone; ***Pol.***: Biotrakson; Lendacin; Oframax; Rocephin†; Tartriakson; ***Port.***: Betasporina; Cefilan; Ceriax; Kemudin; Mesporin; Rocephin; ***Rus.***: Axone (Аксоне); Azaran (Азаран); Betasporina (Бетаспорина); Biotrakson (Биотраксон); Cefatrin (Цефатрин); Cefaxone (Цефаксон); Cefogram (Цефограм); Cefson (Цефсон); Ceftriabol (Цефтриабол); Ceftrifin (Цефтрифин); Hizone (Хизон); Ificef (Ифицеф); Lendacin (Лендацин); Lifaxon (Лифаксон); Loraxone (Лораксон); Medaxone (Медаксов); Megion (Мегион); Movigip (Мовигип); Novosef (Новосеф); Oframax (Офрамакс); Rocepherin (Роцеферин); Rocephin (Роцефин); Sterlcef (Стерицеф); Tercef (Терцеф); Torocef (Тороцеф); Triaxone (Триаксон); ***S.Afr.***: Kocef; Medaxone; Oframax; Rocephin; Rocicct; Triaphin; Triaxiphin; ***Singapore***: Antibacin; Cefaxone; Ceftriphine; Oframax; Rocephin; Trexofin; Triaxone; Tricefin; Trizon; ***Spain***: Rocefalin†; ***Swed.***: Cefonova†; Rocephalin; ***Switz.***: Rocephin; ***Thai.***: CEF-3; Cef-Zone; Ceftrex; Ceftriphin; Gomcephin; Oframax; Rinxolay†; Rocephin; Sedalin; Triacef†; Tricephin†; Trixone; Trixophin; Utofin; Zefaxone; ***Turk.***: Armaseft; Baktiscf; Cefaday; Cefridem; Cephaxon; Desefin; Equicefi; Forsef; Iesef; Nevakson; Novosef; Rocephin; Triaxon; Unacefin; ***UAE***: Triaxone; ***UK***: Rocephin; ***Ukr.***: Cefaxone (Цефаксон); Cefogram (Цефограм); Lendacin (Лендацин)†; Noraxon (Нораксон); Oframax (Офрамакс); Parcef (Парцеф)†; ***USA***: Rocephin; ***Venez.***: Bioceftrax; Cefin; Cefix; Ceftrialin; Ciplacef; Eftrival; Megion; Rocephin; Strixone; Tricefi.

Multi-ingredient Preparations. ***China***: Xin Junbizhi (新君必治); ***India***: Acticef-SB; Adesul; Afzone-S; Alitax-S; Alkaceff-S; Alnacef-S; Alnacef-T; Amceft-S; Arixon-SB; Arixon-TZB; Augtaz; Avcef-S; Avcef-TZ; Axocare-S; Axocare-T; Axon-SB; Axone-SB; Axtrum-S; Bactosul; Big-Tum; Broadcef-S; Broadcef-T; C-Fort; C-Tab-SB; C-Tum; Cadizone-S; Cadizone-XP; Cafage-S; Cameo-S; Cearium; Cebactum; Cef-S; Cefa-T Kit; Cefaday-S; Cefaday-TZ; Cefcin-SB; Cefcin-TJ; Cefirone T; Cefirone-V; Cefjoy; Cefmol-SF; Cefmol-TZ; Cefritz-TZ; Cefrose-S; Cefs-T; Cefset-S; Cefset-TX; Cefsine-S; Cefsine-TZ; Ceftichek; Ceftraset-S; Ceftril-S; Ceftrimax; Ceftrol-S; Cefurin; Cefwon-S; Cefzone-S; Cefzox-SF; Cefzox-TZ; Cepoxit-S; Cesafe-TZ; Cetriax-S; Cetzone-S; Cetzone-TZ; Cezone Plus; Champione-S; Chuncif-S; Corcef-SB; Cotyx-S; Crucef; CSI-S; CT Ceff SM; CT Ceff-TZ; CTMor-TZ; CTrisana-SB; CTX-TZ; Cucef-S; Cuxone-SL; Deczone-S; Deczone-T; Deczone-TP; Dewcef-S; Dibact; Eftanu-S; Ekcef-S; Emtri-S; Estxone-SB; Extacef-Tazo; Extacef-XL; Finecef-T; Finetriax-S; Formic; Forone-SB; Geminate Plus; Glen-SB; Glen-TZB; Glicef-S; Glicef-T; Gloriax-SB; Gramocef-S; Hicef-T; Hocef-S; Hocef-T; Ifytrox-SB; Ifytrox-TB; Incef-SB; Incef-TZ; Indocef-SB; Indoxone-S; Infoxon-S; Infoxon-T; Kafi-S; Kafi-TBZ; Keftragard; Kexone Plus; Kxone-SL; Labxone-SB; Lezone-S; Lezone-XP; Lifecare-A; Lifecare-C; Lifecare-SB; Lifecare-T; Lisel-S; Lisel-TBZ; Lyceft Plus; Mahacef-SB; Mat-CS; Mepef-S; Mintrax-S; Mocef-S; Mocef-TZ; Monobact; Montaz; Nexef-SB; Nexef-TBZ; Nizotrax-S; NKCef+S; Novaceft-S; Nutracip-SB; Oframax Forte; Onbact; Opticef-S; Oritiz; Oxy-S; Pancef-S.

Pharmacopoeial Preparations
BP 2014: Ceftriaxone Injection;
USP 36: Ceftriaxone for Injection; Ceftriaxone Injection.

Cefuroxime *(BAN, USAN, rINN)*

640/359; Cefuroxim; Cefuroxima; Céfuroxime; Cefuroximum; Kefuroksiimi; Sefuroksim; Цефуроксим.

(*Z*)-3-Carbamoyloxymethyl-7-[2-(2-furyl)-2-methoxyiminoacetamido]-3-cephem-4-carboxylic acid.

$C_{16}H_{16}N_4O_8S$=424.4

CAS — 55268-75-2.

ATC — J01DC02; S01AA27.

ATC Vet — QJ01DC02; QJ51DA06; QS01AA27.

UNII — O1R9FJ93ED.

Cefuroxime Axetil *(BANM, USAN, rINNM)*

CCI-15641; Cefuroksimas aksetilas; Cefuroksymu aksetyl; Cefuroxima axetilo; Cefuroxim-axetil; Céfuroximaxetil; Céfuroxime axétil; Cefuroxime, Axétil de; Cefuroximi Axetilum; Cefuroximum Axetili; Cefuroximum Axetilum; Kefuroksiimiaksetiili; Sefuroksim Aksetil; Цефуроксима Аксетил.

$C_{20}H_{22}N_4O_{10}S$=510.5

CAS — 64544-07-6.

ATC — J01DC02; S01AA27.

ATC Vet — QJ01DC02; QS01AA27.

UNII — Z49QDT0J8Z.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Cefuroxime Axetil). A white or almost white powder. Slightly soluble in water and in alcohol; soluble in acetone, in ethyl acetate, and in methyl alcohol. Store in airtight containers. Protect from light.

USP 36: (Cefuroxime Axetil). A mixture of the diastereoisomers of cefuroxime axetil. A white or almost white powder. The amorphous form is insoluble in water and in ether; slightly soluble in dehydrated alcohol; freely soluble in acetone; soluble in chloroform, in ethyl acetate, and in methyl alcohol. The crystalline form is insoluble in water and in ether; slightly soluble in dehydrated alcohol; freely soluble in acetone; sparingly soluble in chloroform, in ethyl acetate, and in methyl alcohol. Store in airtight containers.

Cefuroxime Sodium *(BANM, rINNM)*

Cefuroksimo natrio druska; Cefuroksym sodowy; Cefuroxim-Natrium; Cefuroxim sodná sůl; Cefuroxima sódica; Céfuroxime Sodique; Cefuroximnatrium; Cefuroxim-nátrium; Cefuroximum Natricum; Kefuroksiiminatrium; Natrii Cefuroximum; Sefuroksim Sodyum; Натрий Цефуроксим.

$C_{16}H_{15}N_4NaO_8S$=446.4

CAS — 56238-63-2.

ATC — J01DC02; S01AA27.

ATC Vet — QJ01DC02; QS01AA27.

UNII — R8A7M9MY61.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Cefuroxime Sodium). A white or almost white slightly hygroscopic powder. Freely soluble in water; very slightly soluble in alcohol. A 1% solution in water has a pH of 5.5 to 8.5. Store in airtight containers.

USP 36: (Cefuroxime Sodium). A white or faintly yellow powder. Freely soluble in water; very slightly soluble in alcohol, in chloroform, in ether, and in ethyl acetate; soluble in methyl alcohol. pH of a 10% solution in water is between 6.0 and 8.5. Store in airtight containers.

Incompatibility and stability. Cefuroxime sodium may be incompatible with aminoglycosides.

References.
1. Barnes AR. Chemical stabilities of cefuroxime sodium and metronidazole in an admixture for intravenous infusion. *J Clin Pharm Ther* 1990; 15: 187–96.
2. Stiles ML, *et al.* Stability of ceftazidime (with arginine) and of cefuroxime sodium in infusion-pump reservoirs. *Am J Hosp Pharm* 1992; 49: 2761–4.
3. Hebron B, Scott H. Shelf life of cefuroxime eye-drops when dispensed in artificial tear preparations. *Int J Pharm Pract* 1993; 2: 163–7.

Uses and Administration

Cefuroxime is a second-generation cephalosporin antibacterial used in the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria, including infections of the bones and joints, CNS, skin and skin structures, respiratory tract, genito-urinary tract (including gonorrhoea), and Lyme disease. It is also used for surgical infection prophylaxis. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Cefuroxime is given orally as the acetoxyethyl ester, cefuroxime axetil, in the form of tablets or suspension with or after food, or by injection as the sodium salt. Cefuroxime sodium may be given by deep intramuscular injection, by slow intravenous injection over 3 to 5 minutes, or by intermittent or continuous intravenous infusion; it can also be given by intracameral injection. Doses of cefuroxime axetil and cefuroxime sodium are expressed in terms of the equivalent amount of cefuroxime; 1.20 g of cefuroxime axetil and 1.05 g of cefuroxime sodium are each equivalent to about 1 g of cefuroxime.

The usual oral dose is 250 mg twice daily; for uncomplicated urinary-tract infections 125 mg twice daily may be adequate and for respiratory-tract infections 250 to 500 mg twice daily is recommended. For Lyme disease an oral dose of 500 mg is given twice daily for 20 days.

By injection the usual dose is 750 mg of cefuroxime every 8 hours but in more severe infections 1.5 g may be given intravenously every 8, or in some cases every 6 hours.

Those with pneumonia or with acute exacerbations of chronic bronchitis may respond to sequential therapy with parenteral cefuroxime 1.5 g twice daily or 750 mg twice daily respectively, followed by oral cefuroxime 500 mg twice daily in each case.

For the treatment of meningitis due to sensitive strains of bacteria, cefuroxime is given intravenously in doses of 3 g every 8 hours.

In the treatment of gonorrhoea, a single dose of 1.5 g by intramuscular injection, divided between 2 injection sites, has been used. A single 1-g oral dose of cefuroxime has been given for uncomplicated gonorrhoea. In each case an oral dose of probenecid 1 g may be given with cefuroxime.

For surgical infection prophylaxis, the usual dose is 1.5 g of cefuroxime intravenously before the procedure; this may be supplemented by 750 mg intramuscularly every 8 hours for up to 24 to 48 hours depending upon the procedure. For

total joint replacement, 1.5 g of cefuroxime powder may be mixed with the methylmethacrylate cement.

Cefuroxime may be given by intracameral injection for the prophylaxis of postoperative endophthalmitis; a dose of 1 mg is slowly injected into the anterior chamber of the eye at the end of cataract surgery.

The dose of cefuroxime may need to be reduced in patients with renal impairment, see p. 258.1. For details of doses in children, see also p. 258.1.

Reviews.
1. Perry CM, Brogden RN. Cefuroxime axetil: a review of its antibacterial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1996; **52**: 125–58.
2. Scott LJ, *et al.* Cefuroxime axetil: an updated review of its use in the management of bacterial infections. *Drugs* 2001; **61**: 1455–1500.
3. Keating GM. Intracameral cefuroxime: prophylaxis of postoperative endophthalmitis after cataract surgery. *Drugs* 2013; **73**: 179–86.

Administration in children. Cefuroxime may be given to neonates and children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria and for surgical prophylaxis. It is given orally as cefuroxime axetil; the sodium salt is given parenterally either by intramuscular injection or intravenously, by slow injection over 3 to 5 minutes, or intermittent or continuous infusion.

The *BNFC* suggests the following treatment doses for cefuroxime:

given *orally*
- children 3 months to 2 years of age: 10 mg/kg (to a maximum dose of 125 mg) twice daily
- those over 2 years of age: 15 mg/kg (to a maximum dose of 250 mg) twice daily, *or*

given *parenterally*
- neonates under 7 days of age: 25 mg/kg every 12 hours
- neonates 7 to 21 days of age: 25 mg/kg every 8 hours
- neonate 21 to 28 days of age: 25 mg/kg every 6 hours
- these doses may be doubled in neonates with severe infections, but should be given intravenously
- children from 1 month of age: 20 mg/kg (to a maximum dose of 750 mg) every 8 hours; this dose may be increased to 50 to 60 mg/kg (to a maximum dose of 1.5 g) every 6 or 8 hours in severe infection and cystic fibrosis

For surgical prophylaxis the *BNFC* suggests that children from the age of 1 month may be given a dose of 50 mg/kg (to a maximum dose of 1.5 g) intravenously before the procedure; this may be supplemented by up to 3 further doses of 30 mg/kg (to a maximum dose of 750 mg) intramuscularly or intravenously at 8-hour intervals for high-risk procedures.

In the USA, the American Academy of Pediatrics[1] suggests the following doses:

orally
- children 1 month and older: 20 to 30 mg/kg daily in 2 divided doses (to a maximum daily dose of 0.5 to 1 g) for mild to moderate infections

intravenously or *intramuscularly*
- for neonates aged ⩽7 days (irrespective of body weight): 50 mg/kg every 12 hours
- for neonates aged 8 to 28 days and weighing ⩽2 kg: 50 mg/kg every 8 to 12 hours; a dosing interval of 12 hours may be used until 2 weeks of life in extremely low birth-weight neonates (weighing less than 1 kg)
- for neonates aged 8 to 28 days and weighing >2 kg: 50 mg/kg every 8 hours
- children 1 month and older: 75 to 100 mg/kg daily in 3 divided doses (to a maximum daily dose of 2.25 to 4.5 g) for mild to moderate infections, or 100 to 200 mg/kg daily in 3 or 4 divided doses (to a maximum daily dose of 3 to 6 g) in severe infections

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Administration in renal impairment. Parenteral doses of cefuroxime may need to be reduced in renal impairment. Licensed product information suggests the following doses based on creatinine clearance (CC):
- CC 10 to 20 mL/minute: 750 mg twice daily
- CC less than 10 mL/minute: 750 mg once daily

Patients undergoing haemodialysis should receive an additional 750-mg dose following each dialysis; those undergoing continuous peritoneal dialysis may be given 750 mg twice daily.

Adverse Effects and Precautions

As for Cefalotin Sodium, p. 235.2.

Gastrointestinal disturbances, including diarrhoea, nausea, and vomiting, have occurred in some patients receiving cefuroxime axetil. There have been rare reports of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Mild to moderate hearing loss has been reported in some children given cefuroxime for the treatment of meningitis.

Antibiotic-associated colitis. For reports of pseudomembranous colitis associated with cefuroxime axetil, see Cefalotin, p. 235.2.

Hypersensitivity. A report[1] of a serum sickness-like reaction to cefuroxime. Similar reactions have occurred with cefaclor (p. 233.1), although it is unclear whether they represent a class effect.

A patient who developed a type-1 hypersensitivity reaction to cefuroxime, characterised by itchy maculopapular rash, exhibited cross-sensitivity to cefotaxime and ceftriaxone on patch testing, possibly because of similarities in the side-chain;[2] no cross-sensitivity to cefazolin, cefepime, cefoxitin, or ceftazidime, or to various penicillins, was seen on testing and the patient subsequently tolerated doses of amoxicillin and ceftazidime. The authors noted that cefuroxime had been found in another study to be the most frequent cause of immediate-type hypersensitivity reactions to cephalosporins.

1. Katta R, Anusuri V. Serum sickness-like reaction to cefuroxime: a case report and review of the literature. *J Drugs Dermatol* 2007; **6**: 747–8.
2. Varela Losada S, *et al.* Immediate-type allergic reaction to cefuroxime: cross-reactivity with other cephalosporins, and good tolerance to ceftazidime. *J Investig Allergol Clin Immunol* 2009; **19**: 164–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cefuroxime as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 15/10/11)

Sodium content. Each g of cefuroxime sodium contains about 2.2 mmol of sodium.

Interactions

Probenecid reduces the renal clearance of cefuroxime.

Antimicrobial Action

Cefuroxime is bactericidal and has a similar spectrum of antimicrobial action and pattern of resistance to those of cefamandole (p. 237.1). It is more resistant to hydrolysis by beta-lactamases than cefamandole, and therefore may be more active against beta-lactamase-producing strains of, for example, *Haemophilus influenzae* and *Neisseria gonorrhoeae*. However, treatment failures have occurred in patients with *H. influenzae* meningitis given cefuroxime and might be associated with a relatively high minimum bactericidal concentration when compared with the minimum inhibitory concentration or with a significant inoculum effect. Reduced affinity of penicillin-binding proteins for cefuroxime has also been reported to be responsible for resistance in a beta-lactamase-negative strain of *H. influenzae*.

References.
1. Aditi M, *et al.* Cefuroxime treatment failure and Haemophilus influenzae meningitis: case report and review of literature. *Pediatrics* 1989; **84**: 132–5.
2. Mendelman PM, *et al.* Cefuroxime treatment failure of nontypable Haemophilus influenzae meningitis associated with alteration of penicillin-binding proteins. *J Infect Dis* 1990; **162**: 1118–23.
3. Brown NM, *et al.* Cefuroxime resistance in Haemophilus influenzae. *Lancet* 1992; **340**: 552.

Pharmacokinetics

Cefuroxime axetil is absorbed from the gastrointestinal tract and is rapidly hydrolysed in the intestinal mucosa and blood to cefuroxime; absorption is enhanced in the presence of food. Peak plasma concentrations occur about 2 to 3 hours after an oral dose. The sodium salt is given by intramuscular or intravenous injection. Peak plasma concentrations of about 27 micrograms/mL have been achieved 45 minutes after an intramuscular dose of 750 mg with measurable amounts present 8 hours after a dose. Up to 50% of cefuroxime in the circulation is bound to plasma proteins. The plasma half-life is about 70 minutes and is prolonged in patients with renal impairment and in neonates.

Cefuroxime is widely distributed in the body including pleural fluid, sputum, bone, synovial fluid, and aqueous humour, but only achieves therapeutic concentrations in the CSF when the meninges are inflamed. It crosses the placenta and has been detected in breast milk.

Cefuroxime is excreted unchanged, by glomerular filtration and renal tubular secretion, and high concentrations occur in the urine. On injection, most of a dose of cefuroxime is excreted within 24 hours, the majority within 6 hours. Probenecid competes for renal tubular secretion with cefuroxime resulting in higher and more prolonged plasma concentrations of cefuroxime. Small amounts of cefuroxime are excreted in bile.

Plasma concentrations are reduced by dialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cefurox; ***Austral.***: Zinnat; ***Austria***: Curocef; Zinnat; ***Belg.***: Cefurim; Doccefuro†; Kefuro; Zinacef; Zinnat; ***Braz.***: Keroxime; Medcef; Monocef; Zinacef; Zinnat; ***Canad.***: Ceftin; ***Chile***: Cerevax; Curocef; Zinnat; ***Chin.***: AoShu (澳舒); Axetine (安可欣); Ba Xin (巴欣); Ceroxim (协信); Dalbxin (达力新); Fulexin (伏乐新); Jia Nuo Xin (嘉诺欣); Jin Mao (金茂); Kaidixin (凯帝欣); Ku Xin (库欣); Li Fu Xin (利扶欣); Li Jian Xin (立健新); Lifurox (力复乐); Monacef (明可欣); Pai Wei Xin (派威欣); Rui Fu Xin (瑞呋欣); Sipeiding (司佩定); Supero (舒贝洛); Xi Lu Xin (希路信); Xin Li Xin (信立欣); Xin Lu Xin (欣路信); Xinfuxin (新福欣); Yaxing (亚星); Youlexin (优乐新); Yun Tai (运泰); Zinacef (西力欣); ***Cz.***: Axetin; Medoxin; Miksor; Xorimax; Zinacef; Zinnat; Zinoxime†; ***Denm.***: Zinacef; Zinnat; ***Fin.***: Aprokam; Zinacef; Zinnat; ***Fr.***: Cepazine; Zinnat; ***Ger.***: Cefuhexal†; Cefuro-Puren†; Cefurox-Wolff; Cefurox†; Elobact; Zinnat†; ***Gr.***: Anaptivan; Cefoprim; Cefuretil; Cefuroprol; Cerofene; Ceruxim; Cupax; Ecoline; Fecef; Foucacillin; Fredyr; Furaxil; Galemin; Genephoxal; Goni; Helatocil; Interbion; Lyprovir; Medoxem; Mevecan; Mosalar; Nelabocin; Nipogalin; Normafenac; Receant; Saxetil; Sedopar; Vekfazolin; Yokel; Zagorine; Zetagal; Zilisten; Zinacef; Zinadc; ***Hong Kong***: Axacef; Axim; Ceflour; Quali-Cefurnat; Sefuxin; Xorimax; Zinacef; Zinnat; ***Hung.***: Cefurin†; Ceroxim; Xorin; Xorimax; Zinacef; Zinnat; ***India***: Actum; Adexim; Altace; Altum; Anorex; Arixime; Atom; Aucee; Axacef; Axeptil; Axeti; Axetim; Axti; Bacticef; Barocef; Bencef; Bigcef; Biocef; Bullce; C-Furo; C-Tri-T; Cascef; Ceax; Cef-Vepan; Cefakind; Cefan; Cefar; Cefasyn; Cefexl; Cefies; Cefking; Ceflet; Cefob; Cefoget; Cefoprim; Ceforim; Ceforox; Cefos; Cefoxim; Cefpil; Cefta; Cetab; Ceftal; Ceftra; Ceftum; Cefu; Cefubir; Cefucin; Cefuco; Cefunis; Cefupet; Cefurin; Cefusym; Cefutab-O; Cefuvik; Cefyrex; Cefzim; Ceplex; Cepokem; Cerom; Ceroxitum; Cesai; Ceti; Ceurox; Cilixem; CTrox; Curoxim; Cutil; Cuxim; Daltum; Dercef; Difu; Duxim; Edrucef; Ethicef; Evercef; Exeption; Eximc; Flamicef; Forcef; Forcez; Forex; Forkem; Fucef; Furion; Furrbid; Furomax; Furome; Furox; Furoxil; Fydoroxim; Glyph-ZN; Gocef; I-M-Sure; Iflacef; Insifu; Intracef; Iviroxime; Jaxe; Joxcy; Kaircef; Kaxitel; Kefstar; Kefuel; Kem; Kincef; Klime; L-Turn; Lazocin; Luroxime; Magna; Magnacef; Martec; Maxim; Maxtum; Metump; Milcef; Neftum-AXT; Neroxim; Nifoxime; Novaroxim; Ocef; Omnixim; Oruf; Supacef; ***Indon.***: Anbacim; Cefurox†; Celocid; Cethixim; Kalcef; Kenacef†; Oxtercic; Roxbi†; Sharox; Soxime; Zinacef†; Zinnat; ***Irl.***: Ceftal; Zinace; Zinnat; ***Israel***: Cefurax; Ceroxim†; Kefurim; Pan-Cefuroxime; Zinacef; Zinnat; ***Ital.***: Biocidin†; Cefoprim†; Cefurin; Curoxim; Duxima; Itorex; Lafurex†; Oraxim; Supero; Tilexim; Zinnat; Zinocep; Zoref; ***Malaysia***: Altacef; Anikef; Ceflour; Efurox; Furoxime; Vaxcel Cefuroxime; Xorimax; Xylid; Zinacef; Zinnat; Zocef; ***Mex.***: Cefabiot; Cefagen; Cefuracet; Cetoxil; Froxal; Fucerox; Furobioxin; Magnaspor; Novador; Ximaken; Xorufec; Zinnat; ***Neth.***: Aprokam; Zinacef; Zinnat; ***Norw.***: Zinacef; ***NZ***: Axetine; Zinacef; Zinnat; ***Philipp.***: Aeruginox; Altacef; Ambixime; Axet; Axurocef; Bactipoz; Betcef; C-Tri T; Cefogen; Ceftil; Cefucil†; Cefumax; Cefurex; Cefuzime; Cervin; Cesavess; Cidokez; Cimex; Clovixime; Curecef; Darcef; Ecocef; Educef; Elixime; Emixor; Eoroxime; Eroxmit; Eurimax; Finax; Fubaxyn†; Furocef; Furocem; Furomax; Furoxim†; Furoxy; Harox; Ifurax; Infekor; Jectocef; Kaftax; Kefezy; Kefox; Kefstar; Kefsyn; Kefurox; Keunzef; Lasuzef; Laxinat; Loxatrel†; Medxil; Medxime; Medzyme; Microzef; Panaxim; Panjecxime; Pheoronex; Pierozef; Profurex; Rexofen; Rezafil; Robisef; Rocef; Romicef; Rovix; Roxetil; Roxicef; Roxime; Roxym†; Rucef; Ruxim; Sharox†; Shincef; Teikeden; Unoximed; Vitaroxima; Xorimax; Zefcid; Zefsur; Zefur; Zefuxim; Zegen; Zenoxim; Zinacef; Zinaf; Zinnat; Zoltax; Zurenix; ***Pol.***: Biofuroksym; Bioracef; Ceroxim; Novocef; Plixym†; Tarsime; Xelacef; Xorim†; Xorimax; Zamur; Zinacef; Zinnat; Zinoxx; ***Port.***: Antibioxime; Axacef; Cefofix†; Condronac; Curoxime; Famicef; Lusocef†; Saracef; Zipos; Zoref; ***Rus.***: Antibioxim (Антибиоксим); Axetine (Аксетин); Cefurabol (Цефурабол); Cefurus (Цефурус); Cetyl (Цетил); Kefstar (Кефстар); Ketocef (Кетоцеф); Proxime (Проксим); Supero (Суперо); Xorim (Ксорим); Zinacef (Зинацеф); Zinnat (Зиннат); ***S.Afr.***: Auroxime; Betaroxime; Cefasyn; Cefu-Hexal; Ceroxim; Cipofix; CuroAx; Intracef†; Medaxime; Zefroxe; Zefurime; Zinacef; Zinnat; Zinoxime; ***Singapore***: Bearcef; Ceftil; Cefxin; Shincef; Xorimax; Zinacef; Zinnat; ***Spain***: Curoxima†; Nivador†; Selan†; Zinnat; ***Swed.***: Zinacef; Zinnat†; ***Switz.***: Cefurim; Zinacef; Zinat; ***Thai.***: Axurocef†; C-Tri T; Cefamart†; Cefurim; Farmacef; Furoxime; Magnaspor; Neurox; Sefuxim; Zinacef; Zinnat; Zocef; Zonef†; ***Turk.***: Aksef; Cefaks; Celatin; Cefurol; Enfexia; Multisef; Oraceftin; Sefaktil; Seffur; Sefuroks; Zinnat; ***UAE***: Cefuzime; ***UK***: Aprokam; Zinacef; Zinnat; ***Ukr.***: Aksef (Аксеф); Biofuroksym (Биофуроксим)†; Cefoctam (Цефоктам); Cefumax (Цефумакс); Cefutil (Цефутил); Cetil (Цетил); Enfexia (Энфексия); Kimacef (Кумацеф); Mikrex (Микрекс); Spizef (Спизеф); Zinacef (Зинацеф); Zinnat (Зиннат); ***USA***: Ceftin; Zinacef; ***Venez.***: Xorim; Zencef; Zinacef; Zinnat.

Multi-ingredient Preparations. ***India***: Bactocef; C-Tri EM; Cefos-S; Covatil-CV; Intracef-CV; Ocef-CV.

Pharmacopoeial Preparations

BP 2014: Cefuroxime Axetil Oral Suspension; Cefuroxime Axetil Tablets; Cefuroxime Eye Drops; Cefuroxime Injection; Cefuroxime Intracameral Injection;

USP 36: Cefuroxime Axetil for Oral Suspension; Cefuroxime Axetil Tablets; Cefuroxime for Injection; Cefuroxime Injection.

Cethromycin *(USAN, rINN)*

A-195773; Abbott-195773; ABT-773; Céthromycine; Cethromycinum; Cetromicina; Цетромицин.

(3a*S*,4*R*,7*R*,9*R*,10*R*,11*R*,13*R*,15*R*,15a*R*)-4-Ethyl-3a,7,9,11,13,15-hexamethyl-11-[[3-(quinolin-3-yl)prop-2-enyl]oxy]-10-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy] octahydro-2*H*-oxacyclotetradecino[4,3-*d*]oxazole-2,6,8,14 (1*H*,7*H*,9*H*)-tetrone.

$C_{42}H_{59}N_3O_{10}$=765.9

CAS — 205110-48-1.

UNII — J0086219X6.

Profile

Cethromycin is a ketolide antibacterial under investigation for the treatment of susceptible respiratory-tract infections.

References.

1. Dougherty TJ, Barrett JF. ABT-773: a new ketolide antibiotic. *Expert Opin Invest Drugs* 2001; 10: 343–51.
2. Zhanel GG, *et al.* The ketolides: a critical review. *Drugs* 2002; 62: 1771–1804.
3. Zhanel GG, *et al.* Ketolides: an emerging treatment for macrolide-resistant respiratory infections, focusing on S. pneumoniae. *Expert Opin Emerg Drugs* 2003; 8: 297–321.
4. Reinert RR. Clinical efficacy of ketolides in the treatment of respiratory tract infections. *J Antimicrob Chemother* 2004; 53: 918–27.
5. Anonymous. Cethromycin: A-195773, A-195773-0, A-1957730, Abbott-195773, ABT 773. *Drugs R D* 2007; 8: 95–102.
6. Hammerschlag MR, Sharma R. Use of cethromycin, a new ketolide, for treatment of community-acquired respiratory infections. *Expert Opin Invest Drugs* 2008; 17: 387–400.
7. Rafie S, *et al.* Cethromycin: a promising new ketolide antibiotic for respiratory infections. *Pharmacotherapy* 2010; 30: 290–303.

Chloramphenicol *(BAN, rINN)*

Chloramfenikol; Chloramfenikolis; Chloramphénicol; Chloramphenicolum; Chloranfenicol; Cloranfenicol; Kloramfenikol; Kloramfenikol; Kloramfenikoli; Laevomycetinum; Хлорамфеникол.

2,2-Dichloro-*N*-[(a*R*,β*R*)-β-hydroxy-α-hydroxymethyl-4-nitrophenethyl]acetamide.

$C_{11}H_{12}Cl_2N_2O_5$=323.1

CAS — 56-75-7.

ATC — D06AX02; D10AF03; G01AA05; J01BA01; S01AA01; S02AA01; S03AA08.

ATC Vet — QD06AX02; QD10AF03; QG01AA05; QJ01BA01; QJ51BA01; QS01AA01; QS02AA01; QS03AA08.

UNII — 66974FR9Q1.

NOTE. CPL is a code approved by the BP 2014 for use on single unit doses of eye drops containing chloramphenicol where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Chloramphenicol). A substance produced by the growth of certain strains of *Streptomyces venezuelae*, but now mainly prepared synthetically. A white, greyish-white or yellowish-white, fine crystalline powder or fine crystals, needles, or elongated plates. Slightly soluble in water; freely soluble in alcohol and in propylene glycol. Protect from light.

USP 36: (Chloramphenicol). Fine, white to greyish-white or yellowish-white, needle-like crystals or elongated plates. Soluble 1 in 400 of water; freely soluble in alcohol, in acetone, in ethyl acetate, and in propylene glycol. pH of a 2.5% suspension in water is between 4.5 and 7.5. Its solutions are practically neutral to litmus. It is reasonably stable in neutral or moderately acid solutions. Store in airtight containers.

Chloramphenicol Palmitate *(BANM, rINNM)*

Chloramfenikolio palmitatas; Chloramfenikol-palmitát; Chloramfenikolu palmitynian; Chloramphenicol α-Palmitate; Chloramphénicol, Palmitate de; Chloramphenicoli Palmitas; Chloramphenicolpalmitat; Cloranfenicol, palmitato de; Kloramfenikolipalmitaatti; Kloramfenikolpalmitat; Kloramfenikol-palmitát; Palmitato de cloranfenicol; Palmitylchloramphenicol; Хлорамфеникола Пальмитат.

$C_{27}H_{42}Cl_2N_2O_6$=561.5

CAS — 530-43-8.

ATC — D06AX02; D10AF03; G01AA05; J01BA01; S01AA01; S02AA01; S03AA08.

ATC Vet — QD06AX02; QD10AF03; QG01AA05; QJ01BA01; QS01AA01; QS02AA01; QS03AA08.

UNII — 43VU4207NW.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Chloramphenicol Palmitate). A fine, white or almost white, unctuous, powder. M.p. 87 degrees to 95 degrees. Chloramphenicol palmitate shows polymorphism and the thermodynamically stable form has low bioavailability following oral administration. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in acetone; very slightly soluble in hexane. Protect from light.

USP 36: (Chloramphenicol Palmitate). A fine, white, unctuous, crystalline powder, having a faint odour. M.p. 87 degrees to 95 degrees. Insoluble in water; sparingly soluble in alcohol; freely soluble in acetone and in chloroform; soluble in ether; very slightly soluble in hexane. Store in airtight containers.

Chloramphenicol Sodium Succinate

(BANM, rINNM)

Chloramfenikolio natrio sukcinatas; Chloramfenikol-sukcinát sodná sůl; Chloramphenicol α-Sodium Succinate; Chloramphénicol, Succinate Sodique de; Chloramphenicolhydrogensuccinat-Natrium; Chloramphenicoli Natrii Succinas; Cloranfenicol, succinato sódico de; Kloramfenikol Süksinat Sodyum; Kloramfenikol-hidrogénszukcinátnátrium; Kloramfenikolinatriumsuksinaatti; Kloramfenikolnatriumsuccinat; Succinato sódico de cloranfenicol; Хлорамфеникола Натрия Сукцинат.

$C_{15}H_{15}Cl_2N_2NaO_8$=445.2

CAS — 982-57-0.

ATC — D06AX02; D10AF03; G01AA05; J01BA01; S01AA01; S02AA01; S03AA08.

ATC Vet — QD06AX02; QD10AF03; QG01AA05; QJ01BA01; QS01AA01; QS02AA01; QS03AA08.

UNII — 872109HX6B.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet. Chin.* includes Chloramphenicol Hydrogen Succinate.

Ph. Eur. 8: (Chloramphenicol Sodium Succinate). A white or yellowish-white hygroscopic powder. Very soluble in water; freely soluble in alcohol. A 25% solution in water has a pH of 6.4 to 7.0. Store in airtight containers. Protect from light.

USP 36: (Chloramphenicol Sodium Succinate). A light yellow powder. Freely soluble in water and in alcohol. pH of a solution in water containing the equivalent of chloramphenicol 25% is between 6.4 and 7.0. Store in airtight containers.

Incompatibility. Incompatibility or loss of activity has been reported between chloramphenicol and many other substances. Other factors, especially drug concentration, may play a part and incompatibilities are most often seen with concentrated solutions.

Uses and Administration

The risk of life-threatening adverse effects, particularly bone-marrow aplasia, has severely limited the clinical usefulness of chloramphenicol, although it is still widely used in some countries. It should never be given systemically for minor infections and regular blood counts are usually advisable during treatment. The third-generation cephalosporins replaced chloramphenicol for many of its former uses, and there are consequently few unambiguous indications for its use. It has been used in severe typhoid and other salmonellal infections, although it does not eliminate the carrier state. Chloramphenicol is an alternative to a third-generation cephalosporin in the treatment of bacterial meningitis, both empirically and against sensitive organisms such as *Haemophilus influenzae*. It may be used as part of a multidrug regimen for the treatment of inhalation and gastrointestinal anthrax. It has been used in the treatment of severe anaerobic infections, particularly in brain abscesses, and in infections below the diaphragm where *Bacteroides fragilis* is often implicated; however, other drugs are usually preferred. Although the tetracyclines remain the treatment of choice in rickettsial infections such as typhus and the spotted fevers, chloramphenicol is also used as an alternative where the tetracyclines cannot be given.

Other bacterial infections in which chloramphenicol may be used as an alternative or adjunct to other drugs include actinomycosis, ehrlichiosis, cystic fibrosis, severe gastroenteritis (including *Salmonella* enteritis, cholera, and *Yersinia* enteritis), gas gangrene, granuloma inguinale, severe *Haemophilus influenzae* infections (for example in epiglottitis), severe melioidosis, pelvic inflammatory disease, plague (especially if meningitis develops), pneumonia, psittacosis, Q fever, relapsing fever, tularaemia (especially when meningitis is suspected), and Whipple's disease. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Chloramphenicol is extensively used in the topical treatment of ear and, in particular, eye infections, despite the fact that many of these are mild and self-limiting. It has also been used topically in the treatment of skin infections.

When given *systemically*, chloramphenicol is usually used orally as capsules or as a suspension of chloramphenicol palmitate. When oral use is not feasible, water-soluble chloramphenicol sodium succinate may be given intravenously, but oral therapy should be substituted as soon as possible; an intravenous dose should be injected over at least 1 minute or given by slow intravenous infusion. Intramuscular injection is controversial because of doubts whether absorption is adequate.

Doses are expressed in terms of chloramphenicol base and are similar whether given orally or intravenously. Chloramphenicol palmitate 1.7 g and chloramphenicol sodium succinate 1.4 g are each equivalent to about 1 g of chloramphenicol base.

The usual dose is 50 mg/kg daily in divided doses every 6 or 8 hours; up to 100 mg/kg daily may be given in meningitis or severe infections due to moderately resistant organisms, although these higher doses should be reduced as soon as possible. It has been recommended that treatment should be continued after the patient's temperature has returned to normal for a further 4 days in rickettsial diseases, and for 8 to 10 days in typhoid fever, to minimise the risk of relapse.

In the *topical* treatment of eye infections, chloramphenicol is usually applied as a 0.5% solution or as a 1% ointment. Generally, drops are applied up to 6 times daily. Severe infections may need more frequent dosing initially, reducing gradually once the infection is controlled. When ointment is used, it may be applied once daily at night if drops are used during the day, or 3 or 4 times daily if used alone.

For bacterial infections in otitis externa, chloramphenicol has been given as ear drops in a strength of 5 or 10%. A dose of 2 or 3 drops to the affected ear 2 or 3 times daily has been used.

Chloramphenicol has also been used in the form of *other derivatives* including the glycinate, the palmitoylglycolate, the pantothenate, the steaglate, the stearate, and the hydrogen succinate.

Administration. When parenteral use of chloramphenicol is necessary the intravenous route is generally preferred, although the intramuscular route has been advocated. Adequate serum concentrations after intramuscular injection have been reported,[1,2] although this is contrary to the widely held belief that chloramphenicol sodium succinate is poorly absorbed by this route. Pain on injection was also claimed to be minimal.[1] After a study in children with bacterial meningitis,[3] treatment with intramuscular chloramphenicol for 2 or 3 days followed by oral therapy has been suggested, although a later study[2] found that the intramuscular route produced therapeutic concentrations when the oral route did not. However, it has been said[4] that children describe intramuscular chloramphenicol as amongst the worst treatments they ever receive, and certainly much worse than the insertion of intravenous cannulae.

1. Shann F, *et al.* Absorption of chloramphenicol sodium succinate after intramuscular administration in children. *N Engl J Med* 1985; 313: 410–14.
2. Weber MW, *et al.* Chloramphenicol pharmacokinetics in infants less than three months of age in the Philippines and The Gambia. *Pediatr Infect Dis J* 1999; 18: 896–901.
3. Shann F, *et al.* Chloramphenicol alone versus chloramphenicol plus penicillin for bacterial meningitis in children. *Lancet* 1985; ii 681–3.
4. Coulthard MG, Lamb WH. Antibiotics: intramuscular or intravenous? *Lancet* 1985; ii: 1015.

Administration in children. Because of metabolic differences, neonates and premature infants will generally require lower systemic doses than older infants and children. Where there is no alternative to the use of chloramphenicol, the doses recommended according to age and maturity are as follows:

- *all neonates up to 2 weeks old:* 25 mg/kg daily in divided doses (the *BNFC* suggests 2 divided doses at intervals of 12 hours) by intravenous injection
- *full-term neonates 2 weeks of age and older:* 25 to 50 mg/kg daily given in divided doses of 12.5 mg/kg every 6 to 12 hours
- *premature neonates 2 weeks of age or older, and infants with suspected immature metabolic processes:* 25 mg/kg daily intravenously in divided doses
- *infants and children aged 1 month to 18 years:* where metabolic processes are mature, as for adults (see Uses and Administration, above). Where immature metabolic processes are suspected a reduced dose of 25 mg/kg daily in divided doses has again been recommended

Blood concentration monitoring is recommended when using parenteral or oral chloramphenicol in neonates, children with immature metabolic processes, and for children receiving higher dose ranges for serious infections. It is also preferred for those under 4 years of age. For details of recommended plasma concentrations, see Precautions, p. 260.2.

Chloramphenicol **topical** eye and ear preparations are used similarly to use in adults (see Uses and Administration, p. 257.2).

Enterococcal infections. The emergence of resistance to vancomycin among enterococcal isolates has required the development of new therapeutic options such as linezolid, daptomycin, tigecycline, and quinupristin/dalfopristin for the treatment of vancomycin-resistant enterococcal infections (p. 181.1). There is, however, no standard treatment and choice of antibacterial depends on local patterns of resistance and antibacterial sensitivity tests. Some reports have indicated that chloramphenicol may be effective against vancomycin-resistant *Enterococcus faecium*.[1-3] Although no significant effect of chloramphenicol on mortality was found in one small study,[4] a retrospective analysis[5] of the outcomes of 6 patients with bacteraemia due to vancomycin-resistant *Enterococcus faecium* concluded that chloramphenicol was effective and should be considered as a treatment option. However, vancomycin-resistant enterococci also resistant to chloramphenicol have been reported.[6]

1. Norris AH, *et al.* Chloramphenicol for the treatment of vancomycin-resistant enterococcal infections. *Clin Infect Dis* 1995; **20**: 1137–44.
2. Papanicolaou GA, *et al.* Nosocomial infections with vancomycin-resistant Enterococcus faecium in liver transplant recipients: risk factors for acquisition and mortality. *Clin Infect Dis* 1996; **23**: 760–6.
3. Mato SP, *et al.* Vancomycin-resistant Enterococcus faecium meningitis successfully treated with chloramphenicol. *Pediatr Infect Dis J* 1999; **18**: 483–4.
4. Lautenbach E, *et al.* The role of chloramphenicol in the treatment of bloodstream infection due to vancomycin-resistant Enterococcus. *Clin Infect Dis* 1998; **27**: 1259–65.
5. Ricaurte JC, *et al.* Chloramphenicol treatment for vancomycin-resistant Enterococcus faecium bacteremia. *Clin Microbiol Infect* 2001; **7**: 17–21.
6. Lautenbach E, *et al.* Emergence of resistance to chloramphenicol among vancomycin-resistant enterococcal (VRE) bloodstream isolates. *Int J Antimicrob Agents* 2004; **23**: 200–3.

Adverse Effects and Treatment

Chloramphenicol may cause severe and sometimes fatal adverse effects. The most serious of these is bone-marrow depression, which can take two different forms. The first is a fairly common dose-related reversible depression occurring usually when plasma-chloramphenicol concentrations exceed 25 micrograms/mL or when adult doses are greater than 4 g daily, and is characterised by morphological changes in the bone marrow, decreased iron utilisation, reticulocytopenia, anaemia, leucopenia, and thrombocytopenia. This effect may be due to inhibition of protein synthesis in the mitochondria of bone marrow cells.

The second and apparently unrelated form of bone-marrow toxicity is severe irreversible aplastic anaemia. This is fairly rare, with a suggested incidence of about 1:18 000 to 1:50 000, although the incidence varies throughout the world, and is not considered to be dose-related. The aplasia usually develops after a latent period of weeks or even months and has been suggested to be the result of a nitrated benzene radical produced *in vivo*. It is considered that there may be some genetic or biochemical predisposition, but there is no way of identifying susceptible patients. Although most cases follow oral use, aplasia has also occurred after intravenous and topical (eye drops) use of chloramphenicol. Survival is most likely in those with early onset aplasia, but they may subsequently develop acute myeloid leukaemia.

A toxic manifestation—the 'grey syndrome' or 'grey baby syndrome'—characterised by abdominal distension, vomiting, ashen colour, hypothermia, progressive pallid cyanosis, irregular respiration, and circulatory collapse, followed by death in a few hours or days, has occurred in premature and other newborn infants given large doses of chloramphenicol. The syndrome is associated with high plasma concentrations of chloramphenicol, due to reduced capacity for glucuronidation and decreased glomerular filtration in children of this age, leading to drug accumulation. Recovery is usually complete if the drug is withdrawn early enough after onset, but up to 40% of infants with the full-blown syndrome may die. The syndrome has also been reported in infants born to mothers given chloramphenicol in late pregnancy or labour. A similar syndrome has been reported in adults and older children given very high doses.

Prolonged oral use of chloramphenicol may induce bleeding, either by bone-marrow depression or by reducing the intestinal flora with consequent inhibition of vitamin K synthesis. Haemolytic anaemia has occurred in some patients with the Mediterranean form of glucose 6-phosphate dehydrogenase deficiency, but is rare in patients with milder forms of the deficiency. Paroxysmal nocturnal haemoglobinuria has also been reported.

Peripheral as well as optic neuritis has been reported, usually in patients treated over prolonged periods. Although ocular symptoms are often reversible if treatment is withdrawn early, permanent visual impairment or blindness has occurred.

Other neurological symptoms have included encephalopathy with confusion and delirium, depression, and headache. Ototoxicity has also occurred, especially after the use of ear drops.

Hypersensitivity reactions including rashes, fever, and angioedema may occur especially after topical use; anaphylaxis has occurred but is rare. Jarisch-Herxheimer reactions may also occur. Gastrointestinal symptoms including nausea, vomiting, and diarrhoea can follow oral use. Disturbances of the oral and intestinal flora may cause stomatitis, glossitis, and rectal irritation. Patients may experience an intensely bitter taste after rapid intravenous use of chloramphenicol sodium succinate.

Aplastic anaemia. A review[1] of the toxicity of chloramphenicol and related drugs, including the potential role of the *p*-nitro group in producing aplastic anaemia, indicated that derivatives such as thiamphenicol, which lack this grouping, are not associated with increased incidence of aplastic anaemia.

For a discussion of the risk of aplastic anaemia associated with topical use of chloramphenicol eye drops, see under Ocular Use, p. 260.3.

1. Yunis AA. Chloramphenicol: relation of structure to activity and toxicity. *Ann Rev Pharmacol Toxicol* 1988; **28**: 83–100.

Effects on the liver. Isolated cases of hepatotoxicity, including hepatitis and jaundice, have been reported after systemic use of chloramphenicol.

In a case report[1] hepatitis also occurred in a 37-year-old patient after a 5-day course of chloramphenicol 0.5% eye drops; the patient presented 7 days after the end of treatment with lethargy, pruritus, dark urine, scleral icterus, and elevated liver-transaminase values. A liver biopsy 6 weeks after stopping chloramphenicol was highly suggestive of drug-induced hepatitis, and transaminase values returned to normal within 10 months of stopping the eye drops.

1. Doshi B, Sarkar S. Topical administration of chloramphenicol can induce acute hepatitis. *BMJ* 2009; **339**: 574.

Overdosage. Charcoal haemoperfusion was found to be far superior to exchange transfusion in the removal of chloramphenicol from blood, although it did not prevent death in a 7-week-old infant with the 'grey syndrome' after a dosage error.[1]

1. Freundlich M, *et al.* Management of chloramphenicol intoxication in infancy by charcoal hemoperfusion. *J Pediatr* 1983; **103**: 485–7.

Precautions

Chloramphenicol is contra-indicated in patients with a history of hypersensitivity or toxic reaction to the drug. It should never be given systemically for minor infections, prophylaxis, or where less toxic antibacterials could be used. Repeated courses and prolonged treatment should be avoided and it should not be used in patients with pre-existing bone-marrow depression or blood dyscrasias. Routine periodic blood examinations are advisable in all patients, but will not warn of aplastic anaemia.

Use of chloramphenicol with other drugs liable to depress bone-marrow function should be avoided.

Excessive blood concentrations may occur after usual doses in patients with hepatic or renal impairment, or in premature and full-term neonates who have immature metabolic processes. Licensed product information recommends dose reduction in such patients, based on monitoring of serum chloramphenicol concentrations; a suggested range for peak plasma concentrations is 10 to 25 micrograms/mL, and for trough concentrations, 5 to 15 micrograms/mL. In addition, specific dosage guidance is given for neonates (see Administration in Children, p. 257.3), although they should never be given chloramphenicol systemically (unless it may be life-saving and there is no alternative treatment) because of the risk of 'grey syndrome'.

Chloramphenicol readily crosses the placenta and US licensed product information recommends that use during pregnancy or at term should be undertaken with caution due to potential toxic effects on the fetus. Equivalent UK information lists pregnancy as a contra-indication to the systemic use of chloramphenicol. However, see also p. 260.3.

Chloramphenicol may interfere with the development of immunity and it should not be given during active immunisation.

Breast feeding. Chloramphenicol is distributed into breast milk[1] and the last available guidance from the American Academy of Pediatrics[2] considered that its use by mothers during breast feeding might be of concern, since there have been reports of possible idiosyncratic bone-marrow suppression in the infant.

1. Havelka J, *et al.* Excretion of chloramphenicol in human milk. *Chemotherapy* 1968; **13**: 204–11.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)

Ocular use. Ocular chloramphenicol is widely used in the UK for the treatment of superficial eye infections. In view of the potential for serious toxicity, such as aplastic anaemia, after systemic absorption some, particularly in the USA, have advised that its ocular use should be restricted to situations where there is no alternative treatment.[1] However, apart from patients with a personal or family history of blood dyscrasias, the use, particularly of short courses, was defended by several specialists in the UK,[2-4] and the arguments have been the subject of several reviews.[5-7] Prospective case-control studies were considered necessary to clarify the risk.[8] One such study,[9] involving 145 patients with aplastic anaemia and 1226 controls, found that only 3 of the patients had been exposed to ocular chloramphenicol, and calculated that the absolute risk was no more than 0.5 cases per million treatment courses. Similarly, data[10] from 2 other studies revealed that none of 426 patients with aplastic anaemia and 7 of 3118 controls had used chloramphenicol eye drops. In a survey[11] of patients who received prescriptions for chloramphenicol eye drops the risk of serious haematological toxicity was 3 per 442 543 patients or 3 per 674 148 prescriptions.

1. Doona M, Walsh JB. Use of chloramphenicol as topical eye medication: time to cry halt? *BMJ* 1995; **310**: 1217–18.
2. Mulla RJ, *et al.* Is it time to stop using chloramphenicol on the eye: fears are based on only six cases. *BMJ* 1995; **311**: 450.
3. Buckley RJK, *et al.* Is it time to stop using chloramphenicol on the eye: safe in patients with no history of blood dyscrasia *BMJ* 1995; **311**: 450.
4. Hall AV, *et al.* Is it time to stop using chloramphenicol on the eye: risk is low in short courses. *BMJ* 1995; **311**: 450–1.
5. McGhee CNJ, Anastas CN. Widespread ocular use of topical chloramphenicol: is there justifiable concern regarding idiosyncratic aplastic anaemia? *Br J Ophthalmol* 1996; **80**: 182–4.
6. Rayner SA, Buckley RJ. Ocular chloramphenicol and aplastic anaemia: is there a link? *Drug Safety* 1996; **14**: 273–6.
7. Tucomb L. Ophthalmic chloramphenicol and blood dyscrasias: a review. *Pharm J* 1997; **258**: 28–35.
8. Gordon-Smith EC, *et al.* Is it time to stop using chloramphenicol on the eye: prospective study of aplastic anaemia should give definitive answer. *BMJ* 1995; **311**: 451.
9. Laporte J-R, *et al.* Possible association between ocular chloramphenicol and aplastic anaemia—the absolute risk is very low. *Br J Clin Pharmacol* 1998; **46**: 181–4.
10. Wiholm B-E, *et al.* Relation of aplastic anaemia to use of chloramphenicol eye drops in two international case-control studies. *BMJ* 1998; **316**: 666.
11. Lancaster T, *et al.* Risk of serious haematological toxicity with use of chloramphenicol eye drops in a British general practice database. *BMJ* 1998; **316**: 667.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies chloramphenicol as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 09/08/11)

Pregnancy. A case-control study involving 22 865 women whose babies had congenital abnormalities and 38 151 controls found that 52 of the former and 51 of the latter had taken oral chloramphenicol (usually with other drugs) during pregnancy.[1] There was no evidence of a teratogenic effect of chloramphenicol, and it was thought to pose little risk in early pregnancy.

1. Czeizel AE, *et al.* A population-based case-control teratologic study of oral chloramphenicol treatment during pregnancy. *Eur J Epidemiol* 2000; **16**: 323–7.

Sodium content. Each g of chloramphenicol sodium succinate represents about 2.2 mmol of sodium.

Interactions

The use of chloramphenicol with other drugs that can cause bone-marrow depression may increase the risk of haematological toxicity, and should be avoided.

Chloramphenicol is inactivated in the liver and may, therefore, interact with drugs that are metabolised by hepatic microsomal enzymes. For example, it enhances the effects of coumarin anticoagulants, such as dicoumarol and warfarin, some hypoglycaemics such as chlorpropamide and tolbutamide, and antiepileptics such as phenytoin. Conversely, the metabolism of chloramphenicol may be increased by inducers of hepatic enzymes such as phenobarbital or rifampicin. Some other interactions affecting the activity of chloramphenicol are discussed below.

Chloramphenicol may decrease the effects of iron and vitamin B_{12} in anaemic patients and has occasionally impaired the action of oral contraceptives.

For the effects of chloramphenicol on the activity of other antibacterials, see Antimicrobial Action, p. 261.1.

Analgesics. A report of an increase in chloramphenicol half-life from 3.25 to 15 hours when intravenous *paracetamol* was given to 6 patients in intensive care 2 hours after intravenous chloramphenicol[1] was not confirmed by subsequent studies in patients receiving oral paracetamol. A study in 5 children found that the half-life of intravenous

chloramphenicol was reduced from 3 to 1.2 hours, with an increase in clearance, when oral paracetamol was given 30 minutes beforehand.[2] Furthermore, a study in 26 children found no evidence of altered disposition when oral paracetamol was given to patients receiving intravenous chloramphenicol,[3] and no significant change in chloramphenicol pharmacokinetics was found in 5 patients given oral chloramphenicol and paracetamol.[4]

1. Buchanan N, Moodley GP. Interaction between chloramphenicol and paracetamol. *BMJ* 1979; **2**: 307–8.
2. Spika JS, *et al.* Interaction between chloramphenicol and acetaminophen. *Arch Dis Child* 1986; **61**: 1121–4.
3. Kearns GL, *et al.* Absence of a pharmacokinetic interaction between chloramphenicol and acetaminophen in children. *J Pediatr* 1985; **107**: 134–9.
4. Stein CM, *et al.* Lack of effect of paracetamol on the pharmacokinetics of chloramphenicol. *Br J Clin Pharmacol* 1989; **27**: 262–4.

Antiepileptics. Serum concentrations of chloramphenicol are usually reduced by the hepatic enzyme induction that occurs with *phenobarbital*,[1,2] and similar reductions have been reported in a case study during *phenytoin* use.[3] Conversely, elevated and potentially toxic serum-chloramphenicol concentrations have resulted during phenytoin use,[2] apparently due to competition for binding sites, although increased metabolism may alternatively lead to decreased serum-chloramphenicol concentrations.

For reference to the effects of chloramphenicol on phenobarbital and phenytoin, see p. 537.2 and p. 542.3, respectively.

1. Bloxham RA, *et al.* Chloramphenicol and phenobarbitone—a drug interaction. *Arch Dis Child* 1979; **54**: 76–7.
2. Krasinski K, *et al.* Pharmacologic interactions among chloramphenicol, phenytoin and phenobarbital. *Pediatr Infect Dis* 1982; **1**: 232–5.
3. Powell DA, *et al.* Interactions among chloramphenicol, phenytoin, and phenobarbital in a pediatric patient. *J Pediatr* 1981; **98**: 1001–3.

Antineoplastics. For the effect of chloramphenicol on *cyclophosphamide*, see p. 773.2.

Gastrointestinal drugs. Fatal aplastic anaemia of rapid onset has occurred in 2 patients who received intravenous chloramphenicol and *cimetidine*.[1,2] As there is usually a latent period of 2 weeks to 12 months before aplastic anaemia develops after chloramphenicol therapy it is plausible that an additive or synergistic effect may have occurred between the 2 drugs to cause bone-marrow toxicity.

1. Farber BF, Brody JP. Rapid development of aplastic anemia after intravenous chloramphenicol and cimetidine therapy. *South Med J* 1981; **74**: 1257–8.
2. West BC, *et al.* Aplastic anemia associated with parenteral chloramphenicol: review of 10 cases, including the second case of possible increased risk with cimetidine. *Rev Infect Dis* 1988; **10**: 1048–51.

Immunosuppressants. For the effect of chloramphenicol on *ciclosporin* and on *tacrolimus*, see p. 1956.1 and p. 1977.3, respectively.

Oral contraceptives. For the effect of chloramphenicol on oral contraceptives, see Hormonal Contraceptives, p. 2243.1.

Antimicrobial Action

Chloramphenicol is a bacteriostatic antibiotic with a broad spectrum of action against both Gram-positive and Gram-negative bacteria, as well as some other organisms.

Mechanism of action. Chloramphenicol is thought to enter sensitive cells by an active transport process. Within the cell it binds to the 50S subunit of the bacterial ribosome at a site adjacent to the site of action of the macrolides and clindamycin, and inhibits bacterial protein synthesis by preventing attachment of aminoacyl transfer RNA to its acceptor site on the ribosome, thus preventing peptide bond formation by peptidyl transferase. The block in protein synthesis results in a mainly bacteriostatic action, although it may be bactericidal to some organisms, including *Haemophilus influenzae*, *Neisseria meningitidis*, and *Streptococcus pneumoniae*, at higher concentrations.

Spectrum of activity. Chloramphenicol has activity against many types of bacteria, although in most cases there are less toxic alternatives available. The following pathogens are usually susceptible (but see also Resistance, below):

- Gram-positive cocci including streptococci such as *Str., pneumoniae*, *Str. pyogenes*, and the viridans streptococci. Strains of *Staphylococcus aureus* may be less susceptible, and meticillin-resistant staphylococci are commonly found to be resistant. Enterococcal species are often resistant, but activity against some strains of vancomycin-resistant enterococci has been reported
- other Gram-positive species including *Bacillus anthracis*, *Corynebacterium diphtheriae*, *Listeria monocytogenes*, and anaerobes such as *Actinomyces* spp., *Peptococcus*, and *Peptostreptococcus* spp. are usually susceptible. While most *Clostridium* spp. are susceptible, many strains of *C. difficile*, particularly those of serogroup C, are resistant
- Gram-negative cocci such as *Neisseria meningitidis* and *N. gonorrhoeae* are usually highly sensitive, as are *Haemophilus influenzae* and a variety of other Gram-negative bacteria including *Bordetella pertussis*, *Brucella abortus*, *Campylobacter* spp., *Pasteurella*, and *Vibrio* spp. Despite good *in-vitro* activity against *Legionella* spp., chloramphenicol is not as active *in-vivo* as many other antibacterials (particularly macrolides and fluoroquinolones) against *L. pneumophila*

  The Enterobacteriaceae vary in their susceptibility, and many strains have shown acquired resistance (see below). The susceptibility of *Escherichia coli* has marked geographic variability, but other Enterobacteriaceae, including *Citrobacter*, *Enterobacter*, *Klebsiella*, *Proteus*, *Shigella*, *Salmonella*, and *Yersinia* spp. are generally susceptible. Chloramphenicol has poor activity against *Serratia* spp., and *Pseudomonas aeruginosa* are invariably resistant, although *Burkholderia* (formerly *Pseudomonas*) spp. are often susceptible
- Gram-negative anaerobes are generally susceptible including *Bacteroides fragilis*, *Veillonella*, and *Fusobacterium* spp.
- other susceptible organisms include *Leptospira* spp., spirochaetes such as *Treponema pallidum*, Chlamydiaceae, Mycoplasma spp., and Rickettsia spp.
- *Nocardia* spp. are resistant
- Chloramphenicol is ineffective against protozoa and viruses. However, its reported activity against *Batrachochytrium dendrobatitis*, a fungus affecting frogs, has suggested the possibility of activity against other fungi

Activity with other antimicrobials. As with other bacteriostatic antimicrobials, the possibility exists of an antagonistic effect if chloramphenicol is given with a bactericidal drug, and some antagonism has been shown *in vitro* between chloramphenicol and various beta lactams and aminoglycosides. The clinical significance of most of these interactions is usually held to be doubtful, but care is advisable where patient factors or infection severity make bactericidal activity desirable. Chloramphenicol may competitively inhibit the effects of macrolides or lincosamides such as clindamycin because of the adjacency of their binding sites on the ribosome.

Resistance. Acquired resistance has been widely reported, although the prevalence of resistance has tended to decline where use of the drug has become less frequent. The most commonly seen form of resistance has been the production of an acetyltransferase that inactivates the drug. Such resistance is usually plasmid-mediated and may be associated with resistance to other drugs such as the tetracyclines. Other mechanisms that may reduce sensitivity to chloramphenicol include reduced permeability or uptake, and ribosomal mutation.

The actual incidence of resistance varies considerably in different countries and different centres. Epidemics of chloramphenicol-resistant *Salmonella* and *Shigella* spp. have occurred in many areas of the world, particularly in South and South-east Asia and Central and South America, and often reflect local usage patterns of chloramphenicol. Greater use of alternative antibacterials has more recently resulted in a decline in chloramphenicol resistance in some countries where it was formerly common. Resistance among *Haemophilus* and *Neisseria* spp. occurs, and the latter may be problematic in developing countries, although it does not yet seem to be widespread. Acquired resistance has also been reported in *Staph. aureus*, *Str. pneumoniae*, and *Str. pyogenes*.

Pharmacokinetics

Chloramphenicol is readily absorbed when given orally. Blood concentrations of 10 micrograms/mL or more may occur about 1 or 2 hours after a single oral dose of 1 g. Chloramphenicol palmitate is hydrolysed to chloramphenicol in the gastrointestinal tract before absorption, and the sodium succinate, which is given parenterally, is probably hydrolysed to free drug mainly in the liver, lungs, kidneys, and plasma; such hydrolysis may be incomplete in infants and neonates, contributing to the variable pharmacokinetics in this age group. Chloramphenicol sodium succinate is, even in adults, only partially and variably hydrolysed, so that blood concentrations of chloramphenicol obtained after the sodium succinate is given parenterally are often lower than those obtained after oral chloramphenicol, with up to 30% of a dose excreted unchanged in the urine before hydrolysis can take place (but see under Administration, p. 257.3).

Chloramphenicol is widely distributed in body tissues and fluids; it enters the CSF, giving concentrations of about 50% of those existing in the blood even in the absence of inflamed meninges; it diffuses across the placenta into the fetal circulation, into breast milk, and into the aqueous and vitreous humours of the eye. It also enters the aqueous humour after topical application. Up to about 60% in the circulation is bound to plasma protein. The half-life of chloramphenicol has been reported to range from 1.5 to 4 hours; the half-life is prolonged in patients with severe hepatic impairment and is also much longer in neonates. Renal impairment has relatively little effect on the half-life of the active drug, due to its extensive metabolism, but may lead to accumulation of the inactive metabolites.

Chloramphenicol is excreted mainly in the urine but only 5 to 10% of an oral dose appears unchanged; the remainder is inactivated in the liver, mostly by conjugation with glucuronic acid. About 3% is excreted in the bile. However, most is reabsorbed and only about 1%, mainly in the inactive form, is excreted in the faeces.

The absorption, metabolism, and excretion of chloramphenicol are subject to considerable interindividual variation, especially in infants and children, making monitoring of plasma concentrations necessary to determine pharmacokinetics in a given patient.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Anuar; Bioticaps; Chloromycetin; Farmicetina; Isopto Fenicol; Klonalfenicol; Pluscloran†; Poenfenicol; Quemicetina‡; ***Austral.***: Chloromycetin; Chlorsig; ***Austria***: Halomycetin; Kemicetin†; Oleomycetin†; ***Braz.***: Arifenicol; Cloralenil; Neo Fenicol; Profenicol†; Quemicetina; Sintomicetina; Uni Fenicol†; Visalmin; Vixmicina; ***Canad.***: Ak-Chlor; Chloromycetin; Chloroptic†; Diochloram; Pentamycetin; ***Chile***: Chloromycetin†; Clorampast; Gemitin; ***China***: Moisten (润舒); ShuEr (舒尔); Tianli Runzhu (天力润珠); ***Fin.***: Chloromycetin; Oftan Akvakol; Oftan Chlora; ***Ger.***: Posifenicol C; ***Gr.***: Chloranic; Chlorocollyre; Chloromyk; Chloroptic; Kemicetine; Kemipen; Kramerin; Maltogen; Niamycétine; Ursa-Fenol; ***Hong Kong***: Aristophen; Chloroph; Chlorsig; Elisca; Europhenicol; Isopto Fenicol†; Kemicetine; Optivis; Venicol†; Xepanicol; ***India***: Aglomycetin; Andrecin; Biophenicol; Chemocetin; Chloraxin; Chlormet; Chlorocin; Chloromycetin; Daclor; Decol; Dexoren; Enclor; Enteromycetin; Eptico; Fencol; Kemicetine; Labchlor; Larmycetin; Ocuchlor; Oculor; Optocol; Paraxin; Reclor; Vanmycetin; Vitamycetin; ***Indon.***: Chloramex; Chlorbiotic†; Cloramidina; Colain†; Colme; Colsancetine; Combicetin; Empeecetin; Enkacetyn; Fenicol; Ikamicetin; Isotic Salmicol; Kalmicetine; Kemicetine; Lanacetine; Licoklor; Microtina†; Neophenicol†; Palmicol; RECO; Ribocine; Spersanicol†; Suprachlor; Xepanicol; ***Irl.***: Chloromycetin; ***Israel***: Chlorphenicol; Phenicol; Synthomycine; ***Ital.***: Chemicetina; Mycetin; Sificetina; Vitamfenicolo; ***Malaysia***: Beaphenicol; Chloramex; Nicol; Xepanicol†; ***Mex.***: Abefen; Bariclor†; Brocil; Chloromycetin; Clomicin†; Clorafen†; Cloramed†; Cloramfeni; Clorampler; Cloran; Cloranmicron; Cloratenol; Clorazin; Clordil†; Clorfenil†; Clorofunon; Clorotan; Diarman; Dilclor†; Enteromicin; Estreptopal; Exacol; Fenicol; Fenisol; Fenizzard†; Lebrocetin; Leclor A†; Naxo†; Oftadil; Omycet†; Palcol†; Palmiclor; Palmifer; Palmisol; Procloril†; Pronicol; Quemicetina; Solvaris; Uniclor; ***NZ***: Chlorafast; Chloromycetin; Chlorsig; ***Philipp.***: Alphagram Otic; Anpheclor; Aphrenil; Biomycetin; C-Phenicol; Chloro-S; Chloro-V; Chlorocaire; Chloromycetin; Chlorsig; CLM; Clovicol; Esnicol†; Fen-Alcon†; Forastrol†; Genphenil; Gerafen; Kemicetine†; Klorfen; Klornik; Medimycetin; Medoptic; Metrophenicol; Oliphenicol; Optomycin; Pediachlor; Penachlor; Septicyn; Typhiclor; Venimicetin; Vistachlor; ***Pol.***: Detreomycyna; ***Port.***: Clorocil; Micetinoftalmina; ***Rus.***: Levomycetin (Левомицетин); Synthomycin (Синтомицин); ***S.Afr.***: Chloramex; Chlorchol; Chlorcol; Chlornicol; Chloromycetin; Chlorphen; Lennacol†; Spersanicol; ***Singapore***: Beaphenicol; Enclor; Isopto Fenicol; Kemicetine†; Optichlor; Xepanicol; ***Swed.***: Chloromycetin; ***Switz.***: Septicol†; ***Thai.***: Antibi-Otic; Archifen; Chlor-Pyrad; Chloracil; Chloram-P; Chloramno†; Chloroph; Chlorosin†; Cogenate†; Cogetine; Fenicol; Genercin†; Levomycetin†; Med-Chloramp; Mycochlorin†; Pharmacetin; Pisalin; Silmycetin; Synchlolim; Unison Ointment; Vanafen; ***Turk.***: Armisetin†; Kemicetine; Klorasuksinat; ***UK***: Brochlor; Chloromycetin; Clorogen; Golden Eye; Kemicetine; Optrex Infected Eyes; ***Ukr.***: Laevomycetin (Левомицетин); ***USA***: Chloromycetin†; ***Venez.***: Cloftal.

Multi-ingredient Preparations. ***Arg.***: Acnoxin; Antiflogol; Bioftal; Clorfibrase; Colirio Antibiotico CNH; Colirio Oftalmico; Esodar; Fluoropoen; Iruxol; Klonovan; Neocortizul†; Oftal-D; Poenbioptal; Quemicetina con Hidrocortisona; Quemicetina Nasal Compuesta; ***Austria***: Cortison Kemicetin†; Oleomycetin-Prednison†; ***Belg.***: De Icol; ***Braz.***: Dexafenicol; Epitezan; Fenidex; Fibrase; Fibrinase c/Cloranfenicol; Gino Fibrase; Gino Kollagenase; Gyno Iruxol; Iruxol; Kollagenase com cloranfenicol; Naxogin Composto; Otomicina; Ouvidonal; Profenicol†; Regencel; Regenom; Sulnil; ***Canad.***: Pentamycetin-HC; ***Chile***: Gemitin con Prednisolona; Naxogin Compositum†; Otandrol; Sintofotona; ***China***: Fukexin (复可欣); ***Cz.***: Spersadex Compositum; ***Denm.***: Spersadex Comp; ***Fin.***: Iruxol†; Oftan C-C; Oftan Dexa-Chlora; ***Fr.***: Cebedexacol†; ***Ger.***: Aquapred†; Ichthoseptal†; ***Gr.***: Chlorapred; Cortiphenol H; Dexachlor; Dispersadron-C; Geypirina; Neo-Otil; Nezefib; Otenor; Spersadexoline; Sulfachlor; Sulfachloramphenicol; Sulfanicole; ***Hong Kong***: Anlina†; Cortiphenol H†; Dexanicol†; Eurodron; Neo-Dex (Improved); Sonexa-C; Spersadex Comp; ***India***: A-Cof; Adcort; Advin-NC; Arima; Bactisone; Beclocin-O; Belmycetin-C†; Bestec; Biomycetin; Candibiotic; CBL; Chloramsone; Chlormet-DM; Chlormixin†; Chloromycetin Ear Drops; CLCD; Clobiotic; Deco-AT; Deco; Decol-C; Decol-F; Dendor; Dexamon; Dexoren-S; Dexosyn-C†; Eligao; Enteromycetin Otic; Eptico-D; Excan; Eyclor-Dexa; Eyclor; Flubichlor; Fungi-BC; Infabact; Kemicetine Antiozena; LBC; Mycin; Mycotic; Ocupol-D; Ocupol; Olotic; Otek-AC Plus; Otiden; Otiderm; Otina; Otocin; Otocos; Otosym; Perfocyn†; Pyrimon; ***Indon.***: Chloramphecort-H; Chloramphecort;

The symbol † denotes a preparation no longer actively marketed

Gynoxa; Indoson; Kemiderm; Kloramixin D; Kloramixin; Klorfeson; Naxogin Complex; Otolin; Particol†; Ramicort; Spersadex Comp; *Israel*: Phenimixin; Tarocidin D; Tarocidin; Threolone; *Ital.*: Antibioptal; Betabioptal; Cloradex; Colbiocin; Colbiocin; Cortison Chemicetina; Cosmiciclina; Eubetal Antibiotico; Eubetal Antibiotico; Idracemi; Iruxol; Vasofen; Xantervit Antibiotico; *Malaysia*: De Icol; Spersadexoline†; *Mex.*: Cloramfeni Otico; Cloran Otico†; Cloxona-O; Fibrase; Levodexan; Levofenil; Nispil; Ofodex; Otalgan; Otifar; Otiser; Poral; Pre Clor; Soldrin; Solfranicol; Sulfa Cloran; Trecloran†; Ulcoderma†; *Norw.*: Spersadex med kloramfenikol; *Philipp.*: Dexanicol; Idodex; Ipecor; Spersadex Compound; *Port.*: Predniftalmina; *Rus.*: Candibiotic (Кандибиотик); Colbiocin (Колбиоцин); Colbiocin (Колбиоцин); Cortomycetin (Кортомицетин); Iruxol (Ируксол)†; Levomecol (Левомеколь); Levometil (Левометил); Levosin (Левосин); Netran (Нетран); Olasol (Олазоль); Saledez (Саледез); *S.Afr.*: Covomycin-D; Covomycin; Covotop†; Spersadex Comp; Spersadexoline†; *Singapore*: Spersadex Comp; Spersadexoline; *Spain*: Blefaridat†; Cloram Hemidex†; Cloram Zinc†; Cortison Chemicet Topica; Dermisone Epitelizante†; Icol; Medrivas Antib; *Switz.*: Spersadex Comp; *Thai.*: Archifen; CD-Oph; Chlorotracin†; Dermasol; Levoptin; Spersadexoline†; Vagicin; *UK*: Actinac†; *Ukr.*: Candibiotic (Кандибиотик); Micogynax (Микожинакс); *Venez.*: Clorasona.

Pharmacopoeial Preparations

BP 2014: Chloramphenicol Capsules; Chloramphenicol Ear Drops; Chloramphenicol Eye Drops; Chloramphenicol Eye Ointment; Chloramphenicol Sodium Succinate Injection:

USP 36: Chloramphenicol and Hydrocortisone Acetate for Ophthalmic Suspension; Chloramphenicol and Polymyxin B Sulfate Ophthalmic Ointment; Chloramphenicol and Prednisolone Ophthalmic Ointment; Chloramphenicol Capsules; Chloramphenicol Cream; Chloramphenicol for Ophthalmic Solution; Chloramphenicol Ophthalmic Ointment; Chloramphenicol Ophthalmic Solution; Chloramphenicol Otic Solution; Chloramphenicol Palmitate Oral Suspension; Chloramphenicol Sodium Succinate for Injection; Chloramphenicol, Polymyxin B Sulfate, and Hydrocortisone Acetate Ophthalmic Ointment.

Chloroxine *(USAN)*

Cloroxinum; 5,7-Dichlorochinolin-8-ol; 5,7-Dichloroquinolin-8-ol; Kloroxin; Хлороксин.

$C_9H_5Cl_2NO$=214.0

CAS — 773-76-2.

UNII — 2I8BD50I88.

Profile

Chloroxine is a halogenated hydroxyquinoline with antibacterial and antifungal properties similar to those of clioquinol (p. 275.1). It is given orally in preparations for acute infectious diarrhoea. It has also been used topically in the treatment of dandruff and seborrhoeic dermatitis of the scalp.

Chloroxine is a component of halquinol (p. 311.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Endiaron; Endioderm; *USA*: Capitrol†.

Multi-ingredient Preparations. *Cz.*: Triaderm†; Triamcinolon E; *Ital.*: Beben Clorossina.

Chlorquinaldol *(BAN, rINN)*

Chlorochinaldol; Chlorquinaldolum; Clorquinaldol; Kloorikinaldoli; Klorkinaldol; Хлорхинальдол.

5,7-Dichloro-2-methylquinolin-8-ol.

$C_{10}H_7Cl_2NO$=228.1

CAS — 72-80-0.

ATC — D08AH02; G01AC03; P01AA04; R02AA11.

ATC Vet — QD08AH02; QG01AC03; QR02AA11.

UNII — D6VHC87LLS.

Pharmacopoeias. In *Pol.*

Profile

Chlorquinaldol is a halogenated hydroxyquinoline with properties similar to those of clioquinol (p. 275.1). It is mainly applied topically in infected skin conditions and in vaginal infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Gynosan; *Ukr.*: Chinofucin-LH (Хинофуцин-ЛХ); Chlorchinaldin (Хлорхинальдин)†.

Multi-ingredient Preparations. *Arg.*: Nerisona C; *Braz.*: Bi-Nerisona; *Chile*: Bi-Nerisona†; *China*: Colposeptine (可宝净); *Denm.*: Locoidol†; *Fr.*: Nerisone C; *Gr.*: Nerisona C; *Hong Kong*: Colposeptine; Nerisone C; *Indon.*: Nerisona Combi; *Irl.*: Locoid C†; *Israel*: Multiderm; *Ital.*: Impetex; Nerisona C; *Mex.*: Bi-Nerisona; *Mon.*: Colposeptine; *Norw.*: Locoidol†; *NZ*: Locoid C; Nerisone C; *Philipp.*: Nerisona Combi; *Pol.*: Chlorchinaldin H; Gynalgin; Laticort-CH†; *Port.*: Nerisona C; Trophoseptine; *Rus.*: Gynalgin (Гиналгин); *Spain*: Claral Plus; *Switz.*: Anginazol; *Turk.*: Colposeptine; Impetex; Nerisona C; *Ukr.*: Colposeptine (Колпосептин); Gynalgin (Гиналгин); *Venez.*: Binerisona.

Chlortetracycline *(BAN, rINN)*

Chlortetracyclin; Chlortétracycline; Chlortetracyclinum; Chlortetracyklin; Clortetraciclina; Klooritetrasykliini; Klortetracyclin; Хлортетрациклин.

(4*S*,4a*S*,5a*S*,6*S*,12a*S*)-7-Chloro-4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxonaphthacene-2-carboxamide; 7-Chlorotetracycline.

$C_{22}H_{23}ClN_2O_8$=478.9

CAS — 57-62-5.

ATC — A01AB21; D06AA02; J01AA03; S01AA02.

ATC Vet — QA01AB21; QD06AA02; QJ01AA03; QJ51AA03; QS01AA02.

UNII — WCK1KIQ23Q.

Chlortetracycline Bisulfate *(BANM, rINNM)*

Bisulfato de clortetraciclina; Chlortétracycline, Bisulfate de; Chlortetracycline Bisulphate; Chlortetracyclini Bisulfas; Clortetraciclina, bisulfato de; Хлортетрациклина бисульфат.

UNII — 1D06KZ672I.

Pharmacopoeias. In *US* for veterinary use only.

USP 36: (Chlortetracycline Bisulfate). Store in airtight containers. Protect from light.

Chlortetracycline Hydrochloride *(BANM, rINNM)*

Chlorotetracykliny chlorowodorek; Chlortetraciklino hidrochloridas; Chlortétracycline, Chlorhydrate de; Chlortetracyclinhydrochlorid; Chlortetracyclini Hydrochloridum; Chlortetracyklin-hydrochlorid; Clortetraciclina, hidrocloruro de; Hidrocloruro de clortetraciclina; Klooritetrasykliinihydrokloridi; Klórtetraciklin-hidroklorid; Klortetracyklinhydroklorid; Хлортетрациклина гидрохлорид.

$C_{22}H_{23}ClN_2O_8HCl$=515.3

CAS — 64-72-2.

ATC — A01AB21; D06AA02; J01AA03; S01AA02.

ATC Vet — QA01AB21; QD06AA02; QJ01AA03; QS01AA02.

UNII — O1GX33ON8R.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US*.

Ph. Eur. 8: (Chlortetracycline Hydrochloride). The hydrochloride of a substance produced by the growth of certain strains of *Streptomyces aureofaciens* or by any other means. A yellow powder. Slightly soluble in water and in alcohol; it dissolves in solutions of alkali hydroxides and carbonates. A 1% solution in water has a pH of 2.3 to 3.3. Protect from light.

USP 36: (Chlortetracycline Hydrochloride). A yellow, odourless crystalline powder. Soluble 1 in 75 of water and 1 in 560 of alcohol; practically insoluble in acetone, in chloroform, in dioxan, and in ether; soluble in solutions of alkali hydroxides and carbonates. pH of a 1% solution in water is between 2.3 and 3.3. Store in airtight containers. Protect from light.

Profile

Chlortetracycline is a tetracycline derivative with general properties similar to those of tetracycline (p. 375.1) and is used as the hydrochloride, more often topically than orally. It is used as a 1% ophthalmic ointment and as a 3% ointment for application to the skin. It is poorly absorbed from the gastrointestinal tract compared with other tetracyclines but it has sometimes been given orally with other tetracycline derivatives.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies chlortetracycline as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 15/08/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Aureomycin; Aureomycine†; *Fr.*: Aureomycine; *Ger.*: Aureomycin; *Gr.*: Aureomycin; *Hong Kong*: Chlortralim; *Ital.*: Aureomicina; *Malaysia*: Chlortralim; *Pol.*: Chlorocyclinum; *Singapore*: Chlortralim; *Spain*: Aureomicina; Dermosa Aureomicina; *Thai.*: Aureomycin†; Chlortralim.

Multi-ingredient Preparations. *Austria*: Aureocort; *Braz.*: Cortaciclen; *Ital.*: Aureocort; Aureomix; *S.Afr.*: Tritet†; *UK*: Aureocort.

Pharmacopoeial Preparations

BP 2014: Chlortetracycline Eye Ointment; Chlortetracycline Ointment;

USP 36: Chlortetracycline Hydrochloride Ointment; Chlortetracycline Hydrochloride Ophthalmic Ointment.

Ciclacillin *(BAN, rINN)*

Ciclacilina; Ciclacilline; Ciclacillinum; Ciklacillin; Cyclacillin (USAN); Siklasilliini; Wy-4508; Циклациллин.

(6*R*)-6-(1-Aminocyclohexanecarboxamido)penicillanic acid.

$C_{15}H_{23}N_3O_4S$=341.4

CAS — 3485-14-1.

UNII — 72ZJ154X86.

Pharmacopoeias. In *Jpn*.

Profile

Ciclacillin is an aminopenicillin with properties similar to those of ampicillin (p. 218.2), although it is generally less active *in vitro*.

Cilastatin Sodium *(BANM, USAN, rINNM)*

Cilastatin-Natrium; Cilastatin sodná sůl; Cilastatina sódica; Cilastatine Sodique; Cilastatinnatrium; Cilastatino natrio druska; Cilastatinum Natricum; Cilasztatin-nátrium; L-64295?; MK-791; Natrii Cilastatinas; Natrii Cilastatinum; Natriumsilastatinaatti; Natriumsilastatinat; Silastatininatrium; Silastatin Sodyum; Натрий Циластатин.

(*Z*)-(*S*)-6-Carboxy-6-[(*S*)-2,2-dimethylcyclopropanecarboxamido]hex-5-enyl-L-cysteine, monosodium salt.

$C_{16}H_{25}N_2NaO_5S$=380.4

CAS — 82009-34-5 (cilastatin); 81129-83-1 (cilastatin sodium).

UNII — 5428WXZ74M.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Cilastatin Sodium). A white or light yellow, hygroscopic, amorphous powder. Very soluble in water and in methyl alcohol; slightly soluble in dehydrated alcohol; practically insoluble in acetone and in dichloromethane; very slightly soluble in dimethyl sulfoxide. A 1% solution in water has a pH of 6.5 to 7.5. Store at a temperature not exceeding 8 degrees in airtight containers.

USP 36: (Cilastatin Sodium). A white to tan-coloured powder. Soluble in water and in methyl alcohol. pH of a 1% solution in water is between 6.5 and 7.5. Store at a temperature less than 8 degrees.

Profile

Cilastatin is an inhibitor of dehydropeptidase I, an enzyme found in the brush border of the renal tubules. It is given as the sodium salt with the antibacterial imipenem (p. 311.2) to prevent its renal metabolism to microbiologically inactive and potentially nephrotoxic products. This increases the concentrations of imipenem achieved in the urine and protects against any nephrotoxic effects, which were seen with high doses of imipenem given experimentally to *animals*.

Cilastatin has no antibacterial activity itself, and does not affect the antibacterial activity of imipenem.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Dixabiox; Imipecil; Imistatin; Klonam; Zienam; *Austral.*: Primaxin; *Austria*: Zienam; *Belg.*: Tienam; *Braz.*: Tienam; Tiepem; *Canad.*: Primaxin; *Chile*: Inem; Tienam; *China*: Bacqure (齐佩能); Prepenem (诸能); Tienam (泰能); *Cz.*: Cilanem; Imecitin; Tienam; *Fin.*: Tienam; *Fr.*: Tienam; *Ger.*: Zienam; *Gr.*: Imicil; Nimedine; Primagal; Primalix; Primaxin; *Hong Kong*: Prepenem; Tienam; *Hung.*: Cilanem; Tienam; *India*: Cilanem; Cilaspene; Cimispect; Flaminim; I-Nem; Ime-Cila; Imelastin; Imi-Cila; Iminem; Imitop; Lastinem; *Indon.*: Elastyn; Pelastin; Tienam; Timipen; *Israel*: Tienam; *Ital.*: Imipem; Tenacid; Tienam; *Malaysia*: Bacqure; Tienam; *Mex.*: Arzomeba; Iminen†; Lemibet†; Opostibac; Tienam; *Neth.*: Tienam; *Norw.*: Tienam; *NZ*: Primaxin; *Philipp.*: Anipen; Penam; Plastin; Tienam; *Pol.*: Ransetron; Tienam; *Port.*: Tienam; *Rus.*: Cilaspen (ЦИЛАСТЕН); Grimipenem (Гримипенем); Tienam (Тиенам); *S.Afr.*: Tienam; *Singapore*: Tienam; *Spain*: Tienam; *Swed.*: Tienam; *Switz.*: Tienam; *Thai.*: Bacqure; Cilapenem; Prepenem; Tienam; *Turk.*: Silanem; Tienam; *UAE*: Maxinem; *UK*: Primaxin; *Ukr.*: Lastinem (Ластинем)†; Sinerpen (Синерпен); Tienam (Тиенам); *USA*: Primaxin; *Venez.*: Zienam.

Pharmacopoeial Preparations

USP 36: Imipenem and Cilastatin for Injectable Suspension; Imipenem and Cilastatin for Injection.

Cinoxacin *(BAN, USAN, rINN)*

64716; Azolinic Acid; Cinoxacine; Cinoxacino; Cinoxacinum; Compound 64716; Sinoksasiini; Циноксацин.

1-Ethyl-1,4-dihydro-4-oxo-1,3-dioxolo[4,5-*g*]cinnoline-3-carboxylic acid.

$C_{12}H_{10}N_2O_5$=262.2

CAS — 28657-80-9.

ATC — J01MB06.

ATC Vet — QJ01MB06.

UNII — LMK22VUH23.

Pharmacopoeias. In *US.*

USP 36: (Cinoxacin). A white to yellowish-white, odourless crystalline solid. Insoluble in water and in most common organic solvents; soluble in alkaline solution. Store in airtight containers.

Uses and Administration

Cinoxacin is a 4-quinolone antibacterial with actions and uses similar to those of nalidixic acid (p. 330.3). In the treatment of urinary-tract infections the usual oral dose is 500 mg twice daily; for prophylaxis 500 mg is given at bedtime.

Administration in renal impairment. Cinoxacin should be used in reduced dosage, or not at all, in patients with renal impairment.

Adverse Effects and Precautions

As for Nalidixic Acid, p. 331.1.

Caution is needed in patients with renal impairment (see above).

References.

1. Stricker BHC, *et al.* Anaphylactic reactions to cinoxacin. *BMJ* 1988; 297: 1434–5.

Interactions

As for Nalidixic Acid, p. 331.2.

Antimicrobial Action

As for Nalidixic Acid, p. 331.2. Cross-resistance with nalidixic acid has been shown.

Pharmacokinetics

Cinoxacin is rapidly and almost completely absorbed after oral doses. Peak serum concentrations of about 15 micrograms/mL occur 2 to 3 hours after a 500-mg dose. The plasma half-life is about 1 to 2 hours. Cinoxacin is more than 60% bound to plasma proteins.

Cinoxacin appears to be metabolised in the liver and is excreted via the kidney. Over 95% of a dose appears in the urine within 24 hours, over half as unaltered drug and the remainder as inactive metabolites. Mean urinary concentrations of about 300 micrograms/mL have been achieved during the first 4 hours after a 500-mg oral dose. Urinary excretion is reduced by probenecid and in patients with renal impairment.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Cinobactin; Fleryl; Iristan-V; Londolife; Panafen; Simarlen; *Ital.*: Cinobac; Cinocil; Cinoxen†; Uroc†; Urocinox.

Pharmacopoeial Preparations

USP 36: Cinoxacin Capsules.

Ciprofloxacin *(BAN, USAN, rINN)*

Bay-q-3939; Ciprofloksacinas; Ciprofloxacine; Ciprofloxacino; Ciprofloxacinum; Siprofloksasiini; Siprofloksasin; Siprofloxacin; Ципрофлоксацин.

1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazin-1-ylquinoline-3-carboxylic acid.

$C_{17}H_{18}FN_3O_3$=331.3

CAS — 85721-33-1.

ATC — J01MA02; S01AE03; S02AA15; S03AA07.

ATC Vet — QJ01MA02; QS01AE03; QS02AA15; QS03AA07.

UNII — 5E8K9I0O4U.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Ciprofloxacin). An almost white or pale yellow, slightly hygroscopic, crystalline powder. Practically insoluble in water; very slightly soluble in dehydrated alcohol and in dichloromethane. Store in airtight containers. Protect from light.

USP 36: (Ciprofloxacin). Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Avoid temperatures above 40 degrees. Protect from light.

Ciprofloxacin Hydrochloride

(BANM, USAN, rINNM)

Bay-o-9867; Ciprofloksacino hidrochloridas; Ciprofloxacine, chlorhydrate de; Ciprofloxacin-hidroklorid; Ciprofloxacin-hydrochlorid; Ciprofloxacinhydrochlorid; Ciprofloxacinhydroklorid; Ciprofloxacini Hydrochloridum; Ciprofloxacino, hidrocloruro de; Cyprofloksacyny chlorowodorek; Hidrocloruro de ciprofloxacino; Siprofloksasiinihydrokloridi; Siprofloksasin Hidroklorür; Ципрофлоксацина Гидрохлорид.

Ciprofloxacin hydrochloride monohydrate.

$C_{17}H_{18}FN_3O_3HCl,H_2O$=385.8

CAS — 86483-48-9 (anhydrous ciprofloxacin hydrochloride); 86393-32-0 (ciprofloxacin hydrochloride monohydrate).

ATC — J01MA02; S01AE03; S02AA15; S03AA07.

ATC Vet — QJ01MA02; QS01AE03; QS02AA15; QS03AA07.

UNII — 4BA73M5E37.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 8: (Ciprofloxacin Hydrochloride). A pale yellow, slightly hygroscopic, crystalline powder. It contains a variable quantity of water. Soluble in water; very slightly soluble in dehydrated alcohol; practically insoluble in acetone, in dichloromethane, and in ethyl acetate; slightly soluble in methyl alcohol. A 2.5% solution in water has a pH of 3.5 to 4.5. Store in airtight containers. Protect from light.

USP 36: (Ciprofloxacin Hydrochloride). Faintly yellowish to light yellow crystals. Sparingly soluble in water; very slightly soluble in dehydrated alcohol; slightly soluble in acetic acid and in methyl alcohol; practically insoluble in acetone, in acetonitrile, in dichloromethane, in ethyl acetate, and in hexane. pH of a 2.5% solution in water is between 3.0 and 4.5. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Ciprofloxacin Lactate *(BANM, rINNM)*

Ciprofloxacine, Lactate de; Ciprofloxacini Lactas; Ciprofloxacino, lactato de; Lactato de ciprofloxacino; Ципрофлоксацина Лактат.

$C_{17}H_{18}FN_3O_3,C_3H_6O_3$=421.4

CAS — 97867-33-9.

ATC — J01MA02; S01AE03; S02AA15; S03AA07.

ATC Vet — QJ01MA02; QS01AE03; QS02AA15; QS03AA07.

UNII — UEY6XFC224.

Incompatibility. Ciprofloxacin infusion is stated in UK licensed product information to have a pH of 3.9 to 4.5 and to be incompatible with injections chemically or physically unstable at this pH range. Incompatibility has been reported between ciprofloxacin and other drugs including some antibacterials.[1-5]

1. Lyall D, Blythe J. Ciprofloxacin lactate infusion. *Pharm J* 1987; 238: 290.
2. Janknegt R, *et al.* Quinolones and penicillins incompatibility. *DICP Ann Pharmacother* 1989; 23: 91–2.
3. Goodwin SD, *et al.* Compatibility of ciprofloxacin injection with selected drugs and solutions. *Am J Hosp Pharm* 1991; 48: 2166–71.
4. Jim LK. Physical and chemical compatibility of intravenous ciprofloxacin with other drugs. *Ann Pharmacother* 1993; 27: 704–7.
5. Elmore RL, *et al.* Stability and compatibility of admixtures of intravenous ciprofloxacin and selected drugs. *Clin Ther* 1996; 18: 246–55.

Stability. For mention of loss of activity in ciprofloxacin solutions exposed to ultraviolet light see under Precautions, p. 266.2.

Uses and Administration

Ciprofloxacin is a fluorinated 4-quinolone or fluoroquinolone antibacterial with a wider spectrum of activity than nalidixic acid (see Antimicrobial Action, p. 267.2) and more favourable pharmacokinetics allowing its use in systemic infections. It has been used in the treatment of infections caused by susceptible bacteria, including in anthrax, biliary-tract infections, infected bites and stings, bone and joint infections, cat scratch disease, chancroid, exacerbations of cystic fibrosis, ear, nose, and throat infections (including otitis externa, otitis media, and sinusitis), HACEK endocarditis, gastro-enteritis (including travellers' diarrhoea and campylobacter enteritis, cholera, salmonella enteritis, shigellosis, and yersinia enteritis), gonorrhoea, granuloma inguinale, infections in immunocompromised patients (neutropenia), legionnaires' disease, pelvic inflammatory disease, peritonitis, plague, lower respiratory-tract infections (including pseudomonal infections in cystic fibrosis, but excluding infections due to *Streptococcus pneumoniae* such as pneumococcal pneumonia), rickettsial infections (including Q fever, spotted fevers, and typhus), septicaemia, typhoid and paratyphoid fever, and urinary-tract infections including chronic bacterial prostatitis. It may be used for infections of skin or skin structures due to Gram-negative bacteria, although a fluoroquinolone which also has good activity against Gram-positive organisms may be preferred. Ciprofloxacin is also used for meningococcal meningitis prophylaxis, surgical infection prophylaxis, and in the treatment of nontuberculous mycobacterial infections; it has also been used to treat tuberculosis, but has largely been replaced in this role by more effective fluoroquinolones (see p. 264.2). Ciprofloxacin is used topically in the treatment of eye and ear infections.

For details of all these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Administration and dosage. Ciprofloxacin is given orally as the hydrochloride or base, by intravenous infusion as the lactate, and in eye drops, eye ointment, or ear drops as the hydrochloride. Doses and strengths are expressed in terms of the base. Ciprofloxacin hydrochloride 291.1 mg is equivalent to about 250 mg of ciprofloxacin. Ciprofloxacin lactate 127 mg is equivalent to about 100 mg of ciprofloxacin.

The usual oral dose of ciprofloxacin ranges from 250 to 750 mg twice daily depending on the severity and nature of the infection. Modified-release preparations for once-daily dosage are available in some countries. The usual intravenous dose is 200 mg twice daily to 400 mg 3 times daily, generally given over 60 minutes as a solution containing the equivalent of 1 to 2 mg/mL. A 28-day course of treatment with an oral dose of 500 mg twice daily or an intravenous dose of 400 mg twice daily should be given for chronic bacterial prostatitis. Bone and joint infections should be treated with an oral dose of 500 to 750 mg twice daily or an intravenous dose of 400 mg two or three times daily for 4 to 12 weeks; for malignant otitis externa, the higher doses are recommended for up to 3 months. Intravenous infusions of 400 mg three times daily have also been recommended in severe or complicated lower respiratory tract or skin infections, nosocomial pneumonia, and with piperacillin for empirical treatment of febrile neutropenic patients.

For treatment and postexposure prophylaxis of inhalation **anthrax**, a 60-day course of treatment with either intravenous doses of 400 mg twice daily or oral doses of 500 mg twice daily is recommended; although unlicensed, the same regimen is recommended by UK and US public health agencies for the treatment of gastrointestinal anthrax. In the treatment of cutaneous anthrax (also unlicensed), a 7- to 10-day course of treatment with an oral dose of 500 to 750 mg twice daily is similarly recommended; treatment may need to be extended to 60 days if infection is due to aerosol exposure.

Doses should be reduced in patients with severe renal impairment (see p. 264.1).

Single oral doses of 500 mg may be used for the treatment of **gonorrhoea**, depending upon patterns of resistance. A single oral dose of 750 mg has been used for surgical infection prophylaxis, given 60 minutes before the procedure. For **meningococcal meningitis** prophylaxis a single oral dose of 500 mg is recommended.

For details of doses in children, including adolescents, see p. 263.3.

For corneal ulcers and superficial **ocular infections** caused by susceptible strains of bacteria ciprofloxacin is given as the hydrochloride in eye drops and eye ointment containing the equivalent of 0.3% of ciprofloxacin.

Ciprofloxacin is also used topically as the hydrochloride in ear drops containing the equivalent of 0.2 or 0.3% of ciprofloxacin, usually with a corticosteroid such as dexamethasone or hydrocortisone, for the treatment of otitis externa and chronic suppurative otitis media caused by susceptible strains of bacteria.

General references to fluoroquinolones[1-8] including ciprofloxacin specifically.[9-12]

1. Balfour JA, Goa KL, eds. Proceedings of the 5th International symposium on new quinolones. *Drugs* 1995; 49 (suppl 2): 1–505.
2. Walker RC. The fluoroquinolones. *Mayo Clin Proc* 1999; 74: 1030–7.
3. Smith A, *et al.* Fluoroquinolones: place in ocular therapy. *Drugs* 2001; 61: 747–61.
4. Schaeffer AJ. The expanding role of fluoroquinolones. *Am J Med* 2002; 113 (suppl 1A): 45S–54S.
5. Zhanel GG, *et al.* A critical review of the fluoroquinolones: focus on respiratory infections. *Drugs* 2002; 62: 13–59.
6. Carson C, Naber KG. Role of fluoroquinolones in the treatment of serious bacterial urinary tract infections. *Drugs* 2004; 64: 1359–73.
7. Shams WE, Evans ME. Guide to selection of fluoroquinolones in patients with lower respiratory tract infections. *Drugs* 2005; 65: 949–91.
8. Andriole VT. The quinolones: past, present, and future. *Clin Infect Dis* 2005; 41 (suppl 2): S113–S119.
9. Davis R, *et al.* Ciprofloxacin: an updated review of its pharmacology, therapeutic efficacy and tolerability. *Drugs* 1996; 51: 1019–74.
10. Campoll-Richards DM, *et al.* Ciprofloxacin: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1998; 35: 373–447.
11. Gould FK, *et al.*, eds. Ten years of ciprofloxacin: the past, present and future. *J Antimicrob Chemother* 1999; 43 (suppl A): 1–134.
12. Blondeau JM. Current issues in the management of urinary tract infections: extended-release ciprofloxacin as a novel treatment option. *Drugs* 2004; 64: 611–28.

Administration in children. Ciprofloxacin is not recommended for general use in children and adolescents (see

under Precautions, p. 266.1) but, if considered essential, it may be given orally or by intravenous infusion over 60 minutes. UK licensed product information recommends that for serious infections, oral doses of 20 mg/kg (maximum 750 mg) twice daily, or intravenous doses of 10 mg/kg (maximum 400 mg) three times daily may be used in those aged 1 year and older. For younger children, the *BNFC* recommends the following doses:

- neonates: 15 mg/kg orally, or 10 mg/kg intravenously, both twice daily
- from 1 month to 18 years: 20 mg/kg (maximum 750 mg) orally twice daily or 10 mg/kg (maximum 400 mg) three times daily

Ciprofloxacin is also licensed in different doses for specific indications as outlined below.

In the UK and the USA ciprofloxacin is licensed for the treatment and postexposure prophylaxis of inhalation **anthrax** in children and adolescents. A 60-day course of treatment with either intravenous doses of 10 mg/kg (to a maximum of 400 mg) twice daily or oral doses of 15 mg/kg (to a maximum of 500 mg) twice daily is recommended; the *BNFC* suggests that similar doses may be given to those as young as 1 month of age. Although unlicensed, the same regimen is recommended by UK and US public health agencies for the treatment of gastrointestinal anthrax. In the treatment of cutaneous anthrax (also unlicensed), a 7- to 10-day course of treatment with an oral dose of up to 15 mg/kg twice daily is similarly recommended; treatment may need to be extended to 60 days if infection is due to aerosol exposure.

It is also licensed in the UK for acute exacerbations of **cystic fibrosis** associated with *Pseudomonas aeruginosa* infection in those aged 1 year and older. An oral dose of 20 mg/kg (to a maximum of 750 mg) twice daily or an intravenous dose of 10 mg/kg (to a maximum of 400 mg) three times daily is recommended. Although not licensed for younger children, the *BNFC* suggests these doses are suitable for those aged 1 month and older.

Ciprofloxacin is also licensed in the UK and the USA for complicated **urinary-tract infections** or **pyelonephritis** in those aged 1 year and older. An oral dose of 10 to 20 mg/kg (to a maximum of 750 mg) twice daily or an intravenous dose of 6 to 10 mg/kg (to a maximum of 400 mg) three times daily is recommended. The *BNFC* suggests the following doses for younger children:

- neonates: 10 mg/kg orally or 6 mg/kg intravenously, both twice daily
- children from 1 month to 18 years of age: 10 to 20 mg/kg (maximum 750 mg) orally twice daily or 6 to 10 mg/kg intravenously (maximum 400 mg) three times daily

Although unlicensed in the UK, the *BNFC* suggests a single oral dose of 125 mg for **meningococcal meningitis prophylaxis** in children aged 1 month to 5 years; children aged 5 to 12 years may be given a single oral dose of 250 mg, and those aged over 12 years a single oral dose of 500 mg. Single oral doses of 500 mg have also been suggested for the treatment of **gonorrhoea** in those over 12 years of age.

Administration in renal impairment. The dose of ciprofloxacin should be reduced in ***adult patients*** with renal impairment by either reducing the total daily dose and/or by increasing the dosage interval in accordance with their creatinine clearance (CC); ideally plasma concentrations of ciprofloxacin should be monitored.

In the UK, usual doses may be used for those with a CC greater than 60 mL/minute; for lower CC, up to 500 mg orally or up to 400 mg intravenously may be given at the following intervals:

- CC 30 to 60 mL/minute: twice daily
- CC less than 30 mL/minute: once daily

For haemodialysis or peritoneal dialysis patients, up to 500 mg orally or 400 mg intravenously every 24 hours has been recommended; for haemodialysis patients, doses should be given after the dialysis run.

Alternatively, in the USA the following doses are recommended:

- CC 30 to 50 mL/minute: up to 500 mg orally every 12 hours or the usual dose intravenously
- CC 5 to 29 mL/minute: up to 500 mg orally every 18 hours or up to 400 mg intravenously every 18 to 24 hours

A pharmacokinetic study in 10 critically ill patients undergoing continuous renal replacement therapy with continuous venovenous haemofiltration or haemodiafiltration suggested that an intravenous dose of ciprofloxacin 400 mg every 24 hours would be suitable in such situations.[1] Other authors have suggested that up to 400 mg twice daily may be necessary for patients undergoing continuous venovenous haemodialysis or haemofiltration.[2]

1. Malone RS, *et al.* Pharmacokinetics of levofloxacin and ciprofloxacin during continuous renal replacement therapy in critically ill patients. *Antimicrob Agents Chemother* 2001; 45: 2949–54.
2. Trotman RL, *et al.* Antibiotic dosing in critically ill adult patients receiving continuous renal replacement therapy. *Clin Infect Dis* 2005; 41: 1159–66.

Inflammatory bowel disease. Ciprofloxacin has been given, sometimes with metronidazole, in the management of active Crohn's disease[1,2] (see Inflammatory Bowel Disease, p. 1811.3), particularly for perianal fistulae.[3,4]

1. Prantera C, *et al.* An antibiotic regimen for the treatment of active Crohn's disease: a randomized, controlled clinical trial of metronidazole plus ciprofloxacin. *Am J Gastroenterol* 1996; 91: 328–32.
2. Ishikawa T, *et al.* Metronidazole plus ciprofloxacin therapy for active Crohn's disease. *Intern Med* 2003; 42: 318–21.
3. West RL, *et al.* Clinical and endosonographic effect of ciprofloxacin on the treatment of perianal fistulae in Crohn's disease with infliximab: a double-blind placebo-controlled study. *Aliment Pharmacol Ther* 2004; 20: 1329–36.
4. Thia KT, *et al.* Ciprofloxacin or metronidazole for the treatment of perianal fistulas in patients with Crohn's disease: a randomized, double-blind, placebo-controlled pilot study. *Inflamm Bowel Dis* 2009; 15: 17–24.

Tuberculosis. Although the newer fluoroquinolones are reported to have good *in-vitro* (levofloxacin, gatifloxacin, moxifloxacin) and *in-vivo* (gatifloxacin and moxifloxacin) bactericidal activity against *Mycobacterium tuberculosis*,[1] reviews[1,2] of data obtained from controlled studies, cohorts, and case series, published up to March 2006, evaluating the clinical efficacy of fluoroquinolones for the treatment of tuberculosis (p. 210.2) concluded that substituting or adding fluoroquinolones (in particular the older fluoroquinolones such as ciprofloxacin or ofloxacin) to established first-line treatment regimens did not confer additional benefits. In a later study,[3] substitution of moxifloxacin for ethambutol in a first-line treatment regimen (including isoniazid, rifampicin, and pyrazinamide) resulted in a significantly higher rate of negative culture conversion at 8 weeks, suggesting that use of moxifloxacin with other first-line drugs might shorten the time needed to cure tuberculosis by several months, although further study is needed.

There are very few controlled studies evaluating the use of fluoroquinolones in multidrug-resistant tuberculosis (MDR-TB), but 2 retrospective studies support their efficacy.[1] WHO guidelines[4,5] recommend that patients with suspected or confirmed MDR-TB should receive second-line antituberculous drugs as part of a DOTS-plus regimen; such drugs include ofloxacin, levofloxacin, and moxifloxacin. The usual recommended oral doses are as follows:[5]

- moxifloxacin: 400 mg daily
- levofloxacin: 750 mg to 1 g daily
- ofloxacin: 800 mg to 1 g daily

Because of its relatively weak efficacy compared with other fluoroquinolones, ciprofloxacin is no longer recommended by WHO for the treatment of either susceptible or drug-resistant tuberculosis.

1. Moadebi S, *et al.* Fluoroquinolones for the treatment of pulmonary tuberculosis. *Drugs* 2007; 67: 2077–99.
2. Ziganshina LE, Squire SB. Fluoroquinolones for treating tuberculosis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 07/07/08).
3. Sellier P, *et al.* Moxifloxacin versus ethambutol in initial tuberculosis treatment. *Lancet* 2009; 373: 1183–9.
4. WHO. *Treatment of tuberculosis: guidelines—4th edition.* Geneva: WHO, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf (accessed 08/02/10)
5. WHO. *Guidelines for the programmatic management of drug-resistant tuberculosis: emergency update 2008.* Geneva: WHO, 2008. Available at: http://whqlibdoc.who.int/publications/2008/9789241547581_eng.pdf (accessed 08/02/10)

Adverse Effects

Ciprofloxacin is generally well tolerated. The range of adverse effects associated with ciprofloxacin and the other fluoroquinolones is broadly similar to that of earlier quinolones such as nalidixic acid (p. 331.1). They most often involve the gastrointestinal tract, CNS, or skin.

Gastrointestinal disturbances include nausea, vomiting, diarrhoea, abdominal pain, and dyspepsia and are the most frequent adverse effects. Pseudomembranous colitis, pancreatitis, and dysphagia have been reported rarely.

Headache, dizziness, confusion, insomnia, and restlessness are among the commonest effects on the CNS. Others include tremor, drowsiness, nightmares, visual and other sensory disturbances, hallucinations, psychotic reactions, depression, convulsions, and intracranial hypertension. Paraesthesia and peripheral neuropathy have also been reported.

In addition to rash and pruritus, hypersensitivity-type reactions affecting the skin have included, rarely, vasculitis, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Photosensitivity has occurred, although it may be more frequent with some other fluoroquinolones such as lomefloxacin and sparfloxacin. Anaphylaxis has been associated with ciprofloxacin and some other quinolones. As with other quinolones, reversible arthralgia or myalgia has sometimes occurred and joint erosions have been documented in immature *animals*. Tendon damage has also been reported.

Fluoroquinolones have neuromuscular-blocking activity, which may exacerbate muscle weakness in patients with myasthenia gravis. In rare cases, severe exacerbations leading to respiratory failure or death have occurred.

Other adverse effects reported with ciprofloxacin include crystalluria, transient increases in serum creatinine or blood urea nitrogen and, rarely, acute renal failure secondary to interstitial nephritis. Elevated liver enzyme values, jaundice, and hepatitis have occurred, as have haematological disturbances including eosinophilia, leucopenia, thrombocytopenia and, very rarely, pancytopenia, haemolytic anaemia or agranulocytosis. Cardiovascular adverse effects include tachycardia, hypotension, oedema, syncope, hot flushes, and sweating. Some fluoroquinolones may rarely cause prolongation of the QT interval and ventricular arrhythmias, including torsade de pointes (see p. 264.3).

As with other antibacterials, superinfection with organisms not very susceptible to ciprofloxacin is possible. Such organisms include *Candida*, *Clostridium difficile*, and *Streptococcus pneumoniae*. There is some evidence that fluoroquinolone use may be associated with an increased risk of colonisation by MRSA.

Pain and irritation may occur at the site of infusion accompanied rarely by phlebitis or thrombophlebitis.

Adverse effects reported after ocular use of ciprofloxacin include local burning or discomfort, keratopathy, corneal staining, corneal precipitates or infiltrates, and photophobia.

Local discomfort, pain, or pruritus have occurred after use of ear drops containing ciprofloxacin.

General reviews of the adverse effects of fluoroquinolones[1-7] and ciprofloxacin specifically.[8,9]

1. Lipsky BA, Baker CA. Fluoroquinolone toxicity profiles: a review focusing on newer agents. *Clin Infect Dis* 1999; 28: 352–64.
2. Ball P, *et al.* Comparative tolerability of the newer fluoroquinolone antibacterials. *Drug Safety* 1999; 21: 407–21.
3. Rubinstein E. History of quinolones and their side effects. *Chemotherapy* 2001; 47 (suppl 3): 3–8.
4. Leone R, *et al.* Adverse drug reactions related to the use of fluoroquinolone antimicrobials: an analysis of spontaneous reports and fluoroquinolone consumption data from three Italian regions. *Drug Safety* 2003; 26: 109–20.
5. Stahlmann R, Lode H. Fluoroquinolones in the elderly: safety considerations. *Drugs Aging* 2003; 20: 289–302.
6. Owens RC, Ambrose PG. Antimicrobial safety: focus on fluoroquinolones. *Clin Infect Dis* 2005; 41 (suppl 2): S144–S157.
7. Mehlhorn AJ, Brown DA. Safety concerns with fluoroquinolones. *Ann Pharmacother* 2007; 41: 1859–66.
8. Segev S, *et al.* Safety of long-term therapy with ciprofloxacin: data analysis of controlled clinical trials and review. *Clin Infect Dis* 1999; 28: 299–308.
9. Heyd A, Haverstock D. Retrospective analysis of the safety profile of oral and intravenous ciprofloxacin in a geriatric population. *Clin Ther* 2000; 22: 1239–50.

Effects on the blood. Haematological disturbances including thrombocytopenia,[1] eosinophilia,[2] leucopenia, and, very rarely, pancytopenia,[3] haemolytic anaemia,[4] or agranulocytosis have been reported with ciprofloxacin and some other fluoroquinolones. There has also been a case report[5] of haemolytic-uraemic syndrome associated with ciprofloxacin therapy; the patient recovered with routine supportive treatment (haemodialysis and plasma exchange) after the drug was stopped. In addition, transient reductions in factor VIII and von Willebrand's factor leading to bleeding in 2 patients receiving ciprofloxacin has been reported.[6] Neutropenia that developed in an elderly patient a few days after starting treatment with intravenous moxifloxacin resolved on stopping the drug.[7]

1. Starr JA, Ragucci KR. Thrombocytopenia associated with intravenous ciprofloxacin. *Pharmacotherapy* 2005; 25: 1030–4.
2. Mofredj A, *et al.* Norfloxacin-induced eosinophilia in a cirrhotic patient. *Ann Pharmacother* 2002; 36: 1107–8.
3. Deng JY, Tovar JM. Pancytopenia with levofloxacin therapy for pelvic inflammatory disease in an otherwise healthy young patient. *Ann Pharmacother* 2006; 40: 1692–3.
4. Oh YR, *et al.* Levofloxacin-induced autoimmune hemolytic anemia. *Ann Pharmacother* 2003; 37: 1010–13.
5. Allan DS, *et al.* Ciprofloxacin-associated hemolytic-uremic syndrome. *Ann Pharmacother* 2002; 36: 1000–1002.
6. Castaman G, Rodeghiero F. Acquired transitory von Willebrand syndrome with ciprofloxacin. *Lancet* 1994; 343: 492.
7. Chang C-M, *et al.* Moxifloxacin-associated neutropenia in a cirrhotic elderly woman with lower extremity cellulitis. *Ann Pharmacother* 2008; 42: 580–3.

Effects on the cardiovascular system. Prolongation of the QT interval,[1,2] sometimes progressing to torsade de pointes,[3-8] has been associated with ciprofloxacin and other fluoroquinolones although a review[9] considered that ciprofloxacin was least likely to produce this effect. A subsequent observational, population-based, case-control study[10] of patients who had had ventricular arrhythmia or cardiac arrest supported an association between an increased risk of these events and the recent use of a fluoroquinolone. Licensed product information recommends that gatifloxacin, gemifloxacin, levofloxacin, lomefloxacin, moxifloxacin, ofloxacin, and sparfloxacin should be avoided in patients with predisposing factors or who are also receiving other drugs that are known to cause this effect and that norfloxacin should be used with caution in such situations.

1. Noel GJ, *et al.* Effects of three fluoroquinolones on QT interval in healthy adults after single doses. *Clin Pharmacol Ther* 2003; 73: 292–303.
2. Nykamp DL, *et al.* QTc prolongation associated with combination therapy of levofloxacin, imipramine, and fluoxetine. *Ann Pharmacother* 2005; 39: 543–6.

3. Frothingham R. Rates of torsades de pointes associated with ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin, and moxifloxacin. *Pharmacotherapy* 2001; 21: 1468–72.
4. Owens RC, Ambrose PG. Torsades de pointes associated with fluoroquinolones. *Pharmacotherapy* 2002; 22: 663–8.
5. Bertino JS, *et al.* Gatifloxacin-associated corrected QT interval prolongation, torsades de pointes, and ventricular fibrillation in patients with known risk factors. *Clin Infect Dis* 2002; 34: 861–3.
6. Amankwa K, *et al.* Torsades de pointes associated with fluoroquinolones: importance of concomitant risk factors. *Clin Pharmacol Ther* 2004; 75: 242–7.
7. Dale KM, *et al.* Moxifloxacin and torsade de pointes. *Ann Pharmacother* 2007; 41: 336–40.
8. Knorr JP, *et al.* Ciprofloxacin-induced Q-T interval prolongation. *Am J Health-Syst Pharm* 2008; 65: 547–51.
9. Owens RC. QT prolongation with antimicrobial agents: understanding the significance. *Drugs* 2004; 64: 1091–1124.
10. Zambon A, *et al.* Effect of macrolide and fluoroquinolone antibacterials on the risk of ventricular arrhythmia and cardiac arrest: an observational study in Italy using case-control, case-crossover and case-time-control designs. *Drug Safety* 2009; 32: 159–67.

Effects on the gastrointestinal tract. There have been several case reports and studies supporting an association between pseudomembranous colitis or superinfection with *Clostridium difficile* and use of ciprofloxacin[1,2] and other fluoroquinolones.[3-7]

1. McFarland LV, *et al.* Ciprofloxacin-associated Clostridium difficile disease. *Lancet* 1995; 346: 977–8.
2. Angel CA, *et al.* Severe ciprofloxacin-associated pseudomembranous colitis in an eight-year-old child. *J Pediatr Surg* 2004; 39: 1590–2.
3. Dan M, Samra Z. Clostridium difficile colitis associated with ofloxacin therapy. *Am J Med* 1989; 87: 479.
4. Ortiz-de-Saracho J, *et al.* Moxifloxacin-induced Clostridium difficile diarrhea. *Ann Pharmacother* 2003; 37: 452–3.
5. Gaynes R, *et al.* Outbreak of Clostridium difficile infection in a long-term care facility: association with gatifloxacin use. *Clin Infect Dis* 2004; 38: 640–5.
6. Pépin J, *et al.* Emergence of fluoroquinolones as the predominant risk factor for Clostridium difficile-associated diarrhea: a cohort study during an epidemic in Quebec. *Clin Infect Dis* 2005; 41: 1254–60.
7. Gallagher JC, *et al.* Severe pseudomembranous colitis after moxifloxacin use: a case series. *Ann Pharmacother* 2009; 43: 123–8.

Effects on glucose metabolism. For the effects of fluoroquinolones (in particular gatifloxacin) on blood glucose see under Gatifloxacin, p. 305.3.

Effects on the kidneys. A review[1] of case reports of renal toxicity (including interstitial nephritis, acute renal failure, acute tubular necrosis, and crystalluria) associated with ciprofloxacin and other fluoroquinolones indicated that such toxicity, although potentially serious, was rare. It was also noted that nearly all patients developing acute renal failure were over 50 years of age. Another review,[2] confirming that the problem remained rare, noted that risk factors for quinolone-induced nephrotoxicity seemed to include the particular quinolone chosen, with ciprofloxacin the most often involved, as well as the use of high doses, patient age, inadequate hydration, and use of other nephrotoxic drugs or the presence of other processes likely to contribute to renal damage such as diabetes.

1. Lomaestro BM. Fluoroquinolone-induced renal failure. *Drug Safety* 2000; 22: 479–85.
2. Montagnac R, *et al.* Les insuffisances rénales aiguës aux quinolones: revue générale à propos d'une observation avec cristallisation liée à la ciprofloxacine. *Nephrol Ther* 2005; 1: 44–51.

Effects on the liver. Fluoroquinolones, including ciprofloxacin, may cause elevated liver enzyme values. In most patients this effect is transient and reversible without stopping the drug.

More serious cases of hepatotoxicity, including fatalities, have been reported both with ciprofloxacin[1-6] and with other fluoroquinolones[4,7-13] but they are rare. In many cases the patients were elderly and had comorbid conditions.

1. Grassmick BK, *et al.* Fulminant hepatic failure possibly related to ciprofloxacin. *Ann Pharmacother* 1992; 26: 636–9.
2. Sherman O, Beizer JL. Possible ciprofloxacin-induced acute cholestatic jaundice. *Ann Pharmacother* 1994; 28: 1162–4.
3. Villeneuve J-P, *et al.* Suspected ciprofloxacin-induced hepatotoxicity. *Ann Pharmacother* 1995; 29: 257–9.
4. Jones SE, Smith RH. Quinolones may induce hepatitis. *BMJ* 1997; 314: 869.
5. Contreras MÁ, *et al.* Severe ciprofloxacin-induced acute hepatitis. *Eur J Clin Microbiol Infect Dis* 2001; 20: 434–5.
6. Dichiara AJ, *et al.* Ciprofloxacin-induced acute cholestatic liver injury and associated renal failure: case report and review. *Minerva Gastroenterol Dietol* 2008; 54: 307–15.
7. González Carro P, *et al.* Fatal subfulminant hepatic failure with ofloxacin. *Am J Gastroenterol* 2000; 95: 1606.
8. Björnsson E, *et al.* Norfloxacin-induced eosinophilic necrotizing granulomatous hepatitis. *Am J Gastroenterol* 2000; 95: 3662–4.
9. Spahr L, *et al.* Acute fatal hepatitis related to levofloxacin. *J Hepatol* 2001; 35: 308–9.
10. Karim A, *et al.* Possible levofloxacin-induced acute hepatocellular injury in a patient with chronic obstructive lung disease. *Clin Infect Dis* 2001; 33: 2088–90.
11. Soto S, *et al.* Moxifloxacin-induced acute liver injury. *Am J Gastroenterol* 2002; 97: 1853–4.
12. Coleman CI, *et al.* Possible gatifloxacin-induced fulminant hepatic failure. *Ann Pharmacother* 2002; 36: 1162–7.
13. Schwalm J-D, Lee CH. Acute hepatitis associated with oral levofloxacin therapy in a hemodialysis patient. *CMAJ* 2003; 168: 847–8.
14. Cheung O, *et al.* Gatifloxacin-induced hepatotoxicity and acute pancreatitis. *Ann Intern Med* 2004; 140: 73–4.
15. Çoban Ş, *et al.* Levofloxacin-induced acute fulminant hepatic failure in a patient with chronic hepatitis B infection. *Ann Pharmacother* 2005; 39: 1737–40.

Effects on the musculoskeletal system. Reversible arthralgia has sometimes occurred with the fluoroquinolones;[1] joint erosions have been documented in immature *animals*. In a report,[2] treatment with pefloxacin may have contributed to the destructive arthropathy that occurred in a 17-year-old youth. For a discussion of the use of fluoroquinolones in children and adolescents, see Administration in Children, under Precautions, p. 266.1.

There have been reports[3-7] of tendinitis and tendon rupture associated with fluoroquinolones. By July 1995, the UK CSM[5] had received 21 reports of tendon damage, often of the Achilles tendon, associated with these antibacterials—11 with ciprofloxacin and 10 with ofloxacin. In a later case-control study[8] of a cohort of 46 776 users of fluoroquinolones between July 1992 to June 1998, 704 had Achilles tendinitis and 38 had Achilles tendon rupture; the adjusted relative risk of Achilles tendon disorders with current use was 1.9. The risk of tendon damage is increased by use with corticosteroids and is more common with increasing age:[5] the case-control study[8] found that the relative risk for current users rose to 3.2 among those aged 60 and over, and to 6.2 in those in this age group also using corticosteroids. Another case-control study[9] using data from 1988 to 1998 held on a different UK general practice database reported similar findings and concluded that ofloxacin was associated with a higher risk of tendon damage than other fluoroquinolones. A review[10] of the literature between 1966 and 2001 revealed 98 case reports of fluoroquinolone-associated tendon damage. Of these, 36 were associated with pefloxacin therapy and 25 with ciprofloxacin; ofloxacin was associated with 6 cases. Renal disease or impairment was also considered as a risk factor.

Onset may be rapid: rupture has occurred within 48 hours of starting therapy.[11] It can, however, also occur after therapy has been completed, in some cases up to several months later. The CSM[5] warned that at the first sign of pain or inflammation the fluoroquinolone should be withdrawn and the affected limb rested until the tendon symptoms had resolved. Similar warnings have been issued in other countries, but some cases have continued to be reported.[12,13] In the USA the FDA has required a warning to be added to prescribing information for the fluoroquinolones stating that there is an increased risk in patients over 60, in kidney, heart, and lung transplant recipients, and with use of concomitant corticosteroid therapy.[14]

There have been reports[15,16] of rhabdomyolysis in patients given fluoroquinolones, including one fatality associated with levofloxacin therapy.[15] Acute myalgia without signs of rhabdomyolysis has also been reported with ciprofloxacin.[17]

1. Alfaham M, *et al.* Arthropathy in a patient with cystic fibrosis taking ciprofloxacin. *BMJ* 1987; 295: 699.
2. Chevalier X, *et al.* A case of destructive polyarthropathy in a 17-year-old youth following pefloxacin treatment. *Drug Safety* 1992; 7: 310–14.
3. Huston KA. Achilles tendinitis and tendon rupture due to fluoroquinolone antibiotics. *N Engl J Med* 1994; 331: 748.
4. Szarfman A, *et al.* More on fluoroquinolone antibiotics and tendon rupture. *N Engl J Med* 1995; 332: 193.
5. CSM/MCA. Tendon damage associated with quinolone antibiotics. *Current Problems* 1995; 21: 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE6dDocName=CON20156196RevisionSelectionMethod=LatestReleased (accessed 12/07/06)
6. Carrasco JM, *et al.* Tendinitis associated with ciprofloxacin. *Ann Pharmacother* 1997; 31: 120.
7. Mathis AS, *et al.* Levofloxacin-associated Achilles tendon rupture. *Ann Pharmacother* 2003; 37: 1014–17.
8. van der Linden PD, *et al.* Fluoroquinolones and risk of Achilles tendon disorders: case-control study. *BMJ* 2002; 324: 1306–7.
9. van der Linden PD, *et al.* Increased risk of Achilles tendon rupture with quinolone antibacterial use, especially in elderly patients taking oral corticosteroids. *Arch Intern Med* 2003; 163: 1801–7.
10. Khaliq Y, Zhanel GG. Fluoroquinolone-associated tendinopathy: a critical review of the literature. *Clin Infect Dis* 2003; 36: 1404–10.
11. CSM/MCA. Reminder: fluoroquinolone antibiotics and tendon disorders. *Current Problems* 2002; 28: 3–4. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE6dDocName=CON0074346RevisionSelectionMethod=LatestReleased (accessed 12/07/06)
12. Adverse Drug Reactions Advisory Committee (ADRAC). Fluoroquinolone antibiotics: remember tendon disorders. *Aust Adverse Drug React Bull* 2006; 25: 3. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0602.pdf (accessed 12/07/06)
13. Akali AU, Niranjan NS. Management of bilateral Achilles tendon rupture associated with ciprofloxacin: a review and case presentation. *J Plast Reconstr Aesthet Surg* 2008; 61: 830–4.
14. FDA. Fluoroquinolone Antimicrobial Drugs [ciprofloxacin (marketed as Cipro and generic ciprofloxacin), ciprofloxacin extended release (marketed as Cipro XR and Proquin XR), gemifloxacin (marketed as Factive), levofloxacin (marketed as Levaquin), moxifloxacin (marketed as Avelox), norfloxacin (marketed as Noroxin), and ofloxacin (marketed as Floxin and generic ofloxacin)] (issued 8th July, 2008). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/fluoroquinolonesHCP.htm (accessed 12/08/08)
15. Petitjeans F, *et al.* A case of rhabdomyolysis with fatal outcome after a treatment with levofloxacin. *Eur J Clin Pharmacol* 2003; 59: 779–80.
16. Hsiao S-H, *et al.* Acute rhabdomyolysis associated with ofloxacin/levofloxacin therapy. *Ann Pharmacother* 2005; 39: 146–9.
17. Eisele S, *et al.* Ciprofloxacin-related acute severe myalgia necessitating emergency care treatment: a case report and review of the literature. *Int J Clin Pharmacol Ther* 2009; 47: 165–8.

Effects on the nervous system. By 1991 the UK CSM[1] had received 26 reports of convulsions associated with ciprofloxacin, 1 with norfloxacin, and 1 with ofloxacin. It was noted that convulsions could occur both in patients with epilepsy and in those with no history of convulsions. Generalised seizures have been reported in patients given gatifloxacin[2] and levofloxacin.[3,4] Seizures have also been associated with the use of ear drops containing ciprofloxacin.[5] All 5 case reports[2-5] involved patients aged 65 years and over; of these, 1 had a history (although unclear) of seizures,[2] 3 had chronic renal impairment,[3-5] and 1 had neither.[3] Ciprofloxacin-associated seizures have also been reported[6] in a patient with thyrotoxicosis.

Other reports of CNS toxicity associated with ciprofloxacin have included eosinophilic meningitis,[7] delirium,[8] and acute psychoses.[9,10] Peripheral neuropathy,[11] dysaesthesia,[12] catatonia[13] (also with levofloxacin[14]), hemiparesis,[15] and tinnitus[16] have also been reported. Acute psychosis occurred[17] in a patient using ciprofloxacin eye drops. A review[18] of published and spontaneous reports found an association between adverse manic reactions and the use of certain antibacterials including ciprofloxacin and ofloxacin. Levofloxacin has also been reported to have possibly unmasked a hereditary motor and sensory neuropathy (Charcot-Marie-Tooth disease).[19]

There have also been reports of sleep disturbances[20] and of a Tourette-like syndrome[21] associated with ofloxacin. Ataxia[22] and hallucinations[23] have been reported with the use of gatifloxacin. In one case report, acute encephalopathy occurred in an elderly woman after ingestion of a single dose of gemifloxacin.[24]

A literature review[25] (up to 31st October 2010) found that the most commonly reported psychiatric adverse events with the fluoroquinolones were mania, insomnia, acute psychosis, and delirium, while the most commonly reported neurological events were convulsions (including grand mal convulsion), confusional state, and myoclonus.

1. CSM. Convulsions due to quinolone antimicrobial agents. *Current Problems* 32 1991. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE6dDocName=CON20244506RevisionSelectionMethod=LatestReleased (accessed 02/03/07)
2. Quigley CA, Lederman JR. Possible gatifloxacin-induced seizure. *Ann Pharmacother* 2004; 38: 235–7.
3. Kushner JM, *et al.* Seizures associated with fluoroquinolones. *Ann Pharmacother* 2001; 35: 1194–8.
4. Christie MJ, *et al.* Generalized seizure and toxic epidermal necrolysis following levofloxacin exposure. *Ann Pharmacother* 2005; 39: 953–5.
5. Orr CF, Rowe DB. Eardrop attacks: seizures triggered by ciprofloxacin eardrops. *Med J Aust* 2003; 178: 343.
6. Aghahi K, *et al.* Ciprofloxacin-associated seizures in a patient with underlying thyrotoxicosis: case report and literature review. *Int J Clin Pharmacol Ther* 2009; 47: 303–10.
7. Asperilla MO, *et al.* Eosinophilic meningitis associated with ciprofloxacin. *Am J Med* 1989; 87: 589–90.
8. Jay GT, Fitzgerald JM. Ciprofloxacin-induced delirium. *Ann Pharmacother* 1997; 31: 252.
9. McCue JD, Zandt JR. Acute psychoses associated with the use of ciprofloxacin and trimethoprim-sulfamethoxazole. *Am J Med* 1991; 90: 528–9.
10. Reeves RR. Ciprofloxacin-induced psychosis. *Ann Pharmacother* 1992; 26: 930–1.
11. Aoun M, *et al.* Peripheral neuropathy associated with fluoroquinolones. *Lancet* 1992; 340: 127.
12. Zehnder D, *et al.* Painful dysaesthesia with ciprofloxacin. *BMJ* 1995; 311: 1204.
13. Akhtar S, Ahmad H. Ciprofloxacin-induced catatonia. *J Clin Psychiatry* 1993; 54: 115–16.
14. Youssef NA, *et al.* Levofloxacin-induced catatonia. *Prog Neuropsychopharmacol Biol Psychiatry* 2009; 33: 741–2.
15. Rosolen A, *et al.* Acute hemiparesis associated with ciprofloxacin. *BMJ* 1994; 309: 1411.
16. Paul J, Brown NM. Tinnitus and ciprofloxacin. *BMJ* 1995; 311: 232.
17. Tripathi A, *et al.* Acute psychosis following the use of topical ciprofloxacin. *Arch Ophthalmol* 2002; 120: 665–6.
18. Abouesh A, *et al.* Antimicrobial-induced mania (antibiomania): a review of spontaneous reports. *J Clin Psychopharmacol* 2002; 22: 71–81.
19. Panas M, *et al.* Hereditary neuropathy unmasked by levofloxacin. *Ann Pharmacother* 2011; 45: 1312–13.
20. Upton C. Sleep disturbance in children treated with ofloxacin. *BMJ* 1994; 309: 1411.
21. Thomas RJ, Reagan DR. Association of a Tourette-like syndrome with ofloxacin. *Ann Pharmacother* 1996; 30: 138–41.
22. Mohan N, *et al.* Oral gatifloxacin-induced ataxia. *Am J Health-Syst Pharm* 2002; 59: 1894.
23. Adams M, Tavakoli H. Gatifloxacin-induced hallucinations in a 19-year-old man. *Psychosomatics* 2006; 47: 360.
24. Barrett MJ, Login IS. Gemifloxacin-associated neurotoxicity presenting as encephalopathy. *Ann Pharmacother* 2009; 43: 782–4.
25. Tomé AM, Filipe A. Quinolones: review of psychiatric and neurological adverse reactions. *Drug Safety* 2011; 34: 465–88.

Hypersensitivity. Hypersensitivity and skin reactions have been associated with ciprofloxacin and other fluoroquinolones. Reports have included anaphylaxis (which has sometimes been fatal, and may occur after the first dose),[1-4] serum sickness,[5] Stevens-Johnson syndrome,[6] toxic epidermal necrolysis (sometimes fatal),[7-13] laryngeal oedema,[14] and vasculitis.[15-17] Fatal vasculitis has been reported with ofloxacin.[18] Radiation recall reactions have also been reported.[19,20]

1. Assouad M, *et al.* Anaphylactoid reactions to ciprofloxacin. *Ann Intern Med* 1995; 122: 396–7.
2. Smythe MA, Cappelletty DM. Anaphylactoid reaction to levofloxacin. *Pharmacotherapy* 2000; 20: 1520–3.
3. Ho DY, *et al.* Anaphylactoid reaction to ciprofloxacin. *Ann Pharmacother* 2003; 37: 1018–23.
4. Sachs B, *et al.* Fluoroquinolone-associated anaphylaxis in spontaneous adverse drug reaction reports in Germany: differences in reporting rates between individual fluoroquinolones and occurrence after first-ever use. *Drug Safety* 2006; 29: 1087–1100.

5. Slama TG. Serum sickness-like illness associated with ciprofloxacin. *Antimicrob Agents Chemother* 1990; **34**: 904–5.
6. Hällgren J, *et al.* Stevens-Johnson syndrome associated with ciprofloxacin: a review of adverse cutaneous events reported in Sweden as associated with this drug. *J Am Acad Dermatol* 2003; **49** (suppl): S267–S269.
7. Yerasi AB, Oertel MD. Ciprofloxacin-induced toxic epidermal necrolysis. *Ann Pharmacother* 1996; **30**: 297.
8. Livasy CA, Kaplan AM. Ciprofloxacin-induced toxic epidermal necrolysis: a case report. *Dermatology* 1997; **195**: 173–5.
9. Melde SL. Ofloxacin: a probable cause of toxic epidermal necrolysis. *Ann Pharmacother* 2001; **35**: 1388–90.
10. Sahin MT, *et al.* Norfloxacin-induced toxic epidermal necrolysis. *Ann Pharmacother* 2005; **39**: 768–70.
11. Christie MJ, *et al.* Generalized seizure and toxic epidermal necrolysis following levofloxacin exposure. *Ann Pharmacother* 2005; **39**: 953–5.
12. Islam AFMS, Rahman MS. Levofloxacin-induced fatal toxic epidermal necrolysis. *Ann Pharmacother* 2005; **39**: 1136–7.
13. Davila G, *et al.* Toxic epidermal necrolysis induced by levofloxacin. *Ann Allergy Asthma Immunol* 2009; **102**: 441–2.
14. Baciewicz AM, *et al.* Laryngeal edema related to ciprofloxacin therapy. *Ann Pharmacother* 1992; **26**: 1456.
15. Choe U, *et al.* Ciprofloxacin-induced vasculitis. *N Engl J Med* 1989; **320**: 257–8.
16. Stubbings J, *et al.* Cutaneous vasculitis due to ciprofloxacin. *BMJ* 1992; **305**: 29.
17. Drago F, *et al.* Henoch-Schönlein purpura induced by fluoroquinolones. *Br J Dermatol* 1994; **131**: 448.
18. Pace JL, Gatti P. Fatal vasculitis associated with ofloxacin. *BMJ* 1989; **299**: 658.
19. Cho S, *et al.* Radiation recall reaction induced by levofloxacin. *J Drugs Dermatol* 2008; **7**: 64–7.
20. Jain S, *et al.* Radiation recall dermatitis with gatifloxacin: a review of literature. *J Med Imaging Radiat Oncol* 2008; **52**: 191–3.

Superinfection. Superinfection with *Streptococcus pneumoniae* has been reported in patients receiving ciprofloxacin.[1-3] For references to superinfection with *Clostridium difficile* and associated pseudomembranous colitis, see under Effects on the Gastrointestinal Tract, p. 263.1.

Fungal otitis externa is also associated with the use of ear drops containing fluoroquinolones.[4]

1. Righter J. Pneumococcal meningitis during intravenous ciprofloxacin therapy. *Am J Med* 1990; **88**: 548.
2. Gordon JJ, Kauffman CA. Superinfection with Streptococcus pneumoniae during therapy with ciprofloxacin. *Am J Med* 1990; **89**: 383–4.
3. Lee BL, *et al.* Infectious complications with respiratory pathogens despite ciprofloxacin therapy. *N Engl J Med* 1991; **325**: 520–1.
4. Schrader N, Isaacson G. Fungal otitis externa: its association with fluoroquinolone eardrops. *Pediatrics* 2003; **111**: 1123.

Precautions

Ciprofloxacin should be used with caution in patients with epilepsy or a history of CNS disorders. Care is also necessary in those with renal impairment or G6PD deficiency (see also p. 266.2). An adequate fluid intake should be maintained during treatment with ciprofloxacin and excessive alkalinity of the urine avoided because of the risk of crystalluria.

Since ciprofloxacin and related fluoroquinolones have, like nalidixic acid, been shown to cause degenerative changes in weight-bearing joints of young *animals*, it has been suggested that these drugs should not generally be used in patients aged under 18 years (see also p. 266.1), pregnant women, or breast-feeding mothers (but see also p. 266.2) unless the benefits outweigh the risks. Tendon damage may occur rarely with fluoroquinolones (see Effects on the Musculoskeletal System, p. 263.2) and treatment should be stopped if patients have tendon pain, inflammation, or rupture; subsequent use of fluoroquinolones is contra-indicated in these patients. Fluoroquinolones should also be avoided in patients with a history of myasthenia gravis, as severe muscle weakness may occur (see Adverse Effects, p. 262.2).

Exposure to strong sunlight or sunlamps should be avoided during treatment with ciprofloxacin. The ability to drive or operate machinery may be impaired, especially when alcohol is also taken.

Some fluoroquinolones have the potential to prolong the QT interval (see Effects on the Cardiovascular System, p. 262.3) and should be avoided or used with caution in patients with QT prolongation or relevant risk factors such as uncorrected electrolyte disturbances, bradycardia, or pre-existing cardiac disease. Certain drugs may also increase the risk (see Interactions, p. 266.3).

Ciprofloxacin and other fluoroquinolones should be avoided in MRSA infections because of the high level of resistance.

Administration in children. Since ciprofloxacin and other fluoroquinolones can cause degenerative changes in weight-bearing joints of young *animals* they should only be used in children and adolescents where their use may be justified if the benefits outweigh the risks.[1-4] For example, ciprofloxacin is licensed in some countries for use in the prophylaxis and treatment of inhalational anthrax and also in the treatment of certain infections in those under 18 years of age (see under Uses and Administration, p. 261.3). A systematic review[4] of the use of ciprofloxacin in more than 16 000 children (7 months to 17 years) found that musculoskeletal adverse events were most frequent; 258 events were reported in 232 patients, giving an estimated risk of 1.6%. Of these musculoskeletal events 50% were arthralgia, 19% tendon or joint disorder, and 15% reduced movement or stiffness. The review also found no dose-dependent or duration-dependent risk of toxicity and no significant effect on growth; adverse events were reversible on stopping medication.

A comparative cohort study[2] involving about 500 children and adolescents found that the incidence of musculoskeletal adverse effects was higher (10 cases out of 264 patients) in those taking fluoroquinolones (ciprofloxacin, ofloxacin, or pefloxacin) than in those taking other antibacterials (1 out of 237). In the former group of patients, these adverse effects, mainly arthralgias, were reversible and were most frequent with pefloxacin therapy.

1. Burstein GR, *et al.* Ciprofloxacin for the treatment of uncomplicated gonorrhea infection in adolescents: does the benefit outweigh the risk? *Clin Infect Dis* 2002; **35** (suppl 2): S191–S199.
2. Chalumeau M, *et al.* Fluoroquinolone safety in pediatric patients: a prospective, multicenter, comparative cohort study in France. Abstract: *Pediatrics* 2003; **111**: 1427–8. Full version: http://pediatrics.aappublications.org/cgi/reprint/111/6/e714 (accessed 01/11/06)
3. American Academy of Pediatrics Committee on Infectious Diseases. The use of systemic fluoroquinolones. *Pediatrics* 2006; **118**: 1287–92.
4. Adefurin A, *et al.* Ciprofloxacin safety in paediatrics: a systematic review. *Arch Dis Child* 2011; **96**: 874–80.

Breast feeding. Ciprofloxacin was found to be undetectable in the serum of a breast-fed infant whose mother took ciprofloxacin 500 mg daily for 10 days.[1] In another study[2] involving 30 women who underwent termination of pregnancy, 10 each were given ciprofloxacin, ofloxacin, or pefloxacin respectively, and all 3 drugs were found to be highly concentrated in breast milk with ratios exceeding 75% of the simultaneous serum concentrations 2 hours after a dose. It was concluded that, because fluoroquinolones had been shown to cause arthropathy in young *animals*, their potential benefits should be weighed against the risk to the infant before they were considered for use in breast-feeding women. The American Academy of Pediatrics[3] considers that the use of ciprofloxacin is usually compatible with breast feeding.

1. Gardner DK, *et al.* Simultaneous concentrations of ciprofloxacin in breast milk and in serum in mother and breast-fed infant. *Clin Pharm* 1992; **11**: 352–4.
2. Giamarellou H, *et al.* Pharmacokinetics of three newer quinolones in pregnant and lactating women. *Am J Med* 1989; **87** (suppl 5A): 49S–51S.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. [Retired May 2010] Correction, *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)

Exposure to UV light. Loss of antibacterial activity has been reported after irradiation of ciprofloxacin solutions by UV light.[1] In addition to the possible hazard of photosensitivity reactions, a reduction in both cutaneous and circulating levels of ciprofloxacin was predicted in patients exposed to sunlight through window glass or the longer wavelength UVA radiation from sunbeds.[1]

1. Phillips G, *et al.* The loss of antibiotic activity of ciprofloxacin by photodegradation. *J Antimicrob Chemother* 1990; **26**: 783–9.

G6PD deficiency. Licensed product information for ciprofloxacin and other fluoroquinolones advises that these drugs be used with caution in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency as there may be a risk of haemolysis. This cautionary advice is based on similar warnings for nalidixic acid, a non-fluorinated quinolone. However, a review[1] found no reports of haemolysis in G6PD-deficient patients given fluoroquinolones.

1. Youngster I, *et al.* Medications and glucose-6-phosphate dehydrogenase deficiency: an evidence-based review. *Drug Safety* 2010; **33**: 713–26.

Myasthenia gravis. Caution is advised in patients with myasthenia gravis given fluoroquinolones after a few reports of the possible exacerbation of symptoms[1,2] or unmasking of subclinical myasthenia gravis[3] by ciprofloxacin. Exacerbation of myasthenia gravis is considered to be a class effect;[2] it has also been reported with other fluoroquinolones including norfloxacin, ofloxacin, pefloxacin, gatifloxacin, levofloxacin, and moxifloxacin.[2,4-6] Exacerbations usually occurred within 1 to 2 days of systemic fluoroquinolone use, but have not been reported with non-systemic formulations. Dyspnoea was the most commonly reported adverse event (50% of cases) followed by muscle weakness or fatigue (48%). More serious, although less frequent, were cases of respiratory failure requiring mechanical ventilation (30% of reports). Nearly all patients improved when the fluoroquinolone dose was reduced or stopped, although some required additional supportive treatment.

1. Moore B, *et al.* Possible exacerbation of myasthenia gravis by ciprofloxacin. *Lancet* 1988; **i**: 882.
2. Jones SC, *et al.* Fluoroquinolone-associated myasthenia gravis exacerbation: evaluation of postmarketing reports from the US FDA adverse event reporting system and a literature review. *Drug Safety* 2011; **34**: 839–47.
3. Mumford CJ, Ginsberg L. Ciprofloxacin and myasthenia gravis. *BMJ* 1990; **301**: 818.
4. Rauser EH, *et al.* Exacerbation of myasthenia gravis by norfloxacin. *DICP Ann Pharmacother* 1990; **24**: 207–8.
5. Azevedo E, *et al.* Probable exacerbation of myasthenia gravis by ofloxacin. *J Neurol* 1993; **240**: 508.
6. Vial T, *et al.* Aggravation d'une myasthénie sous péfloxacine. *Rev Neurol (Paris)* 1995; **151**: 286–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ciprofloxacin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Pregnancy. Although there are no controlled studies on the use of ciprofloxacin in pregnant women, data available shows no increased risk of congenital malformations or other adverse fetal events. However, the UK teratology information service (UKTIS) and the US Teratogen Information System (TERIS) consider the data to be too limited to state that there is no increased risk of adverse outcomes. UK licensed product information recommends that it is preferable to avoid the use of ciprofloxacin during pregnancy.

Interactions

Fluoroquinolones, including ciprofloxacin, are known to inhibit the cytochrome P450 isoenzyme CYP1A2 and may increase plasma concentrations of drugs, such as clozapine, ropinirole, theophylline, and tizanidine, that are metabolised by this isoenzyme. Use of ciprofloxacin with tizanidine is contra-indicated, although theophylline may be used providing its dose is reduced and concentrations monitored. Clozapine or ropinirole may also be used, providing appropriate clinical surveillance occurs with subsequent dose adjustment where necessary.

Ciprofloxacin is reported to enhance the effect of oral anticoagulants such as warfarin and the oral antidiabetic glibenclamide. Severe hypoglycaemia, sometimes fatal, has occurred in patients also taking glibenclamide. Renal tubular secretion of methotrexate may be inhibited by ciprofloxacin, potentially increasing its toxicity.

The excretion of ciprofloxacin or related drugs is reduced and plasma concentrations may be increased by probenecid. Cations such as aluminium, calcium, magnesium, or iron reduce the absorption of oral ciprofloxacin or related drugs when given together. Changes in the pharmacokinetics of fluoroquinolones have been reported when given with histamine H_2 antagonists, possibly due to changes in gastric pH, but do not seem to be of much clinical significance.

Transient increases in serum creatinine have occurred when ciprofloxacin is given with ciclosporin; monitoring of serum creatinine concentrations is recommended. Altered serum concentrations of phenytoin have been reported in patients also receiving ciprofloxacin.

Further details concerning some of these interactions, and others, are given below.

Some fluoroquinolones have the potential to prolong the QT interval (see Effects on the Cardiovascular System, p. 262.3) and should be avoided in patients also receiving class Ia antiarrhythmic drugs (such as quinidine and procainamide) or class III antiarrhythmics (such as amiodarone and sotalol). In addition, caution should be exercised when they are used with other drugs known to have this effect (such as the antihistamines astemizole and terfenadine, cisapride, erythromycin, pentamidine, phenothiazines, or tricyclic antidepressants).

For physical or chemical incompatibilities with ciprofloxacin, see p. 261.2.

Analgesics. Use of *fenbufen* with fluoroquinolones may increase the incidence of fluoroquinolone CNS adverse effects. Reviews[1,2] have noted cases of convulsions associated with the use of fenbufen and enoxacin reported to the Japanese regulatory authorities. The UK CSM[3] has recognised that convulsions may occur due to an interaction between the fluoroquinolones and *NSAIDs*; by 1991, 3 such interactions had been reported to them. Adverse neurological effects have also been reported in a patient receiving *naproxen* and chloroquine when ciprofloxacin was given, which abated when the antirheumatic drugs were stopped.[4]

Ciprofloxacin also interacts with *opioid analgesics*; peak serum concentrations of oral ciprofloxacin given preoperatively were significantly reduced when intramuscular *papaveretum* was injected.[5] In the UK, licensed product information for ciprofloxacin tablets recommends that opioid premedication should not be used if ciprofloxacin is given for surgical infection prophylaxis.

1. Janknegt R. Drug interactions with quinolones. *J Antimicrob Chemother* 1990; **26** (suppl D): 7–29.
2. Christ W. Central nervous system toxicity of quinolones: human and animal findings. *J Antimicrob Chemother* 1990; **26** (suppl B): 219–25.
3. CSM. Convulsions due to quinolone antimicrobial agents. *Current Problems 32* 1991. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024450&RevisionSelectionMethod=LatestReleased (accessed 02/03/07)

4. Rollof J, Vinge E. Neurologic adverse effects during concomitant treatment with ciprofloxacin, NSAIDs, and chloroquine: possible drug interaction. *Ann Pharmacother* 1993; 27: 1058–9.
5. Morran C, *et al.* Brief report: pharmacokinetics of orally administered ciprofloxacin in abdominal surgery. *Am J Med* 1989; 87 (suppl 5A): 86S–88S.

Antacids and metal ions. The absorption of ciprofloxacin and other fluoroquinolones is reduced by *antacids* containing *aluminium* or *magnesium* and also by *calcium*, *iron*, and *zinc* salts.[1] *Sucralfate* releases aluminium ions in the stomach and thereby reduces the absorption of ciprofloxacin[2,3] and other fluoroquinolones, including norfloxacin,[4] ofloxacin, and sparfloxacin.[5] In addition, antacids or oral iron preparations might antagonise the antibacterial activity of fluoroquinolones within the gut lumen.[6] *Dairy products* with a high calcium content may also interfere with the absorption of some fluoroquinolones.[7–9] *Enteral feeds*, which contain cations, have also been found to reduce absorption of ciprofloxacin.[10] Exposure to ciprofloxacin was also reduced by *lanthanum carbonate*, and was thought to be due to the lanthanum ion forming a non-absorbable complex with ciprofloxacin.[11] A reduction in ciprofloxacin bioavailability has also been reported after *chewable tablets* of didanosine which contain aluminium and magnesium ion buffering agents.[12]

It is recommended that oral ciprofloxacin should be given at least 2 hours before or 6 hours after such products; similar advice also applies to other fluoroquinolones.

1. Lomaestro BM, Bailie GR. Absorption interactions with fluoroquinolones: 1995 update. *Drug Safety* 1995; 12: 314–33.
2. Garrelts JC, *et al.* Sucralfate significantly reduces ciprofloxacin concentrations in serum. *Antimicrob Agents Chemother* 1990; 34: 931–3.
3. Van Slooten AD, *et al.* Combined use of ciprofloxacin and sucralfate. *DICP Ann Pharmacother* 1991; 25: 578–82.
4. Parpia SH, *et al.* Sucralfate reduces the gastrointestinal absorption of norfloxacin. *Antimicrob Agents Chemother* 1989; 33: 99–102.
5. Kamberi M, *et al.* The effect of staggered dosing of sucralfate on oral bioavailability of sparfloxacin. *Br J Clin Pharmacol* 2000; 49: 98–103.
6. Lewin CS, Smith JT. 4-Quinolones and multivalent ions. *J Antimicrob Chemother* 1990; 26: 149.
7. Neuvonen PJ, *et al.* Interference of dairy products with the absorption of ciprofloxacin. *Clin Pharmacol Ther* 1991; 50: 498–502.
8. Kivistö KT, *et al.* Inhibition of norfloxacin absorption by dairy products. *Antimicrob Agents Chemother* 1992; 36: 489–91.
9. Neuvonen PJ, Kivistö KT. Milk and yoghurt do not impair the absorption of ofloxacin. *Br J Clin Pharmacol* 1992; 33: 346–8.
10. Healy DP, *et al.* Ciprofloxacin absorption is impaired in patients given enteral feedings orally and via gastrostomy and jejunostomy tubes. *Antimicrob Agents Chemother* 1996; 40: 6–10.
11. How PP, *et al.* Effects of lanthanum carbonate on the absorption and oral bioavailability of ciprofloxacin. *Clin J Am Soc Nephrol* 2007; 2: 1235–40.
12. Sahai J, *et al.* Cations in the didanosine tablet reduce ciprofloxacin bioavailability. *Clin Pharmacol Ther* 1993; 53: 292–7.

Antibacterials. The simultaneous use of parenteral ciprofloxacin and *azlocillin* has resulted in higher and more prolonged serum concentrations of ciprofloxacin.[1] Steady-state plasma concentrations of moxifloxacin are significantly reduced when given with *rifampicin* and *isoniazid* for the treatment of tuberculosis.[2]

1. Barriere SL, *et al.* Alteration in the pharmacokinetic disposition of ciprofloxacin by simultaneous administration of azlocillin. *Antimicrob Agents Chemother* 1990; 34: 823–6.
2. Nijland HMJ, *et al.* Rifampicin reduces plasma concentrations of moxifloxacin in patients with tuberculosis. *Clin Infect Dis* 2007; 45: 1001–7.

Anticoagulants. For reports of ciprofloxacin and other fluoroquinolones enhancing the effect of oral anticoagulants, see under *Warfarin*, p. 1531.1.

Antidiabetics. For reference to elevated *glibenclamide* concentrations in patients who were also given ciprofloxacin, see p. 505.3.

Antiepileptics. For conflicting reports of the effect of ciprofloxacin on serum-*phenytoin* concentrations, see p. 542.3.

Antifungals. Both *fluconazole* and levofloxacin can prolong the QT interval. The simultaneous use of intravenous levofloxacin and fluconazole resulted in an episode of torsade de pointes in a patient on haemodialysis.[1]

1. Gandhi PJ, *et al.* Fluconazole- and levofloxacin-induced torsades de pointes in an intensive care unit patient. *Am J Health-Syst Pharm* 2003; 60: 2479–83.

Antimigraine drugs. For a recommendation to reduce the dosage of *zolmitriptan* when given with ciprofloxacin, see p. 682.3.

Antineoplastics. Absorption of oral ciprofloxacin appears to be reduced after cytotoxic chemotherapy.[1]

For reference to the effect of ciprofloxacin on the pharmacokinetics of *cyclophosphamide*, see p. 773.2.

1. Johnson EJ, *et al.* Reduced absorption of oral ciprofloxacin after chemotherapy for haematological malignancy. *J Antimicrob Chemother* 1990; 25: 837–42.

Antivirals. Both ciprofloxacin and *foscarnet* can cause convulsions and 2 patients developed generalised tonic-clonic seizures while receiving the drugs together.[1]

For reference to reduction of ciprofloxacin bioavailability due to the antacid content of chewable *didanosine* tablets, see under Antacids and Metal Ions, above.

1. Fan-Havard P, *et al.* Concurrent use of foscarnet and ciprofloxacin may increase the propensity for seizures. *Ann Pharmacother* 1994; 28: 869–72.

Anxiolytics. For reference to the effect of ciprofloxacin on the pharmacokinetics of *diazepam*, *midazolam*, and *temazepam*, see under Diazepam, p. 1068.2.

Immunosuppressants. For reference to possible interaction between fluoroquinolones and *ciclosporin*, see Quinolones, p. 1956.1. For a pharmacokinetic study reporting reduced exposure to *mycophenolate mofetil* when given with norfloxacin or norfloxacin plus metronidazole, see p. 1968.2.

Muscle relaxants. For a report of ciprofloxacin increasing the plasma concentrations of *tizanidine*, see p. 2027.1.

Sevelamer. The bioavailability of ciprofloxacin was decreased by about 50% when it was given with sevelamer.[1] Licensed product information for sevelamer suggests that it should be given at least 3 hours before or 1 hour after drugs for which a reduction in bioavailability could be clinically significant.

1. Kays MB, *et al.* Effects of sevelamer hydrochloride and calcium acetate on the oral bioavailability of ciprofloxacin. *Am J Kidney Dis* 2003; 42: 1253–9.

Xanthines. Ciprofloxacin and other fluoroquinolones (to a greater or lesser extent) decrease the clearance of *theophylline* (p. 1234.2) and *caffeine* (p. 1206.1) from the body. Seizures have occurred in patients given ciprofloxacin and theophylline and in one such report[1] serum-theophylline concentrations were normal.

1. Bader MB. Role of ciprofloxacin in fatal seizures. *Chest* 1992; 101: 883–4.

Antimicrobial Action

Ciprofloxacin is bactericidal and acts by inhibiting DNA gyrase and topoisomerase IV, which are essential enzymes in the reproduction of bacterial DNA. It has a broader spectrum of activity and is more potent *in vitro* than the non-fluorinated quinolone nalidixic acid although resistance to many species or strains previously sensitive is emerging. Activity may be reduced in acid media and in the presence of urine but not of serum.

Spectrum of activity.

- Among Gram-negative aerobic bacteria, ciprofloxacin may be active *in vitro* against Enterobacteriaceae, including *Escherichia coli* and *Citrobacter*, *Enterobacter*, *Klebsiella*, *Proteus*, *Providencia*, *Salmonella*, *Serratia*, *Shigella*, and *Yersinia* spp.
  It may also have activity against *Pseudomonas aeruginosa* and *Neisseria gonorrhoeae*. *H. influenzae*, *Moraxella catarrhalis* (*Branhamella catarrhalis*), and *N. meningitidis* are all sensitive.
  Other Gram-negative aerobic bacteria reported to be sensitive to ciprofloxacin have included *Gardnerella vaginalis*, *Helicobacter pylori*, *Legionella* spp., *Pasteurella multocida*, and *Vibrio* spp.
  Variable activity has been reported against *Acinetobacter* spp., *Brucella melitensis*, and *Campylobacter* spp.
- Among Gram-positive aerobic bacteria, ciprofloxacin is active against staphylococci, including penicillinase-producing and penicillinase-nonproducing strains, and against some MRSA. Streptococci, in particular *Streptococcus pneumoniae* and enterococci, are less susceptible.
  Other Gram-positive bacteria sensitive to ciprofloxacin *in vitro* are *Bacillus* spp.; variable activity has been noted for *Corynebacterium* spp.
- Most anaerobic bacteria, including *Bacteroides fragilis* and *Clostridium difficile*, are resistant to ciprofloxacin, although some other *Clostridium* spp. may be susceptible.
- Ciprofloxacin has some activity against mycobacteria, mycoplasmas, rickettsias, *Chlamydia trachomatis*, and *Ureaplasma urealyticum*.

Acquired resistance. Resistant strains, particularly of MRSA, *Ps. aeruginosa*, *E. coli*, *Klebsiella pneumoniae*, *C. jejuni*, *N. gonorrhoeae*, and *Str. pneumoniae* have emerged during treatment with ciprofloxacin although there are widely differing patterns of resistance geographically. Resistance to ciprofloxacin has usually been chromosomally mediated although plasma-mediated resistance has recently been noted.

Pharmacokinetics

Ciprofloxacin is rapidly and well absorbed from the gastrointestinal tract. Oral bioavailability is about 70 to 80% and a peak serum concentration of about 2.4 micrograms/mL occurs 1 to 2 hours after a 500-mg oral dose. Absorption of ciprofloxacin tablets may be delayed by the presence of food, but is not substantially affected overall.

Plasma protein binding ranges from 20 to 40%. Ciprofloxacin is widely distributed in the body and tissue penetration is generally good. It appears in the CSF, but concentrations are only about 10% of those in serum when the meninges are not inflamed. Ciprofloxacin crosses the placenta and is also distributed into breast milk. High concentrations occur in bile.

The elimination half-life is about 3 to 5 hours and there is evidence of modest accumulation. Half-life may be prolonged in renal impairment (a value of 8 hours has been reported in end-stage renal disease) and to some extent in the elderly. However, no dose adjustment is usually necessary in patients with renal impairment unless it is severe; similarly, usual doses can be given to the elderly except in those with severe renal impairment. There is limited information on the effect of hepatic impairment; the half-life of ciprofloxacin has been reported to be slightly prolonged in patients with severe cirrhosis of the liver. With one or two exceptions, most studies have shown that the pharmacokinetics of ciprofloxacin are not markedly affected by cystic fibrosis.

Ciprofloxacin is eliminated principally by urinary excretion, but non-renal clearance may account for about one-third of elimination and includes hepatic metabolism, biliary excretion, and possibly transluminal secretion across the intestinal mucosa. At least 4 active metabolites have been identified. Oxociprofloxacin appears to be the major urinary metabolite and sulfociprofloxacin the primary faecal metabolite. Urinary excretion is by active tubular secretion as well as glomerular filtration and is reduced by probenecid; it is virtually complete within 24 hours. About 40 to 50% of an oral dose is excreted unchanged in the urine and about 15% as metabolites. Up to 70% of a parenteral dose may be excreted unchanged within 24 hours and 10% as metabolites. Faecal excretion over 5 days has accounted for 20 to 35% of an oral dose and 15% of an intravenous dose.

Only small amounts of ciprofloxacin are removed by haemodialysis or peritoneal dialysis.

General pharmacokinetics. Reviews of the pharmacokinetics of ciprofloxacin[1] and the fluoroquinolones in general.[2,3]

1. Vance-Bryan K, *et al.* Clinical pharmacokinetics of ciprofloxacin. *Clin Pharmacokinet* 1990; 19: 434–61.
2. Aminimanizani A, *et al.* Comparative pharmacokinetics and pharmacodynamics of the newer fluoroquinolone antibacterials. *Clin Pharmacokinet* 2001; 40: 169–187.
3. Wispelwey B. Clinical implications of pharmacokinetics and pharmacodynamics of fluoroquinolones. *Clin Infect Dis* 2005; 41 (suppl 2): S127–S135.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Argeflox; Atibax C; Biotic; Ciapar; Ciloxan; Cipro Otico; Cipro; Ciprolabsa; Cipromed; Ciprotenk; Cirflox-G; Ciriax; Crisacide; Exertial; Floraxina; Gino Ciriax†; Golysine; Lorbifloxacina; Medaflox; Microsulf; Neflox†; Nexofloxacin; Novidat; Ocefax; Omaflaxina; Quisegen; Rexner; Safoxen; Septicide; Ultramicina; ***Austral.***: C-Flox; Cifran; Ciloquin; Ciloxan; Ciprol; Ciproxin; Profloxin; Proquin†; ***Austria***: Ciflox; Ciloxan; Cipromed; Ciprostad; Ciproxin; Otanol; Utiminx; Vegarex†; ***Belg.***: Ciloxan; Ciprobel; Ciproflomed†; Ciproxine; Docciproflo†; ***Braz.***: Biamotil; Ciclatry; Cifloxt; Cifloxatil; Cifloxtron; Ciloxan; Cinoflax; Ciprix; Cipro; Ciprocilin; Ciprodine; Ciprofar; Ciprofloxil; Cipronid; Ciprono; Ciproxen; Ductocina; Floxan†; Floxocip; Maxiflox; Nixin†; Ofoxin; Otofoxin; Proflox; Proxacin; Quiflox; Quinoflox; ***Canad.***: Apo-Ciproflox; Ciloxan; Cipro; ***Chile***: Baycip; Cifloxin; Ciloxacin; Ciproval; Ciproxino; Grifociprox; Oflono; Oftaciprox†; Sophixin; Tigina; ***China***: Bei Si Te (贝斯特); Cifran (悉复欣); Ciprobay (西普乐); Da Wei Bang (达维邦); Guang Yi Sha (广易沙); Huayu (华昱); Jia Ke (佳可); Kuinuoxian (奎诺仙); Kun Ning (坤宁); Lin Qing (林青); Qiu Lu (秋露); Rui Kang (瑞康); Rui Xin Chao (瑞欣超); Sai Ke Xing (赛克星); Shi Pu Huan (世普欢); Xin Jie Ming (新洁明); Xipofuxing (希珀福星); Xipuxing (希普欣); ***Cz.***: Cifloxinal; Cifran†; Ciloxan; Ciphin; Ciplox; Ciprinol; Ciprobay; Ciprum†; ***Denm.***: Cifin; Ciloxan; Ciprinomyl; Ciproflomyl†; Ciproscope; Ciproten; Ciproxin†; ***Fin.***: Cetraxal; Cipromed†; Ciproxin; Siprion; ***Fr.***: Ciflox; Ciloxan; Uniflox; ***Ger.***: Ciloxan; Cipro-Q†; Cipro-saar; Ciprot; Ciprobay; Ciprobeta; Ciprodoc†; Ciprofat†; Ciprofloxpuren†; Ciproflox†; Ciprohexal†; Gyracip†; InfectoCipro†; Keciflox; Panotile cipro; ***Gr.***: Afenoxin; Alciprocin; Aristin-C; Balepton; Biocipro; Bivorilan; Cidrops; Cifloxacin; Ciloxan; Ciprocton; Ciprofal; Cipromycin; Ciprospes; Ciprovian; *Ciproxin*; *Citrovenot*; Droll; Edestis; Flociprin; Forterra; Ginorectol; Glossyfin; Grenis-Cipro; Infectina; Labentrol; Ladinin; Limox; Nafloxin; Ravalton; Remena; Revion; Revionorm; Superspor; Topistin; Ufexil; Uritent; Urodixin; Utiminx; ***Hong Kong***: Aprocin; Cifloxin; Cifran†; Ciloxan; Cipide†; Ciplox†; Cipmax; Ciprofrankin†; Ciprol; Ciproxin; Ciproxyl; Cirok†; Cyfloxin†; Duflomex†; Enoxin; Gonning; Hippro†; Medociprin; Proxacin; Quidex†; Quinocin†; Uroxin; Utahzone†; Viprolox†; ***Hung.***: Cifloxin; Cifran; Ciloxan; Ciphin†; Ciplox; Ciprinol; Ciprobay; Ciprolen; Cipropharm†; Ciprum; Cydonin; ***India***: Abact; Adcip; Adiflox; Alcip; Alcipro; Alquin; Aniflox; Aricip; Atocip; Avcip; Avilox; Bactoquin; Baycip; Bekaycin; Bicipro;

Bio Cipron; Biocip; C-Flox; C-Lox; C-OD; C-Plus; C-Pro; Cadiwin; Caniron; Caspro; Cbic; Cebect; Cebran; Ceepro; Ceeptalib; Ceflox; Cefobac; Celox; Ceplox; Ceprolen; Cibiotic; Cif; Ciflon; Cifomed; Clfran; Cigram; Cina; Cinant; Cinodin; Cip; Cipact; Cipad; Cipcin; Cipcot; Cipgen; Cipglow; Cipic; Cipkind; Ciporic; Ciprex; Cipride; Ciprind; Cipro-Cent; Ciproace; Ciprobid; Ciprobiotic; Ciprocap; Ciprocure; Ciprodac; Ciprodel; Ciprodex; Ciprofen; Ciprolar; Ciproleb; Ciprolen; Ciprolet; Cipromark; Cipromax; Cipromed; Cipromycetine; Cipronat; Cipronex-E; Cipronova; Cipropan; Ciropet; Ciproquin; Ciprosia; Ciprosym; Ciprotek; Ciprotum; Ciprova; Ciprovar; Ciprovec; Ciprovit; Ciprowin; Ciprox; Ciprozen; Ciprozet; Ciprozol; Cips; Ciptam; Ciptar; Ciptec; Cipure; Cipven; Cipwin; Cipzone; Cipzy; Ciral; Ciwi; Coflox; Corgard; Cosflox; Coutim; Cymex; Cyprin; Depci; Disquin; E-Cip; Eldequin; Elquin; Flocin; Flocy; Floxaquin-C; Floxip; Fulgram; Glocip; Hicip; Icip; K-Cip; Kaicip; Kera; Kocip; Kurecip; Lacipron; Lakcip; Lexflox; Locip; Lucipro; Lypro; Maflo; Mapci; Mencip; Mericip; Microcip; Microflox; Mintocip; Miz; Nayacip; Neocip; Nexcip; NTBec; Nucip; Ormiback; Omniflox; Orpic; Panzer; Quinobact; Strox; Zoxan; ***Indon.***: Bactiprox; Baquinor; Bernoflox; Bidiprox†; Cetafloxo; Ciflos; Cilox; Ciprec; Ciproxin; Civell; Coroflox; Corsacin; Cylowam†; Disfabac†; Duflomex†; Etacin; Floksid; Floxbio; Floxigra; Girabloc†; Interflox; Isotic Renator; Jayacin; Kifarox; Lapiflox; Licoprox; Meflosin; Mensipox; Nilaflox; Phaproxin; Poncoflox; Proxcip; Proxitor; Qinox; Quamiprox; Quidex; Quinobiotic; Renator; Rindoflox; Scanax; Siflox; Tequinol; Vidintal†; Viflox; Vioquin; Volinol; Wiaflox; Ximex Cylowam; Zeniflox; Zumaflox; ***Irl.***: Biofloxcin; Cifloxager; Clfox; Ciloxan; Ciproxin; Profloxin; Truoxin; ***Israel***: Cifran; Ciloxan; Ciplox; Ciprot†; Ciprodex; Ciprogis; Ciproxin; Giroflox; Ufexil; ***Ital.***: Battizer; Chinocid; Ciperus; Ciprosol; Ciproxin; Cuspis; Eoxin; Flontalexin; Generflon; Ibixacin; Kinox; Macar; Oftaclox; Prociflor; Samper; Unicexal; ***Jpn***: Ciproxan; ***Malaysia***: Bactiflox; Cifloxin; Cifran; Ciloxan; Ciprobay; Ciproflo; Ciprox; Ciproxol; Enoxin; Serviflox; ***Mex.***: Antimed; Apoflox; Arfloxina; Bacproin; Bioflox; Ci-Sons; Cifran; Ciloxan; Cimogal; Ciprain; Cipro; Ciprobac; Ciprobiotic; Ciprofloxc; Ciprofurt; Ciprohexal†; Ciproser; Ciprotec; Ciproxina; Ciqfadin; Ciriax; Dinaflox; Eni; Eufloxin; Flovin; Floxager; Floxantina; Floxelena†; Floxitul; Gibac; Infloxa†; Italnik; Kenzoflex; Lemiflox; Lemyflox†; Liferxina; Microrgan; Mitroken; Novoquin; Opthaflox; Patox; Pharcina; Profluxol; Provay; Quinoflox; Rancif; Rictor†; Sinfexina†; Sophixin; Suiflox; Trigen; Vifloxina; Wasiprobil; Z-Xin; Zipra; ***Neth.***: Cetraxal; Ciloxan†; Ciprinol; Ciproxin; Otiflox; ***Norw.***: Cilox; Ciproxin; ***NZ***: Cifran; Ciloxan; Cipflox; Ciproxin; DP-Cipro; Topistin; Ufexil: ***Philipp.***: Alcipro; Bacipro; Baxolyn; Brelcip†; Ciclodin; Cidrolex; Cidroxal†; Ciflodal; Cifloxin; Ciloxan; Ciplox; Cipro-V; Ciprobach; Ciprobay; Ciprobet; Ciprobiotic; Ciprofen; Ciproflox; Ciproglen; Ciprolet; Cipromac; Cipromax; Cipromet; Ciprotal; Ciprotor; Ciproxel; Ciprozef; Cirok; Floroc†; Flosicron; Floxacet; Floxil; Floxzu†; Genoflox; Holdestin; Hyprocel; Ifloxin; Inoxzel; Iprobac; Iprolan; Ipromax; Kinogen; Kinoves; Laitun; Nexproxyn; Oflobay; Optaflox; Probact; Profilox; Proseloc; Proviflox; Proxazin; Proxco; Proxidin; Proxivex; Prozin; Qinosyn; Quidex; Quilox; Quinocip; Quinoryl; Quiprime; Rancif; Rapiqure; Rexfobys; Savedar; Sigmacip; Sutid; Uniflox; Uticin; Vistaflox; Xenoflox; Xipro; Xypen; Xyprody; Zalvos; Ziprocap; Zomrac Zyflox; ***Pol.***: Cifran†; Ciloxan; Ciphin; Ciprinol; Ciprobay; Ciproneх; Cipropol; Ciproquin; Ciprum†; Proxacin; ***Port.***: Ciflan†; Ciplox; Ciproxina; Colintil; Estecina; Giroflox; ISINO; Megaflox; Nivoflox; Nixin; Oftaclox; Quinox; ***Rus.***: Cifloxinal (Ципфлоксинал); Cifran (Ципфран); Ciloxan (Ципоксан); Ciplox (Циплокс); Cipraz (Ципраз); Ciprex (Ципрекс); Ciprinol (Ципринол); Ciprobay (Ципробай); Ciprobid (Ципробид); Ciprobrin (Ципробрин); Ciprocin (Ципросин); Ciprodox (Ципродокс); Ciprolacare (Ципролакэр); Ciprolet (Ципролет); Ciprolone (Ципролон); Cipromed (Ципромед); Cipronat (Ципронат); Ciprosun (Ципросан)†; Ciprova (Ципрова); Ifidpro (Ифидпро); Medociprin (Медоциприн); Procipro (Проципро); Quintor (Квинтор); Sifloks (Сифлокс); ***S.Afr.***: Adco-Ciprin; Biocip; Cifloc; Cifran; Ciloflоc; Ciloxan; Ciploxx; Cipro-Hexal; Ciprobay; Ciprocina; Ciprogen; Ciprol; Dynafloc Loxip; Orpic; Spec-Topistin; ***Singapore***: Ciloxan; Ciprobay; Ciprohexal; Ciprolet; Cycin; Enoxin; Ginorectol; Microflox; Neofloxin; Novaflox; Qupron; Serviflox; Topistin; Uroxin; ***Spain***: Aceoto; Araxacina; Baycip; Belmacina†; Cetraflux; Cetraxal; Ciflot; Ciprenit Otico†; Ciproactin; Ciproctal†; Ciproxina Simple; Cunesin; Doriman; Estecina; Felixene; Giroflox†; Globuce; Numen; Oftaclox; Otociprin; Otosat; Piprol†; Rigoran; Sepcen; Septocipro; Tam†; Ultramicina; ***Swed.***: Ciloxan; Ciproxin; ***Switz.***: Ciloxan; Cip eco; Ciprofiox; Ciproxine; ***Thai.***: C-Floxacin†; Ciflex; Ciflo; Ciflolan; Cifloxin; Cifloxno: Cifolox; Cifran; Cilab†; Ciloxan; Cinfloxine; Cipflocin; Cipon; Cipro; Ciprobay; Ciprobid; Ciprocep; Ciprofex; Ciprofin; Ciprogen; Ciprohof; Ciprolet†; Ciprom-M; Ciproquin; Ciprovid†; Ciproxan; Ciproxin; Ciproxyl; Cobay; Cyflox; Enoxin; Forexin; Hippro; Ifidpro; Microflox†; Opral-Pro; Pharproxin; Poli-Cifloxin; Proflox; Supraflox; Tulipt†; Ultraflox†; Uroxin; Vesprocin; Xyrocin; ***Turk.***: Ciflosin; Cifluron; Ciloxan; Ciprasid; Cipro; Ciproktan; Cipronatin; Ciproxin; Loxasid; Proxacin; Roflazin; Roxtin; Sanfloks; Sanset; Sifloks; Siprobel; Siprogut; Siprosan; Sispres†; UroCiproxin†; ***UAE***: Sarf; ***UK***: Ciloxan; Ciproxin; ***Ukr.***: Bactiflox (Бактифлокс)†; Cifran (Ципфран); Ciprinol (Ципринол); Cipro (Ципро); Ciprobay (Ципробай); Ciprobel (Ципробел); Ciprofarm (Ципрофарм); Ciprohexal (Ципрогексал)†; Cipromed (Ципромед); Ciproxol (Ципроксол); Floximed (Флоксимед); Ifidpro (Ифидпро); Sifloks (Сифлокс); ***USA***: Cetraxal; Ciloxan; Cipro; ***Venez.***: Bacipro; Baflox; Ciflox; Ciloxan; Ciprivax; Ciproflox; Cipronax; Ciproquin; Ciproxina; Cirok; Cypral; Iproxin; Lisipin; Oxtin; Quinoftal; Quinotic; Serviflox; Sophixin; Zolina.

Multi-ingredient Preparations. ***Arg.***: Aibrex; Ciloxadex; Cipro HC; Ciprofiox-Otic†; Ciprofloxacina D; Cirflox Oftal; Cirflox Otic; Ciriax Otic L; Ciriax Otic; Decadron con Ciprofloxina; Delos Otic; Fotamicin; Labsa Otic L; Labsa Otic; Medaflox Dol; Omaflaxina D; Otex HC; Oto Biotaer†; Otobiotic; Otocipro; Otolef HC; Otosporin C; Otosporin Dexa; Procalm; Prootocipro; Quidex; Tacines; ***Austral.***: Ciproxin HC; ***Braz.***: Biamotil-D; Biancort; Cilodex; Ciprixin Dexa; Cipro HC; Cylocort; Maxiflox D; Otociriax; ***Canad.***: Ciprodex; ***Chile***: Cilodex; Ciprodex; Oflono-D; Otex HC; ***Cz.***: Ciprobay HC Otic†; ***Denm.***: Ciflox; Cilodex; ***Fin.***: Cetraxal Comp; Ciproxin-Hydrocortison; ***Gr.***: Ciprobay; Otospon; ***Hong Kong***: Cipro HC; ***India***: AC; Adcip-TZ; Alcip-TZ; Alcipro-TN; Aricip-TZ; Atocip-TZ; Avilox-M; Avilox-TZ; Baycip-TZ; Biocip-TZ; Caniron-TZ; Caspro-TZ; Cbic-TZ; Cebect-TZ; Cebran-TN; Ceepro-TZ; Ceflox-CF; Ceflox-D; Ceflox-TZ; Cefobac-TD; Cefobac-TDH; Ceplox-TZ; Ceprolen-D; Cidalox-TZ; Ciflon-TZ; Cifomed-D; Cifomed-TZ; Cifran-CT-H; Cifran-CT; Cifran-OZ; Cina-TZ; Cinant-TZ; Cinodin-TZ; Cip-TZ; Cipcin-TNZ; Cipcot-TZ; Cipflox-TZ; Cipgen TZ; Cipglow-TZ; Ciplox D; Ciplox TZ; Ciplox; Cipnet-OZ; Cipro-TZ; Ciprobid-TZ; Ciprobiotic-FC; Ciprobiotic-TN; Ciprodac-TZ; Ciprodex-TZ; Ciprogyl; Ciprolar-F; Ciprolar-FC; Ciprolar-T; Ciprolet-A; Ciprolet-AH; Cipromark-DX; Cipronat-TZ; Cipronij-TZ; Ciropet-TZ; Ciprosia-D; Ciprosym-TZ; Ciprotini; Ciprotiz; Ciprotum-TZ; Ciprova-T; Ciprovec-TZ; Ciprowin-TZ; Ciprozee-TZ; Ciprozen-D; Ciptam-CT; Ciptech-CT; Cipti; Ciptini; Cipure-TZ; Cipven-TZ; Cipwin-TZ; Cipzone-TN; Cipzy-TZ; Ciral-TZ; Citi; Citibid; Citizol; Ciwi-TZ; CPF-TZ; CT-Robes; Cymex-TZ; Cyprin-D; Cyprin-TD; Depci-TZ; Diarlop-CT; Donnagyl-H; E-Cip-TZ; Elquin-TZ; Flocin-TZ; Flocipron-T; Flocy TZ; Flucocip; Formax; Gastrogyl Plus; Gastrogyl; Glocip-TZ; Hicip-TZ; K-Cip-TZ; Kurecip-TZ; Labocip-TZ; Lexflox-TZ; Locip-TZ; Lomet-CT; Loxtin; Lucipro-T; Mapci-TZ; Microcip-TZ; Microflox-CT; Microflox-DX; Miflox-DM; Mini-Citizol; Mintocip-TZ; Neocip FC; Neocip M; Nexcip-TZ; Normide-CZ; Nucip-TZ; Nugen Eye/Ear; Ocimix; Odicip-OZ; Omibact-TZ; Omniflox-CT; Orpic-T; Panzer-TZ; Tinvista-CF; ***Israel***: Cilodex†; Ciproxin HC†; ***Ital.***: Mediflox: ***Mex.***: Cilodex; Ciproxina HC; Ciriax D; Combiquine-C; Dinill-D; Oto Eni; Quinoflox Otico; Sodrimax; Softramc; Sophixin DX; Vodelan; ***NZ***: Cilodex; Ciproxin HC; ***Rus.***: Ciprolet A (Ципролет А); Kombinil-Duo (Комбинил-Дуо); ***S.Afr.***: Cilodex; Ciprobay HC; ***Singapore***: Cilodex; Ciprobay HC; ***Spain***: Aceoto Plus; Cetraxal Plus; Ciproxina; Synalotic; Ultramicina Plus; ***Switz.***: Ciproxin HC; ***Ukr.***: Cetraxal Plus (Цетраксал Плюс); Cifran CT (Ципфран CT); Orcipol (Орципол); ***USA***: Cipro HC; Ciprodex; ***Venez.***: Otalex; Quinocort; Quinotic HC.

Pharmacopoeial Preparations

BP 2014: Ciprofloxacin Infusion; Ciprofloxacin Tablets;

USP 36: Ciprofloxacin and Dexamethasone Otic Suspension; Ciprofloxacin Extended-Release Tablets; Ciprofloxacin Injection; Ciprofloxacin Ophthalmic Ointment; Ciprofloxacin Ophthalmic Solution; Ciprofloxacin Tablets.

Clarithromycin *(BAN, USAN, rINN)*

A-56268; Abbott-56268; Clarithromycine; Clarithromycinum; Claritromicina; Klarithromycin; Klaritromicinas; Klaritromlsin; Klaritromycin; Klaritromysiini; TE-031; Кларитромицин.

(2*R*,3*S*,4*S*,5*R*,6*R*,8*R*,10*R*,11*R*,12*S*,13*R*)-3-[2,6-Dideoxy-3-*C*,3*O*-dimethyl-α-L-*ribo*-hexopyranosyloxy)-11,12-dihydroxy-6-methoxy-2,4,6,8,10,12-hexamethyl-9-oxo-5-(3,4,6-trideoxy-3-dimethylamino-β-D-*xylo*-hexopyranosyloxy)pentadecan-13-olide; 6-*O*-Methylerythromycin.

$C_{38}H_{69}NO_{13}$=748.0

CAS — 81103-11-9.

ATC — J01FA09.

ATC Vet — QJ01FA09.

UNII — H1250JIK0A.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Clarithromycin). A white or almost white, crystalline powder. Practically insoluble in water; soluble in acetone and in dichloromethane; slightly soluble in methyl alcohol.

USP 36: (Clarithromycin). A white to off-white crystalline powder. Practically insoluble in water; slightly soluble in dehydrated alcohol, in methyl alcohol, and in acetonitrile; soluble in acetone; slightly soluble in phosphate buffer at pH values of 2 to 5. pH of a 0.2% suspension in a mixture of water and methyl alcohol (19:1) is between 8.0 and 10.0. Store in airtight containers.

Uses and Administration

Clarithromycin is a macrolide derived from erythromycin with similar actions and uses (p. 294.1). It is given in the treatment of respiratory-tract infections (including otitis media) and in skin and soft-tissue infections. Clarithromycin is also used for the prophylaxis and treatment of nontuberculous mycobacterial infections and has been used as a second-line drug in the treatment of leprosy. It is used in some countries as an alternative to penicillins for prophylaxis of endocarditis.

For details of all these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Clarithromycin may be given to eradicate *Helicobacter pylori* in treatment regimens for peptic ulcer disease (p. 1816.2). It is used with pyrimethamine as an alternative regimen in the treatment of toxoplasmosis (p. 926.1).

Clarithromycin is given orally or by intravenous infusion. Some clarithromycin preparations are prepared with the aid of lactobionic acid and may be stated to contain clarithromycin lactobionate; others may contain clarithromycin citrate. Doses are expressed in terms of the equivalent amount of clarithromycin.

Usual oral doses in adults are 250 mg twice daily, increased to 500 mg twice daily if necessary in severe infection. Modified-release tablets allowing once-daily use are available in some countries.

The usual intravenous dose is 500 mg twice daily, given as an infusion over 60 minutes using a solution containing about 0.2% of clarithromycin. Intravenous treatment may continue for 2 to 5 days, but should be changed to oral clarithromycin when possible.

For treatment and prophylaxis of disseminated infection due to *Mycobacterium avium* complex, clarithromycin may be given in an oral dose of 500 mg twice daily; for treatment, it should be given with other antimycobacterials. For leprosy, oral clarithromycin 500 mg daily has been given as part of an alternative multidrug therapy regimen.

For the eradication of *H. pylori* associated with peptic ulcer disease, clarithromycin, usually in an oral dose of 500 mg twice daily, is given with another antibacterial and either a proton pump inhibitor or a histamine H_2-receptor antagonist, for 7 to 14 days.

Doses may need to be reduced in patients with severe renal impairment (see p. 268.3).

For details of doses in children, see p. 268.3.

Reviews.

1. Peters DH, Clissold SP. Clarithromycin: a review of its antimicrobial acuvity, pharmacokinetic properties and therapeutic potential. *Drugs* 1992; 44: 117–64.
2. Barradell LB, *et al.* Clarithromycin: a review of its pharmacological properties and therapeutic use in Mycobacterium avium-intracellulare complex infection in patients with acquired immune deficiency syndrome. *Drugs* 1993; 46: 289–312.
3. Markham A, McTavish D. Clarithromycin and omeprazole: as Helicobacter pylori eradication therapy in patients with H. pylori-associated gastric disorders. *Drugs* 1996; 51: 161–78.
4. Alvarez-Elcoro S, Enzler MJ. The macrolides: erythromycin, clarithromycin, and azithromycin. *Mayo Clin Proc* 1999; 74: 613–34.
5. Zuckerman JM. Macrolides and ketolides: azithromycin, clarithromycin, telithromycin. *Infect Dis Clin North Am* 2004; 18: 621–49.
6. Anonymous. Clarithromycin. *Tuberculosis (Edinb)* 2008; 88: 92–5.

Administration in children. The usual oral dose of clarithromycin for infants and children is 7.5 mg/kg twice daily; this dose has also been suggested by the *BNFC* for neonates. Those over 12 years of age may be given the usual adult dose (see Uses and Administration, above).

Although intravenous use is not licensed for children in the UK the *BNFC* suggests a dose of 7.5 mg/kg twice daily for those aged from 1 month to 12 years; older children may be given the adult dose (see Uses and Administration, above).

For prophylaxis of disseminated infection due to *Mycobacterium avium* complex, US guidelines suggest clarithromycin may be given in an oral dose of 7.5 mg/kg twice daily; when used for treatment, it should be given with other antimycobacterials and the dose may be increased to 15 mg/kg (to a maximum of 500 mg) twice daily.[1]

For the **prevention of secondary cases of pertussis** the *BNFC* suggests that clarithromycin may be given twice daily for 7 days in the following oral doses:

- neonates: 7.5 mg/kg
- children 1 month to 12 years of age, according to bodyweight:
  - under 8 kg: 7.5 mg/kg
  - 8 to 11 kg: 62.5 mg
  - 12 to 19 kg: 125 mg
  - 20 to 29 kg: 187.5 mg
  - 30 to 40 kg: 250 mg
- children from 12 years of age: 500 mg

For the eradication of *Helicobacter pylori* associated with peptic ulcer disease, the *BNFC* suggests that 7.5 mg/kg (to a maximum of 500 mg) twice daily may also be given orally with another antibacterial and a proton pump inhibitor for 7 days to children aged 1 year and over.

1. Panel on Opportunistic Infections in HIV-Exposed and HIV-Infected Children. Guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and HIV-infected children: recommendations from the National Institutes of Health, CDC, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics (issued 6th November, 2013). Available at: http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/oi_guidelines_pediatrics.pdf (accessed 09/12/13)

Administration in renal impairment. Licensed product information states that in patients with severe renal impairment (creatinine clearance of less than 30 mL/minute) oral and intravenous doses of clarithromycin may need to be halved or the dosing interval doubled.

Ischaemic heart disease. For mention of studies investigating clarithromycin in the prevention of ischaemic heart disease, see under Azithromycin, p. 222.1.

Multiple myeloma. Clarithromycin 500 mg orally twice daily has been added[1] to a regimen of lenalidomide and dexamethasone in treatment-naive patients with multiple myeloma (p. 699.2). The regimen (BiRD) was considered effective and well tolerated, with a higher response rate at lower dexamethasone doses than had been previously reported with lenalidomide and dexamethasone alone. A regimen of clarithromycin, low-dose thalidomide, and dexamethasone (BLT-D) has also been evaluated.[2]

1. Niesvizky R, *et al.* BiRD (Biaxin [clarithromycin]/Revlimid [lenalidomide]/dexamethasone) combination therapy results in high complete- and overall-response rates in treatment-naive symptomatic multiple myeloma. *Blood* 2008; 111: 1101–9.
2. Coleman M, *et al.* BLT-D (clarithromycin [Biaxin], low-dose thalidomide, and dexamethasone) for the treatment of myeloma and Waldenström's macroglobulinemia. *Leuk Lymphoma* 2002; 43: 1777–82.

Respiratory disorders. For reference to the use of clarithromycin in the management of respiratory disorders, see under Erythromycin, p. 294.3.

Adverse Effects and Precautions

As for Erythromycin, p. 295.1. Gastrointestinal disturbances are the most frequent adverse effect but are usually mild and less frequent with clarithromycin than with erythromycin. Smell and taste disturbances, stomatitis, glossitis, tongue and tooth discoloration, and headache have occurred. There have also been reports of transient CNS effects. Other adverse effects include arthralgia, myalgia, hypoglycaemia, leucopenia, and thrombocytopenia. Interstitial nephritis and renal failure have been reported rarely. Clarithromycin may aggravate muscle weakness in patients with myasthenia gravis and new onset of myasthenic syndromes has been reported.

Intravenous doses may cause phlebitis and pain at the injection site.

Caution is required in patients with hepatic or renal impairment and doses should be reduced in those with renal impairment (see under Uses and Administration p. 266.3). It should not be used during pregnancy if possible as high doses have been associated with embryotoxicity in *animal* studies.

Effects on the blood. Single cases of thrombocytopenia[1] and thrombocytopenic purpura[2,3] associated with clarithromycin have been reported. Cases of agranulocytosis have also been reported.[4] A case of thrombocytopenia accompanied by interstitial nephritis, hepatitis, and elevated serum amylase levels was attributed to an allergic reaction to clarithromycin.[5] Toxic epidermal necrolysis and subsequent death due to aplastic anaemia have been reported in a patient after taking clarithromycin for 3 days.[6]

1. Price TA, Tuazon CU. Clarithromycin-induced thrombocytopenia. *Clin Infect Dis* 1992; 15: 563–4.
2. Oteo JA, *et al.* Clarithromycin-induced thrombocytopenic purpura. *Clin Infect Dis* 1994; 19: 1170–1.
3. Alexopoulou A, *et al.* Thrombotic thrombocytopenic purpura in a patient treated with clarithromycin. *Eur J Haematol* 2002; 69: 191–2.
4. Jacobs P, *et al.* Immune agranulocytosis and clarithromycin. *Hematology* 2004; 9: 291–6.
5. Baylor P, Williams K. Interstitial nephritis, thrombocytopenia, hepatitis, and elevated serum amylase levels in a patient receiving clarithromycin therapy. *Clin Infect Dis* 1999; 29: 1350–1.
6. Baz K, *et al.* Fatal aplastic anaemia in a patient with clarithromycin-induced toxic epidermal necrolysis. *J Eur Acad Dermatol Venereol* 2004; 18: 104–5.

Effects on the cardiovascular system. QT prolongation and torsade de pointes were associated with use of clarithromycin in 2 patients.[1] Renal impairment in 1 of the patients and hepatic impairment and organic heart disease in both could have increased their susceptibility to these effects.

For mention of an unexpected increase in cardiovascular mortality in patients with stable coronary heart disease given clarithromycin, see Ischaemic Heart Disease, in Uses and Administration of Azithromycin, p. 222.1.

1. Lee KL, *et al.* QT prolongation and torsades de pointes associated with clarithromycin. *Am J Med* 1998; 104: 395–6.

Effects on the eyes. Corneal opacities, reversible on stopping treatment, were reported in a patient receiving oral clarithromycin as part of a regimen for disseminated *Mycobacterium avium* complex infection.[1] Corneal subepithelial deposits have also been reported in a patient after prolonged use of clarithromycin eye drops for *Mycobacterium avium* complex keratitis. The deposits did not cause any ocular discomfort and resolved on stopping therapy.[2]

1. Dorrell L, *et al.* Toxicity of clarithromycin in the treatment of Mycobacterium avium complex infection in a patient with AIDS. *J Antimicrob Chemother* 1994; 34: 605–6.
2. Tyagi AK, *et al.* An unreported side effect of topical clarithromycin when used successfully to treat Mycobacterium avium-intracellulare keratitis. *Cornea* 1999; 18: 606–7.

Effects on the gastrointestinal tract. Pseudomembranous colitis associated with *Clostridium difficile* developed in a child receiving clarithromycin.[1]

1. Braegger CP, Nadal D. Clarithromycin and pseudomembranous enterocolitis. *Lancet* 1994; 343: 241–2.

Effects on the liver. Progressive cholestatic jaundice, which subsequently proved fatal, developed in a 59-year-old woman after 3 days of clarithromycin therapy for acute maxillary sinusitis.[1] Fulminant hepatic failure in another patient, which developed during clarithromycin therapy, resolved once the drug was withdrawn.[2] Clarithromycin itself was considered responsible although there was the possibility that it had increased concentrations of isradipine, another known hepatotoxic drug that the patient was also receiving.

1. Fox JC, *et al.* Progressive cholestatic liver disease associated with clarithromycin treatment. *J Clin Pharmacol* 2002; 42: 676–80.
2. Tietz A, *et al.* Fulminant liver failure associated with clarithromycin. *Ann Pharmacother* 2003; 37: 57–60.

Effects on the lungs. On 2 occasions fever and pulmonary infiltration with eosinophilia occurred in a patient given clarithromycin.[1] Another patient developed eosinophilic pneumonia 3 days after starting clarithromycin; symptoms improved when the drug was stopped.[2]

1. Terzano C, Petroianni A. Clarithromycin and pulmonary infiltration with eosinophilia. *BMJ* 2003; 326: 1377–8.
2. Ohnishi H, *et al.* Clarithromycin-induced eosinophilic pneumonia. *Intern Med* 2004; 43: 231–5.

Effects on mental state. Acute psychoses occurred in 2 patients receiving clarithromycin as part of prophylactic treatment for *Helicobacter pylori* infection and were similar to 3 previously reported cases in either AIDS patients or elderly subjects.[1] Delirium[2] has also been associated with clarithromycin monotherapy in an elderly patient, and visual hallucinations have occurred in a 37-year-old woman being treated with ceftriaxone and clarithromycin for suspected pneumonia;[3] and in 2 children taking standard doses of clarithromycin.[4] Mania associated with clarithromycin use has also been reported in a child.[5] A review[6] of published and spontaneous reports found an association between adverse manic reactions and the use of certain antibacterials; clarithromycin was found to be the antibacterial most frequently implicated.

1. Gómez-Gil E, *et al.* Clarithromycin-induced acute psychoses in peptic ulcer disease. *Eur J Clin Microbiol Infect Dis* 1999; 18: 70–1.
2. Özsoylar G, *et al.* Clarithromycin monotherapy-induced delirium. *J Antimicrob Chemother* 2007; 59: 331.
3. Fernández Arenas O, *et al.* Alucinaciones por administración de una pauta estándar de claritromicina. *Farm Hosp* 2007; 31: 315–16.
4. Erkek N, *et al.* Visual hallucinations possibly associated with clarithromycin administration at therapeutic dosage in two children. *Med Princ Pract* 2009; 18: 332–4.
5. Fidan T, Fidan V. Clarithromycin-induced mania in a child. *Int J Clin Pharmacol Ther* 2009; 47: 402–4.
6. Abouesh A, *et al.* Antimicrobial-induced mania (antibiomania): a review of spontaneous reports. *J Clin Psychopharmacol* 2002; 22: 71–81.

Effects on the pancreas. Pancreatitis has been reported in patients receiving clarithromycin.[1-3]

1. Liviu L, *et al.* Pancreatitis induced by clarithromycin. *Ann Intern Med* 1996; 125: 701.
2. Schouwenberg BJJW, Deitcum J. Acute pancreatitis after a course of clarithromycin. *Neth J Med* 2003; 61: 266–7.
3. González Carro P, *et al.* Acute pancreatitis and modified-release clarithromycin. *Ann Pharmacother* 2004; 38: 508–509.

Hypersensitivity. In addition to rashes and other hypersensitivity reactions, which occasionally occur in patients receiving macrolides, leucocytoclastic vasculitis,[1] Henoch-Schönlein purpura,[2] and toxic epidermal necrolysis[3,4] have been reported in patients receiving clarithromycin.

1. Gavura SR, Nusinowitz S. Leukocytoclastic vasculitis associated with clarithromycin. *Ann Pharmacother* 1998; 32: 543–5.
2. Borrás-Blasco J, *et al.* Henoch-Schönlein purpura associated with clarithromycin: case report and review of literature. *Int J Clin Pharmacol Ther* 2003; 41: 213–16. Correction. *ibid.*; 420.
3. Khaldi N, *et al.* Toxic epidermal necrolysis and clarithromycin. *Can J Clin Pharmacol* 2005; 12: e264–e268.
4. Clayton TH, *et al.* Clarithromycin suspension-associated toxic epidermal necrolysis in a 2-year-old girl. *Clin Exp Dermatol* 2007; 32: 755–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies clarithromycin as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

For a discussion of drug interactions of macrolide antibacterials, see Erythromycin, p. 296.2.

Antidepressants. For a report of delirium following use of clarithromycin with *fluoxetine*, see Antibacterials, p. 426.1.

Antidiabetics. For reference to hypoglycaemia resulting from the addition of clarithromycin to *glibenclamide* or *glipizide*, see Antibacterials, p. 505.3.

Antigout drugs. For mention of fatal *colchicine* toxicity associated with concomitant use of clarithromycin, see Macrolides, p. 606.3.

Antivirals. Due to its effect on the cytochrome P450 isoenzyme CYP3A4, *ritonavir* markedly inhibits the metabolism of clarithromycin to its 14-hydroxy metabolite; other HIV-protease inhibitors are expected to interact similarly, albeit to lesser degrees. Clarithromycin becomes more dependent on renal clearance when hepatic metabolism is strongly inhibited; as a result, interactions may be more significant for those with renal impairment. Licensed product information for clarithromycin recommends an extra reduction in dose in patients with renal impairment receiving ritonavir, over and above any reduction that may be needed for the renal impairment alone: doses of clarithromycin should be reduced by 50% in patients with a creatinine clearance (CC) of 30 to 60 mL/minute and reduced by 75% in those with a CC below 30 mL/minute; the daily dose should not exceed 1 g.

Similar dose reductions have been recommended when given with most other ritonavir-boosted HIV-protease inhibitors. However, US licensed product information for *atazanavir* advises considering a 50% dose reduction of clarithromycin, regardless of renal status, to reduce the risk of QT-interval prolongation. It should be noted that this reduction may also substantially reduce levels of the active metabolite 14-hydroxyclarithromycin (which may be of clinical relevance in the treatment of Gram-negative infections such as those due to *Haemophilus influenzae*), and therefore alternatives to clarithromycin should be considered for treatment of infections other than those caused by *Mycobacterium avium complex* (MAC).

The NNRTI *delavirdine* may have similar effects on clarithromycin to those of the HIV-protease inhibitors, and clarithromycin doses should be reduced in patients with renal impairment as above. Use of *efavirenz*, *etravirine*, or *nevirapine* with clarithromycin may decrease plasma concentrations of the macrolide while increasing its hydroxy metabolite. UK licensed information for etravirine and nevirapine advises that alternatives to clarithromycin should be considered for treatment of MAC infections, given the reduced activity of the hydroxy metabolite against this organism. Co-administration of efavirenz with clarithromycin has been associated with a high incidence of rash.

Decreased concentrations of *zidovudine* (p. 1026.2) have been reported in patients also taking clarithromycin and clarithromycin product information recommends that doses of the two drugs should be separated by 1 to 2 hours.

Disulfiram. For a report of an interaction between clarithromycin and disulfiram, see Macrolides, p. 2496.3.

Gastrointestinal drugs. In a study[1] in healthy subjects, concentrations of clarithromycin and its active metabolite were increased in gastric tissue and mucus and, to a lesser extent, in plasma during use of *omeprazole*. In addition, use of clarithromycin with omeprazole resulted in higher and more prolonged plasma concentrations of omeprazole. The investigators suggest that this interaction could account for the synergistic action seen with this combination when used for eradication of *Helicobacter pylori*. However, licensed product information for clarithromycin states that no dosage adjustment to either drug is necessary.

Although a study[2] in healthy subjects suggested that some pharmacokinetic parameters of clarithromycin are altered by *cimetidine*, the clinical significance of such changes are unknown.

1. Gustavson LE, *et al.* Effect of omeprazole on concentrations of clarithromycin in plasma and gastric tissue at steady state. *Antimicrob Agents Chemother* 1995; 39: 2078–83.
2. Amsden GW, *et al.* Oral cimetidine prolongs clarithromycin absorption. *Antimicrob Agents Chemother* 1998; 42: 1578–80.

Antimicrobial Action

As for Erythromycin, p. 297.1.

Clarithromycin is reported to be more active than erythromycin against susceptible streptococci and staphylococci *in vitro*, as well as against some other species including *Moraxella catarrhalis* (*Branhamella catarrhalis*), *Legionella* spp., *Chlamydia trachomatis*, and *Ureaplasma urealyticum*. Clarithromycin is reported to be more active than erythromycin or azithromycin against some mycobacteria, including *Mycobacterium avium* complex and *M. leprae*. It is reported to have some *in-vitro* activity against the protozoan *Toxoplasma gondii*. The major metabolite, 14-hydroxyclarithromycin, is also active, and may enhance the activity of clarithromycin *in vivo*, notably against *Haemophilus influenzae*. The MICs of this metabolite are equal or twofold higher than those of the parent drug; the former is twofold more active than the latter against *H. influenzae*.

Activity with other antimicrobials. Clarithromycin has been reported to enhance the activity of some antimycobacterials including ethambutol, isoniazid, pyrazinamide, and rifampicin against *Mycobacterium tuberculosis*.[1,2]

1. Cavalieri SJ, *et al.* Synergistic activities of clarithromycin and antituberculous drugs against multi drug-resistant Mycobacterium tuberculosis. *Antimicrob Agents Chemother* 1995; 39: 1542–5.
2. Mor N, Estandiari A. Synergistic activities of clarithromycin and pyrazinamide against Mycobacterium tuberculosis in human macrophages. *Antimicrob Agents Chemother* 1997; 41: 2035–6.

Resistance. Erythromycin-resistant isolates of *Streptococcus pneumoniae* are commonly cross-resistant to clarithromycin.[1] The incidence of resistance to clarithromycin and other macrolides is higher among penicillin-resistant strains than among penicillin-sensitive strains.[2] Clarithromycin-resistant isolates of *Helicobacter pylori* have also emerged.[3-7] Genetic mutations responsible for clarithromycin resistance have been identified in *H. pylori*[8] and in *Mycobacterium* spp.[9,10] Since resistance develops rapidly in *M. avium* during clarithromycin monotherapy, combination therapy is usually recommended. However, resistance to clarithromycin in an AIDS patient with systemic *M. avium* complex infection, despite combined treatment with clofazimine, has been described.[11]

1. Lonks JR, Medeiros AA. High rate of erythromycin and clarithromycin resistance among Streptococcus pneumoniae isolates from blood cultures from Providence, RI. *Antimicrob Agents Chemother* 1993; 37: 1742–5.
2. Barry AL, *et al.* Macrolide resistance among Streptococcus pneumoniae and Streptococcus pyogenes isolates from out-patients in the USA. *J Antimicrob Chemother* 1997; 40: 139–40.
3. López-Brea M, *et al.* Evolution of resistance to metronidazole and clarithromycin in Helicobacter pylori clinical isolates from Spain. *J Antimicrob Chemother* 1997; 40: 279–81.
4. Hultén K, *et al.* Macrolide resistance in Helicobacter pylori: mechanism and stability in strains from clarithromycin-treated patients. *Antimicrob Agents Chemother* 1997; 41: 2550–3.
5. Kalach N, *et al.* High levels of resistance to metronidazole and clarithromycin in Helicobacter pylori strains in children. *J Clin Microbiol* 2001; 39: 394–7.
6. Grove DI, Koutsouridis G. Increasing resistance of Helicobacter pylori to clarithromycin: is the horse bolting? *Pathology* 2002; 34: 71–3.
7. Megraud F, *et al.* Helicobacter pylori resistance to antibiotics in Europe and its relationship to antibiotic consumption. *Gut* 2013 62: 34–42.
8. Versalovic J, *et al.* Mutations in 23S rRNA are associated with clarithromycin resistance in Helicobacter pylori. *Antimicrob Agents Chemother* 1996; 40: 477–80.
9. Nash KA, Inderlied CB. Genetic basis of macrolide resistance in Mycobacterium avium isolated from patients with disseminated disease. *Antimicrob Agents Chemother* 1995; 39: 2625–30.
10. Wallace RJ, *et al.* Genetic basis for clarithromycin resistance among isolates of Mycobacterium chelonae and Mycobacterium abscessus. *Antimicrob Agents Chemother* 1996; 40: 1676–81.
11. De Wit S, *et al.* Acquired resistance to clarithromycin as combined therapy in Mycobacterium avium intracellulare infection. *Lancet* 1993; 341: 53–4.

Pharmacokinetics

Clarithromycin is rapidly absorbed from the gastrointestinal tract, and undergoes first-pass metabolism; the bioavailability of the parent drug is about 55%. The extent of absorption is relatively unaffected by the presence of food. Peak plasma concentrations occur 2 to 3 hours after an oral dose. Steady-state concentrations are reached within 3 to 4 days and peak plasma concentrations of clarithromycin and its principal active metabolite, 14-hydroxyclarithromycin, are then about 1 and 0.6 micrograms/mL, respectively, after 250 mg orally every 12 hours as tablets. The same dose given as a suspension to fasting subjects produces steady-state plasma concentrations of about 2 micrograms/mL of clarithromycin and about 0.7 micrograms/mL of 14-hydroxyclarithromycin.

The pharmacokinetics of clarithromycin are non-linear and dose dependent; high doses may produce disproportionate increases in peak concentrations of the parent drug, due to saturation of the metabolic pathways. However, the non-linearity is slight at the recommended doses of 250 to 500 mg every 8 to 12 hours.

Clarithromycin and 14-hydroxyclarithromycin are widely distributed, and tissue concentrations exceed those in serum, in part because of intracellular uptake. Plasma protein binding has been reported to be about 80%. Clarithromycin has been detected in breast milk. It is extensively metabolised in the liver, and excreted in faeces via the bile; 5 to 10% of the parent drug is recovered from the faeces. At steady state, about 20% and 30% of a 250-mg or 500-mg dose as tablets, respectively, and about 40% of a 250-mg dose as suspension, is excreted in the urine as unchanged drug. 14-Hydroxyclarithromycin as well as other metabolites are also excreted in the urine, accounting for 10 to 15% of the dose. The elimination half-lives of clarithromycin and 14-hydroxyclarithromycin are about 3 to 4 and 5 to 6 hours, respectively in patients receiving 250 mg every 12 hours, and about 5 to 7 and 7 to 9 hours, respectively, in those receiving 500 mg every 8 to 12 hours. The half-life is prolonged in renal impairment.

Reviews.

1. Rodvold KA. Clinical pharmacokinetics of clarithromycin. *Clin Pharmacokinet* 1999; 37: 385–98.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aeroxina; Claribiotic; Claricina; Clarimax; Clarimid†; Clarovil; Corixa; Fadamicina; Finasept; Ira; Iset; Kailasa; Klaricid; Klonacid; Macromicina; Quotal; Soferax; Windar; ***Austral.***: Clarac; Clarihexal; Clarithro; Kalixocin; Klacid; ***Austria***: Klacid; Maclar†; ***Belg.***: Bidar; Clarithromed†; Heliclar; Maclar; Monoclarium; ***Braz.***: Clamicin; Clarineo; Claritromax†; Klaricid; Klaroxil; ***Canad.***: Biaxin; ***Chile***: Clarimax; Clarosip†; Clatic; Euromicina; Infex; Klaricid; Mus-TC; Pre-Clar; ***China***: A Rui (阿瑞); Ai Er Bei (艾尔贝); An Ji Er Ning (安吉尔宁); An Ji Er Shu (安吉尔舒); Ang Ke (昂克); Ao Fu An (奥扶安); Ao Ni Ya (奥尼亚); Baihongyou (百红优); Bao Nuo (保诺); Bing Ke (冰克); Chang Di (长迪); Claricin (甲力); Feng Rui (锋锐); Fu Ke Xing (福可星); Gui Long Nuo Ke (桂龙诺克); Jia Ji Ning (甲吉宁); Jia Nuo Qi (佳诺奇); Jin Yang Bo Tai (金阳博泰); Jun Ran (君然); Ka Mai (卡迈); Ka Rui Si (卡瑞斯); Ka Tai Ka (卡太卡); Kai Mai (开迈); Kang Ka (康卡); Kasimaixin (卡斯迈欣); Ke Li Xian (柯力仙); Ke Man Xin (科曼欣); Ke Mei Xin (可枚辛); Ke Ni Bang (克尼邦); Klabax (卡迈士); Klacid (克拉仙); Li Xin (立辛); Limaixian (利迈先); Lu Xian Tong (路仙同); Lv Shu (绿舒); Mei Bo (美博); Mo Xin (莫欣); Nai Er (奈尔); Nuo Bang (诺邦); Nuo Sha (诺沙); Pi Ke (匹刻); Pu Mai (普迈); Rui Yuan (瑞源); Sai Hong (赛红); Sang Mei (桑美); Sen Ke (森克); Sha Di (沙迪); Shen Mai Qi (申迈奇); Sheng Nuo De (圣诺得); Shuang Chuan (双川); Tai Bi Jie (泰必捷); Tai Fei (泰菲); Tai Mei La (泰每拉); Wei Peng (维朋); Wo Ka (沃卡); Yi Chuang (怡川); Yi Ren (宜仁); Yu Jun Xian (裕君先); Zhen Ke (臻克); ZhenKe (珍可); ***Cz.***: Clarexid†; Clarosip†; Fromilid; Klabax; Klacid; Lekoklar; ***Denm.***: Klacid; Klaricid; ***Fin.***: Clarium; Cymoklar; Klacid; Zeclar; ***Fr.***: Mononaxy; Monozeclar; Naxy; Zeciar; ***Ger.***: Biaxin†; Clarithrobeta; Clarosip†; Cyllind†; Klacid; Mavid†; ***Gr.***: Althromicin; Arecid; Brevil; Chlamydicin; Claribactron; Claridus; Clarimex; Clarimil; Claripen; Clarithrocin; Claromycin; Derizic; Egelif; Eliben; Ezumycin; Geromycin; Glartin; Klaretop; Klarexyl; Klaribros; Klaricid; Klarifar; Klarifect; Klarimac; Klarithrin; Klaroxin; Klazidem; Larithro; Laromin; Lyoclar; Maciadin; Maxigan; Maxilin; Mythrocin; Odycin; Pharicid; Pharlemyron; Primocid; Riclemed; Rithroprol; Ritran; Sanicet; Sythro; Thriamox; Tromypen; Zeclar; Zeclaren; ***Hong Kong***: Binoclar; Clacin; Claricin; Clarsin; Cleron†; Fascar; Klacid; Klerimed; Synclar; Vick-Clarcid; ***Hung.***: Cidoclar†; Fromilid; Klabax; Klacid; Klarigen; Lekoklar; ***India***: Acem; Acgel: Acnesol-CL; Bioclar; Celex-OD; Celex; Clamycin; Clar; Clarbact; Claribid; Claricin; Claricip; Clarics; Claridase; Clarie; Clarigen; Clarigo; Clarimac; Clarithro; Clarivir; Clariwin; Clear; Clycin; Crixan; F-Clar; Heliclar; Klacid; Klacin; Klarim; Larit; Maclar; Macmax; Macroclar; Monoclar; Mythro; Mythrocin; Neuclar; Novaciar; Synclar; ***Indon.***: Abbotic; Bicrolid; Binoklar†; Clacine; Clapharma†; Comtro; Hecobac; Orixal; ***Irl.***: Clarie; Claripsine; Clarosip†; Claryl; Clonocid; Clorom; Klacid; Klaram; Klariger; ***Israel***: Karin; Klacid; Klaridex; ***Ital.***: Klacid; Macladin; Madiclar; Soriclar; Veclam; Winclar; ***Jpn***: Clarith; ***Malaysia***: Avexus; Binocular; Clarem; Clarimycin; Crixan; Klacid; Klerimed; Maciar; ***Mex.***: Adel; Arlecyn-K; Claritral; Clatrocin†; Collitred; Crixan†; Crolisil; Doycur; Fhisfal; Gervaken; Klabet; Klaricid; Klarix; Klarmyn; Klarpharma; Krobicin; Mabicrol; Neo-Clarosip; Quedox; Rolicytin; Torvic†; Trimeba; Vikrol; Xuclamin; ***Neth.***: Biaxin†; Clarosip†; Klacid; Klaricid†; Kloreniss; ***Norw.***: Klacid; ***NZ***: Clarac; Klacid; Klamycin; ***Philipp.***: Baclecin; Bysclas; Clabet; Clamycin; Clarania; Clarie; Clariget; Clarithrocid; Clariwin; Claryl; Clistanex; Galemin; Hamun; Klaret; Klargen; Klaricid; Klarid; Klarimac; Klarix; Klarmyn; Klaryz; Klaz; Larizin; Maclar; Macrodin; Macrolin; Macronox; Maxulid; Neo-klar; Onexid; Oracid; Rithrocin†; Ritromax; Supalide†; ***Pol.***: Fromilid; Klabax; Klabion; Klacid; Klarigen; Klarmin; Lekoklar; Taclar; ***Port.***: Ciclinil; Cladina; Cladia; Clarbac; Clarobiotico; Klacid; Zeclar†; Zocid; ***Rus.***: Arvicin (Арвицин); Binoclar (Биноклар); Clarbact (Кларбакт); Clarithrosin (Кларитросин); Clarosip (Кларосил); Ecozitrin (Экозитрин); Fromilid (Фромилид); Klabax (Клабакс); Klacid (Клацид); Klarexid (Кларексид); Klaricin (Кларицин); Klaricit (Кларицит); Klaromin (Кларомин); Klasine (Класине); Klerimed (Клеримед); Lekoklar (Лекоклар); Seidon (Сейдон); ***S. Afr.***: Clacee; ClariHexal; Klacid; Klarithran; Klarizon; ***Singapore***: Bicrolid; Clari; Claripen; Clariwin; Cleron; Crixan; Klacid; Klerimed; Monoclarium; ***Spain***: Bremon; Klacid; Kofron; ***Swed.***: Klacid; ***Switz.***: Clamycin†; Clarithrocine; Claromycine; Klacid; Klaciped; ***Thai.***: Clacina: Claciniа; Clarith; Claron; Crixan; Fascar; Klacid; ***Turk.***: Clabel; Claricide; Cleanomisin; Deklarit; Klacid; Klamaxin; Klamer; Klarolid; Klaromin; Klasol; Klax; Klerant; Laricid; Macrol; Maxiclar; Megasid; Uniklar; ***UAE***: Clamycin; ***UK***: Clarosip†; Febzin; Klaricid; Mycifor; ***Ukr.***: Clabax (Клабакс OD); Clabel (Клабел); Fromilid (Фромилид); Klacid (Клацид); Kleron (Клерон); Lekoklar (Лекоклар)†; ***USA***: Biaxin; ***Venez.***: Binoclar: Claranta; Claritic; Claritron; Clarivax; Klaricid.

Multi-ingredient Preparations. ***Austral.***: Klacid HP 7; Losec Hp 7†; Nexium Hp; Probitor Hp7; Pylorid-KA†; ***Braz.***: Erradic; H Bacter; Helicopac; Heliklar; Omepramix; Pylorikit; Pyloripac; Pyloriset; Pyloritrat; ***Canad.***: Hp-Pac; Losec 1-2-3 A; Losec 1-2-3 M; Nexium 1-2-3 A; ***Chile***: Lanzopral Heli-Pack; Pylopac; ***China***: Weisanlian (胃三联); Yi Hong (怡弘); ***Fin.***: Helipak K; ***Ger.***: ZacPac; ***India***: Claridase; GI Kit; Heligo; L-Cot; LTC-Kit; OTC HP Kit; Pantocid-HP; Pantop-HP Kit; Pantop-HP; Pylokit; ***Malaysia***: Klacid HP 7; Pylobact Combi; ***Mex.***: Pylopac; Rezplen; ***Neth.***: PantoPAC; ***NZ***: Losec Hp7; ***Philipp.***: OAC Hp7†; ***Rus.***: Pylobact (Пилобакт); ***Swed.***: Nexium Hp; ***Turk.***: Helipak; Trio; ***Ukr.***: β-Klatinol (β-КЛАТИНОЛ); Clamed (Кламед); Esoxium Combi (Эзоксиум Комби); Onristat (Орнистат)†; Pylobact Neo (Пилобакт Нео); ***USA***: Omeclamox-Pak; Prevpac.

Pharmacopoeial Preparations

BP 2014: Clarithromycin for Infusion; Clarithromycin Tablet; Prolonged-release Clarithromycin Tablets;
USP 36: Clarithromycin Extended-Release Tablets; Clarithromycin for Oral Suspension; Clarithromycin Tablets.

Clavulanic Acid *(BAN, rINN)*

Acide Clavulanique; Ácido clavulánico; Acidum Clavulanicum; BRL-14151; Clavulánico, ácido; Klavulanik Asit; MM 14151; Клавулановая Кислота.

(*Z*)-(2*R*,5*R*)-3-(2-Hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

$C_8H_9NO_5$=199.2

CAS — 58001-44-8 (clavulanic acid); 57943-81-4 (sodium clavulanate).

UNII — 23521W1S24.

Potassium Clavulanate *(BANM, rINNM)*

Potasu klawulanian; BRL-14151K; Clavulanate de Potassium; Clavulanate Potassium (USAN); Clavulanato potásico; Kalii Clavulanas; Kalio klavulanatas; Kaliumclavulanat; Kaliumklavulanaatti; Kaliumklavulanat; Kalium-klavulanát; Kálium-klavulanát; Potassium, clavulanate de; Калия Клавуланат.

$C_8H_8KNO_5$=237.3

CAS — 61177-45-5.

UNII — Q42OMW3AT8.

NOTE. Compounded preparations of potassium clavulanate may be represented by the following names:

- Co-amoxiclav *x/y* (*BAN*)—amoxicillin (as the trihydrate or the sodium salt) and potassium clavulanate; *x* and *y* are the strengths in milligrams of amoxicillin and clavulanic acid respectively
- Co-amoxiclav (*PEN*)—amoxicillin trihydrate and potassium clavulanate.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Eur. also includes Diluted Potassium Clavulanate.

Ph. Eur. 8: (Potassium Clavulanate). The potassium salt of a substance produced by the growth of certain strains of *Streptomyces clavuligerus* or by any other means. A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; slightly soluble in alcohol; very slightly soluble in acetone. A 1% solution in water has a pH of 5.5 to 8.0. Store in airtight containers at a temperature of 2 degrees to 8 degrees.

Ph. Eur. 8: (Potassium Clavulanate, Diluted; Kalii Clavulanas Dilutus). A dry mixture of potassium clavulanate and microcrystalline cellulose or anhydrous or hydrated colloidal silicon dioxide. A white or almost white, hygroscopic, powder. A suspension corresponding to 1% of potassium clavulanate in water has a pH of 4.8 to 8.0. Store in airtight containers.

USP 36: (Clavulanate Potassium). A white to off-white powder. Freely soluble in water; soluble in methyl alcohol with decomposition. Stability in aqueous solutions is not good, optimum stability at a pH of 6.0 to 6.3. pH of a 1% solution in water is between 5.5 and 8.0. Store in airtight containers.

Profile

Clavulanic acid is produced by cultures of *Streptomyces clavuligerus*. It has a beta-lactam structure resembling that of the penicillin nucleus, except that the fused thiazolidine ring of the penicillins is replaced by an oxazolidine ring. In general, clavulanic acid has only weak antibacterial activity. It is a potent progressive inhibitor of plasmid-mediated and some chromosomal beta-lactamases produced by Gram-negative bacteria including *Haemophilus ducreyi*, *H. influenzae*, *Neisseria gonorrhoeae*, *Moraxella catarrhalis* (*Branhamella catarrhalis*), *Bacteroides fragilis*, and some Enterobacteriaccae. It is also an inhibitor of the beta-lactamases produced by *Staphylococcus aureus*. Clavulanic acid can permeate bacterial cell walls and can therefore inactivate both extracellular enzymes and those that are bound to the cell. Its mode of action depends on the particular enzyme inhibited, but it generally acts as a competitive, and often irreversible, inhibitor. Clavulanic acid consequently enhances the activity of penicillin and cephalosporin antibacterials against many resistant strains of bacteria. However, it is generally less effective against chromosomally mediated type 1 beta-lactamases; therefore, many *Citrobacter*, *Enterobacter*, *Morganella*, and *Serratia* spp., and *Pseudomonas aeruginosa* remain resistant. Some plasmid-mediated extended-spectrum beta-lactamases in *Klebsiella pneumoniae*, some other Enterobacteriaceae, and *Ps. aeruginosa* are also not inhibited by beta-lactamase inhibitors.

Clavulanic acid is given as potassium clavulanate orally and by injection with amoxicillin (co-amoxiclav) (p. 216.2), and by injection with ticarcillin (p. 380.2).

Use of clavulanate with penicillins has been associated with the development of cholestatic jaundice and hepatitis (see under Adverse Effects of Amoxicillin, p. 217.2) and therefore restrictions on the use of co-amoxiclav have been suggested in some countries (see p. 271.1).

Because of the risk of cholestatic jaundice the UK CSM[1] recommended that co-amoxiclav should be reserved for bacterial infections likely to be caused by amoxicillin-resistant beta-lactamase-producing strains and that treatment should not usually exceed 14 days. It may be considered for the following main indications:

- sinusitis, otitis media, recurrent tonsillitis
- acute exacerbations of chronic bronchitis
- bronchopneumonia
- urinary-tract infections, especially when recurrent or complicated, but not prostatitis
- septic abortion, pelvic or puerperal sepsis, and intra-abdominal sepsis
- cellulitis, animal bites, and severe dental abscess with spreading cellulitis.

1. CSM/MCA. Revised indications for co-amoxiclav (Augmentin). *Current Problems* 1997; 23: 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023230&RevisionSelectionMethod=LatestReleased (accessed 11/07/06)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Optamox; ***Austral.***: Moxiclav; ***Indon.***: Aclam; ***Philipp.***: Agpen; Koact; ***Thai.***: Clanoxy; Rapiclav; ***Turk.***: Amoksilav.

Multi-ingredient Preparations. ***Arg.***: Aclav†; Amixen Clavulanico; Amoclav Duo; Amoclav; Amoxi Plus; Amoxigrand Compuesto; Amoxitenk Plus; Bi Moxal Duo; Bi Moxal; Bioclavid; Bioxilina Plus; Clamoxol Bio; Clamoxol; Clavulox Duo; Clavulox; Cloximar Duo†; Darzitil Plus Duo; Darzitil Plus; Dibional; Fabamox Duo; Grinsil Clavulanico; Klonalmox; Nobactam Clavulanico; Optamox Duo; Plenobiotic Duo; Ultrabiotic Duo; Ultrabiotic; ***Austral.***: Augmentin; Clamohexal†; Clamoxyl; Clavulin; Clavycillin; Curam; GA-Amclav; Timentin; ***Austria***: AmoclanHexal; AmoxiClavulan; Amoxicomp; Amoxiplus; Amoxistad plus; Augmentin; Clavamox; Xiclav; ***Belg.***: Amoclane; Amoxiclav; Augmentin; Clavucid; Co-Amoxi†; Docamoclaf†; Timentin; ***Braz.***: Amplamox AC; Augmentin†; Betaclav†; Clavulin; Claxam; Novamox; Policlavumoxil; Sigma Clav; Timentin; ***Canad.***: Apo-Amoxi Clav; Clavulin; Novo-Clavamoxin; ratio-Aclavulanate; Timentin; ***Chile***: Ambilan Bid; Ambilan; Amolex; Augmentin Bid; Augmentin; Clavinex Duo: Clavinex; Clavoxilina Bid; ***China***: A Le Xian (阿乐仙); Aikeer (艾克儿); Amoksiklav (莱得怡); An Ke (安克); An Qi (安奇); Anmiejun (安灭菌); Ao Ge Men Ding (奥格门汀); Ao Xian (奥先)†; Augmentin (力百汀); Bang Lin (棒林); Bi Lin (毕林); Bi Qi Er (比奇尔); Chao Qing (超青); Curam (克瑞兰); Fengkelin (锋克林); Haikela (海可拉); Jian Ao (健澳); Jin Li Chen (今利辰); Jin Li Shu (金力舒); Ju Tai (巨泰); Jun Er Qing (君尔清); Keng Qiang (铿锵); Lieqi (列其); Luo De (洛得); Nuoke (诺可); Rui Si (瑞思); Sheng Ai (胜艾); Sheng Xi Kai (盛西凯); Shu Xian Lin (舒仙琳); Te Di (特迪); Timentin (特美汀); Wei An Ke Xin (维安可欣); You Lin Jia (尤林加); Cz.: Amoclabene; Amoksiklav; Augmentin Duo; Augmentin; Betaklav†; Clamox; Curam; Enhancin†; Forcid†; Medoclav; Megamox; Timentin†; ***Denm.***: Bioclavid; Spektraforte; Spektramox; ***Fin.***: Amorion Comp; Amoxin Comp; Augmentin; Bioclavid; Clavumed†; Clavurion†; Yamoxiclav†; ***Fr.***: Augmentin; Ciblor†; Claventin; ***Ger.***: Amoclav†; Amoxclav†; Amoxi-Clavulan†; Amoxi-saar plus; Amoxicillin comp; Amoxiclav; Augmentan; InfectoSupramox; ***Gr.***: Augmentin; Bioclavid; Forcid; Frolicin; Fugentin; Moxiclav; Tenervan; Timentin; ***Hong Kong***: Amoksiklav; Augmentin; Clamovid; Curam; Fleming; Moxiclav; Quali-Mentin; Timentin; ***Hung.***: Aktil; Amoclav; Augmentin-Duo; Augmentin-Extra†; Augmentin; Co-Amoxi; Curam; Enhancin; Forcid; ***India***: Aclav; Acticlav; Adclav; Adpax; Advent; Aelxim-CL; Afixim Clav; Afymox-Clav; Alepam; Alfi-CV; Amclaid; Ament; Amo-C Plus; Amo-Nate; Amoclavs-LB; Amoclavs; Amonit Plus; Amoxytek; Amstar-Clav; Arclav; Ariclav; Astute-CV; Atmox-CL; Augclav; Augmentin; Augmexx; Augnic; Augpen-LB; Augpen; Augpod; Aulanic; Avclav; Bactoclav; Belfix-CV; Benzoclav; Bestomax 375; Bestomax; Betmox-CV; Bilactam-XL; Bilin Plus; Bixigard-C; Blumox-CA; Bodimox-CV; Boostim-LB; Boostim; C Mox; C-Fix-XT; C-Moxy; Cadmentin; Cafage-CL; Canmox; Capiclav; Casclav; CDCV; Cefchamp; Cefexy-CV; Cefit-XL; Cefix-CV; Cefoclav; Ceftyl-CV; Cefupop-CV; Ceme-CV; Ceximе-CL; CGV-DS; Cifilac-CV; Cinclav; Clafel; Clamchek; Clamox; Clamoxy A; Clamoxy; Clamp; Clanex; Clanic; Clanoxy; Clapex; Clatimox Syr; Clatimox; Clauvmentin; Clav-II; Clavactum; Clavage; Clavam; Clavbel; Claver; Clavid-A; Clavimox; Clavipen; Clavitrax; Clavnic; Clavogard; Clavotrol; Clavox; Clavtax-O; Clavter-LB; Clavu-M; Clavunate; Cleblo-CL; Cleblo-CL; Cliver-A; Clomid-CL; Co-Symoxyl; Coax; Cobex-CL; Comentin; Cosmoxyl; Covatil-CV; Cuclav; Curam; CV-Cef; Daczim-CL; Demoxin-CB; Dewmox-CV; Doxiclav; Doxinis-CV; Droxyl Clav; Duclav; E-Amox CL; Edoxim-CV; Elclav; Emclav; Emtax-CL; Enhancin; Esclox-CL; Etoclav; Everclav; Exario; Exlla-CV; Expodox-CV; Fightox; Fimi-CV; Finecef-CV; Fixcef-CL; Fixx Clav; Flamclov; Flemiclav-LB; Flemiclav; Forticlav; Geclave; Germox; Glomox-C; Glyph-C; Goclav; Gramclav; Gramocef-CV; GSClav; Hibrid; Hifen-CV; Hofim-C; Hosiclav; Incef-CV; Indcel; Indclav; Infactum; Inmox Clav; Intracef-CV; Ipodex-CV; IV Augclav; Jidox-C; Kalmox; Kindclav; Kinopox-CV; Kistan; Klamoric; Klavoclav; Krusade; Labocef-CV; Labzone; Laciclav; Lacom-CV 625; Lacom-CV; Lactoclav; Lakmox-CL; Lamna-C; Laxclav-LB; Laxclav; Laximo-XL; Lebzone; Leclav; Lemna-C Kid; Letix-C; Leximе-CV; Linaox-Clav; LMX Forte; Logcef-CV; M-Clav; M-Klav; Mahacef-CV; Maxclav; Maximizin; MDCef-CV; Mediclav; Mega-CV; Megaclav; Megamentin; Megox; Mikclav; Miliximе-CV; Minoclav; Mintclav; Mintodox-CL; Monamox-CL; Mordica; Mordica; Moxclav; Moxifast-CV; Moxigem; Moxikare; Moxikind-CV; Moxinova CV; Moxiphar-CV; Moxipil-CL; Moxipil-CV; Moxiplus-CV; Moxitrac-CV; Moxiz CV; Moxnic; Moxsav; Moxspen-CL; Moxtive-Clav; Moxxil-Duo; Moxy Plus-CV; Moxycare; Moxyclav; Moxynic; Moxyvent; Mpx-CV; Mucodav; Myclav; Nayaclav; Neclav; Netclav; Netflox-OZ; Neucomox; Nikomox-CV; Nipp-CA; Nismentin; Nizoclav; Noir; Novaclav; Novamox-CV; Nuclav; Nufex Beta; Nupod-CV; O-Moxy-CL; Ocef-CV; Oclam; Ogmen; Omlar-CV; Omnapil-CV; Omnatax-CV; Onamox-CL; One Clav; Opox-CV; Orgamox-CL BD; Orgamox-CL; Osclav; Oxipod-CV; Pamclav; Papcef-CV; Timentin†; ***Indon.***: Amocomb; Ancla; Augmentin; Auspilic; Bellamox; Betaclav; Biditin†; Capsinat; Clabat; Claneksi; Clavamox; Claxy; Comsikla; Danoclav; Daxet; Dexyclav; Ikamoxyl Plus; Improvox; Lansiclav; Nufaclav; Nuvoclav; Palentin; Prafamoc†; Protamox; Surpas; Syneclav; Viaclav; Vibranat; Vulamox; Zumafen†; ***Irl.***: Amoclav; Augmentin; Bellmentin†; Clavamel; Germentin; Pinaclav; ***Israel***: Amoxiclav; Augmentin; Clavamox; Clavenir; Claventin; Moclav; Timentin; ***Ital.***: Abba; Acadimox; Aklav; Anival; Augmentin; Aveggio; Clavulin; Euticlavir; Homer; Klavux; Kruxade; Levantes; Mondex; Moxivul; Neoduplamox; Puriclav; Servamox†; Timentin; Xinamod; ***Malaysia***: Augmentin; Cavumox; Clamentin; Clamovid; Clavam; Clavomid; Curam; Enhancin; Moxiclav; Myclav; ***Mex.***: Acarbixin; Acimox AC; Alvi-Tec; Amobay CL; Amoxiclav; Amoxiclide; Ampliron Duo; Apoclavox; Augmentin; Avuxilan; Clambusil; Clamoxin; Clavant; Clavucyd; Clavulin; Clavuser; Crizmat; Enhancin; Gramaxin; Moxlin CLV; Rapiclav; Riclasip; Servamox CLV; Sinufin; Timentin; Valclan†; ***Neth.***: Amoclan†; Amuclan†; Augmentin; Bioclavid; Forcid; Zymolav; ***NZ***: Alpha-Amoxyclav†; Augmentin; Curam; Synermox; Timentin; ***Philipp.***: Addex; Agcomen; Alvonal; Amoclav; Anbicyn; Atadar; Augmentin; Augmex†; Augurcin; Bactiv; Bactoclav; Bioclav; Bioclavid; Cax; Clamovid; Clamoxil; Claneksi; Clavasul; Claventin; Clavimox; Clavmex; Clavomax; Clavorex; Clavox; Clavoxel; Clavoxin; Clovimax; CO-AX; Comxicla; Duotak; Enhamox; Enhancin; Exten; Globantin; Gloclav; Julmentin; Klavic; Luvmox; Natravox; Nexilav; Penhance; Proxiclav; Rafonex; Sanmox†; Solclav; Sovlan; Sullivan; Suplentin†; Ticarcin; Timentin; Valmocel†; Vamox; Xilanic; ***Pol.***: Amoclan; Amoksiklav; Augmentin; Curam†; Forcid; Ramoclav†; Taromentin; Timentin; ***Port.***: Amoclavam; Amplamox Plus†; Augmentin; Betamox; Clavamox; Clavepen; Forcid; Noprilam; Penilan; ***Rus.***: Amoclan (Амоклан)†; Amoksiklav (Амоксиклав); Arlet (Арлет); Augmentin (Аугментин); Clamosar (Кламосар); Ecoclav (Экоклав); Flemoclav (Флемоклав); Liclav (Ликлав); Medoclav (Медоклав); Panklav (Панклав); Ranclav (Ранклав); Rapiclav (Рапиклав); Timentin (Тиментин); ***S.Afr.***: Adco-Amoclav; Amoclan; Apex-Clavutin; AugMaxcil; Augmentin; Auro-Amoxiclav; Bindoclav; Bio-Amoksiclav; Bio-Amoksiklav; Clamentin; Clavumox; Co-Amoxyclav; Curam; Forcid; Ranclav; Rolab-Amoclav†; ***Singapore***: Amocla; Augmentin; Clamonex; Clamovid; Curam; Enhancin; Fugentin†; Moxiclav; ***Spain***: Amoclave†; Augmentine; Duonasa; Odontobiotic; ***Swed.***: Bioclavid; Spektramox; ***Switz.***: Augmentin; Aziclav; Clavamox†; Co-Amoxi; Co-Amoxicillin; Co-Amoxicilline; CoAmox; ***Thai.***: AMK; Amocla†; Amoksiklav; Anbicyn; Augclav; Augmentin; Augpen†; Biclav; Cavumox; Clavmoxy; Clavomid; Curam; Ind Clav; Klamoks†; Manclamine; Moxiclav; Moxicle; Pencla†; Ranclav; Verclav; ***Turk.***: Amoklavin; Augmentin; Bioment; Croxilex; Klamoks; Klavunat; Klavupen; Timentin; ***UAE***: Julmentin; ***UK***: Augmentin-Duo; Augmentin; Timentin; ***Ukr.***: Amoksiklav (Амоксиклав); Amoxicomb (Амоксикомб); Amoxil-K (Амоксилу-К); Augmentin (Аугментин); Bactoklav (Бактоклав); Betaklav (Бетаклав)†; Clavam (Клавам); Flemoclav (Флемоклав); Klamox (Кламокс)†; Panclav (Панклав)†; Timentin (Тиментин); ***USA***: Amoclan; Augmentin; Timentin; ***Venez.***: Augmentin; Clavumox; Curam; Fulgram.

Pharmacopoeial Preparations

BP 2014: Co-amoxiclav Injection; Co-amoxiclav Oral Suspension; Co-amoxiclav Tablets; Dispersible Co-amoxiclav Tablets; Ticarcillin and Clavulanic Acid Infusion;

USP 36: Amoxicillin and Clavulanate Potassium for Oral Suspension; Amoxicillin and Clavulanate Potassium Tablets; Amoxicillin and Clavulanic Acid Extended-Release Tablets; Ticarcillin and Clavulanic Acid for Injection; Ticarcillin and Clavulanic Acid Injection.

Clemizole Penicillin *(BAN, rINN)*

Clemizol penicilina; Clemizole Benzylpenicillin; Clémizole Pénicilline; Clemizolum Penicillinum; Klemitsolipenisillini; Klemizolpenicillin; Penicillin G Clemizole; Клемизол Пенициллин.

1-[1-(4-Chlorobenzyl)benzimidazol-2-ylmethyl]pyrrolidinium (6*R*)-6-(2-phenylacetamido)penicillanate.

$C_{16}H_{18}N_2O_4S,C_{19}H_{20}ClN_3$=660.2

CAS — 6011-39-8.

UNII — 5UL276H6TF.

Profile

Clemizole penicillin is a long-acting preparation of benzylpenicillin (p. 228.1) with similar properties and uses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Prevepen†; ***Mex.***: Megapenil†.

Multi-ingredient Preparations. ***Chile***: Prevepen Forte; ***Mex.***: Alivin Plus; Anapenil; Megapenil Forte†.

Clindamycin *(BAN, USAN, rINN)*

Clindamicina; Clindamycine; Clindamycinum; Klindamisin; Klindamycin; Klindamysiini; U-21251; Клиндамицин.

Methyl 6-amino-7-chloro-6,7,8-trideoxy-*N*-[(2*S*,4*R*)-1-methyl-4-propylprolyl]-1-thio-L-*threo*-D-*galacto*-octopyranoside.

$C_{18}H_{33}ClN_2O_5S$=425.0

CAS — 18323-44-9.

ATC — D10AF01; G01AA10; J01FF01.

ATC Vet — QD10AF01; QG01AA10; QJ01FF01.

UNII — 3U02EL437C.

NOTE. The name Clinimycin, which was formerly used for clindamycin, has also been used for a preparation of oxytetracycline.

Clindamycin Hydrochloride *(BANM, rINNM)*

(7*S*)-Chloro-7-deoxylincomycin Hydrochloride; Chlorodeoxylincomycin Hydrochloride; Clindamicina, hidrocloruro de; Clindamycine, Chlorhydrate de; Clindamycinhydrochlorid; Clindamycyni Hydrochloridum; Hidrocloruro de clindamicina; Klindamicin-hidroklorid; Klindamicino hidrochloridas; Klindamisin Hidroklorür; Klindamycin-hydrochlorid; Klindamycinhydroklorid; Klindamycyny chlorowodorek; Klindamysiinihydrokloridi; Клиндамицина Гидрохлорид.

$C_{18}H_{33}ClN_2O_5S,HCl$=461.4

CAS — 21462-39-5 (anhydrous clindamycin hydrochloride); 58207-19-5 (clindamycin hydrochloride monohydrate).

ATC — D10AF01; G01AA10; J01FF01.

ATC Vet — QD10AF01; QG01AA10; QJ01FF01.

UNII — T20OQ1YN1W (clindamycin hydrochloride); ZNC153389R (clindamycin hydrochloride monohydrate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Clindamycin Hydrochloride). A white or almost white, crystalline powder. It contains a variable quantity of water. Very soluble in water; slightly soluble in alcohol. A 10% solution in water has a pH of 3.0 to 5.0. Store in airtight containers.

USP 36: (Clindamycin Hydrochloride). A white or practically white crystalline powder, odourless or has a faint mercaptan-like odour. Freely soluble in water, in dimethylformamide, and in methyl alcohol; soluble in alcohol; practically insoluble in acetone. pH of a 10% solution in water is between 3.0 and 5.5. Store in airtight containers.

Clindamycin Palmitate Hydrochloride

(BANM, USAN, rINNM)

Clindamicina, hidrocloruro del palmitato de; Clindamycine, Chlorhydrate de Palmitate de; Clindamycini Palmitatis Hydrochloridum; Hidrocloruro del palmitato de clindamicina; U-25179E; Клиндамицина Пальмитата Гидрохлорид.

Clindamycin 2-palmitate hydrochloride.

$C_{34}H_{63}ClN_2O_6S,HCl$=699.9

CAS — 36688-78-5 (clindamycin palmitate); 25507-04-4 (clindamycin palmitate hydrochloride).

ATC — D10AF01; G01AA10; J01FF01.

ATC Vet — QD10AF01; QG01AA10; QJ01FF01.

UNII — VN9A8JM7M7.

Pharmacopoeias. In *US*.

USP 36: (Clindamycin Palmitate Hydrochloride). A white to off-white amorphous powder having a characteristic odour. Freely soluble in water, in chloroform, in ether, and in benzene; soluble 1 in 3 of alcohol and 1 in 9 of ethyl acetate; very soluble in dimethylformamide. pH of a 1% solution in water is between 2.8 and 3.8. Store in airtight containers.

Clindamycin Phosphate *(BANM, USAN, rINNM)*

Clindamicina, fosfato de; Clindamycin-2-dihydrogenphosphat; Clindamycine, Phosphate de; Clindamycini Dihydrogenophosphas; Clindamycini Phosphas; Fosfato de clindamicina; Klindamicin-foszfát; Klindamicino fosfatas; Klindamisin Fosfat; Klindamycin dihydrogen fosfat; Klindamycinfosfat; Klindamysiinifosfaatti; U-28508; Клиндамицина Фосфат.

Clindamycin 2-(dihydrogen phosphate).
$C_{18}H_{34}ClN_2O_8PS$=505.0
CAS — 24729-96-2.
ATC — D10AF01; G01AA10; J01FF01.
ATC Vet — QD10AF01; QG01AA10; QJ01FF01.
UNII — EH6D7113I8.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Clindamycin Phosphate). A white or almost white, slightly hygroscopic powder. It shows polymorphism. Freely soluble in water; very slightly soluble in alcohol; practically insoluble in dichloromethane. A 1% solution in water has a pH of 3.5 to 4.5. Store at a temperature not exceeding 30 degrees in airtight containers.

USP 36: (Clindamycin Phosphate). A white to off-white, odourless or practically odourless, hygroscopic, crystalline powder. Soluble 1 in 2.5 of water; slightly soluble in dehydrated alcohol; very slightly soluble in acetone; practically insoluble in chloroform, in ether, and in benzene. pH of a 1% solution in water is between 3.5 and 4.5. Store in airtight containers.

Incompatibility. Solutions of clindamycin salts have an acid pH and incompatibility may reasonably be expected with alkaline preparations, or with drugs unstable at low pH. Licensed product information for the injectable solution of clindamycin states that incompatibility has been reported between clindamycin and the following drugs: ampicillin, aminophylline, barbiturates, calcium gluconate, ceftriaxone, ciprofloxacin, idarubicin, magnesium sulfate, phenytoin, and ranitidine.

Clindamycin phosphate is incompatible with natural rubber closures.

Uses and Administration

Clindamycin is a chlorinated derivative of the lincosamide antibacterial lincomycin. It is a mainly bacteriostatic drug used in the treatment of serious anaerobic infections, notably due to *Bacteroides fragilis*. Clindamycin is also used for some Gram-positive infections due to pneumococci, staphylococci (including meticillin-resistant forms), and streptococci. However, because of its potential for causing pseudomembranous colitis (see Adverse Effects, p. 273.2) it is usually used only when alternative drugs are unsuitable.

Amongst the conditions that it may be used to treat (either alone, or with other antibacterials) are liver abscess, actinomycosis, biliary-tract infections, staphylococcal bone and joint infections, the carrier state of diphtheria, endophthalmitis, gas gangrene, various gynaecological infections including bacterial vaginosis, endometritis, and pelvic inflammatory disease, intra-abdominal infections including secondary peritonitis, streptococcal pharyngitis (usually to treat the carrier state), serious respiratory-tract infections including empyema and pneumonia (especially lung abscess), septicaemia, and skin and soft-tissue infections involving heavy colonisation with streptococci or anaerobes such as necrotising fasciitis. It is used in the prophylaxis of endocarditis in penicillin-allergic patients, in the prevention of perinatal streptococcal infections, and with other drugs for the prophylaxis of surgical infection. It may be used as part of a multidrug regimen for the treatment of inhalation and gastrointestinal anthrax.

For details of these bacterial infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Clindamycin is also applied topically in the treatment of acne (see Skin Disorders, p. 273.1) and rosacea (see Skin Disorders, p. 273.1).

Clindamycin has some antiprotozoal actions, and has been used, usually with other antiprotozoals, in various infections including babesiosis (p. 272.3), malaria (p. 272.3), and toxoplasmosis (p. 273.1). It may also be used with primaquine in the treatment of pneumocystis pneumonia (p. 273.1).

Clindamycin is given **orally** as capsules containing the hydrochloride or as oral liquid preparations containing the palmitate hydrochloride. The capsules should be taken with a glass of water. Doses are expressed in terms of the base; 1.1 g of clindamycin hydrochloride and 1.6 g of clindamycin palmitate hydrochloride are each equivalent to about 1 g of clindamycin. The usual adult oral dose is 150 to 300 mg every 6 hours; in severe infections the dose may be increased to 450 mg every 6 hours.

Clindamycin is given **parenterally** as the phosphate by deep intramuscular injection or by intermittent or continuous intravenous infusion. Doses are again expressed in terms of the base; 1.2 g of clindamycin phosphate is equivalent to about 1 g of clindamycin. For intravenous use, the concentration of clindamycin in diluent for infusion should not exceed 18 mg/mL and the rate of infusion should be not more than 30 mg/minute with a maximum of 1.2 g given in a single one-hour infusion. Continuous intravenous infusions may begin with a single rapid infusion of the first dose (generally over 30 minutes), followed by a continuous infusion of 0.75 to 1.25 mg/minute. Not more than 600 mg should be given as a single intramuscular injection.

The usual parenteral dose is the equivalent of 0.6 to 1.2 g of clindamycin daily in two to four divided doses; in severe infections the dose may be increased to 2.7 g daily and up to 4.8 g daily may be given intravenously in life-threatening situations.

For *prophylaxis* in adult patients at high risk of developing endocarditis and who cannot be given a penicillin, US experts suggest a single 600 mg dose of clindamycin, given orally, intramuscularly, or by intravenous infusion, 30 to 60 minutes before dental procedures involving manipulation of the gums, perforation of the oral mucosa, or work on the periapical areas of the teeth. However, in the UK the *BNF* and NICE now suggest that such prophylaxis is unnecessary (see p. 179.2).

For details of doses in children, including infants and adolescents, see p. 272.2.

Topical formulations containing clindamycin phosphate equivalent to 1% of clindamycin are used for the treatment of acne. The hydrochloride may be applied similarly, but systemic absorption may be greater (see Pharmacokinetics, p. 274.2). Clindamycin phosphate is also available in combination preparations with adapalene, benzoyl peroxide, and tretinoin.

Clindamycin phosphate may be given **intravaginally** as pessaries or as a 2% cream for the treatment of bacterial vaginosis; the equivalent of about 100 mg of clindamycin is given at night for 3 to 7 days.

Administration. Some studies have suggested that a parenteral regimen of clindamycin 600 mg three times daily is as effective as giving the same dose four times daily,[1] or as giving 900 mg three times daily.[2,3] In a meta-analysis[4] of parenteral clindamycin dosing regimens, 600 or 900 mg three times daily were similarly effective in the treatment of pelvic infection. For intra-abdominal infections, the two regimens showed similar rates of clinical success (defined as either improvement or cure), but the 600-mg regimen showed a significantly lower rate of definitive cure. The authors suggested that, although 600 mg three times daily was likely to be acceptable for most pelvic infections, dose recommendations for intra-abdominal infections should remain patient specific.

A population *pharmacokinetic model* in 50 patients treated with either oral or intravenous clindamycin for osteomyelitis found that clindamycin clearance increases with body weight; it was suggested that for patients weighing more than 75 kg a dose of 900 mg three times daily may be considered.[5]

1. Buchwald D, *et al.* Effect of hospitalwide change in clindamycin dosing schedule on clinical outcome. *Rev Infect Dis* 1989; **11**: 619–24.
2. Chin A, *et al.* Cost analysis of two clindamycin dosing regimens. *DICP Ann Pharmacother* 1989; **23**: 980–3.
3. Chatwani A, *et al.* Clindamycin dosage scheduling for acute pelvic infection. *Am J Obstet Gynecol* 1990; **163**: 240.
4. Rovers JP, *et al.* Meta-analysis of parenteral clindamycin dosing regimens. *Ann Pharmacother* 1995; **29**: 852–8.
5. Bouazza N, *et al.* Population pharmacokinetics of clindamycin orally and intravenously administered in patients with osteomyelitis. *Br J Clin Pharmacol* 2012; **74**: 971–7.

INTRAVITREAL ROUTE. Intravitreal injection of clindamycin 1 mg, alone or with surgical intervention, was successfully used in 6 patients with toxoplasmic retinochoroiditis.[1] Favourable outcomes and good tolerance were also noted in patients treated with intravitreal clindamycin and dexamethasone.[2,3] Intravitreal injection of clindamycin with gentamicin has been reported[4] to be of benefit in preventing acute bacterial endophthalmitis in patients with retained intra-ocular foreign bodies after penetrating eye injury.

1. Sobrin L, *et al.* Intravitreal clindamycin for toxoplasmic retinochoroiditis. *Retina* 2007; **27**: 952–7.
2. Kishore K, *et al.* Intravitreal clindamycin and dexamethasone for toxoplasmic retinochoroiditis. *Ophthalmic Surg Lasers* 2001; **32**: 183–92.
3. Lasave AF, *et al.* Intravitreal clindamycin and dexamethasone for zone 1 toxoplasmic retinochoroiditis at twenty-four months. *Ophthalmology* 2010; **117**: 1831–8.
4. Soheilian M, *et al.* Prophylaxis of acute posttraumatic bacterial endophthalmitis: a multicenter, randomized clinical trial of intraocular antibiotic injection, report 2. *Arch Ophthalmol* 2007; **125**: 460–5.

SUBCONJUNCTIVAL ROUTE. It has been suggested, should periocular use of clindamycin be necessary, that the injection solution can be given in doses of 15 to 50 mg by subconjunctival injection.[1]

1. Moorfields Eye Hospital NHS Foundation Trust. *Pharmacists Handbook 2006*. London: Moorfields Pharmaceuticals, 2006.

Administration in children. The usual oral dose for infants and children under 12 years of age is the equivalent of 3 to 6 mg/kg of clindamycin every 6 hours; children over 12 years of age may be given the usual adult dose (see Uses and Administration, above). In the UK, the *BNFC* suggests that neonates aged 14 to 28 days may also be given an oral dose of 3 to 6 mg/kg every 6 hours while those aged under 14 days may be given this dose every 8 hours. US authorities recommend that neonates are given oral clindamycin in the same doses as those used parenterally (see below).

The usual **parenteral** dose for infants and children aged from 1 month to 12 years is the equivalent of 15 to 25 mg/kg of clindamycin daily in 3 or 4 divided doses; in severe infections the dose may be increased to 40 mg/kg daily and a minimum dose of 300 mg daily should be given regardless of body-weight. Children over 12 years of age may be given the usual adult dose (see Uses and Administration, above). In the USA, the following parenteral doses have been suggested by the American Academy of Pediatrics[1] for use in those aged less than 1 month; these doses may also be given orally:

- for neonates aged ⩽7 days and weighing ⩽2 kg: 5 mg/kg every 12 hours
- for neonates aged ⩽7 days and weighing >2 kg: 5 mg/kg every 8 hours
- for neonates aged 8 to 28 days and weighing ⩽2 kg: 5 mg/kg every 8 hours; a dosing interval of 12 hours may be used until 2 weeks of life in extremely low birth-weight neonates (those weighing less than 1 kg)
- for neonates aged 8 to 28 days and weighing >2 kg: 5 mg/kg every 6 hours

It should be borne in mind that some parenteral formulations contain benzyl alcohol, which may cause fatal 'gasping syndrome' in neonates (see p. 1741.1).

For the treatment of staphylococcal lung infection in children aged from 1 month to 18 years with cystic fibrosis, the *BNFC* recommends oral doses of 5 to 7 mg/kg (to a maximum of 600 mg) every 6 hours.

For children's doses in babesiosis, malaria, and toxoplasmosis, see below.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*. 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Babesiosis. Clindamycin, given with quinine, both for 7 to 10 days, is recommended by some experts in the USA for the treatment of babesiosis (p. 922.2) caused by *Babesia microti*. Dosage regimens include:

- clindamycin 1.2 g intravenously twice daily, with quinine 650 mg orally three or four times daily
- clindamycin 300 to 600 mg intravenously every 6 hours with quinine as above
- clindamycin 600 mg orally three times daily, with quinine as above

Children may be given clindamycin 20 to 40 mg/kg daily intravenously or orally in 3 or 4 divided doses with quinine 25 mg/kg daily orally in 3 divided doses, both for 7 to 10 days.

1. Wormser GP, *et al.* The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2006; **43**: 1089–1134. Correction. *ibid.* 2007; **45**: 941. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/508667 (accessed 23/03/09)

Malaria. Quinine sulfate plus follow-on treatment with doxycycline, tetracycline, or clindamycin are recommended regimens for the treatment of chloroquine-resistant falciparum malaria (p. 644.1) in non-endemic malaria areas. Doxycycline is generally preferred because it can be given once daily, and there are more data on the efficacy of quinine combined with the tetracyclines than with clindamycin.[1] However, tetracyclines are contra-indicated in children under 8 years of age and in pregnant women, and these groups may be given clindamycin. Clindamycin is given in a usual *adult* dose of 20 mg/kg daily in 3 divided doses (or 450 mg 3 times daily) for 7 days with quinine sulfate 600 to 650 mg 3 times daily for 3 or 7 days (depending on where the infection was acquired), both orally.[1-5] Parenteral quinine (or quinidine) plus follow-on treatment with a tetracycline or clindamycin may be used for severe falciparum malaria in both endemic and non-endemic malaria areas.[1,3-6] Patients unable to tolerate oral treatment may begin follow-on therapy intravenously.[6]

In the UK[5] public health authorities recommend that *children* be given clindamycin at a dose of 7 to 13 mg/kg 3 times daily for 7 days; US[1] public health authorities recommend giving 20 mg/kg daily in 3 divided doses.

1. CDC. Treatment guidelines: treatment of malaria (guidelines for clinicians) (updated April 2011). Available at: http://www.cdc.gov/malaria/resources/pdf/clinicalguidance.pdf (accessed 27/07/11)
2. Abramowicz M, ed. *Drugs for parasitic infections*. 3rd ed. New Rochelle NY: The Medical Letter, 2013.
3. British Infection Society. Algorithm for initial assessment and management of malaria in adults (issued February 2007). Available at: http://www.britishinfection.org/drupal/sites/default/files/MalariaAlgorithm07.pdf (accessed 17/01/11)
4. WHO. *Guidelines for the treatment of malaria*. 2nd ed. Geneva: WHO, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf (accessed 18/08/10) Update (issued April 2011), available at: http://www.who.int/malaria/publications/atoz/mal_treatchild_revised.pdf (accessed 20/05/11)
5. Lalloo DG, *et al.* HPA Advisory Committee on Malaria Prevention in UK Travellers. UK malaria treatment guidelines. *J Infect* 2007; **54**: 111–21. Correction. [primaquine dose]. Corrected version available at: http://

www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1194947343507 (accessed 25/05/10)
6. CDC. Guidelines for treatment of malaria in the United States: based on drugs currently available for use in the United States (updated 18th May, 2009). Available at: http://www.cdc.gov/malaria/pdf/treatmenttable.pdf (accessed 18/08/10)

Pneumocystis pneumonia. Clindamycin may be used with primaquine as an alternative to co-trimoxazole for the treatment of pneumocystis pneumonia (p. 567.2). In the USA, some experts[1,2] recommend giving clindamycin 600 to 900 mg intravenously, or 300 to 450 mg orally, every 6 or 8 hours with primaquine 30 mg orally once daily, both for 21 days. In the UK the *BNF* suggests giving clindamycin 600 mg every 8 hours with primaquine 30 mg daily, both orally, for mild to moderate disease (but notes that this combination is associated with considerable toxicity).

A meta-analysis[3] of literature published between January 1975 to August 1999 found that, when compared with other salvage agents (such as atovaquone, co-trimoxazole, eflornithine, pentamidine, and trimetrexate), clindamycin with primaquine was the most effective regimen in patients unresponsive to conventional treatment. The authors also concluded that this latter regimen was effective as primary treatment of mild to moderately severe disease and suggested that it had fewer adverse effects than co-trimoxazole. However, a later systematic review[4] of second-line salvage treatments for AIDS-related pneumocystis pneumonia considered co-trimoxazole to be the drug of choice in most settings; clindamycin with primaquine was recommended as a suitable salvage option where initial treatment with co-trimoxazole has failed or been poorly tolerated.

Clindamycin with primaquine is not normally recommended for **prophylaxis** although there are reports of it being tried.[5] A retrospective examination[6] of the records of patients who had received prophylaxis found that clindamycin with primaquine was less effective than co-trimoxazole or dapsone, although this could have been due in part to underdosing.

1. Abramowicz M, ed. *Drugs for parasitic infections*. 3rd ed. New Rochelle NY: The Medical Letter, 2013.
2. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America (issued 8th July, 2013). Available at: http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf (accessed 12/09/13)
3. Smego RA, *et al.* A meta-analysis of salvage therapy for Pneumocystis carinii pneumonia. *Arch Intern Med* 2001; **161**: 1529–33.
4. Benfield T, *et al.* Second-line salvage treatment of AIDS-associated Pneumocystis jirovecii pneumonia: a case series and systematic review. *J Acquir Immune Defic Syndr* 2008; **48**: 63–7.
5. Kay R, DuBois RE. Clindamycin/primaquine therapy and secondary prophylaxis against Pneumocystis carinii pneumonia in patients with AIDS. *South Med J* 1990; **83**: 403–4.
6. Barber BA, *et al.* Clindamycin/primaquine as prophylaxis for Pneumocystis carinii pneumonia. *Clin Infect Dis* 1996; **23**: 718–22.

Skin disorders. *ACNE.* Clindamycin is one of the most widely used topical antibacterials in the treatment of acne vulgaris (p. 1682.2), usually with other topical drugs to reduce the development of resistance.

Some references.

1. Schlessinger J, *et al.* ZIANA Study Group. Clinical safety and efficacy studies of a novel formulation combining 1.2% clindamycin phosphate and 0.025% tretinoin for the treatment of acne vulgaris. *J Drugs Dermatol* 2007; **6**: 607–15.
2. Guay DR. Topical clindamycin in the management of acne vulgaris. *Expert Opin Pharmacother* 2007; **8**: 2625–64.
3. McKeage K, Keating GM. Clindamycin/benzoyl peroxide gel (BenzaClin): a review of its use in the management of acne. *Am J Clin Dermatol* 2008; **9**: 193–204.
4. Korting HC, Schöllmann C. Management der Acne vulgaris: Fokus auf Clindamycin und Zink. *Hautarzt* 2009; **60**: 42–7.
5. Del Rosso JQ, Schmidt NF. A review of the anti-inflammatory properties of clindamycin in the treatment of acne vulgaris. *Cutis* 2010; **85**: 15–24.

ROSACEA. Topical clindamycin[1] has improved inflammatory episodes of rosacea (p. 1688.3), although other features of the skin disorder may not respond. A small study[2] showed that once-daily application of clindamycin 1% plus benzoyl peroxide 5% was effective in the treatment of moderate to severe rosacea.

1. Wilkin JK, DeWitt S. Treatment of rosacea: topical clindamycin versus oral tetracycline. *Int J Dermatol* 1993; **32**: 65–7.
2. Breneman D, *et al.* Double-blind, randomized, vehicle-controlled clinical trial of once-daily benzoyl peroxide/clindamycin topical gel in the treatment of patients with moderate to severe rosacea. *Int J Dermatol* 2004; **43**: 381–7.

Toxoplasmosis. Clindamycin with pyrimethamine has been used for the treatment and secondary prophylaxis (chronic maintenance) of toxoplasmosis (p. 926.1) instead of the more usual treatment with pyrimethamine plus sulfadiazine, in patients unable to tolerate sulfonamides; folinic acid is also given to counteract the megaloblastic anaemia associated with pyrimethamine. In adult patients with AIDS and toxoplasmic encephalitis, US recommendations[1] are:

- *treatment* with clindamycin 600 mg every 6 hours orally or intravenously for at least 6 weeks, *then*
- *chronic maintenance* therapy with oral clindamycin 600 mg every 8 hours

For corresponding doses of pyrimethamine, see under Pyrimethamine p. 663.1.

Children may be given oral or intravenous clindamycin 5 to 7.5 mg/kg 4 times daily for at least 6 weeks, followed by chronic maintenance therapy.[2]

Two studies have found acute therapy with pyrimethamine and oral clindamycin, 600 mg 4 times daily[3] or 1200 mg every 6 hours intravenously,[4] to be as effective as pyrimethamine and sulfadiazine. Oral maintenance therapy with pyrimethamine and clindamycin 300 mg 4 times daily was, however, found to be less effective than pyrimethamine and sulfadiazine at preventing relapses in a population followed for 3 years or more[3] and consequently higher maintenance doses of clindamycin are now recommended (see above). Clindamycin with fluorouracil produced beneficial responses in a study involving 16 patients.[5]

In contrast, another study, comparing clindamycin alone (in lower oral doses—300 mg twice daily) with pyrimethamine alone for prophylaxis of toxoplasmic encephalitis, reported an unacceptably high incidence of adverse effects with clindamycin, which forced premature termination of the clindamycin arm—see AIDS under Precautions, p. 273.3.

Intravitreal injections of clindamycin have also been used to treat toxoplasmic retinochoroiditis, usually where systemic therapy has failed or been poorly tolerated—see Intravitreal Route, p. 270.2.

1. CDC. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America. *MMWR* 2009; **58** (RR-4): 1–207. Also available at: http://www.cdc.gov/mmwr/PDF/RR/RR5804.pdf (accessed 11/05/09)
2. CDC. Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. *MMWR* 2009; **58** (RR-11): 1–166. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5811.pdf (accessed 10/11/10)
3. Katlama C, *et al.* Pyrimethamine-clindamycin vs pyrimethamine-sulphadiazine as acute and long-term therapy for toxoplasmic encephalitis in patients with AIDS. *Clin Infect Dis* 1996; **22**: 268–75.
4. Dannemann B, *et al.* Treatment of toxoplasmic encephalitis in patients with AIDS: a randomized trial comparing pyrimethamine plus clindamycin to pyrimethamine plus sulfadiazine. *Ann Intern Med* 1992; **116**: 33–43.
5. Dhiver C, *et al.* 5-Fluoro-uracil-clindamycin for treatment of cerebral toxoplasmosis. *AIDS* 1993; **7**: 143–4.

Adverse Effects and Treatment

Use of clindamycin has been associated with the development of diarrhoea in up to 20% of patients; symptoms have occurred with topical as well as oral or parenteral formulations. In about 2 to 10% of patients severe or even fatal antibiotic-associated or pseudomembranous colitis may develop during therapy or up to several weeks afterwards. Early reports showed that it occurred more frequently in middle-aged and elderly women, particularly after abdominal surgery; it may also occur rarely after vaginal use. Clindamycin should be stopped immediately if significant diarrhoea or colitis occurs; recovery usually occurs within 3 weeks of stopping the drug. Protein supplementation and use of an antibacterial active against *Clostridium* spp. should be considered for severe antibiotic-associated colitis. For further information on the treatment of antibiotic-associated colitis see p. 183.1.

Other gastrointestinal effects include nausea, vomiting, abdominal pain or cramps; an unpleasant or metallic taste has occasionally been reported after high intravenous doses. Oesophagitis and oesophageal ulceration has been reported particularly after ingestion of capsules with insufficient water. Taste disturbances may also be associated with oral and topical use of clindamycin.

Rashes and urticaria, the most common hypersensitivity reactions, occur in up to 10% of patients usually after 1 to 2 weeks of therapy. Erythema multiforme, Stevens-Johnson syndrome, and exfoliative and vesiculobullous dermatitis have been reported rarely, and a few cases of anaphylaxis have occurred.

Other adverse effects include transient leucopenia or occasionally agranulocytosis, eosinophilia, thrombocytopenia, polyarthritis, and abnormalities of liver function tests; in some cases overt jaundice and hepatic damage have been reported. Renal dysfunction, shown by azotaemia, oliguria, and/or proteinuria, has been reported rarely.

Although local irritation is rare, intramuscular injection has led to induration and sterile abscess, and thrombophlebitis may occur after intravenous use. Too rapid intravenous infusion can result in rare instances of cardiopulmonary arrest and hypotension. Some parenteral formulations contain benzyl alcohol which may cause fatal 'gasping syndrome' in neonates (see p. 1741.1).

Topical application may be associated with local irritation, skin dryness, and contact dermatitis; sufficient clindamycin may be absorbed to produce systemic effects. Cervicitis, vaginitis, vaginal candidiasis, and vulvovaginal irritation have been reported with intravaginal use; a small amount of systemic absorption also occurs.

Effects on the cardiovascular system. Cardiac arrest occurred in a 50-year-old woman after rapid injection of 600 mg of undiluted clindamycin phosphate into a central intravenous line. Further injections were given over 30 minutes without cardiovascular complications.[1] There has also been a case of severely prolonged QT interval attributed to the addition of clindamycin to therapy in an elderly woman;[2] the patient developed AV block and subsequent torsade de pointes, and required resuscitation. When clindamycin was stopped, signs of heart block resolved, and the QT interval returned to normal over several days.

1. Aucoin P, *et al.* Clindamycin-induced cardiac arrest. *South Med J* 1982; **75**: 768.
2. Gabel A, *et al.* Ventricular fibrillation due to long QT syndrome probably caused by clindamycin. *Am J Cardiol* 1999; **83**: 813–15.

Effects on the ears. A 14-year-old boy who was treated with topical clindamycin for acne vulgaris developed unilateral tinnitus during therapy and unilateral sensorineural hearing loss 2 months later;[1] symptoms subsequently recurred upon 2 rechallenges.

1. Scissors B, Shwayder T. Topical clindamycin reproducibly causing tinnitus in a 14-year-old boy. *J Am Acad Dermatol* 2006; **54** (suppl): S243–S244.

Effects on the lymphatic system. Lymphadenopathy was reported in a 54-year-old woman given intravenous clindamycin as part of an antibacterial regimen for osteomyelitis. Symptoms resolved when clindamycin was stopped, but recurred on rechallenge with the drug.[1]

1. Southern PM. Lymphadenitis associated with the administration of clindamycin. *Am J Med* 1997; **103**: 164–5.

Effects on the skin. Toxic epidermal necrosis was reported in a patient about 7 days after starting an oral course of clindamycin; with treatment, the condition resolved within 4 weeks.[1] Acute generalised exanthematous pustulosis associated with oral clindamycin use has also been reported in some patients.[2-4]

Acute febrile neutrophilic dermatosis, or Sweet's syndrome, has been reported in patients given oral, or oral and intravenous, clindamycin for dental infections.[5,6]

1. Paquet P, *et al.* Toxic epidermal necrolysis following clindamycin treatment. *Br J Dermatol* 1995; **132**: 665–6.
2. Valois M, *et al.* Clindamycin-associated acute generalized exanthematous pustulosis. *Contact Dermatitis* 2003; **48**: 169.
3. Kapoor R, *et al.* Acute generalized exanthematous pustulosis induced by clindamycin. *Arch Dermatol* 2006; **142**: 1080–81.
4. Sulewski RJ, *et al.* Acute generalized exanthematous pustulosis due to clindamycin. *Dermatol Online J* 2008; **14**: 14. Available at: http://dermatology.cdlib.org/147/case_presentation/agep/blyumin.html (accessed 06/05/09)
5. Clark BM, *et al.* Clindamycin-induced Sweet's syndrome. *Pharmacotherapy* 2007; **27**: 1343–6.
6. Kandula S, *et al.* Clindamycin-induced Sweet syndrome. *J Am Acad Dermatol* 2010; **62**: 898–900.

Precautions

Clindamycin should not be given to patients hypersensitive to it or to the closely related drug lincomycin. It should be used with caution in patients with a history of gastrointestinal disease, particularly colitis, and stopped immediately if significant diarrhoea or colitis occurs. Middle-aged and elderly female patients may be at greater risk of severe diarrhoea or pseudomembranous colitis, especially after abdominal surgery. Caution has also been advised in atopic patients. Periodic tests of liver and kidney function and blood counts have been recommended in patients on prolonged therapy, and in infants. Caution is required during parenteral use in neonates, since some parenteral formulations contain benzyl alcohol which may cause fatal 'gasping syndrome' (see p. 1741.1).

AIDS. Clindamycin was poorly tolerated by patients with AIDS in a study of its use for *prophylaxis* of toxoplasmic encephalitis.[1] Despite the use of relatively low doses of clindamycin (300 mg twice daily), 23 of 52 patients reported adverse effects that necessitated temporary or permanent withdrawal of the drug, the most frequent adverse reactions being diarrhoea and rash. The clindamycin arm of the study had to be terminated prematurely. Nevertheless, clindamycin has been used successfully in patients with AIDS for the *treatment* of both toxoplasmic encephalitis (see Toxoplasmosis, above) and pneumocystis pneumonia (above).

1. Jacobson MA, *et al.* Toxicity of clindamycin as prophylaxis for AIDS-associated toxoplasmic encephalitis. *Lancet* 1992; **339**: 333–4.

Breast feeding. US licensed product information states that concentrations of clindamycin in breast milk were 0.7 to 3.8 micrograms/mL after doses of 150 mg orally to 600 mg intravenously. The last available guidance from the American Academy of Pediatrics[1] considered that use

of clindamycin was usually compatible with breast feeding. Nevertheless, UK product information states that although it is unlikely that a breast-fed infant could absorb significant amounts, caution should be exercised when clindamycin is given during breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies clindamycin as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 09/08/11)

Interactions

Clindamycin has neuromuscular blocking activity and may enhance the effect of other drugs with this action (see Atracurium, p. 2032.1), leading to a potential danger of respiratory depression. Clindamycin may antagonise the effects of parasympathomimetics.

Clindamycin may competitively inhibit the effects of macrolides, ketolides, streptogramins, linezolid, and chloramphenicol because they all bind to the same subunit of the ribosome. Antagonism between clindamycin and erythromycin has been shown *in vitro*.

Adsorbents. In 16 healthy subjects given clindamycin alone and with a *kaolin-pectin* suspension it was found that the suspension had no effect on the extent of clindamycin absorption but did markedly reduce the absorption rate.[1]

1. Albert KS, *et al.* Pharmacokinetic evaluation of a drug interaction between kaolin-pectin and clindamycin. *J Pharm Sci* 1978; 67: 1579–82.

Immunosuppressants. For the effect of clindamycin on *ciclosporin* disposition, see Lincosamides, under Interactions of Ciclosporin, p. 1956.1.

Antimicrobial Action

Clindamycin is a lincosamide antibacterial with a mainly bacteriostatic action against Gram-positive aerobes and many anaerobic bacteria.

Mechanism of action. Lincosamides such as clindamycin bind to the 50S subunit of the bacterial ribosome, similarly to macrolides such as erythromycin (p. 297.1), and inhibit the early stages of protein synthesis. The action of clindamycin is mainly bacteriostatic, although high concentrations may be slowly bactericidal against sensitive strains.

Spectrum of activity. Clindamycin is active against:

- most aerobic Gram-positive bacteria including streptococci, staphylococci, *Bacillus anthracis, Nocardia* spp., and *Corynebacterium diphtheriae;* enterococci are generally resistant, but clindamycin has some activity against *Enterococcus durans*
- many Gram-positive anaerobes including *Bifidobacterium, Lactobacillus, Eubacterium, Propionibacterium, Peptococcus,* and *Peptostreptococcus* spp., and many strains of *Actinomyces* spp., *Clostridium perfringens,* and *Cl. tetani.* The susceptibility of *Cl. difficile* varies widely, but during outbreaks of diarrhoea associated with *Cl. difficile,* the strains are usually resistant to clindamycin
- Gram-negative anaerobes such as *Fusobacterium* spp. (although *F. varium* is usually resistant), *Prevotella* spp., and *Bacteroides* spp., including the *B. fragilis* group

Most Gram-negative aerobic bacteria, including the Enterobacteriaceae, *Pseudomonas* spp., and *Acinetobacter* spp., are intrinsically resistant to clindamycin; unlike erythromycin, *Neisseria gonorrhoeae, N. meningitidis,* and *Haemophilus influenzae* are generally resistant. *Mycoplasma* spp. are also generally resistant to clindamycin. *Mycobacterium tuberculosis* is resistant, but clindamycin has some activity against *M. leprae.* Fungi, yeasts, and viruses are also resistant; however, clindamycin has been reported to have some antiprotozoal activity against *Toxoplasma gondii* and *Plasmodium* spp.

Resistance. The mechanisms of acquired resistance are the same as those for erythromycin, namely methylation of the ribosomal binding site, chromosomal mutation of the ribosomal protein, and, in a few staphylococcal isolates, enzymic inactivation by a plasmid-mediated adenyltransferase. Methylation of the ribosome leads to cross-resistance between the lincosamides and macrolides and streptogramins (the MLS_B phenotype); this type of resistance is usually plasmid-mediated and inducible. Another resistance pattern (the M phenotype), which is common in the macrolide-resistant streptococci spp. found in the US, does not impart cross-resistance to clindamycin. Complete cross-resistance exists between clindamycin and lincomycin.

The incidence of resistance varies with the organism and the geographical location; it is more frequent in organisms that are also erythromycin-resistant, and some strains of meticillin-resistant *Staph. aureus* are also resistant to clindamycin. In some countries and institutions there is evidence of an increase in resistance amongst the *B. fragilis* group to about 25% of strains or more. Resistance to clindamycin by anaerobes has also been reported in 10 to 20% of *Clostridium* spp. other than *C. perfringens,* 8% of peptostreptococci, 9% of *Fusobacterium* spp., and 11% of *Prevotella* strains.

Action. References suggesting that clindamycin may reduce microbial adherence and enhance phagocytosis by its effects on bacterial slime (glycocalyx)[1-3] and that its antibacterial effects may be independent of plasma concentrations.[4,5]

1. Veringa EM, *et al.* Enhancement of opsonophagocytosis of Bacteroides spp by clindamycin in subinhibitory concentrations. *J Antimicrob Chemother* 1981; 23: 577–87.
2. Veringa EM, *et al.* The role of glycocalyx in surface phagocytosis of Bacteroides spp. in the presence and absence of clindamycin. *J Antimicrob Chemother* 1989; 23: 711–20.
3. Khardori N, *et al.* Effect of subinhibitory concentrations of clindamycin and trospectomycin on the adherence of Staphylococcus epidermidis in an in vitro model of vascular catheter colonization. *J Infect Dis* 1991; 164: 108–13.
4. Xue IB, *et al.* Variation in postantibiotic effect of clindamycin against clinical isolates of Staphylococcus aureus and implications for dosing of patients with osteomyelitis. *Antimicrob Agents Chemother* 1996; 40: 1403–7.
5. Klepser ME, *et al.* Bactericidal activity of low-dose clindamycin administered at 8- and 12-hour intervals against Staphylococcus aureus, Streptococcus pneumoniae, and Bacteroides fragilis. *Antimicrob Agents Chemother* 1997; 41: 630–5.

Pharmacokinetics

About 90% of a dose of clindamycin hydrochloride is absorbed from the gastrointestinal tract; concentrations of 2 to 3 micrograms/mL occur within 1 hour after a 150-mg oral dose, with average concentrations of about 700 nanograms/mL after 6 hours. After doses of 300 and 600 mg, peak plasma concentrations of 4 and 8 micrograms/mL, respectively, have been reported. Absorption is not significantly diminished by food but the rate of absorption may be reduced. Clindamycin palmitate hydrochloride is rapidly hydrolysed to free clindamycin on oral use.

When given parenterally, the biologically inactive clindamycin phosphate is also hydrolysed to clindamycin. When the equivalent of 300 mg of clindamycin is injected intramuscularly, a mean peak plasma concentration of 6 micrograms/mL occurs within 3 hours; 600 mg gives a peak concentration of 9 micrograms/mL. In children, peak concentrations may occur within 1 hour. When the same doses are infused intravenously, peak concentrations of 7 and 10 micrograms/mL occur by the end of infusion.

Small amounts of clindamycin may be absorbed after topical application to the skin; absorption of clindamycin hydrochloride from the skin is about 4 to 5%. Systemic absorption of the phosphate is lower and it is therefore preferred for topical use. About 5% of a dose may be absorbed systemically from an intravaginal cream formulation; systemic absorption appears to be slower in women with bacterial vaginosis than in healthy women. Absorption from vaginal pessaries is reported to be about 30%.

Clindamycin is widely distributed in body fluids and tissues, including bone, but it does not reach the CSF in significant concentrations. It diffuses across the placenta into the fetal circulation and has been reported to appear in breast milk. High concentrations occur in bile. It accumulates in leucocytes and macrophages. Over 90% of clindamycin in the circulation is bound to plasma proteins. The half-life is 2 to 3 hours, but may be prolonged in preterm neonates and in patients with severe renal impairment.

Clindamycin undergoes metabolism, presumably in the liver, to the active *N*-demethyl and sulfoxide metabolites, and also to some inactive metabolites. About 10% of a dose is excreted in the urine as active drug or metabolites and about 4% in the faeces; the remainder is excreted as inactive metabolites. Excretion is slow, and takes place over several days. It is not effectively removed from the blood by dialysis.

AIDS patients. Clindamycin was reported to have higher bioavailability, lower plasma clearance, and a lower volume of distribution in patients with AIDS than in healthy subjects.[1] This may partly be explained by increased binding to plasma proteins.[2]

Although it is generally considered that penetration of clindamycin into the CSF is insignificant, parasiticidal CSF concentrations against *Toxoplasma gondii* were achieved with intravenous clindamycin in patients with AIDS.[3]

1. Gatti G, *et al.* Comparative study of bioavailabilities and pharmacokinetics of clindamycin in healthy volunteers and patients with AIDS. *Antimicrob Agents Chemother* 1993; 37: 1137–43.
2. Flaherty JF, *et al.* Protein binding of clindamycin in sera of patients with AIDS. *Antimicrob Agents Chemother* 1996; 40: 1134–8.
3. Gatti G, *et al.* Penetration of clindamycin and its metabolite N-demethylclindamycin into cerebrospinal fluid following intravenous infusion of clindamycin phosphate in patients with AIDS. *Antimicrob Agents Chemother* 1998; 42: 3014–17.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Acnestop; Clidan; Clindacin; Clindalaf; Clindopax; Clintopic; Dalacin C; Dalacin T; Naxoclinda; Torgyn; *Austral.*: Cleocin; Clindatech; Dalacin C; Dalacin T; Dalacin V; Zindaclin; *Austria*: Clindac; Dalacin C; Dalacin; Lanacine; *Belg.*: Dalacin C; Dalacin; Dalacin; Zindaclin; *Braz.*: Anaerocid; Clinagel; Clindabiotic; Clindacne; Clindamin C; Clindarix; Dalacin C; Dalacin T; Dalacin V; *Canad.*: Clinda-T; Clindets; Dalacin C; Dalacin T; Dalacin Vaginal; *Chile*: Biomicin; Clidets; Clinacnyl; Cluvax; Daclin; Dalacin C; Dalacin T; Dalacin V†; Dalacin; Dermabel; Divanon; *China*: Ao Di (傲地); Ao Li Xian (奥丽先); Bang Wei Lin Xin (邦韦林欣); Bei He (倍禾); Bin Ke (滨可); Bo Le (博乐); Bo Shi Duo Ta (博士多他); Da Fen Rong (达芬蓉); Dalacin C (特丽仙 C); Dalacin T (特丽仙 T); De Bao Sheng (德宝生); Fu Bang (孚邦); Fu Si Ka (福司卡); Heng Xin (恒新); Huashu (华舒); Jianqi (健奇); Jie Li (捷立); Jin Ge Duo Na (金格多那); Jing Dan (景丹); Kai Fu Fei (凯福菲); Ke Er Sheng (可尔生); Ke Ran Fu (恪然福); Ke Su (克苏); Ke Xin Lin (可欣林); Li Bang Te (力邦特); Li Shen (力深); Li pai (力派); LiTai (力泰); Lizhuling (丽珠灵); Long Ge Xin (隆格新); Long Ke Duo (龙可多); Luoqing (洛庆); Mei Di Xing (美迪星); Pu Nai Tong (普耐同); Pu Yuan Xin (普源欣); Qi Er Su (齐尔速); Qin Lin (沁林); Rong Da (容大); She Xin (舍欣); She Yue (舍悦); Shuai Ke Jia Er (帅克佳尔); Shuaijie (帅洁); Tadix an (他迪仙); Tang Ni Wei (汤尼威); Te Na Si (特纳斯); Wei K ng (维康); Xianqing (先清); Xin Fu Neng (欣复能); Xin Lai (信莱); Xin Pu Feng (欣普风); Xin Qi (馨琦); Xin Yi Kang (欣忆康); Xu Luo (旭洛); Yan Le (颜乐); Yi Jun Ding (益君定); You Ni L ng (尤尼灵); ZaiXing (再欣); Zha Wei (札威); Zhi Fu Bao (知芙宝); Zhuo Li (卓力); *Cz.*: Dalacin C; Dalacin T; Dalacin; Klimicin; Zindaclin†; *Denm.*: Dalacin C; Dalacin; Myclin†; *Fin.*: Dalacin; Klindagol†; Myclin†; *Fr.*: Dalacine T; Dalacine; Zindacline; *Ger.*: Basocin; Clin-Sanorania; Clinda-saar; Clinda; Clindabeta; Clindahexal†; Clindasol; Clindastad†; Dentomycin†; Jutaclin†; Sobelin; Turimycin†; *Gr.*: Arfarel; Borophen; Botamycin-N; Clidacin; Climycen; Clindagel; Clindamed; Dalacin C; Edasin; Esteria; Fleminosan; Fouch; Lindasol; Paradis; Skinasol; Sooomycin; Toliken; Updern; Vagiclin; Veldom; Velkaderm; Ygiele; *Hong Kong*: Bittle; Claribel; Clinac; Clindatech; Clinex; Dalacin C; Dalacin T; Delta T†; Frankacin-T†; Kolinclin; Qualiclinda; T3 Mycin; Tidact†; Zindaclin; *Hung.*: Dalacin C; Dalacin T; Dalacin; Klimicin; *India*: Acneclin; Acneris; Clear Gel; Clenz; Clid; Climycin; Clin-Gold; Clincin; Clindac-A; Clindatec; Clindaz; Clinderm; Clindol; Clingard; Clinscar; CTop; Daklin; Dalacin C; Dalacin; Dalcap†; Dalcinex; Daltrex; Erytop; Gynasafe; Labomycin; Magclin; Mimosee; *Indon.*: Albiotin; Anerocid; Biodasin; Cindala†; Clidacor; Climadan; Clinbercin; Clindexcin; Clinex; Clinidac; Clinika; Clinium; Clinjos; Clinmas; Comdasin; Dacin; Daclin; Dalacin C; Ethidan; Indanox; Lando; Librodan†; Lindacyn; Lindan; Mediklin; Milorin; Niladacin; Nufaclind; Opiclam; Probiotin; Prolic Zumatic; *Irl.*: Dalacin C; Dalacin T; Dalacin; Zindaclin; *Israel*: Dalacin C; Dalacin Vaginal; Dalagis T; Zindaclin; *Ital.*: Cleocin; Dalacin C; Dalacin T; Zindaclin; *Malaysia*: Clindac; Dalacin C; Dalacin T; T3 Mycin; Tidact; Topicil; Zindaclin; *Mex.*: Aktufoam; Ancine†; Apomiclin; Biodaclin; Cigmadil†; Clendazaf; Clendix; Clidets; Clinamsa†; Clindazyn†; Clindazyn; Cliran†; Cobatin; Cutaclin; Dalacin C; Dalacin T; Dalacin V; Dalafar; Dalatina V; Dalatina; Damiclin†; Destralina; Feisclin; Foshlenn; Galecin; Indamid†; Klyndaken†; Lindacil; Lisiken; Losertrin; Lyrfhis; Trexen; Ulmicy; *Neth.*: Dalacin C; Dalacin T; *Norw.*: Dalacin; *NZ*: Clindatech; Dalacin C; Topicil; *Philipp.*: Abanxl; Acresil; Anerocin; Clin-D; Clindal; Clindamit; Clindatech; Clinderm; Cliz; Daklin; Dalace; Dalacin C; Dalaclin; Inprosyn-HP; Klincyn: Klindex; Lincyn; Mycilin; Potecin; T3 Mycin; Tidact; Zindal; *Pol.*: Clindacin†; Clindacne; Clindo†; Dalacin C; Dalacin T; Dalacin; Klimicin; Klindacin; Normaclin; Zindaclin; *Port.*: Clincina; Dalacin C; Dalacin T; Dalacin V; Zindaclin; *Rus.*: Clindacin (Клиндацин); Clindovit (Клиндовит); Dalacin (Далацин); Klimicin (Климицин)†; *S.Afr.*: Clindac†; Clindahexal; Dalacin C; Dalacin T; Dalacin VC; *Sing.*: Clindapore; Climadan; Clindagel; Clindatech; Dalacin C; Dalacin T; T3Mycin; Tidact; Topicil; Zindaclin; *Spain*: Clinwas; Dalacin; Zindaclin; *Swed.*: Dalacin; *Switz.*: Dalacin C; Dalacin T; Dalacin V; *Thai.*: Acnegon; Acnocin; Cedelin; Chinacin-T; Clinda V; Clinda; Clindacne; Clindalin; Clindaman; Clindavid; Clinot; Dacin-F; Dalacin C; Dalacin T; Klimicin†; Klinda; Klindan; Klinna; Lacin†; Millda†; Rosil; Todacin; *Turk.*: Clamine; Cleocin T; Clin; Klindan; Klindaver; Klinoksin; Klitopsir; Meneklin; *UK*: Dalacin C; Dalacin T; Dalacin; Zindaclin; *Ukr.*: Clindahexal (Клиндагексал)†; Clindesse (Клиндес); Dalacin (Далацин); Dalacin C (Далацин Ц); Milagin (Милагин); Vagicin (Вагицин-Здоровье); *USA*: Cleocin T; Cleocin; Clindagel; ClindaMax; Clindesse; Clindets†; Evoclin; *Venez.*: Bioclindax; Clindaval; Clindox; Clinfol; Dalacin.

Multi-ingredient Preparations. *Arg.*: Clidan B; Clindacur; Clindoxyl; Colposan; CP-Acne Duo; Dermaclean†; Duo Clindacin; Ovogin; Perclin; Peroxidin Duo; Torgyn Duo; Z-Clindacin; *Austral.*: ClindaBenz; Duac; *Austria*: Indoxyl; *Braz.*: Adacne Clin; Clindoxyl; Vitacid Acne; *Canad.*: Benzadin; Biacna; Clindasol; Clindoxyl; *Chile*: Indoxyl; Klina; Taripel; *Cz.*: Duac; *Denm.* Clindoxyl; *Fin.*: Clindoxyl; *Ger.*: Duac; Refobacin Revision; *Gr.* Indoxyl; *Hong Kong*: Benzolac Cl; Duac; *Hung.*: Duac; *India* Aclin; Acneris-AD; Acrub; Acsolve-C; Adacin; Alesa; Candid CL; Canison-C; Clevyx; Clima-V; Clin-3; Clinagel; Clindapene Clinderm-A; Clingen Plus; Clingen; Clinicare; Clinmide; Clinsoft; Convoy; Deriva-C; Deriva-CMS; Epilene C; Faceclin-A

Faceclin; Feiz; Femcinol-A; Imidil-CV; Labopene-C; Nicolin; Nisacne; Nuforce-CD; *Indon.*: Benzolac Cl; Climadan; Medi-Klin TR; *Irl.*: Duac; *Israel*: Benzaclin†; Duac; *Ital.*: Duac; *Malaysia*: Duac; *Mex.*: Benzaclin†; Clindapack; Femisan; Gynoclin-V; Indoxyl; Loffymix†; Trexen Duo; *Neth.*: Duac; *NZ*: Duac; *Philipp.*: Duac; *Pol.*: Duac; *Port.*: Duac; *Rus.*: Clenzit-C (Клензит-С); *Singapore*: Clindoxyl; *Spain*: Duac; *Swed.*: Duac; *Switz.*: Duac; *Thai.*: Duac; *Turk.*: Benzaclin; Cleocin; Clindoxyl; *UK*: Duac Once Daily; *Ukr.*: Cliran Zinc (Клиран Цинк); Duac (Дуак); Vagiklin (Вагиклин); *USA*: Acanya; Benzaclin; Clindacin ETZ; Clindacin P; Duac; PledgaClin; Ziana.

Pharmacopoeial Preparations

BP 2014: Clindamycin Capsules; Clindamycin Injection;
USP 36: Clindamycin for Injection; Clindamycin Hydrochloride Capsules; Clindamycin Hydrochloride Oral Solution; Clindamycin Injection; Clindamycin Palmitate Hydrochloride for Oral Solution; Clindamycin Phosphate Gel; Clindamycin Phosphate Topical Solution; Clindamycin Phosphate Topical Suspension; Clindamycin Phosphate Vaginal Cream; Clindamycin Phosphate Vaginal Inserts.

Clioquinol *(BAN, rINN)*

Chinoform; Chloroiodoquine; Cliochinolum; Clioquinolum; Iodochlorhydroxyquin; Iodochlorhydroxyquinoline; Kliochinol; Kliokinol; Kliokinoli; Kliokvinolis; PBT-1; Quiniodochlor; Клиохинол.

5-Chloro-7-iodoquinolin-8-ol.

C_9H_5ClINO=305.5

CAS — 130-26-7.

ATC — D08AH30; D09AA10; G01AC02; P01AA02; S02AA05.

ATC Vet — QD08AH30; QD09AA10; QG01AC02; QS02AA05.

UNII — 7BHQ856EJ5.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Clioquinol). An almost white, light yellow, brownish-yellow, or yellowish-grey powder. Practically insoluble in water; very slightly soluble or slightly soluble in alcohol; sparingly soluble in dichloromethane. Protect from light.

USP 36: (Clioquinol). A voluminous, spongy, yellowish-white to brownish-yellow powder having a slight characteristic odour. It darkens on exposure to light. Practically insoluble in water; soluble 1 in 3500 of alcohol, 1 in 120 of chloroform, and 1 in 4500 of ether; soluble in hot ethyl acetate and in hot glacial acetic acid. Store in airtight containers. Protect from light.

Uses and Administration

Clioquinol is a halogenated hydroxyquinoline with antibacterial and antifungal activity and is used in creams and ointments, usually containing 3%, in the treatment of skin infections. It is applied with a corticosteroid in inflammatory skin conditions complicated by bacterial or fungal infections. It is also used in ear drops for otitis externa. The treatment of bacterial and of fungal skin infections is described on p. 207.1 and p. 568.1 respectively.

For a discussion of the risks from topical application of clioquinol, see Adverse Effects and Precautions, p. 275.2.

Clioquinol has been given orally in the treatment of intestinal amoebiasis. It has also been used for the prophylaxis and treatment of traveller's diarrhoea and similar infections but is of doubtful value. Oral preparations have now generally been withdrawn because of neurotoxicity (see Adverse Effects and Precautions, p. 275.1). However, oral clioquinol has been investigated for its action as a chelator of copper and zinc in the treatment of Alzheimer's disease (see p. 275.1).

Alzheimer's disease. A systematic review[1] to evaluate the efficacy of metal protein attenuating compounds, such as clioquinol, for the treatment of cognitive impairment due to Alzheimer's disease, evaluated only one small randomised controlled study comparing clioquinol and placebo; no significant differences were found. Further studies with clioquinol have now been stopped, but studies are ongoing with a successor compound, PBT2.

1. Sampson E, *et al.* Metal protein attenuating compounds for the treatment of Alzheimer's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 03/04/09).

Adverse Effects and Precautions

Clioquinol, which contains iodine, may rarely cause iodism in sensitive patients or interfere with certain thyroid function tests. Local application of clioquinol in ointments or creams may occasionally cause severe irritation or hypersensitivity and there may be cross-sensitivity with other halogenated hydroxyquinolines.

Clioquinol stains clothing and linen yellow on contact and may stain the skin and discolour fair hair.

Clioquinol given orally has been associated with severe neurotoxicity. In Japan, the epidemic development of subacute myelo-opticoneuropathy (SMON) in the 1960s was associated with the ingestion of normal or high doses of clioquinol for prolonged periods, and the sale of clioquinol and related hydroxyquinolines was subsequently banned there. Symptoms of SMON are mainly those of peripheral neuropathy, including optic atrophy, and myelopathy. Abdominal pain and diarrhoea often precede neurological symptoms, which include paraesthesias in the legs progressing to paraplegia in some patients, and loss of visual acuity sometimes leading to blindness. A characteristic green pigment, a chelate of clioquinol with iron, is often seen on the tongue and in the urine and faeces. Cerebral disturbances, including confusion and retrograde amnesia, have also been reported. Although many patients improved when clioquinol was withdrawn, others had residual disability.

It was suggested that the Japanese epidemic might be due to genetic susceptibility, but a few similar cases of SMON associated with clioquinol or related hydroxyquinoline derivatives, such as broxyquinoline or diiodohydroxyquinoline have been reported from other countries. Oral preparations of clioquinol have now been banned in most countries.

General references.

1. Mao X, Schimmer AD. The toxicology of clioquinol. *Toxicol Lett* 2008; **182**: 1–6.

Hypersensitivity. Clioquinol is classified as a contact allergen that can commonly cause sensitisation, especially when applied to eczematous skin; chlorquinaldol can also cause sensitisation, although less frequently.[1] Cross-sensitivity between the two has been reported, and may also exist between clioquinol and some oral quinolines, such as amodiaquine, chloroquine, or quinine, used to treat malaria.[2] It is important to include clioquinol and chlorquinaldol in routine patch testing since the clinical reaction may be relatively mild and sensitivity easily missed, particularly in the presence of a corticosteroid which suppresses or attenuates the reaction.

1. Anonymous. Skin sensitisers in topical corticosteroids. *Drug Ther Bull* 1986; **24**: 57–9.
2. Rodríguez A, *et al.* Contact cross-sensitization among quinolines. *Allergy* 2001; **56**: 795.

Topical application. Absorption of clioquinol through the skin has been noted on topical application.[1,2] Last available guidance from the Committee on Drugs of the American Academy of Pediatrics[3] considered that there was a potential risk of toxicity to infants and children from clioquinol and diiodohydroxyquinoline applied topically. Since alternative effective preparations are available for dermatitis, the Committee recommended that products containing either of these compounds should not be used.

1. Fischer T, Hartvig P. Skin absorption of 8-hydroxyquinolines. *Lancet* 1977; **i**: 603.
2. Stohs SJ, *et al.* Percutaneous absorption of iodochlorhydroxyquin in humans. *J Invest Dermatol* 1984; **82**: 195–8.
3. Kauffman RE, *et al.* American Academy of Pediatrics. Clioquinol (Iodochlorhydroxyquin, Vioform) and iodoquinol (diiodohydroxyquin): blindness and neuropathy. *Pediatrics* 1990; **86**: 797–8.[Re-affirmed October 2006. Retired January 2011] Also available at: http://aappolicy.aappublications.org/cgi/reprint/pediatrics;86/5/797.pdf (accessed 15/02/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Ke Ai Lin (珂艾林); *Ger.*: Linola-sept; *India*: Dermo Quinol; Dermo Quinol; Enteroquinol; Entrozyme Plain; *Mex.*: Bagton; Biondер-C; Cortifung-C; Lasalar-Y Simple; Luzolona Simple; Nolil; Vioformo.

Multi-ingredient Preparations. *Arg.*: Betnovate-C; *Austral.*: Hydroform; Locacorten Vioform; *Austria*: Betnovate-C†; *Braz.*: Betnovate-Q; Cliotisona; Cremederme; Dreniformio; Hidrocorte; Locorten Vioformio; Permut; Poliderms; Predmicin; Quadribeta; Quadriderm; Quadrihexal; Quadrikin†; Quadrilon; Quadriplus†; Qualiderm; Tetraderm; Vioformio-Hidrocortisona; *Canad.*: Locacorten Vioform; Vioform-Hydrocortisone; *Denm.*: Betnovat med Chinoform; Locacorten Vioform; Synalar med Chinoform; *Fin.*: Bemetson-K; Betnovat-C†; Locacorten Vioform; *Fr.*: Alkocortenbioform†; Locacortene Vioforme†; *Ger.*: Locacorten Vioform; *Gr.*: Betnovate-C; Helpogen; Locacorten Vioform; Myco-Synalar; *Hong Kong*: Aplosyn-C†; Cliocort†; Clobeta-G; Dermafacte†; Quadriderm; *Hung.*: Lorinden C; Prednisolon J†; *India*: ABC Derm; Alcoderm; Balderm; Beclate-C; Becloderm-C; Benda; Betnederm C; Betnovate-C; Clobequad; Clobquad; Corge-C; Cortoquinol; Darederm; Derminol; Dermitop; Dexaquin; Dipform; Esgiderm; Fourderm; Fubac; Millicorten-Vioform; Quiss; *Indon.*: Benoson V†; Krimbeson; Viohydrocort; Visancort; *Irl.*: Betnovate-C; Vioform-Hydrocortisone†; *Israel*: Betnovate-C†; *Ital.*: Diproform; Locorten Vioformio†; Locorten; *Mex.*: Bentix; Cetoquina Y; Clio-Betnovate; Clioderm-H†; Cortifung-Y; Cortilona Compuesta; Dealan; Dermatofin; Diprosone Y; Ditayod; Farmacorti YC; Lasalar-Y; Luzolona Y; Sebryl Plus; Sebryl; Sebstopp; Solfurol; Suyodil; Synalar C; Topsyn-Y; Ultracortin†; Vioformo-Cort; Yderm; Yodozona; *Neth.*: Locacorten Vioform; *Norw.*: Betnovat med Chinoform; Synalar med Chinoform; *NZ*: Betnovate-C; Locacorten Vioform; *Philipp.*: Aplosyn C; Betnovate-C; Dermalin†; Diproform; Quadriderm; Quadrotopic; *Pol.*: Betnovate-C; Lorinden C; Viosept†; *Port.*: Betnovate-C; Dexaval V; Quinodermil-AS; *Rus.*: Dermosolon (Дермозолон); Lorinden C (Лоринден С); *S.Afr.*: Betnovate-C†; Cortoderm-C†; Locacorten Vioform; Quadriderm; Synalar C; *Singapore*: Dermanol-C; Hydroderm-C; *Spain*: Cuatroderm; Menaderm Clio; Menaderm Otologico; *Swed.*: Betnovat med Chinoform; Locacorten Vioform; *Switz.*: Betnovate-C; *Thai.*: Banocin; Beta-C; Betnovate-C†; Betosone-CE; Chlorotracin†; Dermaheu; Dertec; Endothalyl; Genquin; Patarvate-C; Quadriderm; Spectroderm; *Turk.*: Betnovate-C; Kortisetin; Locacortene Vioform; Prednol-A; *UK*: Betnovate-C; Locorten Vioform; Synalar C; Vioform-Hydrocortisone†; *Ukr.*: Dermosolon (Дермозолон)†; Lorinden C (Лоринден С); Viosept (Виосепт)†; *USA*: 1 + I-P; Corquel; Hysone; *Venez.*: Dermosuptril C; Diproformo; Locorten Vioformo; Quadriderm; Tridetarmon.

Pharmacopoeial Preparations

BP 2014: Betamethasone and Clioquinol Cream; Betamethasone and Clioquinol Ointment; Hydrocortisone and Clioquinol Cream; Hydrocortisone and Clioquinol Ointment;
USP 36: Clioquinol and Hydrocortisone Cream; Clioquinol and Hydrocortisone Ointment; Clioquinol Cream; Clioquinol Ointment; Compound Clioquinol Topical Powder.

Clofazimine *(BAN, USAN, rINN)*

B-663; Clofazimin; Clofazimina; Clofaziminum; G-30320; Klofatsimiini; Klofatzimin; Klofazimin; Klofaziminas; NSC-141046; Клофазимин.

3-(4-Chloroanilino)-10-(4-chlorophenyl)-2,10-dihydro-2-phenazin-2-ylideneisopropylamine.

$C_{27}H_{22}Cl_2N_4$=473.4

CAS — 2030-63-9.

ATC — J04BA01.

ATC Vet — QJ04BA01.

UNII — D959AE5USF.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Clofazimine). A fine reddish-brown powder. It shows polymorphism. Practically insoluble in water; very slightly soluble in alcohol; soluble in dichloromethane.

USP 36: (Clofazimine). Dark red crystals. Practically insoluble in water; sparingly soluble in alcohol, in acetone, and in ethyl acetate; soluble in chloroform and in benzene. Store in airtight containers. Protect from light.

Uses and Administration

Clofazimine is an antimycobacterial and is used as part of multidrug regimens for the treatment of multibacillary leprosy (p. 188.3). It has anti-inflammatory properties and has been given in chronic Type 2 lepra reactions (erythema nodosum leprosum) and in a variety of skin disorders.

Clofazimine is given orally with, or immediately after, food or milk for optimum absorption.

For multibacillary leprosy the most common regimen is that recommended by WHO, in which rifampicin 600 mg and clofazimine 300 mg are both given *once a month*, with *daily* doses of clofazimine 50 mg and dapsone 100 mg; this treatment continues for 12 months.

For details of doses in children, see p. 275.3.

Clofazimine 50 mg daily is given with ofloxacin and minocycline in patients unable to take rifampicin. Clofazimine is not usually given in paucibacillary leprosy (p. 188.3). However, it may be used in the treatment regimen as a replacement for dapsone when the latter has caused severe toxicity. The clofazimine dose in such regimens is the same as that in multibacillary leprosy, i.e. 300 mg once a month (with rifampicin 600 mg), plus 50 mg clofazimine daily, but is only continued for 6 months.

Clofazimine has been used in the treatment of chronic Type 2 lepra reactions, although the effect may not be evident for 4 to 6 weeks. A dose of up to 300 mg daily has been suggested but it should not be given for longer than 3 months. Corticosteroids may be given with clofazimine, and standard antileprosy treatment should be continued. Clofazimine is not used in Type 1 lepra reactions.

References.

1. Anonymous. Clofazimine. *Tuberculosis (Edinb)* 2008; **88**: 96–9.
2. Gurfinkel P, *et al.* Use of clofazimine in dermatology. *J Drugs Dermatol* 2009; **8**: 846–51.

Administration in children. For the treatment of multibacillary leprosy in children WHO recommends that children aged 10 to 14 years may be given oral clofazimine 150 mg, rifampicin 450 mg, and dapsone 50 mg *once a month*, plus dapsone 50 mg *daily* and clofazimine 50 mg on *alternate days*. For children less than 10 years of age the dose should be adjusted according to body-weight. As for adults, treatment is given for 12 months.

Adverse Effects

Adverse effects to clofazimine are dose related, the most common being red to brown discoloration of the skin especially on areas exposed to sunlight; leprotic lesions may

become mauve to black. These changes are more noticeable in light-skinned people and may limit its acceptance. The conjunctiva and cornea may also show some signs of red to brown pigmentation. The generalised discoloration may take months to years to disappear after stopping therapy. Discoloration of hair, tears, sweat, sputum, breast milk, urine, and faeces may occur, as may nail discoloration with high doses of 300 mg daily. Severe depression related to skin discoloration has been reported rarely.

Gastrointestinal effects are uncommon for doses of clofazimine less than 100 mg daily and usually are not severe. Symptoms of nausea, vomiting, and abdominal pain occurring shortly after the start of treatment may be due to direct irritation of the gastrointestinal tract and such symptoms usually disappear on dose reduction. Use of doses of 300 mg daily or more for several months sometimes produces abdominal pain, diarrhoea, weight loss, gastrointestinal bleeding, and in severe cases the small bowel may become oedematous and symptoms of bowel obstruction may develop. This may be due to deposition of crystals of clofazimine in the wall of the small bowel and in the mesenteric lymph nodes. Crystal deposition may also occur in other organs including the liver and spleen and there have been rare reports of splenic infarction. Symptoms usually regress on withdrawal of treatment although fatalities have been reported.

Clofazimine may produce a dryness of the skin and ichthyosis as well as decreased sweat production and rashes. Pruritus, acneiform eruptions, and photosensitivity reactions have also been reported.

Eye irritation and decreased tear production may occur.

Headache, drowsiness, dizziness, taste disorders, and elevation of blood glucose levels have been reported rarely.

Incidence of adverse effects. The incidence of adverse effects was reviewed in 65 patients[1] who were receiving, or had received, clofazimine in weekly doses of either 700 mg or less as antimycobacterial therapy, or more than 700 mg as anti-inflammatory therapy. Length of treatment ranged from 1 to 83 months. Adverse effects on the skin included discoloration (20% of patients), pigmentation (64.6%), dry skin (35.4%), and pruritus (5%). Ocular adverse effects were conjunctival pigmentation (49.2%), subjective dimness of vision (12.3%), and dry eyes, burning, and other ocular irritation (24.6%). Gastrointestinal adverse effects included abdominal pain (33.8%), nausea (9.2%), diarrhoea (9.2%), and weight loss, vomiting, or loss of appetite (13.8%). The different dose regimens for antimycobacterial therapy or anti-inflammatory effect had similar incidences of adverse effects. Skin pigmentation in 8 patients disappeared on average 8.5 months after stopping therapy with clofazimine, the maximum time required being one year. Adverse effects of clofazimine were considered to be well tolerated.

In another report covering 540 patients receiving clofazimine 100 mg on alternate days or 300 mg daily, the most common adverse effect was skin pigmentation, which occurred in 77.8% of the patients. Ichthyotic changes were reported in 66.7% and pruritus in 20.2%. Gastrointestinal symptoms occurred in 20 patients (about 4%); other effects such as discoloration of sweat, urine, and tears were minor.[2]

1. Moore VJ. A review of side-effects experienced by patients taking clofazimine. *Lepr Rev* 1983; 54: 327–35.
2. Kumar B, *et al.* More about clofazimine—3 years experience and review of the literature. *Indian J Lepr* 1987; 59: 63–74.

Effects on the eyes. Accumulation of clofazimine crystals in the eye can lead to pigmentation of the cornea and conjunctiva. Degeneration of the retinal pigment epithelium has also been attributed to clofazimine therapy in a patient.[1] Slight repigmentation was seen after withdrawal of clofazimine.

1. Forster DJ, *et al.* Bull's eye retinopathy and clofazimine. *Ann Intern Med* 1992; 116: 876–7.

Effects on the gastrointestinal tract. Gastrointestinal effects are uncommon at doses of clofazimine less than 100 mg daily. However, there have been some reports of severe gastrointestinal adverse events, including fatalities, in patients taking clofazimine.[1-4] An 11-year-old child given clofazimine (150 mg daily) for graft-versus-host disease developed severe enteropathy 2 years after starting treatment.[1] Clofazimine was stopped and symptoms resolved after 5 weeks. Enteropathy has also been reported in a 20-year-old patient who had taken 200 mg of clofazimine daily for 4 years.[2] Clofazimine was stopped but his symptoms did not resolve; he developed peripheral oedema and hypoalbuminaemia and died 2 years later due to cerebral thrombosis. In another report,[4] partial intestinal obstruction developed in a patient after 12 months of treatment with clofazimine 100 mg daily for the treatment of multidrug-resistant tuberculosis. The patient recovered 3 weeks after stopping clofazimine. Splenic infarction has been reported after 11 months treatment with high-dose clofazimine for the management of pyoderma gangrenosum.[5] Chronic abdominal pain due to crystal-storing histiocytosis of mesenteric lymph nodes is well recognised, and may mimic the symptoms of gastrointestinal lymphoma or myeloma.[3]

1. Parizhskaya M, *et al.* Clofazimine enteropathy in a pediatric bone marrow transplant recipient. *J Pediatr* 2001; 138: 574–6.
2. Hameed A, *et al.* A case of clofazimine enteropathy. *Int J Clin Pract* 1998; 52: 439–40.
3. Sukpanichnant S, *et al.* Clofazimine-induced crystal-storing histiocytosis producing chronic abdominal pain in a leprosy patient. *Am J Surg Pathol* 2000; 24: 129–35.
4. Üsküdar O, *et al.* Partial intestinal obstruction due to clofazimine in a patient with multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2005; 9: 703–4.
5. McDougall AC, *et al.* Splenic infarction and tissue accumulation of crystals associated with the use of clofazimine (Lamprene; B663) in the treatment of pyoderma gangrenosum. *Br J Dermatol* 1980; 102: 227–30.

Effects on the heart. Ventricular tachycardia, thought to be probably torsade de pointes, was reported to be associated with clofazimine.[1]

1. Choudhri SH, *et al.* Clofazimine induced cardiotoxicity—a case report. *Lepr Rev* 1995; 66: 63–8.

Precautions

Clofazimine should be used with caution in patients with gastrointestinal symptoms such as abdominal pain and diarrhoea. If gastrointestinal symptoms develop during treatment, the dose should be reduced and, if necessary, the interval between doses increased, or the drug should be stopped. Daily doses of more than 100 mg should not be used for more than 3 months because of dose-related adverse effects on the gastrointestinal tract; patients receiving doses above 100 mg daily should be under medical supervision.

Patients should be warned that clofazimine may cause a reddish-brown discoloration of breast milk, hair, skin, conjunctiva, tears, sputum, sweat, urine, and faeces. Nails may be discoloured at higher doses.

As clofazimine crosses the placental barrier, neonates of women receiving clofazimine may have skin discoloration at birth.

Breast feeding. The last available guidance from the American Academy of Pediatrics[1] considered that the use of clofazimine by mothers during breast feeding may be of concern, since there is the possibility of transfer of a high percentage of the maternal dose and a possible increase in skin pigmentation in the infant. A small study in 8 women calculated that up to 30% of a maternal dose may be ingested by a breast-fed infant.[2]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 03/10/07)
2. Venkatesan K, *et al.* Excretion of clofazimine in human milk in leprosy patients. *Lepr Rev* 1997; 68: 242–6.

Pregnancy. Two successful pregnancies in women who received clofazimine throughout pregnancy have been reported[1] but a literature review revealed 3 neonatal deaths in 13 pregnancies, although the deaths could not be directly attributed to clofazimine. However, WHO[2] states that its recommended multiple drug therapy regimens for leprosy, which may include clofazimine, are safe during pregnancy.

1. Farb H, *et al.* Clofazimine in pregnancy complicated by leprosy. *Obstet Gynecol* 1982; 59: 122–3.
2. WHO. *Guide to eliminate leprosy as a public health problem.* 1st ed. Geneva: WHO, 2000. Also available at: http://www.who.int/lep/resources/Guide_Int_E.pdf (accessed 28/07/08)

Interactions

Some preliminary data have suggested that the anti-inflammatory action of clofazimine in Type 2 lepra reactions may be reduced by dapsone, although US licensed product information (*Lamprene; Novartis, USA*) states that these findings have not been confirmed; the antimycobacterial effect was not affected.

Elevated plasma and urine concentrations of clofazimine have been detected in patients receiving high doses of clofazimine with isoniazid, although skin concentrations were found to be lower.

For a report of the effect of clofazimine on rifampicin absorption, see p. 355.2.

Antimicrobial Action

Clofazimine is bacteriostatic and weakly bactericidal against *Mycobacterium leprae*. Tissue antimicrobial activity in humans cannot be found until after about 50 days of therapy. Clofazimine is active *in vitro* against various other species of *Mycobacterium*. Resistance has been reported rarely and no cross-resistance occurs with rifampicin or dapsone.

Pharmacokinetics

Clofazimine is absorbed from the gastrointestinal tract in amounts varying from 45 to 70%. Absorption is greatest when clofazimine is given in microcrystalline formulations and when it is taken immediately after food. The time to steady-state plasma concentrations has not been determined but exceeds 42 days.

Average plasma concentrations in leprosy patients receiving 100 or 300 mg daily are reported as 700 nanograms/mL and 1.0 microgram/mL, respectively.

Because of its lipophilic nature, clofazimine is mainly distributed to fatty tissue and reticuloendothelial cells, including macrophages. Clofazimine is distributed to most organs and tissues and into breast milk; it crosses the placenta but not the blood-brain barrier.

The tissue half-life after a single dose has been reported to be about 10 days; that after multiple oral doses has been variously estimated to be between 25 and 90 days. Clofazimine accumulates in the body and is largely excreted unchanged in the faeces, both as unabsorbed drug and via biliary excretion. About 1% of the dose is excreted in 24 hours in the urine as unchanged clofazimine and metabolites. A small amount of clofazimine is also excreted through sebaceous and sweat glands, and in sputum.

References.

1. Holdiness MR. Clinical pharmacokinetics of clofazimine: a review. *Clin Pharmacokinet* 1989; 16: 74–85.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Lamprene; *Braz.*: Newzimina; *Cz.*: Lamprene; *Fr.*: Lamprene; *Gr.*: Lamprene; *Indi.*: Clofozine; Hansepran; *Jpn*: Lampren; *Neth.*: Lampren; *N.Z.*: Lamprene; *Spain*: Lampren†; *Thai.*: Lamcoin; *USA*: Lamprene

Multi-ingredient Preparations. *Thai.*: Lepromix MB.

Pharmacopoeial Preparations
BP 2014: Clofazimine Capsules;
USP 36: Clofazimine Capsules.

Clofoctol *(rINN)*

Clofoctolum; Клофактол.
2-(2,4-Dichlorobenzyl)-4-(1,1,3,3-tetramethylbutyl)phenol.
$C_{21}H_{26}Cl_2O$=365.3
CAS — 37693-01-9.
ATC — J01XX03.
ATC Vet — QJ01XX03.
UNII — 704083NI0R.

Profile

Clofoctol has bacteriostatic or bactericidal activity against Gram-positive organisms such as staphylococci and streptococci. It is given in doses of 750 mg twice daily rectally in the treatment of respiratory-tract infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Gramplus.

Clometocillin Potassium *(rINNM)*

Clometocilina potásica; Clométocilline Potassique; 3,4-Dichloro-α-methoxybenzylpenicillin Potassium; Kalii Clometocillinum; Penicillin 356 (clometocillin); Калия Клометоциллин.
Potassium (6*R*)-6-[2-(3,4-dichlorophenyl)-2-methoxyacetamido]penicillanate.
$C_{17}H_{17}Cl_2KN_2O_5S$=471.4
CAS — 1926-49-4 (clometocillin); 15433-28-0 (clometocillin potassium).
ATC — J01CE07.
ATC Vet — QJ01CE07.
UNII — 7C71K33PDJ.

Profile

Clometocillin is a penicillin given orally as the potassium salt in the treatment of susceptible bacterial infections. Doses are expressed in terms of the base. The usual adult dose is 500 mg two or three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Rixapen.

Cloxacillin *(BAN, rINN)*

Cloxacilina; Cloxacilline; Cloxacillinum; Kloksasilliini; Kloxacillin; Клоксациллин.
(6*R*)-6-[3-(2-Chlorophenyl)-5-methylisoxazole-4-carboxamido]penicillanic acid.

$C_{19}H_{18}ClN_3O_5S$=435.9
CAS — 61-72-3.
ATC — J01CF02.
ATC Vet — QJ01CF02; QJ51CF02; QS01AA90.
UNII — O6X5QGC2VB.

Cloxacillin Benzathine *(BANM, rINNM)*

Cloxacilina benzatina; Cloxacilline Benzathine; Cloxacillinum Benzathinum; Клоксациллин бензатин.
The *N,N'*-dibenzylethylenediamine salt of cloxacillin.
$C_{16}H_{20}N_2(C_{19}H_{18}ClN_3O_5S)_2$=1112.1
CAS — 23736-58-5; 32222-55-2.
ATC — J01CF02.
ATC Vet — QJ01CF02.
UNII — AC79L7PV2G.

Pharmacopoeias. In *US* for veterinary use only. Also in *BP (Vet)*.

BP(Vet) 2014: (Cloxacillin Benzathine). A white or almost white powder. Slightly soluble in water, in alcohol, and in isopropyl alcohol; freely soluble in methyl alcohol. Store in airtight containers.

USP 36: (Cloxacillin Benzathine). White or almost white, almost odourless, crystals or crystalline powder. Slightly soluble in water, in alcohol, and in isopropyl alcohol; sparingly soluble in acetone; soluble in chloroform and in methyl alcohol. pH of a 1% suspension in water is between 3.0 and 6.5. Store in airtight containers.

Cloxacillin Sodium *(BANM, USAN, rINNM)*

BRL-1621; Cloxacilina sódica; Cloxacillin-Natrium; Cloxacilline sodique; Cloxacillinum Natricum; Cloxacillinum Natricum Monohydricum; Kloksacilino natrio druska; Kloksacylina sodowa; Kloksasilliininatrium; Kloxacilin sodná sůl monohydrát; Kloxacillinnatrium; Kloxacillin-nátrium; Natrii Cloxacillinum; P-25; Натрий Клоксациллин.
$C_{19}H_{17}ClN_3NaO_5S,H_2O$=475.9
CAS — 642-78-4 (anhydrous cloxacillin sodium); 7081-44-9 (cloxacillin sodium monohydrate).
ATC — J01CF02.
ATC Vet — QJ01CF02.
UNII — MWQ645MKMF (anhydrous cloxacillin sodium); 65LCB00B4Y (cloxacillin sodium monohydrate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Cloxacillin Sodium). Semisynthetic product derived from a fermentation product. A white or almost white, hygroscopic, crystalline powder. Freely soluble in water and in methyl alcohol; soluble in alcohol. A 10% solution in water has a pH of 5.0 to 7.0. Store at a temperature not exceeding 25 degrees in airtight containers.

USP 36: (Cloxacillin Sodium). A white, odourless, crystalline powder. Freely soluble in water; soluble in alcohol; slightly soluble in chloroform. pH of a 1% solution in water is between 4.5 and 7.5. Store in airtight containers at a temperature not exceeding 25 degrees.

Incompatibility. Cloxacillin sodium has been reported to be incompatible with aminoglycosides and several other antimicrobials.

Uses and Administration

Cloxacillin is an isoxazolyl penicillin used similarly to flucloxacillin (p. 301.2) in the treatment of infections due to staphylococci resistant to benzylpenicillin.

Cloxacillin is given orally, intramuscularly, or by intravenous injection or infusion as the sodium salt and doses are expressed in terms of the equivalent amount of cloxacillin: 1.09 g of cloxacillin sodium is equivalent to about 1 g of cloxacillin.

Usual oral doses are 250 to 500 mg four times daily and should be given 1 hour before, or 2 hours after meals as the presence of food in the stomach reduces absorption. Parenteral doses usually range from 1 to 2 g every 6 hours; for more severe infections such as meningitis or endocarditis, 2 g every 4 hours may be used. Other routes have included intra-articular or intrapleural injection, and inhalation.

For details of doses in children, see p. 277.1.

Cloxacillin may be used with other antibacterials, including ampicillin, to produce a wider spectrum of activity.

Cloxacillin benzathine is used in veterinary medicine.

Administration in children. Cloxacillin may be given to neonates and children for the treatment of infections caused by susceptible bacteria, particularly beta-lactamase-producing staphylococci, in the following doses:

- neonates 7 days of age and younger, weighing less than 2 kg: 25 mg/kg *orally* or *intravenously* every 12 hours
- neonates 7 to 28 days of age, weighing less than 2 kg, or, neonates 7 days of age and younger weighing 2 kg or more: 25 mg/kg *orally* or *intravenously* every 8 hours
- neonates 7 to 28 days of age weighing 2 kg or more: 25 mg/kg every 6 hours, *orally* or *intravenously*
  For treatment of meningitis, the above doses should be doubled, and given *intravenously*.
- children from 1 month of age, weighing less than 20 kg: 50 to 100 mg/kg daily (maximum 4 g) divided every 6 hours; *orally*, *intravenously*, or *intramuscularly*. For severe infection, up to 200 mg/kg daily (maximum 12 g) in divided doses may be given *intravenously*
- children from 1 month of age, weighing 20 kg or more: as for adults (see Uses and Administration, above)

Adverse Effects and Precautions

As for Flucloxacillin, p. 301.3.

Effects on the kidneys. References.
1. García-Ortiz R, *et al.* Cloxacillin-induced acute tubulo interstitial nephritis. *Ann Pharmacother* 1992; 26: 1241–2.

Effects on the liver. References.
1. Enat R, *et al.* Cholestatic jaundice caused by cloxacillin: macrophage inhibition factor test in preventing rechallenge with hepatotoxic drugs. *BMJ* 1980; 280: 982–3.
2. Konikoff P, *et al.* Cloxacillin-induced cholestatic jaundice. *Am J Gastroenterol* 1986; 81: 1082–3.
3. Goland S, *et al.* Severe cholestatic hepatitis following cloxacillin treatment. *Postgrad Med J* 1998; 74: 59–60.

Phlebitis. For a study indicating that dicloxacillin is associated with a higher incidence of phlebitis than cloxacillin, see p. 288.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cloxacillin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]
1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Sodium content. Each g of cloxacillin sodium contains about 2.1 mmol of sodium.

Interactions

As for Benzylpenicillin, p. 230.1.

Antimicrobial Action

As for Flucloxacillin, p. 302.1.

Pharmacokinetics

Cloxacillin is incompletely absorbed from the gastrointestinal tract, and absorption is reduced by the presence of food in the stomach. After an oral dose of 500 mg, a peak plasma concentration of 7 to 15 micrograms/mL is attained in fasting subjects in 1 to 2 hours. Absorption is more complete when given by intramuscular injection and peak plasma concentrations of about 15 micrograms/mL have occurred 30 minutes after a dose of 500 mg. Doubling the dose can double the plasma concentration. About 94% of cloxacillin in the circulation is bound to plasma proteins. Cloxacillin has been reported to have a plasma half-life of 0.5 to 1 hour. The half-life is prolonged in neonates.

Cloxacillin crosses the placenta and is distributed into breast milk. There is little diffusion into the CSF except when the meninges are inflamed. Therapeutic concentrations can be achieved in pleural and synovial fluids and in bone.

Cloxacillin is metabolised to a limited extent, and the unchanged drug and metabolites are excreted in the urine by glomerular filtration and renal tubular secretion. About 35% of an oral dose is excreted in the urine and up to 10% in the bile. Cloxacillin is not removed by haemodialysis.

Plasma concentrations are enhanced by probenecid. Reduced concentrations in patients with cystic fibrosis have been attributed to both enhanced tubular secretion and enhanced nonrenal clearance of cloxacillin.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Apo-Cloxi; Novo-Cloxin; Nu-Cloxi; ***China***: An Mei Lin (安美林); Gaofen (高芬); ***Fin.***: Staflocil; ***Fr.***: Orbenine; ***Gr.***: Anadosil; Orbenin; Staphyclox; ***Hong Kong***: Apo-Cloxi; Cloxa†; Cloxcin; Lidoxin; Monoclox†; Prostaphlin-A†; ***India***: Aclox; Bioclox; Clocilin; Clopen; Klox; Neoclox; ***Indon.***: Meixam; ***Israel***: Loxavit; Orbenil; ***Malaysia***: Monoclox; ***Norw.***: Ekvacillin; ***Philipp.***: Avastoph; Caxin; Ciclox†; Clocsamed; Clopen; Clox; Cloxaco; Cloxal; Cloxigen†; Cloxil; Cloxin; CLX; Eloxil; Endoxil; Eraclox; Excelox†; Jogen; Kloxitas; Lewinex; Medaclox; Medix; Noxylen; Orbenin; Oxaclen; Pannox; Patriflex; Prostaphilin-A†; Seclоxin; Solaze; Vamcloxil; ***Pol.***: Syntarpen; ***S.Afr.***: Cloxin; Orbenin†; ***Singapore***: Apo-Cloxi; Cloxacap; Cloxcin; Lidoxin; Procap-C; ***Spain***: Anadosil; Orbenin; ***Swed.***: Ekvacillin; ***Thai.***: Clox†; Cloxa; Cloxacel; Cloxalin; Cloxam; Cloxamed; Cloxan; Cloxanbin†; Cloxasian; Cloxgen; Cloxil; *Cloxillin*; Cloxin; Cloxino†; Cloxpac; Cloxstar†; Coclox†; Corbin; Greater-Gloxa†; K-Cil; Lidoxin; Lincox; Loxzalin; Meiclox; Orbenin†; Panoxilin; Procloxin; S-Cloxin; Sanoclox; Socloxin†; Syntoclox†; Theradox†; Vaclox†; Vidoxa.

Multi-ingredient Preparations. ***China***: Jielite (洁利特); Kaifa (凯法); ***Hong Kong***: Cloxamp†; Cloxampi†; Cloxampilin†; Co-Amclox†; Lampicin†; Pamedox†; Rosclox†; ***India***: ABCloxi; ACL; Adilox; Afymox-CL; AK-60; Alclox; Amcl-Clox; Amclo; Amclominus; Amclox-LB; Amclox-LBS; Amclox; Amcloxin; Amiclox Plus; Amolac Plus DT; Amolac Plus; Amphy; Ampicloxa; Ampifort; Ampilox-LB; Ampilox; Amplus; Amplus; Ampoxin-LB; Ampoxin; Ampy C; Ampylox; Amydox-LB; Amyclox; Axcel-L; Axcel-LS; Bacidox; Bacimox; Bactimox Plus; Bactimox; Baxin-LB; Baxin; Bclomox; Betaclox; Biddal Plus; Bicil-P; Biclopen; Bilactam; Bilin-CS; Biplox-SL; Bluclox; Blumox-XL; Broadcure; Broadiclox-LB; Broadiclox; C-Clox; C-Tax-O XL; Cadmoxin-CS; Campilox-LB; Campilox; Capilac XP; Capilac Cefglobe; Cefi XL; Cefo-LX; Cefocef-XL; Cilclox; Clacin; Clax; Climox; Climpen; Clodax-L; Clomentin; Clompic; Clotrop; Cloxam Plus; Cloxapene; Cloxcin; Cluster; Cobacta-S; Combilox-LB; Combilox; Combipen; Cynox; Dabclox; Daze-MX; DC-Ped; DC; Dualcillin; Duoclox; Dupen Ped; Dynaclox; Edomox-C; Elclox Plus; Elclox; Elfi-XL; Emulox; Eradiclox; Eudase-MX; Euphoclox; Famclox; Flemiklox-LBX; G-Clox; Genidox; Glocef-CL; Glymox-Plus; Glymox-Plus; Glymox; Gudcef; Himox Plus; Himox-LS; Hipenox LB; Hipenox; Imox-Clo LB†; Imox-Clo; Inloxy-LB Kid; Inloxy-SLB; Inloxy; Klomox; Kloxamp; Laclomox; Lacom; LC-Mox; Leemoxin-CS; Magclox-LB; Magnacillin; Mahacef-XL; Mediclox Plus; Megaclox LB; Megaclox; Megamox; Megapen; Mikilac Kidtab; Mikilac Plus; Milixim-LX; Moclox; Mokcan-C LB; Mokcan-C; Moxiclox; Moxlox-L; Moxlox; Moxtid-CS; Moxyplus-SL; Mytimox; Nataclox; Nepoclox; Nodimox Plus-LB; Nodimox Plus; Novaclox LB; Novaclox; Nuclox; Numox-LB; Numox; Oleclox; Omnipen; Osoclox; Oxylac; Suprimox; Symbiotik; ***Ital.***: Amplium; ***S.Afr.***: Ampiclox†; Ampoxin; Apen; Cloxam; Megamox; ***Thai.***: Ampcoxin; Ampiclox†; Viccillin-S†.

Pharmacopoeial Preparations
USP 36: Cloxacillin Sodium Capsules; Cloxacillin Sodium for Oral Solution.

Colistin Sulfate *(BANM, pINNM)*

Colistin Sulphate; Colistina, sulfato de; Colistine, Sulfate de; Colistini Sulfas; Colistinsulfat; Kolistiinisulfaatti; Kolistino sulfatas; Kolistinsulfat; Kolistin-sulfát; Kolistyny siarczan; Kolisztin-szulfát; Polymyxin E Sulphate; Sulfato de colistina; Колистина Сулфат.
CAS — 1066-17-7 (colistin); 1264-72-8 (colistin sulfate).
ATC — A07AA10; J01XB01.
ATC Vet — QA07AA10; QJ01XB01.
UNII — WP15DXU577.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Colistin Sulfate). A mixture of the sulfates of polypeptides produced by certain strains of *Bacillus polymyxa* var. *colistinus* or obtained by any other means. It contains not less than 19 000 International Units/mg, calculated with reference to the dried drug. A white or almost white, hygroscopic powder. Freely soluble in water; practically insoluble in alcohol and in acetone. A 1% solution in water has a pH of 4.0 to 6.0. Store in airtight containers. Protect from light.

USP 36: (Colistin Sulfate). The sulfate salt of an antibacterial substance produced by the growth of *Bacillus polymyxa* var. *colistinus*. It has a potency of not less than 500 micrograms of colistin per mg. A white to slightly yellow, odourless, fine powder. Freely soluble in water; insoluble in acetone and in ether; slightly soluble in methyl alcohol. pH of a 1% solution in water is between 4.0 and 7.0. Store in airtight containers.

Stability. Colistin base is precipitated from aqueous solution above pH 7.5.

Colistimethate Sodium *(BANM, USAN, rINN)*

Colistimetato de Sódio; Colistimetato de sodio; Colistimetato sódico; Colistimethat-Natrium; Colistiméthate Sodique; Colistimethatum natricum; Colistimethatum Natrium; Colistin Sulphomethate Sodium; Colistinéméthanesulfonate Sodique; Kolistimetaattinatrium; Kolistimetatnatrium; Kolistimetato natrio druska; Kolistimetát sodná sůl; Kolistymetat sodowy; Koliszтimetát-nátrium; Pentasodium Colistinmethanesulfonate; Sodium Colistimethate; Sodium Colistinmethanesulphonate; W-1929; Колистиметат Натрий.
CAS — 30387-39-4 (colistimethate); 8068-28-8 (colistimethate sodium).
ATC — A07AA10; J01XB01.

ATC Vet — QA07AA10; QJ01XB01.
UNII — XW0E5YS77G.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Colistimethate Sodium). It is prepared from colistin by the action of formaldehyde and sodium bisulfite. The potency is not less than 11 500 units/mg, calculated with reference to the dried substance. A white or almost white, hygroscopic powder. Very soluble in water; slightly soluble in alcohol; practically insoluble in acetone. A 1% solution in water has a pH of 6.5 to 8.5. Store in airtight containers. Protect from light.

USP 36: (Colistimethate Sodium). A white to slightly yellow, odourless, fine powder. It has a potency equivalent to not less than 390 micrograms of colistin per mg. Freely soluble in water; insoluble in acetone and in ether; soluble in methyl alcohol. pH of a 1% solution in water is between 6.5 and 8.5.

Stability. After the death of a patient with cystic fibrosis who had been given a liquid solution of colistimethate premixed for inhalation with a nebuliser (see Cystic Fibrosis, under Adverse Effects, p. 279.1) the US FDA warned[1] that such premixing of colistimethate in an aqueous solution and storing it for longer than 24 hours results in increased concentrations of colistin in solution and increases the potential for lung toxicity. When colistimethate is mixed with water and buffer it undergoes spontaneous hydrolysis to colistin; polymyxin E1, a component of colistin, has been shown to cause pulmonary inflammation in *animal* studies. Inhalation solutions of colistimethate should therefore be given promptly after preparation.

1. FDA. Colistimethate (marketed as Coly-Mycin M and generic products) (issued 28 June 2007). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/colistimethateHCP.htm (accessed 18/01/08)

Units

The first International Standard Preparation (1968) for colistin contains 20 500 units/mg of colistin sulfate and the first International Reference Preparation (1968) for colistimethate contains 12 700 units/mg of colistimethate. Pure colistin base has been assigned a potency of 30 000 units/mg.

Differences in how doses of colistimethate sodium are expressed in different parts of the world (for example, as international units in the UK, or as colistin base in the USA) may cause considerable confusion; it should be noted that doses reported in clinical studies or case reports may vary depending on the country of origin and the preparation used. To avoid confusion, some have suggested that doses of colistimethate sodium be expressed in terms of international units.

Uses and Administration

Colistin is a polymyxin antibacterial that has been used in the treatment of severe Gram-negative infections, especially those due to *Pseudomonas aeruginosa*, although other drugs are usually preferred. Colistimethate sodium is used by inhalation in the management of respiratory infections in patients with cystic fibrosis (p. 177.2). Colistin has been given orally as the sulfate for the treatment of gastrointestinal infections, although in the UK, the *BNF* has advised against its use for this indication. Colistin sulfate is also given orally for bowel preparation before abdominal surgery, and with other drugs in regimens for selective digestive tract decontamination (SDD) in patients at high risk of endogenous infections (see under Intensive Care, p. 187.3).

The usual oral dose of colistin sulfate is 1.5 to 3 million units given 3 times daily. For bowel preparation, the same dose is given for 24 hours with the course being completed 12 hours before surgery.

Colistin is given parenterally, as colistimethate sodium, by intramuscular injection or slow intravenous injection or infusion. In the UK, usual doses are 1 to 2 million units given 3 times daily (maximum dose 6 million units in 24 hours) for patients weighing more than 60 kg; those weighing up to 60 kg may be given 50 000 units/kg daily in 3 divided doses up to a maximum of 75 000 units/kg daily. In the USA, the usual dose is equivalent to colistin base 2.5 to 5 mg/kg daily in 2 to 4 divided doses. Monitoring of plasma concentrations is required in some patients (see Adverse Effects and Precautions, p. 278.3).

Colistimethate sodium may also be given by inhalation in respiratory infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis. A nebulised solution is used in a usual dose of 1 to 2 million units given 2 or 3 times daily. A 3-week course of 2 million units twice daily may be given with other systemic antibacterials for initial colonisation, increased to a maximum of 2 million units given 3 times daily for up to 3 months in frequent recurrent infections; 1 to 2 million units twice daily may be given for chronic infection. Solutions for inhalation should be freshly prepared (see Stability, above). Alternatively, a dry-powder inhaler can be used in the management of chronic infections; a dose of 1.6625 million units is inhaled twice daily.

Doses and dosage intervals should be adjusted in patients with renal impairment (see p. 278.2).

For details of doses in children, see p. 278.2.

Colistimethate sodium has also been given by subconjunctival injection and as a bladder instillation. Both colistin sulfate and colistimethate sodium have been applied topically, often with other antibacterials, in the management of ear, eye, and skin infections.

Reviews.

1. Falagas ME, Kasiakou SK. Colistin: the revival of polymyxins for the management of multidrug-resistant gram-negative bacterial infections. *Clin Infect Dis* 2005; 40: 1333–41. Correction. *Ibid.* 2006; 42: 1819. [dose]
2. Falagas ME, *et al.* The use of intravenous and aerosolized polymyxins for the treatment of infections in critically ill patients: a review of the recent literature. *Clin Med Res* 2006; 4: 138–46.
3. Li J, *et al.* Colistin: the re-emerging antibiotic for multidrug-resistant Gram-negative bacterial infections. *Lancet Infect Dis* 2006; 6: 589–601.
4. Michalopoulos A, Falagas ME. Colistin and polymyxin B in critical care. *Crit Care Clin* 2008; 24: 377–91.
5. Petrosillo N, *et al.* Colistin monotherapy vs. combination therapy: evidence from microbiological, animal and clinical studies. *Clin Microbiol Infect* 2008; 14: 816–27.
6. Falagas ME, Rafailidis PI. Re-emergence of colistin in today's world of multidrug-resistant organisms: personal perspectives. *Expert Opin Invest Drugs* 2008; 17: 973–81.

Administration in children. Colistin sulfate may be used orally in children for selective digestive tract decontamination. Although it is licensed for use in the treatment of gastrointestinal infections caused by Gram-negative bacteria, the *BNFC* has advised against this practice. The following doses may be given orally according to weight:

- up to 15 kg: 250 000 to 500 000 units 3 times daily
- 15 to 30 kg: 0.75 to 1.5 million units 3 times daily
- over 30 kg: the usual adult dose (see Uses and Administration, above)

Colistimethate sodium may be used parenterally in children for the treatment of serious infections caused by susceptible Gram-negative bacteria;[1,2] it may also be used by inhalation for management of *Pseudomonas aeruginosa* infection in cystic fibrosis. Parenteral doses may vary between countries.

UK according to weight:

- up to 60 kg: 50 000 units/kg daily in 3 divided doses up to a maximum of 75 000 units/kg daily (the *BNFC* suggests that this dose may be given to those as young as 1 month of age)
- over 60 kg: the usual adult dose (see above)

USA:

- children may be given the usual adult dose, equivalent to colistin base, of 2.5 to 5 mg/kg daily in 2 to 4 divided doses

Monitoring of plasma concentrations is required in some patients (see Adverse Effects, Treatment, and Precautions, p. 278.3).

For **inhalation** colistimethate sodium may be given as a nebulised solution in the following doses according to age:

- under 2 years: 0.5 to 1 million units twice daily (the *BNFC* suggests that this dose may be given to those as young as 1 month of age and that the dose may be increased to 1 million units three times daily in subsequent infections)
- over 2 years: the usual adult dose (see Uses and Administration, above)

Colistimethate sodium may alternatively be given by dry-powder inhaler for chronic *Pseudomonas aeruginosa* infection in children aged 6 years and older with cystic fibrosis; doses are as for adults (see above).

Doses and dosage intervals should be adjusted in patients with renal impairment (see p. 278.2).

1. Rosanova M, *et al.* Use of colistin in a pediatric burn unit in Argentina. *J Burn Care Res* 2009; 30: 612–5.
2. Falagas ME, *et al.* Systemic colistin use in children without cystic fibrosis: a systematic review of the literature. *Int J Antimicrob Agents* 2009; 33: 503.e1–503.e13.

Administration in renal impairment. Dosage of **parenteral** colistimethate sodium must be adjusted in renal impairment; both reduction in dose and decreased frequency of dosing may be required.

In the UK, the following intravenous doses of colistimethate sodium, based on creatinine clearance (CC), have been suggested with one preparation (*Colomycin; Forest, UK*) for patients weighing 60 kg or more:

- CC 20 to 50 mL/minute: 1 to 2 million units every 8 hours
- CC 10 to 20 mL/minute: 1 million units every 12 to 18 hours
- CC less than 10 mL/minute: 1 million units every 18 to 24 hours

Licensed product information for another preparation (*Promixin; Profile, UK*) recommends the following intravenous dose modifications:

- mild impairment: 1 to 1.5 million units twice daily
- moderate impairment: 1 million units once or twice daily
- severe impairment: 1 to 1.5 million units every 36 hours

US licensed product information suggests the following intravenous or intramuscular doses (equivalent to colistin base) for adults with renal impairment in terms of plasma-creatinine concentrations:

- 1.3 to 1.5 mg/100 mL: 150 to 230 mg given daily in two divided doses
- 1.6 to 2.5 mg/100 mL: 133 to 150 mg given daily as a single dose or in 2 divided doses
- 2.6 to 4.0 mg/100 mL: 100 to 150 mg given every 36 hours

A review[1] of antimicrobial dosing in critically ill patients receiving renal replacement therapy recommends an intravenous dose (equivalent to colistin base) of 2.5 mg/kg every 48 hours for patients undergoing continuous renal replacement therapy (CRRT). The authors note that a shorter dosing interval may be appropriate depending on patient specific factors including the specific type of CRRT used (as well as filter type and flow rate), the site of infection, and the level of antibacterial resistance of the infecting organism, and that close monitoring of pharmacological response, adverse effects, and serum drug concentrations (where possible) should guide dosing. Other authors have suggested that a dose (equivalent to colistin base) of around 2 to 3 mg/kg intravenously every 12 hours may be required to achieve acceptable serum drug concentrations for resistant Gram-negative bacteria in patients receiving continuous venovenous haemodiafiltration (CVVHDF) specifically.[2]

For critically ill patients undergoing intermittent haemodialysis, a dose (equivalent to colistin base) of 1.5 mg/kg every 24 to 48 hours has been suggested.[1]

Although high colistimethate sodium serum concentrations are considered unlikely during **inhaled** therapy, monitoring of serum concentrations has been suggested in those with renal impairment given nebulised drug.

1. Heintz BH, *et al.* Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy* 2009; 29: 562–77.
2. Li J, *et al.* Pharmacokinetics of colistin methanesulfonate and colistin in a critically ill patient receiving continuous venovenous hemodiafiltration. *Antimicrob Agents Chemother* 2005; 49: 4814–5.

Multidrug-resistant Gram-negative infections. A systematic review[1] of 6 controlled studies comparing nebulised or intravenous colistimethate sodium for the treatment of ventilator-associated pneumonia with other antibacterials found that colistin may be as safe and effective as standard antibacterial therapy, and suggested that it could be an alternative treatment for multidrug-resistant Gram-negative organisms. A high-dose extended-interval regimen[2] of intravenous colistimethate sodium has also been used to treat such infections. The dosing schedule was based on a loading dose of colistimethate sodium 9 million units by intravenous infusion, followed by subsequent doses of 4.5 million units, with the dosing interval adjusted according to renal function: every 12 hours for those with a creatinine clearance (CC) above 50 mL/min, every 24 hours for a CC 20 to 50 mL/min, or every 48 hours for a CC below 20 mL/min. High efficacy was seen without significant renal toxicity.

1. Florescu DF, *et al.* What is the efficacy and safety of colistin for the treatment of ventilator-associated pneumonia? A systematic review and meta-regression. *Clin Infect Dis* 2012; 54: 670–80.
2. Dalfino L, *et al.* High-dose, extended-interval colistin administration in critically ill patients: is this the right dosing strategy? A preliminary study. *Clin Infect Dis* 2012; 54: 1720–6.

Adverse Effects, Treatment, and Precautions

As for Polymyxin B Sulfate, p. 345.1.

Colistin sulfate is poorly absorbed from the gastrointestinal tract and adverse effects do not normally occur with usual oral doses. However, gastrointestinal absorption is limited and unpredictable in infants under 6 months of age and systemic adverse effects such as transient sensory disturbances may occur in this patient group.

Cough and bronchospasm are very common following inhalation of colistimethate sodium, but usually disappear or diminish with continued use. Reactions can be treated with an inhaled beta$_2$ agonist used before or after treatment, but withdrawal may be required if symptoms remain problematic. Cases of sore throat or sore mouth, possibly due to hypersensitivity or superinfection with *Candida* spp., have also been reported. After inhalation the mouth may be rinsed with water and the water expelled. Other adverse effects reported after inhalation include tinnitus, haemoptysis, dysphonia, dysgeusia, epistaxis, pharyngolaryngeal pain, gastrointestinal disturbances, and arthralgia.

Neurotoxic reactions such as dizziness, confusion, and visual disturbances can occur during parenteral therapy and patients so affected should not drive or operate machinery. Pain and local irritation are reported to be less troublesome after intramuscular injection of colistimethate sodium than with colistin sulfate or polymyxin B. Overgrowth of

non-susceptible organisms, particularly *Proteus* spp., may occur after prolonged use.

Plasma-concentration monitoring during systemic treatment is recommended in neonates, patients with renal impairment, and those with cystic fibrosis. Peak plasma-colistin concentrations of 10 to 15 mg/litre (about 125 to 200 units/mL) are recommended.

Cystic fibrosis. Intravenous colistin sulfate was reported to be associated with a lower rate of severe nephrotoxicity among 19 patients with cystic fibrosis than has been previously reported in other patient populations.[1] However, fatal acute respiratory distress syndrome (ARDS) has been reported in a cystic fibrosis patient after inhalation of colistimethate sodium 75 mg twice daily.[2] The solution used had been compounded 5 weeks previously, and it was considered that ARDS was caused by the conversion of colistimethate sodium to the active form colistin which may cause airway or alveolar injury. The FDA subsequently warned that inhalation solutions should be used promptly after preparation (see Stability, p. 276.1).

1. Bosso JA, *et al.* Toxicity of colistin in cystic fibrosis patients. *DICP Ann Pharmacother* 1991; **25**: 1168–70.
2. McCoy KS. Compounded colistimethate as possible cause of fatal acute respiratory distress syndrome. *N Engl J Med* 2007; **357**: 2310–1.

Effects on the cardiovascular system. Significant, but transient, hypotension occurred in a patient after starting aerosolised colistin inhalation.[1] Intravenous colistin, alone or with aerosolised amikacin, had no such effect on blood pressure.

1. Hakeam HA, Almohaizeie AM. Hypotension following treatment with aerosolized colistin in a patient with multidrug-resistant Pseudomonas aeruginosa. *Ann Pharmacother* 2006; **40**: 1677–80.

Effects on the kidneys. The rates of colistin-associated nephrotoxicity previously reported in the literature have varied from around 50% in older studies to no toxicity in more recent reports,[1] which may, in part, be due to variable definitions of toxicity.[2] In a retrospective study[1] evaluating the incidence of nephrotoxicity defined by a standardised criteria, intravenous colistimethate sodium was associated with some degree of renal dysfunction in 45% of patients, with 21% subsequently stopping therapy as a result. The risk of toxicity was increased fourfold in those given colistimethate sodium for more than 14 days. A similar rate of nephrotoxicity (43%) was reported from a retrospective study of patients who had received intravenous colistin for 48 hours or longer.[3] Nephrotoxicity occurred in a dose-dependent manner; more than 30% of patients who received between 3 and 4.9 mg/kg of colistin daily (based on ideal body weight) had nephrotoxicity and this increased to 69% when daily doses of 5 mg/kg or more were given. In most patients nephrotoxicity occurred within the first week of therapy and no clear association was seen between cumulative colistin doses and nephrotoxicity. None of the patients had long-term renal failure or required haemodialysis after their treatment with colistin.[3] Another retrospective cohort study of 30 patients treated with intravenous colistin for 48 hours or longer reported that nephrotoxicity occurred in 33% of patients within the first 5 days of treatment. Nephrotoxicity was associated with excessive colistin dosing which was usually due to the daily mg/kg dose of colistin being calculated according to the actual body weight in obese patients rather than the ideal body weight.[4]

See Cystic Fibrosis, above, for the suggestion that nephrotoxicity may be less frequent in this patient group.

1. Hartzell JD, *et al.* Nephrotoxicity associated with intravenous colistin (colistimethate sodium) treatment at a tertiary care medical center. *Clin Infect Dis* 2009; **48**: 1724–8.
2. Falagas ME, Rafailidis PI. Nephrotoxicity of colistin: new insight into an old antibiotic. *Clin Infect Dis* 2009; **48**: 1729–31.
3. Pogue JM, *et al.* Incidence of and risk factors for colistin-associated nephrotoxicity in a large academic health system. *Clin Infect Dis* 2011; **53**: 879–84.
4. Deryke CA, *et al.* Colistin dosing and nephrotoxicity in a large community teaching hospital. *Antimicrob Agents Chemother* 2010; **54**: 4503–5.

Occupational asthma. Occupational asthma has been reported in a 24-year-old man working in a pharmaceutical company transporting and storing raw materials.[1] Three months after starting his job, he developed rhinitis which improved over the weekends; 9 months later, exposure to colistin had caused him to develop a sudden cough, wheeze, and dyspnoea. A specific inhalation challenge confirmed the diagnosis of occupational asthma to colistin and the patient stopped working in the colistin-exposed environment. He was asymptomatic at 6-months follow-up.

1. Gómez-Ollés S, *et al.* Occupational asthma due to colistin in a pharmaceutical worker. *Chest* 2010; **137**: 1200–2.

Porphyria. Although the Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden offers no classification for colistin,[1] UK-licensed product information advises that colistin should be used with extreme caution in patients with porphyria.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

As for Polymyxin B Sulfate, p. 345.2.

Antimicrobial Action

The antimicrobial spectrum and mode of action of colistin is similar to that of polymyxin B (p. 345.2) but colistin sulfate is slightly, and colistimethate significantly, less active.

Pharmacokinetics

Colistin sulfate and colistimethate sodium are poorly absorbed from the gastrointestinal tract of adults and children; however, limited and unpredictable gastrointestinal absorption occurs in infants under 6 months of age. The drugs are not absorbed through mucous membranes, or intact or denuded skin. Transpulmonary absorption of colistimethate sodium is variable following inhalation of nebulised solution or dry powder. Peak plasma concentrations usually occur 2 to 3 hours after an intramuscular injection of colistimethate sodium. Plasma protein binding of colistin is reported to be more than 50% but that of colistimethate sodium is low. Colistin is reversibly bound to body tissues, but binding does not occur with colistimethate. Some colistimethate sodium may be hydrolysed to colistin *in vivo*. The serum half-life of colistimethate sodium is 2 to 3 hours but is prolonged in renal impairment; values of 10 to 20 hours have been reported in patients with a creatinine clearance of less than 20 mL/minute. See also Half-life p. 279.2. Half-life may initially be prolonged in neonates but has been reported to fall to 2 to 3 hours after 3 or 4 days.

Colistimethate is mainly excreted by glomerular filtration as changed and unchanged drug and up to 80% of a parenteral dose may be recovered in the urine within 24 hours. Excretion is more rapid in children than in adults; it is reduced in patients with renal impairment. Colistin crosses the placenta but diffusion into the CSF is negligible. It is distributed into breast milk.

Cystic fibrosis. References.

1. Reed MD, *et al.* The pharmacokinetics of colistin in patients with cystic fibrosis. *J Clin Pharmacol* 2001; **41**: 645–54.
2. Li J, *et al.* Steady-state pharmacokinetics of intravenous colistin methanesulphonate in patients with cystic fibrosis. *J Antimicrob Chemother* 2003; **52**: 987–92.
3. Ratjen F, *et al.* Pharmacokinetics of inhaled colistin in patients with cystic fibrosis. *J Antimicrob Chemother* 2006; **57**: 306–11.

Half-life. A study involving 18 critically-ill patients given intravenous colistimethate sodium found that the pharmacokinetics fitted a single-compartment model with an estimated half-life of 14.4 hours.[1] It was considered that the pharmacokinetics implied that plasma concentrations of the drug would be inadequate in this group until steady state was reached; loading doses might be of benefit in critically-ill patients.

1. Plachouras D, *et al.* Population pharmacokinetic analysis of colistin methanesulfonate and colistin after intravenous administration in critically ill patients with infections caused by gram-negative bacteria. *Antimicrob Agents Chemother* 2009; **53**: 3430–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Alfacolin; Alficetin; Nolisim; Toliscrin; *Austral.*: Coly-Mycin M†; Tadim; *Belg.*: Colistineb; *Canad.*: Coly-Mycin M; *China*: Colmycin (可利迈仙); *Cz.*: Colomycin; *Denm.*: Promixin; *Fr.*: Colimycine; *Ger.*: ColiFin; Diaront mono; Promixin; *Gr.*: Colimycine; Colomycin; Tadim; *Hong Kong*: Colomycin; *Hung.*: Colomycin; *India*: Colgit; Coligyl; Colistop; GDSafe; Harmless; Walamycin; *Indon.*: Colistine; *Irl.*: Colomycin; Promixin; *Israel*: Coliracin; *Ital.*: Colimicina†; Colimicina; *Mex.*: Colmesdant; *Neth.*: ColiFin; Colobreathe; Tadim; *Norw.*: Promixin; *Port.*: Colixin; *Spain*: Colimicina†; Promixin; *Swed.*: Tadim; *Switz.*: ColiFin; *Thai.*: Colistate; *Turk.*: Colistimicin; *UK*: Colobreathe; Colomycin; Promixin; *Ukr.*: Colomycin (Коломицин); *USA*: Coly-Mycin M.

Multi-ingredient Preparations. *Arg.*: Clarex Compuesto; Eristin; *Fr.*: Bacicoline; *Ger.*: Ecolicin; *Ital.*: Colbiocin; Colbiocin; Eubetal Antibiotico; Eubetal Antibiotico; *Mex.*: Colfur†; Colistin Magma†; *Neth.*: Bacicoline-B; *NZ*: Antibiotic Simplex; *Philipp.*: Elicocin; *Rus.*: Colbiocin (Колбиоцин); Colbiocin (Колбиоцин); *USA*: Coly-Mycin S Otic; Cortisporin-TC.

Pharmacopoeial Preparations

BP 2014: Colistimethate Injection; Colistimethate Sodium Powder for Nebuliser Solution; Colistin Tablets;
USP 36: Colistimethate for Injection; Colistin and Neomycin Sulfates and Hydrocortisone Acetate Otic Suspension; Colistin Sulfate for Oral Suspension.

Co-tetroxazine (BAN)

CAS — 73173-12-3.

Profile

Co-tetroxazine, a mixture of tetroxoprim (p. 378.3) and sulfadiazine (p. 363.3) in the proportion of 2:5, has properties similar to those of co-trimoxazole (p. 279.3). It has been given orally, mainly in the treatment of infections of the urinary and respiratory tracts, including pneumocystis pneumonia.

Co-trifamole (BAN)

CN-3123; Cotrifamol.
ATC — J01EE04.

Profile

Co-trifamole, a mixture of 5 parts of sulfamoxole (p. 370.1) and 1 part of trimethoprim (p. 383.2), has properties similar to those of co-trimoxazole (p. 279.3) and has been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Supristol.

Co-trimoxazole (BAN)

Cotrimossazolo; Co-trimoxazol; Cotrimoxazol; Ko-trimoksazol; Kotrimoksazol; Kotrimoxazol; SMX-TMP; SMZ-TMP; TMP-SMX; TMP-SMZ; Ко-тримоксазол.
CAS — 8064-90-2.
ATC — J01EE01.

Description. Co-trimoxazole is defined as a mixture of 5 parts of sulfamethoxazole and 1 part of trimethoprim.

Preparation and stability. Co-trimoxazole concentrate for injection must be diluted before being given as an intravenous infusion. Each 5 mL (80 mg of trimethoprim and 400 mg of sulfamethoxazole) of the concentrate is usually diluted in 125 mL of infusion solution. The recommended diluent is glucose 5%, although other solutions, including sodium chloride 0.9%, may be compatible for adequate periods. In patients who are fluid restricted, each 5 mL of the concentrate may be diluted in 75 mL of glucose 5%.

Diluted infusion solutions of co-trimoxazole have limited stability and eventually form a precipitate: this occurs more rapidly at higher concentrations. If the solution is cloudy or crystallisation appears at any time before or during an infusion, the solution should be discarded. Dilution is best carried out immediately before use; prepared solutions should be kept at room temperature and used within 2 hours of preparation if diluted in 75 mL of diluent, within 4 hours if in 100 mL, or within 6 hours if in 125 mL.

Uses and Administration

Co-trimoxazole is a mixture of the medium-acting sulfonamide, sulfamethoxazole, and the diaminopyrimidine, trimethoprim, in the proportion of 5 parts of sulfamethoxazole to 1 part of trimethoprim. It is used in infections caused by susceptible bacteria, particularly those of the urinary, respiratory, and gastrointestinal tracts, although the indications for its use are restricted in the UK (see p. 280.1). It is used to treat nocardiosis (p. 280.3) and is usually the drug of choice for the management of pneumocystis pneumonia (see p. 280.3).

Its other uses have included the treatment of acne, biliary-tract infections, brucellosis (generally with other drugs), cat scratch disease, *Burkholderia cepacia* (*Pseudomonas cepacia*) infections in cystic fibrosis, granuloma inguinale, listeriosis, melioidosis, mycetoma, otitis media, pertussis, typhoid and paratyphoid fever, and Whipple's disease. It has also been used for the prophylaxis of infections in immunocompromised patients. For details of the bacterial infections listed above and their treatment, see under Choice of Antibacterial, p. 172.2.

Co-trimoxazole is also used in the management of toxoplasmosis (p. 280.3), as well as many other protozoal infections, including blastocystis infection (p. 280.2), cyclosporiasis (p. 280.2), and isosporiasis (p. 280.2). It also may be used in the management of certain granulomatous disorders (p. 280.2).

Co-trimoxazole is usually given orally in a standard dose of 960 mg (trimethoprim 160 mg and sulfamethoxazole 800 mg) twice daily; in severe infections 2.88 g daily in 2 divided doses has been given. Lower doses are given for

long-term treatment and in patients with renal impairment (see Administration in Renal Impairment, p. 280.2).

Higher doses of co-trimoxazole of up to 120 mg/kg daily given in 2 to 4 divided doses for 14 to 21 days are used in the treatment of pneumocystis pneumonia; serum concentrations should be monitored and folate supplementation possibly considered (but see Pneumocystis Pneumonia, p. 280.3). For prophylaxis of pneumocystis pneumonia, the following dose regimens may be used: 960 mg once daily (7 days each week); 960 mg once daily on alternate days (3 days each week); or 960 mg twice daily on alternate days (3 days each week).

For details of doses in children, see p. 280.1.

For serious infections, if oral use is not possible, treatment may begin by intravenous infusion. Each ampoule (containing 480 mg of co-trimoxazole in 5 mL) is typically added to 125 mL of a suitable diluent immediately before use (see also p. 277.3), and the solution infused over 60 to 90 minutes. Doses given are similar to recommended oral doses.

The place of co-trimoxazole in therapy was reviewed by the UK CSM in 1995 (see also Incidence of Adverse Effects, p. 281.1).[1] As a result they recommended that its use should be limited to: pneumocystis pneumonia, toxoplasmosis, and nocardiosis; urinary-tract infections and acute exacerbations of chronic bronchitis, but only when there is bacteriological evidence of sensitivity to co-trimoxazole and good reason to prefer it to a single antibacterial; and acute otitis media in children, but again only when there is good reason to prefer it.

In other countries co-trimoxazole continues to be used for susceptible infections without restriction.

1. CSM. Revised indications for co-trimoxazole (Septrin, Bactrim, various generic preparations). *Current Problems* 1995; **21**: 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015619&RevisionSelectionMethod=LatestReleased (accessed 14/07/06)

Administration in children. Co-trimoxazole may be used in children for the treatment of infections caused by susceptible organisms, or for the prophylaxis of pneumocystis infection in those who are immunocompromised. It may be given orally or by intravenous infusion. Doses are expressed as the total amount of sulfamethoxazole and trimethoprim.

In the UK, co-trimoxazole is generally not recommended for use in infants younger than 6 weeks because of the risk of kernicterus from the sulphonamide component (see under Precautions of Sulfamethoxazole, p. 368.1), although it may be used in infants from 4 weeks of age for the treatment and prophylaxis of pneumocystis pneumonia. For the treatment of most infections, the *BNFC* recommends an *oral* dose of 24 mg/kg twice daily or the following *standard* doses:

- children 6 weeks to 6 months of age: 120 mg twice daily
- children 6 months to 6 years of age: 240 mg twice daily
- children 6 to 12 years of age: 480 mg twice daily

When used *intravenously*, doses of 18 mg/kg every 12 hours are recommended, although in severe infection up to 27 mg/kg (to a maximum of 1.44 g) every 12 hours may be used.

Alternatively, in the USA the American Academy of Pediatrics[1] recommends that children from 1 month of age may be given 48 to 72 mg/kg daily, orally in 2 divided doses.

For ***treatment*** **of pneumocystis pneumonia**, 120 mg/kg daily in 2 to 4 divided doses is recommended, either orally or intravenously for 14 to 21 days. For ***prophylaxis***, a few different regimens have been suggested. The *BNFC* suggests that an oral dose of 450 mg/m^2 (to a maximum of 960 mg) may be given twice daily on 3 alternate or consecutive days each week. US guidelines for prophylaxis of opportunistic infection in HIV-infected children suggest that a dose of 15 to 30 mg/kg twice daily may be given on 2 or 3 days of the week; the dose may be given on consecutive or alternate days of the week. Alternatively, the total daily dose may be given as a single dose on every day of the week.[2] In children with leukaemia or lymphoma, co-trimoxazole 30 mg/kg daily given in 2 divided doses on 2 consecutive days each week has been reported to be an effective alternative regimen.[3]

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.
2. Panel on Opportunistic Infections in HIV-Exposed and HIV-Infected Children. Guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and HIV-infected children: recommendations from the National Institutes of Health, CDC, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics (Issued 6th November, 2013). Available at: http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/oi_guidelines_pediatrics.pdf (accessed 13/12/13)
3. Lindemulder S, Albano E. Successful intermittent prophylaxis with trimethoprim/sulfamethoxazole 2 days per week for Pneumocystis carinii (jirovecii)-pneumonia in pediatric oncology patients. Abstract: *Pediatrics* 2007; **120**: 158. Full version: http://pediatrics.aappublications.org/cgi/reprint/120/1/e47 (accessed 14/08/09)

Administration in renal impairment. Doses of co-trimoxazole, both orally and intravenously, should be reduced in patients with renal impairment. The following recommendations for adults and children over 12 years of age are based on creatinine clearance (CC):

- CC above 30 mL/minute: the standard dose
- CC 15 to 30 mL/minute: half the standard dose
- CC below 15 mL/minute: not recommended.

In a review,[1] the following doses of co-trimoxazole (based on the trimethoprim component) were recommended for critically ill patients undergoing different types of renal replacement therapy:

- intermittent haemodialysis: 2.5 to 10 mg/kg every 24 hours or 5 to 20 mg/kg three times weekly (given after dialysis on dialysis days)
- continuous renal replacement therapy: 2.5 to 7.5 mg/kg every 12 hours; up to 10 mg/kg may be needed for patients with pneumocystis pneumonia who are undergoing continuous venovenous haemodiafiltration (CVVHDF)

1. Heintz BH, *et al.* Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy* 2009; **29**: 562–77.

Blastocystis infection. For a mention of the use of co-trimoxazole in the treatment of *Blastocystis hominis* infection, see p. 922.3.

Cyclosporiasis. Patients with *Cyclospora* infection (p. 923.2) have responded to treatment with co-trimoxazole.[1,2]

1. Hoge CW, *et al.* Placebo-controlled trial of co-trimoxazole for cyclospora infections among travellers and foreign residents in Nepal. *Lancet* 1995; **345**: 691–3. Correction. *ibid.*: 1060.
2. Verdier R-I, *et al.* Trimethoprim-sulfamethoxazole compared with ciprofloxacin for treatment and prophylaxis of Isospora belli and Cyclospora cayetanensis infection in HIV-infected patients: a randomized, controlled trial. *Ann Intern Med* 2000; **132**: 885–8.

Granulomatous diseases. Although co-trimoxazole appears to be effective in reducing the incidence of bacterial infection in patients with chronic granulomatous disease,[1-3] a disorder of leucocyte function associated with recurrent life-threatening infection and granuloma formation, its use in systemic vasculitis is much more controversial. There have been some reports of benefit from co-trimoxazole in patients with Wegener's granulomatosis (p. 1615.2),[4-7] but relapse appears to be common,[6] and an analysis[8] of the experience of the USA National Institutes of Health in 158 patients, was sceptical of its value: only 1 of 9 patients given 960 mg twice daily orally had any prolonged improvement.

Some evidence later emerged that addition of co-trimoxazole to maintenance regimens in patients already in remission reduces the incidence of relapse,[9] although another study suggested that it might actually increase the risk of relapse.[10]

1. Mouy R, *et al.* Incidence, severity, and prevention of infections in chronic granulomatous disease. *J Pediatr* 1989; **114**: 555–60.
2. Margolis DM, *et al.* Trimethoprim-sulfamethoxazole prophylaxis in the management of chronic granulomatous disease. *J Infect Dis* 1990; **162**: 723–6.
3. Gallin JI, Malech HL. Update on chronic granulomatous diseases of childhood: immunotherapy and potential for gene therapy. *JAMA* 1990; **263**: 1533–7.
4. DeRemee RA, *et al.* Wegener's granulomatosis: observations on treatment with antimicrobial agents. *Mayo Clin Proc* 1985; **60**: 27–32.
5. Bowden PJ, Griffiths H. Co-trimoxazole in the treatment of Wegener's granulomatosis. *Med J Aust* 1989; **151**: 303–4.
6. Valeriano-Marcet J, Spiera H. Treatment of Wegener's granulomatosis with sulfamethoxazole-trimethoprim. *Arch Intern Med* 1991; **151**: 1649–52.
7. Ohtake T, *et al.* Generalized Wegener's granulomatosis responding to sulfamethoxazole-trimethoprim monotherapy. *Intern Med* 2001; **40**: 666–70.
8. Hoffman GS, *et al.* Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med* 1992; **116**: 488–98.
9. Stegeman CA, *et al.* Trimethoprim-sulfamethoxazole (co-trimoxazole) for the prevention of relapses of Wegener's granulomatosis. *N Engl J Med* 1996; **335**: 16–20.
10. de Groot K, *et al.* Therapy for the maintenance of remission in sixty-five patients with generalized Wegener's granulomatosis: methotrexate versus trimethoprim/sulfamethoxazole. *Arthritis Rheum* 1996; **39**: 2052–61.

Isosporiasis. A regimen of oral co-trimoxazole 960 mg four times daily for 10 days followed by 960 mg twice daily for 3 weeks was reported to be initially effective in patients with AIDS suffering from isosporiasis (p. 923.3), and produced resolution of diarrhoea within 2 days of beginning treatment; it was, however, associated with a high rate of recurrence.[1] A shorter regimen followed by indefinite prophylaxis may be preferable in persons with AIDS; in a small randomised controlled study, co-trimoxazole 960 mg twice daily for 7 days, followed by 10 weeks of prophylaxis, was effective in HIV-infected patients with isosporiasis.[2]

1. DeHovitz JA, *et al.* Clinical manifestations and therapy of Isospora belli infection in patients with the acquired immunodeficiency syndrome. *N Engl J Med* 1986; **315**: 87–90.
2. Verdier R-I, *et al.* Trimethoprim-sulfamethoxazole compared with ciprofloxacin for treatment and prophylaxis of Isospora belli and Cyclospora cayetanensis infection in HIV-infected patients: a randomized, controlled trial. *Ann Intern Med* 2000; **132**: 885–8.

Nocardiosis. Co-trimoxazole is used in the treatment of nocardiosis (p. 193.3). There is no consensus on the optimum dosage; doses of 2.88 to 3.84 g daily in divided doses for up to 3 months have been used.

Pneumocystis pneumonia. Co-trimoxazole is the preferred drug for both the treatment and prophylaxis of pneumocystis pneumonia (p. 567.2). A single dose of 480 mg daily may be effective and better tolerated for prophylaxis than a daily dose of 960 mg.[1] However, some still prefer the later dose schedule[2] which is also the one preferred by the CDC in the USA[3] and is a licensed dose for prophylaxis in both the UK and USA. Various studies[1,2,4-8] have shown intermittent dosing is also effective for the prophylaxis of pneumonia and is better tolerated than daily dosing; the dose has usually been 960 mg three times each week on alternate days[1,2,4-7] although 960 mg twice daily three times each week has also been given.[8] The addition of folinic acid has no effect on tolerability and may be associated with a higher rate of therapeutic failure (see HIV Infection and AIDS, p. 2067.3).

1. Ioannidis JPA, *et al.* A meta-analysis of the relative efficacy and toxicity of Pneumocystis carinii prophylactic regimens. *Arch Intern Med* 1996; **156**: 177–88.
2. El-Sadr WM, *et al.* A randomized trial of daily and thrice-weekly trimethoprim-sulfamethoxazole for the prevention of Pneumocystis carinii pneumonia in human immunodeficiency virus-infected persons. *Clin Infect Dis* 1999; **29**: 775–83.
3. CDC. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR* 2009; **58** (RR-4): 1–207. Also available at: http://www.cdc.gov/mmwr/pdf/rr/rr5804.pdf (accessed 09/07/09)
4. Wormser GP, *et al.* Low-dose intermittent trimethoprim-sulfamethoxazole for prevention of Pneumocystis carinii pneumonia in patients with human immunodeficiency virus infection. *Arch Intern Med* 1991; **151**: 688–92.
5. Stein DS, *et al.* Use of low-dose trimethoprim-sulfamethoxazole thrice weekly for primary and secondary prophylaxis of Pneumocystis carinii pneumonia in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother* 1991; **35**: 1705–9.
6. Ruskin J, LaRiviere M. Low-dose co-trimoxazole for prevention of Pneumocystis carinii pneumonia in human immunodeficiency virus disease. *Lancet* 1991; **337**: 468–71.
7. Bozzette SA, *et al.* The tolerance for zidovudine plus thrice weekly or daily trimethoprim-sulfamethoxazole with and without leucovorin for primary prophylaxis in advanced HIV disease. *Am J Med* 1995; **98**: 177–82.
8. Podzamczer D, *et al.* Intermittent trimethoprim-sulfamethoxazole compared with dapsone-pyrimethamine for the simultaneous primary prophylaxis of Pneumocystis pneumonia and toxoplasmosis in patients infected with HIV. *Ann Intern Med* 1995; **122**: 755–61.

Toxoplasmosis. There is some evidence that giving co-trimoxazole for prophylaxis of pneumocystis pneumonia produces an additional benefit in acting prophylactically against toxoplasmic encephalitis in persons with HIV infection or AIDS,[1-5] but the evidence (as for other drugs) has been largely anecdotal or from small retrospective studies. In the USA, the CDC recommends[1] that co-trimoxazole 960 mg daily (as for pneumocystis pneumonia prophylaxis, above) be given to HIV-infected patients who are seropositive for *Toxoplasma* and have a CD4+ count below 100 cells/microlitre.

Co-trimoxazole has also produced promising results in preliminary studies for the treatment of toxoplasmic encephalitis in patients with AIDS,[6] and a systematic review[7] considered it an effective treatment, particularly in resource-poor settings where alternatives such as pyrimethamine with sulfadiazine might not be available.

For a discussion of toxoplasmosis and its management, see p. 926.1.

1. CDC. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR* 2009; **58** (RR-4): 1–207. Also available at: http://www.cdc.gov/mmwr/pdf/rr/rr5804.pdf (accessed 14/09/09)
2. Zangerle R, Allerberger F. Effect of prophylaxis against Pneumocystis carinii on toxoplasma encephalitis. *Lancet* 1991; **337**: 1232.
3. Carr A, *et al.* Low-dose trimethoprim-sulfamethoxazole prophylaxis for toxoplasmic encephalitis in patients with AIDS. *Ann Intern Med* 1992; **117**: 106–11.
4. Beaman MH, *et al.* Prophylaxis for toxoplasmosis in AIDS. *Ann Intern Med* 1992; **117**: 163–4.
5. Podzamczer D, *et al.* Intermittent trimethoprim-sulfamethoxazole compared with dapsone-pyrimethamine for the simultaneous primary prophylaxis of pneumocystis pneumonia and toxoplasmosis in patients infected with HIV. *Ann Intern Med* 1995; **122**: 755–61.
6. Torre D, *et al.* Randomized trial of trimethoprim-sulfamethoxazole versus pyrimethamine-sulfadiazine for therapy of toxoplasmic encephalitis in patients with AIDS. *Antimicrob Agents Chemother* 1998; **42**: 1346–9.
7. Dedicoat M, Livesley N. Management of toxoplasmic encephalitis in HIV-infected adults (with an emphasis on resource-poor settings). Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 23/07/08).

Adverse Effects and Treatment

The adverse effects of co-trimoxazole are those of its components; most effects can be attributed to sulfamethoxazole (p. 367.3), although some, including potentially

serious hyperkalaemia, may be caused by trimethoprim (see p. 384.1). Gastrointestinal disturbances (mainly nausea and vomiting) and skin reactions are the most common adverse effects. There have been occasional deaths, especially in elderly patients, mainly due to blood disorders, hepatic necrosis, or severe skin reactions.

A high incidence of adverse effects has been reported in AIDS patients; desensitisation may sometimes be considered (see Immunocompromised Patients under Precautions, p. 281.2).

Incidence of adverse effects. There has been concern over the safety of co-trimoxazole. In 1985, reporting on 85 deaths associated with the use of co-trimoxazole,[1] mainly due to blood dyscrasias (50 reports) and skin reactions (14 reports), the UK CSM found that fatalities showed a marked increase with age: below 40 years, there were 0.25 reported deaths per million prescriptions, but for patients over 65 years of age the number of reported deaths per million prescriptions was more than 15-fold greater. However, at that time the CSM felt that it would be unwise to assume that trimethoprim was substantially less liable than co-trimoxazole to cause fatal adverse reactions.[1] Others suggested[2] that most of the deaths associated with the use of co-trimoxazole were typical of sulfonamide toxicity and that the indications for the use of co-trimoxazole should be reduced; this included the suggestion that it should be contra-indicated in the elderly. The CSM stated that their main message was that the risks of treatment with co-trimoxazole were more apparent in the elderly, but that there was no significant difference between the numbers of reports received for serious adverse reactions to trimethoprim and co-trimoxazole when corrected for prescription volumes.[3] In practice, despite further occasional reports of fatalities in elderly patients,[4] there did not appear to have been a marked reduction in the use of this drug in the UK.[5] A similar warning of increased risk from co-trimoxazole in elderly patients was issued by the Adverse Drug Reactions Advisory Committee in Australia.[6]

A large population-based follow-up study in the UK[7] indicated that the risks of serious liver, blood, skin, and kidney disorders with either co-trimoxazole, trimethoprim, or cefalexin were small and were similar to those with many other antibacterials. Although in 1995 the CSM did restrict the use of co-trimoxazole on the grounds that its place in therapy had changed[8] (see under Uses and Administration, p. 278.1), they also noted that co-trimoxazole continued to show a similar pattern of serious suspected adverse reactions to that reported 10 years earlier and that adverse drug reactions with trimethoprim were similar; blood dyscrasias and generalised skin disorders were the most serious reactions in each case and occurred mainly in elderly patients.

1. CSM. Deaths associated with co-trimoxazole, ampicillin and trimethoprim. *Current Problems 15* 1985. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024422&RevisionSelectionMethod=LatestReleased (accessed 23/07/08)
2. Lacey RW, *et al.* Co-trimoxazole toxicity. *BMJ* 1985; 291: 481.
3. Goldberg A. Co-trimoxazole toxicity. *BMJ* 1985; 291: 673.
4. Whittington RM. Toxic epidermal necrolysis and co-trimoxazole. *Lancet* 1989; ii: 574.
5. Carmichael AJ, Tan CY. Fatal toxic epidermal necrolysis associated with co-trimoxazole. *Lancet* 1989; ii: 808–9.
6. Adverse Drug Reactions Advisory Committee (ADRAC). Trimethoprim-sulphamethoxazole warning on elderly. *Aust Adverse Drug React Bull* February 1990.
7. Jick H, Derby LE. Is co-trimoxazole safe? *Lancet* 1995; 345: 1118–19.
8. CSM. Revised indications for co-trimoxazole (Septrin, Bactrim, various generic preparations). *Current Problems* 1995; 21: 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015619&RevisionSelectionMethod=LatestReleased (accessed 14/07/06)

Effects on the CNS. Higher-level gait disorder and nocturnal delirium were reported in an elderly man given oral co-trimoxazole, up to 1.92 g every 12 hours, for lung infection;[1] dramatic improvement occurred shortly after the drug was stopped. Tremor associated with co-trimoxazole use has also been reported in a patient treated for suspected pneumocystis pneumonia.[2] The trimethoprim component has been proposed as the most likely cause of adverse effects involving the CNS.[2]

1. Dakin LE. Probable trimethoprim/sulfamethoxazole-induced higher-level gait disorder and nocturnal delirium in an elderly man. *Ann Pharmacother* 2009; 43: 129–33.
2. Floris-Moore MA, *et al.* Adverse reactions to trimethoprim/sulfamethoxazole in AIDS. *Ann Pharmacother* 2003; 37: 1810–3.

Precautions

As for Sulfamethoxazole, p. 368.1 and Trimethoprim, p. 384.2.

Co-trimoxazole should not be given to patients with a history of hypersensitivity to it or to the sulfonamides or trimethoprim. It should be stopped at the first appearance of a rash, or if blood disorders develop. It should be avoided in patients with severe hepatic impairment and used with caution in patients with lesser degrees of impairment. Like its components, co-trimoxazole should be used with caution in renal impairment, and dosage adjustment may be necessary; it should not be used in severe renal impairment without monitoring of plasma drug concentrations. An adequate fluid intake should be maintained to reduce the risk of crystalluria, but alkalinisation of the urine, although it increases urinary excretion of the sulfamethoxazole component, decreases urinary trimethoprim excretion. Regular blood counts and urinalyses and renal-function tests should be carried out in patients receiving prolonged treatment with co-trimoxazole. Elderly patients may be more susceptible to adverse effects (see Incidence of Adverse Effects, above). Folate supplementation may be necessary in patients predisposed to folate deficiency, such as elderly patients and when high doses of co-trimoxazole are given for a prolonged period. Co-trimoxazole is contra-indicated in patients with megaloblastic anaemia due to folate deficiency.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were taking co-trimoxazole, and the last available guidance from the American Academy of Pediatrics considered[1] that it was therefore usually compatible with breast feeding. Studies have shown that significant concentrations of trimethoprim and sulfamethoxazole are present in breast milk after maternal doses;[2,3] however, the calculated dose to the infant was deemed unlikely to lead to clinical effects.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/05/04)
2. Arnauld R, *et al.* Étude du passage de la triméthoprime dans le lait maternel. *Ouest Med* 1972; 25: 959–64.
3. Miller RD, Salter AJ. The passage of trimethoprim/sulphamethoxazole into breast milk and its significance. *Hell Soc Chemother* 1974; 1: 687–91.

G6PD deficiency. It has been suggested by some that co-trimoxazole should be avoided by people with G6PD deficiency.[1] Others suggest that therapeutic doses may be given without causing haemolytic anaemia.[2] However, a healthy, 37-year-old man developed haemolytic anaemia, hepatitis, orthostatic hypotension, and aseptic meningitis after taking co-trimoxazole for a urinary-tract infection; the patient was later found to have G6PD deficiency and this was considered to have increased his risk for a co-trimoxazole hypersensitivity reaction as well as for developing haemolytic anaemia.[3]

1. WHO. Glucose-6-phosphate dehydrogenase deficiency. *Bull WHO* 1989; 67: 601–11.
2. Youngster I, *et al.* Medications and glucose-6-phosphate dehydrogenase deficiency: an evidence-based review. *Drug Safety* 2010; 33: 713–26.
3. Chisholm-Burns MA, *et al.* Aseptic meningitis, hemolytic anemia, hepatitis, and orthostatic hypotension in a patient treated with trimethoprim-sulfamethoxazole. *Am J Health-Syst Pharm* 2010; 67: 123–7.

Immunocompromised patients. An extraordinarily high frequency of adverse reactions to co-trimoxazole has been reported in patients with AIDS being treated for pneumocystis pneumonia. The comment has been made that, when therapeutic doses of co-trimoxazole are used, hypersensitivity rashes and leucopenia each develop in 30% of patients, compared with less than 5% for each complication in patients without AIDS.[1] Other studies have reported an even higher incidence of toxicity, and the overall incidence of adverse effects, including fever, malaise, and hepatitis, may be 80% or more.[2-4] Adverse reactions also appear to be unusually frequent when prophylactic doses are used.[4] A lower frequency of cutaneous reactions has been reported among African, Haitian, and American black AIDS patients compared with white AIDS patients, suggesting a genetic susceptibility to such reactions.[5]

High serum concentrations of trimethoprim and sulfamethoxazole may contribute to the incidence of adverse effects,[6,7] and it was noted[6] that adverse effects, and in particular myelosuppression, were kept to tolerable levels in a group of patients in whom the dose of co-trimoxazole was adjusted to maintain serum-trimethoprim concentrations at 5 to 8 micrograms/mL. In a study in HIV-infected patients given co-trimoxazole for the prophylaxis of pneumocystis pneumonia,[8] a gradual start to therapy (increased over 2 weeks to the full therapeutic dose) was found to improve the tolerability of co-trimoxazole, when compared with patients started on full therapeutic doses. However, others[9] found no difference in the frequency of adverse effects when the sulfamethoxazole dose was modified.

It was suggested[10] that it was the reactive hydroxylamine metabolites of sulfamethoxazole that produced the adverse effects in HIV-infected individuals, but later work by the same authors[11] cast some doubt on this hypothesis.

Some workers have used diphenhydramine alone or with adrenaline to manage hypersensitivity reactions associated with co-trimoxazole therapy, thus allowing continuation of treatment,[12,13] while other workers have tried **desensitisation** to co-trimoxazole in patients with AIDS.[14-19] A systematic review[20] based on 3 small studies concluded that desensitisation was a more effective strategy than continuation. For mention of desensitisation to sulfonamides in patients with AIDS, see under Sulfamethoxazole, p. 368.2.

An increased incidence of myelosuppression, although not, apparently, of other adverse effects, has been reported in **patients with leukaemia** receiving maintenance chemotherapy.[21,22] Multifocal myoclonus and bilateral asterixis occurred in an immunocompromised lymphoma patient 4 days after starting treatment with high dose co-trimoxazole for the treatment of *Nocardia asteroides*. Symptoms resolved completely after stopping co-trimoxazole treatment.[23]

1. Masur H. Treatment of infections and immune defects. In: Fauci AS, moderator. Acquired immunodeficiency syndrome: epidemiologic, clinical, immunologic, and therapeutic considerations. *Ann Intern Med* 1984; 100: 92–106.
2. Gordin FM, *et al.* Adverse reactions to trimethoprim-sulfamethoxazole in patients with the acquired immunodeficiency syndrome. *Ann Intern Med* 1984; 100: 495–9.
3. Jaffe HS, *et al.* Complications of co-trimoxazole in treatment of AIDS-associated Pneumocystis carinii pneumonia in homosexual men. *Lancet* 1983; ii: 1109–11.
4. Mitsuyasu R, *et al.* Cutaneous reaction to trimethoprim-sulfamethoxazole in patients with AIDS and Kaposi's sarcoma. *N Engl J Med* 1983; 308: 1535.
5. Colebunders R, *et al.* Cutaneous reactions to trimethoprim-sulfamethoxazole in African patients with the acquired immunodeficiency syndrome. *Ann Intern Med* 1987; 107: 599–600.
6. Sattler FR, *et al.* Trimethoprim-sulfamethoxazole compared with pentamidine for treatment of Pneumocystis carinii pneumonia in the acquired immunodeficiency syndrome. *Ann Intern Med* 1988; 109: 280–7.
7. Stevens RC, *et al.* Pharmacokinetics and adverse effects of 20-mg/kg/day trimethoprim and 100-mg/kg/day sulfamethoxazole in healthy adult subjects. *Antimicrob Agents Chemother* 1991; 35: 1884–90.
8. Para MF, *et al.* Reduced toxicity with gradual initiation of trimethoprim-sulfamethoxazole as primary prophylaxis for Pneumocystis carinii pneumonia: AIDS Clinical Trials Group 268. *J Acquir Immune Defic Syndr* 2000; 24: 337–43.
9. McLean I, *et al.* Modified trimethoprim-sulphamethoxazole doses in Pneumocystis carinii pneumonia. *Lancet* 1987; ii: 857–8.
10. van der Ven AJAM, *et al.* Adverse reactions to co-trimoxazole in HIV infection. *Lancet* 1991; 338: 431–3.
11. ter Hofstede HJM, *et al.* Drug reactions to cotrimoxazole in HIV infection: possibly not due to the hydroxylamine metabolites of sulphamethoxazole. *Br J Clin Pharmacol* 1999; 47: 571–3.
12. Gibbons RB, Lindauer JA. Successful treatment of Pneumocystis carinii pneumonia with trimethoprim-sulfamethoxazole in hypersensitive AIDS patients. *JAMA* 1985; 253: 1259–60.
13. Toma E, Pournier S. Adverse reactions to co-trimoxazole in HIV infection. *Lancet* 1991; 338: 954.
14. Kreuz W, *et al.* "Treating through" hypersensitivity to co-trimoxazole in children with HIV infection. *Lancet* 1990; 336: 908–9.
15. Carr A, *et al.* Efficacy and safety of rechallenge with low-dose trimethoprim-sulphamethoxazole in previously hypersensitive HIV-infected patients. *AIDS* 1993; 7: 65–71.
16. Absar N, *et al.* Desensitization to trimethoprim/sulfamethoxazole in HIV-infected patients. *J Allergy Clin Immunol* 1994; 93: 1001–9.
17. Cortese LM, *et al.* Trimethoprim/sulfamethoxazole desensitization. *Ann Pharmacother* 1996; 30: 184–6.
18. Caumes E, *et al.* Efficacy and safety of desensitization with sulfamethoxazole and trimethoprim in 48 previously hypersensitive patients infected with human immunodeficiency virus. *Arch Dermatol* 1997; 133: 465–9.
19. Demoly P, *et al.* Six-hour trimethoprim-sulfamethoxazole-graded challenge in HIV-infected patients. *J Allergy Clin Immunol* 1998; 102: 1033–6.
20. Lin D, *et al.* Cotrimoxazole for prophylaxis or treatment of opportunistic infections of HIV/AIDS in patients with previous history of hypersensitivity to cotrimoxazole. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 23/07/08).
21. Woods WG, *et al.* Myelosuppression associated with co-trimoxazole as a prophylactic antibiotic in the maintenance phase of childhood acute lymphocytic leukemia. *J Pediatr* 1984; 105: 639–44.
22. Drysdale HC, Jones LP. Co-trimoxazole prophylaxis in leukaemia. *Lancet* 1982; i: 448.
23. Dib EG, *et al.* Multifocal myoclonus induced by trimethoprim-sulfamethoxazole therapy in a patient with nocardia infection. *N Engl J Med* 2004; 350: 88–9.

Interference with diagnostic tests. Co-trimoxazole has been reported[1,2] to cause a small reduction in serum-thyroxine and tri-iodothyronine concentrations, probably due to the sulfonamide component.[2] Although co-trimoxazole had not been shown to be a cause of hypothyroidism (since all concentrations remained within the normal range), tests of thyroid function might need to be interpreted with care in patients on such treatment.

1. Cohen HN, *et al.* Effects on human thyroid function of sulphonamide and trimethoprim combination drugs. *BMJ* 1980; 281: 646–7.
2. Cohen HN, *et al.* Trimethoprim and thyroid function. *Lancet* 1981; i: 676–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies the combination of sulfamethoxazole and trimethoprim as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/08/11)

Interactions

Any of the drug interactions reported with sulfamethoxazole (p. 368.2) or trimethoprim (p. 384.2) may occur with co-trimoxazole.

Antibacterials. For reference to potential interaction between co-trimoxazole and *rifampicin*, see p. 355.2.

Antimicrobial Action

The actions and spectrum of activity of co-trimoxazole are essentially those of its components, sulfamethoxazole (p. 368.3) and trimethoprim (p. 384.3).

Because they act at different points of the folate metabolic pathway a potent synergy exists between its components *in vitro* with an increase of up to about tenfold in antibacterial activity, and a frequently bactericidal action where the components individually are generally bacteriostatic. The optimum effect against most organisms is seen at a ratio of 1 part trimethoprim to 20 of sulfamethoxazole; although co-trimoxazole is formulated as a 1 to 5 ratio, differences in the pharmacokinetics of the two drugs mean that the ratio of the peak concentrations is about 1:20. However, it is not clear that the optimum ratio is achieved at all sites and, given that both drugs are present in therapeutic concentrations, the contribution of synergy to the effects of co-trimoxazole *in vivo* is uncertain.

Although it was originally thought that combining trimethoprim and sulfamethoxazole would prevent resistance developing to either of the two components, this has not proved correct and resistance to co-trimoxazole (in both Gram-positive and Gram-negative organisms) is now widespread. Rates of resistance vary depending on the bacterial species, the type of infection being treated, and geographic location. Resistance is generally chromosome- or plasmid-mediated. Although resistant organisms are usually resistant to both components of the mixture, strains resistant to either the sulfonamide or trimethoprim, and with a reduced sensitivity to co-trimoxazole, have been reported; resistance to co-trimoxazole develops more slowly *in vitro* than to either component alone. Resistance has occurred notably among Enterobacteriaceae; resistant *Salmonella* and *Shigella* are common in many countries, while resistance in *Haemophilus influenzae, H. ducreyi*, and *Streptococcus pneumoniae* tends to vary according to geographic location. Resistance in *Moraxella catarrhalis* has been reported rarely.

References.

1. Martin JN, *et al.* Emergence of trimethoprim-sulfamethoxazole resistance in the AIDS era. *J Infect Dis* 1999; **180**: 1809–18.
2. Huovinen P. Resistance to trimethoprim-sulfamethoxazole. *Clin Infect Dis* 2001; **32**: 1608–14.

Pharmacokinetics

As for sulfamethoxazole (p. 369.1) and trimethoprim (p. 384.3). Co-trimoxazole is rapidly and well absorbed from the gastrointestinal tract and peak plasma concentrations are reached between 1 to 4 hours after an oral dose; effective plasma concentrations are maintained for up to 24 hours after an oral therapeutic dose. Steady-state concentrations are reached after dosing for 2 to 3 days. Plasma concentrations of trimethoprim and sulfamethoxazole are generally around the optimal ratio of 1:20, although they may vary from 1:20 to 1:30 or more. The ratio of the two drugs is usually much lower in the tissues (often around 1:2 to 1:5) since trimethoprim, the more lipophilic drug, penetrates many tissues better than sulfamethoxazole and has a much larger volume of distribution. In urine the ratio may vary from 1:1 to 1:5 depending on the pH. Co-trimoxazole is excreted mainly by the kidneys through both glomerular filtration and tubular secretion; about 50% is excreted in the urine within 24 hours as unchanged drug.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Adrenol; Bacticel; Bactrim; Cotrizol-G; Danferane; Dosulfin Fuerte; Netocur; Novidrine; Sulfagrand; Tritenk; Urisept NP; *Austral.*: Bactrim; Resprim; Septrin; Trimoxazole†; *Austria*: Bactrim; Cotribene; Eusaprim; Oecotrim†; *Belg.*: Bactrim; Cotrim†; Eusaprim; *Braz.*: Assepium; Bac-Sulfitrin; Bacfar; Bacprotin†; Bacteracin; Bactrim; Bactrisan; Bactrizol†; Bactropin; Batrox; Bellacrim P; Benectrin; Dientrin; Ectrin; Gamactrin†; Imuneprim†; Infectrin; Metoprin; Neotrin; Pulkrin†; Qiftrin; Roytrin; Selectrin†; Teutrin; Tricban; Trimexazol; Uropol†; *Canad.*: Apo-Sulfatrim; Novo-Trimel; Nu-Cotrimox; Protrin; Septra; Trisulfa; *Chile*: Bacterol; Bactrimel; Septrin; Trelibec; *China*: Fu Fang Xin Nuo Ming Pian (复方新诺明片); Kui Jian (奎建); Morbifurb (诺德菲); Nuo Da Ming (诺达明); Ou Lin (欧林); Yu An Li Qing (玉安立清); *Cz.*: Biseptol; Bismoral†; Primotren†; Sumetrolim; *Fin.*: Cotrim; *Fr.*: Bactrim; *Ger.*: Berlocid†; Cotrim-Diolan; Cotrim; CotrimHefa†; Cotrimhexal†; Cotrimox-Wolff†; Cotrimstada†; Drylin†; Eusaprim; Kepinol; TMS†; *Gr.*: Bactrimel; Bioprim; Blaxezan; Blexon; Epahol; Oradin; Santafurin; Septrin; Solfoton; Stremycil-T; Sunicol; Trilogan; Ylestrom; *Hong Kong*: Chemoprim; Cotrim; Dhatrin; Letus; Resprim†; Septol†; Septrin†; Suprim†; Synco-SMZT†; Trimetrin†; Trisul†; Uni-Sulfaprim†; *Hung.*: Cotripharm; Sumetrolim; *India*: Alcorim-F; Antrima; Bactrim; Ciplin; Colizole; Cotribid Kid; Cotrimox; Cotrizole; Kombina; L-Trim; Larprim; Methoxaprim; Moly Kid; Mountrim; Okatrim DS; Oriprim; Otrim; Sepmax; Septran; Tabrol; Trisulfose; *Indon.*: Bactoprim Combi; Bactricid; Bactrim; Bactrizol; Cotrim†; Cotrimol†; Dotrim; Dumotrim†; Erphatrim; Ikaprim; Infatrim; Kaftrim; Lapikot; Licoprima; Meditrim†; Meprotrin; Moxalas; Nufaprim; Ottoprim; Pehatrim; Primadex; Primazole; Primsulfon; Sanprima; Septrin; Spectrem; Sulprim†; Sultrimmix†; Trimezol; Triminex†; Trimoxsul; Trixzol†; Trizole; Ulfaprim†; Wiatrim; Xepaprim; Zoltrim; Zultrop; *Irl.*: Septrin; *Israel*: Diseptyl; Resprim; Septrin; *Ital.*: Bactrim; Chemitrim; Eusaprim†; *Jpn*: Bactramin; Baktar; *Malaysia*: Bacin; Bactrim; Chemix; Cotrim; Resprim†; Trimexazole; Trizole; *Mex.*: Andoprim†; Anitrim; Apo-Trinelax; Bacpiryl; Bactelan; Bacterict; Bactidet†; Bactilen; Bactiver; Bactrim; Bactropin; Bateral; Batrizol; Bioprim; Bisultrim; Derrtin; Dibaprim; Ectaprim; Esteprim; Eutrim; Fartropin; Fectri; Kaltrim; Maxtrim; Metoxiprim; Mixange; Neofatrim; Octiban; Odisulfan; Pisatrina†; Polibatrin; Pribac; Protaxol†; Protrim; Septrin; Servitrim; Soltrim; Sulfawal; Sulfoid Trimetho; Sulfort; Sulprim; Sultral; Thriazol; Tribakin; Trimetoger; Trimetox; Trimexazol; Trimexole; Trimzol; TS-Bac Vanadyl; *Neth.*: Bactrimel; *Norw.*: Bactrim; *NZ*: Apo-Sulfatrim†; Deprim; Trisul; *Philipp.*: Bacidal; Bactille; Bactrim; Bactrinol; Bacxal; Baczole†; Bantizol; Chromo-Z; Combi-Methoxan; Comsid; Costazole†; Cozole†; CTR; Doctrimox; Drilozole; Embatrim; Fedimed; Forteprim; Frocimole; Globaxol; Ivatrim†; Kassemox; Kathrex; Lictora†; Macromed; Moxadden; Moxzole; Neotrim; Onetrim; Oprizole†; Pediatrim; Prizogen; Procor; Renatrim; Rimezone; Rotrace; Scribcin; Septrin; Suprex; Syltrifil; Syndal; Synermed; Timizol; Tricomed; Triforam; Trim-S; Trimephar; Trimetazole; Trimitrix; Trimocom; Trimoxis; Triphimox; Trizole; Xanazole; Zamboprim†; Zolmed; *Pol.*: Bactrim; Biseptol; Septrin†; Two-Septol; *Port.*: Bactrim; Microcetim†; Septrin; *Rus.*: Bactrim (Бактрим); Biseptol (Бисептол); Brifeseptol (Брифесептол); Cotrimol (Котримол); Cotripharm (Котрифарм); Groseptol (Гроссептол); Oriprim (Ориприм); Rancotrim (Ранкотрим)†; Sumetrolim (Суметролим); *S.Afr.*: Acuco†; Adco-Bencole; Bactrim; Casicot; Co Trim; Cocydal†; Cozole; Doctrim; Durobac Dynazole; Ilvitrim; Lagatrim; Meditrim; Nucotrim; Purbac Septran; Spectrim; Trimethox; Trimzol†; Trixazole; Ultrasept; Xerazole; *Singapore*: Apo-Sulfatrim; Bacin; BS; Chemix; Dhatrin; Mortin; Primzole; Suprim; Synco-SMZT; *Spain*: Momentol†; Septrin; *Swed.*: Bactrim; Eusaprim; *Switz.*: Bactrim; Cotrim; Escoprim; Lagatrim; Nopil; *Thai.*: Actin; Actrim; Addtrim; Agsulfa; Babyurim; Bacin; Bactin; Bactoprim; Bactrim; Baczole; Co-Fatrim; Co-Star; Co-Tasian; Co-Tri; Co-Trimed; Co-tromoxazole†; Comox; Comoxole; Conprim†; Coprim; Cotamox; Cotrim; GPO-Trim; Herocetine-D; KB Famate; Ko-Cap†; Ko-Kure†; Ladar†; Lastrim; Letus†; M-Moxa; M-Trim; Mano-Trim; Maxitrin; Maxtrim; Medcotrim; Mega-Prim; Metrim; Metxaprim; Mezine; Mycosamthong; Pantrim; Patartim; Po-Trim; Spectrim; Sulbacta†; Sulfometh; Sulprim; Suntrim; Sutrim; Tactrim; Tampo; Toprim; Trifatrim; Trimexazole; Triprim†; Trixzol†; Zoleprim; *Turk.*: Bactrim; Bakton; Co-Tripirim; Cotriver; Kemoprim; Metoprim; Mikrosid; Septrin; Sulfaprim; Trifen; Trimoks; *UAE*: Trimol; *UK*: Fectrim; Septrin; *Ukr.*: Bactrim (Бактрим); Biseptol (Бисептол); Groseptol (Гроссептол); Soluseptol (Солосептол); Sumetrolim (Суметролим); *USA*: Bactrim; Cotrim†; Septra; SMZ-TMP; Sulfatrim; *Venez.*: Bactrimel; Co-Sultrin; Forcrim; Trimecor; Tripur.

Multi-ingredient Preparations. *Arg.*: Bacti-Uril; Bactrim Balsamico; Dosulfin Bronquial; Enterobacticel; Netocur Balsamico; Neumobacticel; *Braz.*: Assepium Balsamico; Benecrin Balsamico; Diazol; Dispeptrin†; Ecrin Balsamico; Metoprin Balsamico†; Selectrin Balsamico; Urocrim; *Chile*: Entero Micinovo; Uro-Micinovo; *China*: Xiaoke 精刻); *India*: Chemotrin; Neoprim; *Mex.*: Bactrim Compositum; Brogamax; Guayaprin; Octex; Sadocin; Trimexole Compositum; *Singapore*: Co-Trimexazole; Trimaxazole; *Spain*: Bactopumon; Balsoprim; Bronco Aseptilex Fuerte†; Broncovir; Bronquicisteina†; Bronquidiazina CR; Bronquimar†; Cotrazol†; Eduprim Mucolitico†.

Pharmacopoeial Preparations

BP 2014: Co-trimoxazole Infusion; Co-trimoxazole Oral Suspension; Co-trimoxazole Tablets; Dispersible Co-trimoxazole Tablets; Paediatric Co-trimoxazole Oral Suspension; Paediatric Co-trimoxazole Tablets;

USP 36: Sulfamethoxazole and Trimethoprim Injection; Sulfamethoxazole and Trimethoprim Oral Suspension; Sulfamethoxazole and Trimethoprim Tablets.

Cycloserine *(BAN, rINN)*

Cicloserina; D-Cycloserin; Cycloserine; D-Cycloserine; Cycloserinum; Cykloserin; SC-49088; Sikloserin; Sykloseriini; Циклосерин.

(+)-(*R*)-4-Aminoisoxazolidin-3-one.

$C_3H_6N_2O_2$=102.1

CAS — 68-41-7.

ATC — J04AB01.

ATC Vet — QJ04AB01.

UNII — 95IKSKI84Z.

Description. Cycloserine is an antimicrobial substance produced by the growth of certain strains of *Streptomyces orchidaceus* or *S. garyphalus*, or obtained by synthesis.

Pharmacopoeias. In *Jpn* and *US*.

USP 36: (Cycloserine). A white to pale yellow, crystalline powder, odourless or has a faint odour. It is hygroscopic and deteriorates upon absorbing water. Freely soluble in water. pH of a 10% solution in water is between 5.5 and 6.5. Store in airtight containers.

Uses and Administration

Cycloserine is a second-line antimycobacterial that may be used in the treatment of tuberculosis (p. 210.2) as part of a multidrug regimen when resistance to primary drugs has developed. It has been used in urinary-tract infections, although less toxic drugs are preferred.

The usual adult oral dose in tuberculosis is 250 mg twice daily for 2 weeks, followed by 0.5 to 1 g daily in divided doses. Dosage in patients with mild to moderate renal impairment should be reduced and doses for all patients should be adjusted by monitoring plasma concentrations (see Precautions, p. 282.3).

For details of doses in children, see p. 282.3.

Cycloserine has been tried for the adjunctive treatment of schizophrenia and anxiety disorders (see p. 282.3). Cycloserine has been investigated for the treatment of Gaucher disease (p. 2433.3).

References.

1. Anonymous. Cycloserine. *Tuberculosis (Edinb)* 2008; **88**: 100–1.

Administration in children. Use of cycloserine is licensed in both the UK and USA for children, although age ranges are not specified in licensed product information. For the treatment of drug-resistant tuberculosis the American Academy of Pediatrics[1] suggests an oral dose of 5 to 10 mg/kg twice daily, to a maximum dose of 1 g daily.

Doses are adjusted according to blood concentrations and response.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Psychological disorders. Cycloserine has been tried as an adjunct in the management of schizophrenia (p. 1031.3) and anxiety disorders (p. 1028.1).

References.

1. Duncan EJ, *et al.* Effects of D-cycloserine on negative symptoms in schizophrenia. *Schizophr Res* 2004; **71**: 239–48.
2. Hofmann SG, *et al.* Augmentation treatment of psychotherapy for anxiety disorders with D-cycloserine. *CNS Drug Rev* 2006; **12**: 208–17.
3. Tuominen HJ, *et al.* Glutamatergic drugs for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 02/07/10).
4. Otto MW, *et al.* Clinical perspectives on the combination of D-cycloserine and cognitive-behavioral therapy for the treatment of anxiety disorders. *CNS Spectr* 2007; **12**: 51–61.
5. Wilhelm S, *et al.* Augmentation of behavior therapy with D-cycloserine for obsessive-compulsive disorder. *Am J Psychiatry* 2008; **165**: 335–41.
6. Goff DC, *et al.* Once-weekly D-cycloserine effects on negative symptoms and cognition in schizophrenia: an exploratory study. *Schizophr Res* 2008; **100**: 320–7.
7. Otto MW, *et al.* Efficacy of d-cycloserine for enhancing response to cognitive-behavior therapy for panic disorder. *Biol Psychiatry* 2010; **67**: 365–70.
8. Heaton LJ, *et al.* Propranolol and D-cycloserine as adjunctive medications in reducing dental fear in sedation practice. *SAAD Dig* 2010; **26**: 27–35.

Adverse Effects and Treatment

The most frequent adverse effects with cycloserine involve the CNS and include anxiety, confusion, disorientation, depression, psychoses possibly with suicidal tendencies, aggression, irritability, and paranoia. Vertigo, headache, drowsiness, speech difficulties, tremor, paresis, hyperreflexia, dysarthria, paraesthesia, coma, and convulsions may also occur. Neurological reactions are dose related and may be reduced by keeping plasma concentrations below 30 micrograms/mL. It has been reported that up to 30% of patients have adverse effects, but these usually subside when cycloserine is stopped or the dosage is reduced. Pyridoxine has been used in an attempt to treat or prevent neurological reactions but its value is unproven.

Hypersensitivity reactions including skin reactions and photosensitivity occur rarely. Serum aminotransferase values may be raised, especially in patients with a history of liver disease. Folate and vitamin B_{12} deficiency, megaloblastic anaemia, and sideroblastic anaemia have been reported occasionally when cycloserine has been used with other antituberculous drugs. Heart failure has occurred in patients receiving daily doses of 1 g or more.

Precautions

Cycloserine is contra-indicated in patients with epilepsy, depression, psychosis, severe anxiety, severe renal impairment, or in those who misuse alcohol. Cycloserine should be stopped, or the dose reduced, if skin reactions or symptoms of CNS toxicity develop.

Cycloserine has a low therapeutic index, and dosage should be adjusted according to plasma concentrations, which should be monitored at least weekly in patients with renal impairment, in those taking doses greater than 500 mg daily, and in patients showing signs of neurotoxicity. Plasma concentrations should be maintained below 30 micrograms/mL. Haematological, renal, and hepatic function should be monitored. Patients with mild to moderate renal impairment require lower doses.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving cycloserine,[1] and the last available guidance from the American Academy of Pediatrics considered[2] that it is therefore usually compatible with breast feeding.

1. Morton RF, *et al.* Studies on the absorption, diffusion, and excretion of cycloserine. *Antibiot Annu* 1955-56; 3: 169–72.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 03/10/07)

Porphyria. UK licensed product information for cycloserine notes that its use has been associated with clinical exacerbations of porphyria and it is not recommended in porphyric patients.

Interactions

Patients receiving cycloserine and taking alcohol are at increased risk of convulsions; for reference to increased blood-alcohol concentrations in patients receiving cycloserine, see p. 1736.2.

Neurotoxic effects may be potentiated by use of cycloserine with ethionamide, and concurrent use of cycloserine and isoniazid may result in increased CNS toxicity, such as dizziness and drowsiness.

Antimicrobial Action

Cycloserine interferes with bacterial cell wall synthesis by competing with D-alanine for incorporation into the cell wall. It has variable activity against Gram-positive and Gram-negative bacteria including *Escherichia coli* and *Staphylococcus aureus*.

Cycloserine is active against *Mycobacterium tuberculosis* and some other mycobacteria. Resistance develops if cycloserine is used alone.

Pharmacokinetics

Cycloserine is readily and almost completely absorbed from the gastrointestinal tract. Peak plasma concentrations of 10 micrograms/mL have been obtained 3 to 4 hours after a dose of 250 mg, rising to 20 to 30 micrograms/mL on repeating the dose every 12 hours. The plasma half-life is about 10 hours and is prolonged in patients with renal impairment.

Cycloserine is widely distributed into body tissues and fluids, including the CSF, placenta, and breast milk, producing fetal blood concentrations approaching those in maternal serum.

Cycloserine is excreted largely unchanged by glomerular filtration. About 50% of a single 250-mg dose is excreted unchanged in the urine within 12 hours and about 70% is excreted within 72 hours. As negligible amounts of cycloserine appear in the faeces, it is assumed that the remainder of a dose is metabolised to unidentified metabolites. It is removed by haemodialysis.

Pregnancy and breast feeding. Cycloserine has been shown to pass to the fetus, into amniotic fluid,[1] and into breast milk.[2] Concentrations in breast milk after 250 mg four times daily have been reported to range from 6 to 19 micrograms/mL.[2]

1. Holdiness MR. Transplacental pharmacokinetics of the antituberculosis drugs. *Clin Pharmacokinet* 1987; 13: 125–9.
2. Morton RF, *et al.* Studies on the absorption, diffusion, and excretion of cycloserine. *Antibiot Annu* 1955-56; 3: 169–72.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Closina†; *Gr.*: D-cycloserin†; Seromycin; *Hong Kong*: Seromycin†; *India*: Coxerin; Cyclokox; Cyclorine; Cyclotec; Cyserin; MDSerine; Myser; Pamserine; *Rus.*: Coxerin (Коксерин); Coxerin Plus (Коксерин Плюс); Myzer (Майзер); *Thai.*: Proserine†; *Turk.*: Siklocap; *UK*: Cycloserine; *USA*: Seromycin.

Multi-ingredient Preparations. *Rus.*: Cyclo Plus (Цикло Плюс).

Pharmacopoeial Preparations
USP 36: Cycloserine Capsules.

Dalbavancin *(BAN, USAN, rINN)*

A-A-1; BI-397; Dalbavancina; Dalbavancine; Dalbavancinum; MDL-63397; VER-001; V-Glycopeptide; Дальбаванцин.
5,31-Dichloro-38-de(methoxycarbonyl)-7-demethyl-19-deoxy-56-O-[2-deoxy-2-[(10-methylundecanoyl)amino]-β-D-glucopyranuronosyl]-38-[[3-(dimethylamino)propyl]carbamoyl]-42-O-α-D-mannopyranosyl-15-*N*-methyl(ristomycin A aglicone) (main component).
$C_{88}H_{100}Cl_2N_{10}O_{28}$=1816.7
CAS — 171500-79-1.
ATC — J01XA04.
ATC Vet — QJ01XA04.
UNII — 808UI9MS5K.

NOTE. The name Zeven has been used as a trade mark for dalbavancin.

Profile

Dalbavancin is a lipoglycopeptide antibacterial under investigation for the treatment of severe infections due to Gram-positive bacteria, including complicated infections of the skin and soft tissues. It has a prolonged terminal elimination half-life and has been given intravenously in a regimen of two doses at an interval of one week.

References.[1-7] See also under Uses and Administration of Telavancin, p. 373.1.

1. Lin S-W, *et al.* Dalbavancin: a new option for the treatment of gram-positive infections. *Ann Pharmacother* 2006; 40: 449–60.
2. Billeter M, *et al.* Dalbavancin: a novel once-weekly lipoglycopeptide antibiotic. *Clin Infect Dis* 2008; 46: 577–83.
3. Anderson VR, Keating GM. Dalbavancin. *Drugs* 2008; 68: 639–48.
4. Bailey J, Summers KM. Dalbavancin: a new lipoglycopeptide antibiotic. *Am J Health-Syst Pharm* 2008; 65: 599–610.
5. Dowell JA, *et al.* Pharmacokinetic-pharmacodynamic modeling of dalbavancin, a novel glycopeptide antibiotic. *J Clin Pharmacol* 2008; 48: 1063–8.
6. Marbury T, *et al.* Pharmacokinetics of dalbavancin in patients with renal or hepatic impairment. *J Clin Pharmacol* 2009; 49: 465–76.
7. Zhanel GG, *et al.* New lipoglycopeptides: a comparative review of dalbavancin, oritavancin and telavancin. *Drugs* 2010; 70: 859–86.

Danofloxacin Mesilate *(BANM, rINNM)*

CP-76136-27 (danofloxacin mesilate); CP-76136 (danofloxacin); Danofloksasiinimesilaatti; Danofloxacin Mesylate (USAN); Danofloxacine, Mésilate de; Danofloxacini Mesilas; Danofloxacinmesilat; Danofloxacino, mesilato de; Mesilato de danofloxacino; Данофлоксацина Мезилат.
1-Cyclopropyl-6-fluoro-1,4-dihydro-7-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]-4-oxo-3-quinolinecarboxylic acid monomethanesulphonate.
$C_{19}H_{20}FN_3O_3.CH_4O_3S$=453.5
CAS — 112398-08-0 (danofloxacin); 119478-55-6 (danofloxacin mesilate).
UNII — 94F3SX3LEM.

Profile

Danofloxacin is a fluoroquinolone antibacterial used as the mesilate in veterinary medicine for the treatment of susceptible infections in cattle and pigs.

Dapsone *(BAN, USAN, rINN)*

DADPS; Dapson; Dapsona; Dapsonas; Dapsoni; Dapsonum; Dapszon; DDS; Diaminodiphenylsulfone; Diaphenylsulfone; Disulone; NSC-6091; Sulphonyldianiline; Дапсон; 4,4'-Sulfonylbis-benzenamine.
Bis(4-aminophenyl) sulphone.
$C_{12}H_{12}N_2O_2S$=248.3
CAS — 80-08-0.
ATC — D10AX05; J04BA02.
ATC Vet — QD10AX05; QJ04BA02.
UNII — 8W5C518302.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 8: (Dapsone). A white or slightly yellowish-white, crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol; freely soluble in acetone. It dissolves freely in dilute mineral acids. Protect from light.

USP 36: (Dapsone). A white or creamy-white, odourless crystalline powder. Very slightly soluble in water, freely soluble in alcohol; soluble in acetone and in dilute mineral acids. Protect from light.

Stability. A study[1] of the stability of two extemporaneous oral suspensions of dapsone prepared from commercially available tablets found them to be stable for 3 months when stored at 4 degrees and at 25 degrees.

1. Nahata MC, *et al.* Stability of dapsone in two oral liquid dosage forms. *Ann Pharmacother* 2000; 34: 848–50.

Uses and Administration

Dapsone is used as part of multidrug regimens in the treatment of all forms of leprosy (p. 188.3). It has also been used in the prophylaxis of leprosy and in the management of household contacts of leprosy patients. Dapsone is used as an alternative to co-trimoxazole or pentamidine for the treatment and prophylaxis of pneumocystis pneumonia (p. 284.1), and has been used with pyrimethamine for the prophylaxis of malaria (see under Pyrimethamine, p. 662.3). It is also used in dermatitis herpetiformis and other dermatoses (see Skin Disorders, p. 284.1) and is applied topically in acne. It is used for the prophylaxis of toxoplasmosis (p. 926.1) and for the treatment of actinomycetoma (see Mycetoma, p. 193.1). It has been tried alone or with topical imiquimod for the treatment of cutaneous leishmaniasis (p. 283.3).

Systemic dapsone is usually given orally. There are some reports of it being given by intramuscular injection, but such injections can be painful and cause abscess formation.

The most common regimens for **leprosy** are those recommended by WHO. For multibacillary leprosy, rifampicin 600 mg and clofazimine 300 mg are both given *once a month* with dapsone 100 mg and clofazimine 50 mg both *daily* for 12 months. Adults weighing less than 35 kg receive reduced doses of rifampicin and dapsone, and in such patients the dapsone dose is 50 mg or 1 to 2 mg/kg daily.

The WHO regimen for paucibacillary leprosy consists of rifampicin 600 mg once a month and dapsone 100 mg daily; both are given for 6 months. Doses are reduced in low-weight patients as for multibacillary leprosy.

The doses of dapsone used for the prophylaxis and treatment of **pneumocystis pneumonia** are discussed in more detail under pneumocystis pneumonia, p. 284.1.

The dose needed to treat **dermatitis herpetiformis** has to be titrated for individual patients, but it is usual to start with an oral dose of 50 mg daily, gradually increased to 300 mg daily or more if required. This dose should be reduced to a minimum as soon as possible. Maintenance dosage can often be reduced in patients receiving a gluten-free diet.

In the treatment of **acne**, dapsone is applied topically as a 5% gel *twice daily*.

For details of doses in children, see p. 283.3.

Administration in children. For the treatment of multibacillary leprosy in children WHO recommends that children aged 10 to 14 years may be given oral dapsone 50 mg plus rifampicin 450 mg and clofazimine 150 mg *once a month*, together with dapsone 50 mg *daily* and clofazimine 50 mg on *alternate days*; both are given for 12 months. For paucibacillary leprosy WHO recommends oral dapsone 50 mg plus rifampicin 450 mg *once a month*, together with dapsone 50 mg *daily*; both are given for 6 months. For children less than 10 years of age the dose should be adjusted according to body weight.

For details of doses for the treatment of pneumocystis pneumonia in children, see p. 284.1.

Connective tissue disorders. Relapsing polychondritis (p. 1610.3) has responded to dapsone, as has Behçet's syndrome (p. 1601.1) and SLE. Vasculitic syndromes such as hypersensitivity vasculitis (p. 1606.1) have also improved following dapsone.

Immune thrombocytopenia. Dapsone has been reported[1-5] to be of benefit in some patients, including children, with refractory immune thrombocytopenia (p. 1606.1).

1. Radaelli F, *et al.* Adult refractory chronic idiopathic thrombocytopenic purpura: can dapsone be proposed as second-line therapy? *Br J Haematol* 1999; 104: 641–2.
2. Dutta TK, *et al.* Dapsone in treatment of chronic idiopathic thrombocytopenic purpura in adults. *J Assoc Physicians India* 2001; 49: 421–5.
3. Meeker ND, *et al.* Dapsone therapy for children with immune thrombocytopenic purpura. *J Pediatr Hematol Oncol* 2003; 25: 173–5.
4. Damodar S, *et al.* Dapsone for chronic idiopathic thrombocytopenic purpura in children and adults—a report on 90 patients. *Eur J Haematol* 2005; 75: 328–31.
5. Vancine-Califani SM, *et al.* Efficacy and safety of dapsone as a second-line treatment in non-splenectomized adults with immune thrombocytopenic purpura. *Platelets* 2008; 19: 489–95.

Leishmaniasis. In early reports from India, treatment of cutaneous leishmaniasis (p. 924.1) with oral dapsone 2 mg/kg daily for several weeks led to cure rates in excess of 80%.[1] However, an open-label study of 11 patients in Columbia[2] reported favourable clinical response in only 2 of 6 patients who completed a 13-week course of oral dapsone 200 mg daily.

In a later study in Kuwait,[3] good or excellent response to therapy was reported for about 43% of patients given oral dapsone, and for about 57% of those given a combination of oral dapsone and topical imiquimod 5%.

1. Mahajan VK, Sharma NL. Therapeutic options for cutaneous leishmaniasis. *J Dermatolog Treat* 2007; 18: 97–104.

2. Osorio LE, *et al.* Treatment of cutaneous leishmaniasis in Colombia with dapsone. *Lancet* 1998; 351: 498–9.
3. Al-Mutairi N, *et al.* Tropical medicine rounds: Treatment of Old World cutaneous leishmaniasis with dapsone, itraconazole, cryotherapy, and imiquimod, alone and in combination. *Int J Dermatol* 2009; 48: 862–9.

Pneumocystis pneumonia. Oral dapsone is used alone or with oral pyrimethamine[1] for *primary and secondary prophylaxis* of pneumocystis pneumonia (p. 567.2) in patients unable to tolerate co-trimoxazole. In adults a dose of dapsone 100 mg daily in one or two doses is commonly used[1] and has been reported to have similar efficacy to co-trimoxazole.[2] Dapsone has also been given with pyrimethamine in various regimens including:

- dapsone 50 mg daily with pyrimethamine 50 mg once weekly[1,3]
- dapsone 100 mg plus pyrimethamine 50 mg both given twice weekly[4]
- dapsone 200 mg plus pyrimethamine 75 mg both given once weekly[1,5]

In children from 1 month of age the recommended dose of dapsone is 2 mg/kg daily (to a maximum of 100 mg daily) or 4 mg/kg weekly (to a maximum of 200 mg weekly).[6]

For *treatment* of adults and adolescents, an oral regimen of dapsone 100 mg once daily with trimethoprim 5 mg/kg three times daily, for 21 days, has been suggested for mild to moderate disease in patients unable to tolerate co-trimoxazole.[1] Infants and children under 13 years of age may be given a dose of dapsone of 2 mg/kg once daily (to a maximum of 100 mg daily) plus trimethoprim 5 mg/kg three times daily.[6]

1. CDC. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR* 2009; 58 (RR-4): 1 207. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5804.pdf (accessed 01/07/09)
2. Bozzette SA, *et al.* A randomized trial of three antipneumocystis agents in patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1995; 332: 693–9.
3. Girard P-M, *et al.* Dapsone-pyrimethamine compared with aerosolized pentamidine as primary prophylaxis against Pneumocystis carinii pneumonia and toxoplasmosis in HIV infection. *N Engl J Med* 1993; 328: 1514–20.
4. Podzamczer D, *et al.* Intermittent trimethoprim-sulfamethoxazole compared with dapsone-pyrimethamine for the simultaneous primary prophylaxis of pneumocystis pneumonia and toxoplasmosis in patients infected with HIV. *Ann Intern Med* 1995; 122: 755–61.
5. Opravil M, *et al.* Once-weekly administration of dapsone/pyrimethamine vs. aerosolized pentamidine as combined prophylaxis for Pneumocystis carinii pneumonia and toxoplasmic encephalitis in human immunodeficiency virus-infected patients. *Clin Infect Dis* 1995; 20: 531–41.
6. CDC. Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. *MMWR* 2009; 58 (RR-11): 1–166. Available at: http://aidsinfo.nih.gov/contentfiles/PediatricOI.pdf (accessed 07/06/10)

Skin disorders. Dapsone is used for the suppression of skin lesions in dermatitis herpetiformis (p. 1683.2). The mechanism of action is unknown but is unrelated to its antimicrobial activity. Reports, generally involving small numbers of patients, suggest that dapsone may also be beneficial for bullous or mucous membrane pemphigoid (p. 1687.1), pyoderma gangrenosum (p. 1688.3), recurrent erythema multiforme (p. 1684.3), and urticaria (p. 1689.2).

References.

1. Gürcan HM, Ahmed AR. Efficacy of dapsone in the treatment of pemphigus and pemphigoid: analysis of current data. *Am J Clin Dermatol* 2009; 10: 383–96.

ACNE. Dapsone is available in the USA as a 5% topical gel for the treatment of acne (p. 1682.2). The use of topical dapsone for acne has been reviewed.[1-5]

1. Stodard M, *et al.* Dapsone 5% gel: a review of its efficacy and safety in the treatment of acne vulgaris. *Am J Clin Dermatol* 2009; 10: 221–7.
2. Pickert A, Raimer S. An evaluation of dapsone gel 5% in the treatment of acne vulgaris. *Expert Opin Pharmacother* 2009; 10: 1515–21.
3. Scheinfeld N. Aczone, a topical gel formulation of the antibacterial, anti-inflammatory dapsone for the treatment of acne. *Curr Opin Investig Drugs* 2009; 10: 474–81.
4. Webster GF. Is topical dapsone safe in glucose-6-phosphate dehydrogenase-deficient and sulfonamide-allergic patients? *J Drugs Dermatol* 2010; 9: 532–6.
5. Kircik LH. Harnessing the anti-inflammatory effects of topical dapsone for management of acne. *J Drugs Dermatol* 2010; 9: 667–71.

Spider bites. As discussed on p. 2420.1, necrotic araneism resulting from the bite of spiders of the genus *Loxosceles* is usually treated conservatively with surgical repair of any persistent defect. A prospective clinical study[1] of 31 patients with brown recluse spider bites indicated that treatment with oral dapsone 100 mg daily for 14 days followed by delayed surgical intervention if necessary reduced the incidence of wound complications and residual scarring compared with treatment by immediate surgical excision. A dose of 100 mg twice daily has also been given for 14 days.[2] An evaluation[3] of the management of brown recluse spider bites found that common treatments did not reduce healing time or scarring; dapsone was associated with slower healing rate and an increased risk of scarring.

1. Rees RS, *et al.* Brown recluse spider bites: a comparison of early surgical excision versus dapsone and delayed surgical excision. *Ann Surg* 1985; 202: 659–63.
2. King LE, Rees RS. Dapsone treatment of a brown recluse bite. *JAMA* 1983; 250: 648.
3. Mold JW, Thompson DM. Management of brown recluse spider bites in primary care. *J Am Board Fam Pract* 2004; 17: 347–52.

Toxoplasmosis. For mention of the use of dapsone in the primary prevention of toxoplasmosis, see under Pyrimethamine, p. 663.1.

Adverse Effects

Varying degrees of dose-related haemolysis and methaemoglobinaemia are the most frequently reported adverse effects of dapsone, and occur in most patients given oral doses of more than 200 mg daily; doses of up to 100 mg daily do not cause significant haemolysis, but patients with G6PD deficiency are affected by doses above about 50 mg daily.

Although agranulocytosis has been reported rarely with dapsone when used alone, reports have been more common when it has been used with other drugs in the prophylaxis of malaria. Deaths due to agranulocytosis, aplastic anaemia, and other blood dyscrasias have been reported.

Rash and pruritus may develop. Serious cutaneous hypersensitivity reactions occur rarely and include maculopapular rash, exfoliative dermatitis, toxic epidermal necrolysis, and Stevens-Johnson syndrome. Fixed drug eruptions have occurred.

A 'dapsone syndrome' may occur after 4 to 8 weeks of treatment and resembles mononucleosis in its presentation (see Hypersensitivity, p. 285.1).

Peripheral neuropathy with motor loss has been reported in patients on dapsone for dermatological conditions. Peripheral neuropathy may occur as part of leprosy reaction states and is not an indication to stop dapsone.

Other adverse effects occur infrequently and include nausea, vomiting, anorexia, headache, hepatitis, insomnia, psychosis, and tachycardia.

Carcinogenicity. A survey of 1678 leprosy patients admitted for treatment to the National Hansen's Disease Center in the USA between 1939 and 1977 indicated that, although dapsone has been implicated as a carcinogen in *animals*, the use of dapsone did not appear to affect significantly the risk of cancer in these patients.[1] The International Agency for Research on Cancer concluded[2] that there was limited evidence for the carcinogenicity of dapsone in *animals* and insufficient data to be able to classify the carcinogenic risk in humans. A subsequent retrospective cohort study[3] also found no significantly increased risk of death or death from cancer among patients who received dapsone for treatment of ocular inflammatory disorders.

1. Brinton LA, *et al.* Cancer mortality among patients with Hansen's disease. *J Natl Cancer Inst* 1984; 72: 109–14.
2. IARC/WHO. Some pharmaceutical drugs. *IARC monographs on the evaluation of carcinogenic risks to humans volume 24* 1980 (updated 07/04/98). Also available at: http://monographs.iarc.fr/ENG/Monographs/vol24/volume24.pdf (accessed 16/07/10)
3. Kempen JH, *et al.* Overall and cancer related mortality among patients with ocular inflammation treated with immunosuppressive drugs: retrospective cohort study. Abridged version: *BMJ* 2009; 339: b2480. Full version: http://www.bmj.com/cgi/content/full/339/jul03_1/b2480?view=long&pmid=19578087 (accessed 07/06/10)

Effects on the blood. *Haemolysis* is the most frequent serious adverse effect of dapsone and may occur at oral doses of 200 mg or higher daily.[1] Red blood cells may contain Heinz bodies and there is a reduction in their life span.[2] Well-known risk factors include G6PD deficiency,[3] methaemoglobin reductase deficiency, and haemoglobin M trait; haemoglobin E trait may also increase susceptibility to haemolytic reactions.[2] Haemolytic anaemia has been reported in a neonate after ingestion of dapsone in breast milk.[4] Clinically relevant haemolysis or anaemia was not reported in patients treated with topical dapsone gel 5% for acne, including patients with G6PD deficiency.[5] However, US licensed product information states that some individuals with G6PD deficiency using dapsone gel have developed laboratory changes suggestive of mild haemolysis.

Methaemoglobinaemia.[6] although common, is rarely symptomatic.[1] However, severe cyanosis was associated with methaemoglobinaemia after an inadvertent overdose with dapsone in an HIV-positive patient with suspected pneumocystis pneumonia.[7] Methaemoglobinaemia has also been reported in an HIV-negative patient with severe renal impairment, who had previously undergone liver and kidney transplantations and who was receiving dapsone for prophylaxis of pneumocystis pneumonia.[8] The metabolite dapsone hydroxylamine is probably responsible for the methaemoglobinaemia and haemolysis associated with dapsone.[3] Studies have shown[9,10] that use of dapsone with cimetidine, which inhibits production of the *N*-hydroxy metabolite, has resulted in a decrease in methaemoglobin levels, at least in the short term.

Agranulocytosis has occurred rarely on use of dapsone in leprosy and skin disease. More cases have been seen with use for malaria prophylaxis[11] (see also under Pyrimethamine, p. 663.2) and dermatitis herpetiformis.[12] The reaction is usually self-limiting once the drug is withdrawn, but fatalities have occurred.[12,13]

Aplastic anaemia has been reported.[14,15] Of 11 fatalities attributed to dapsone reported to the British and Swedish adverse reaction registers[16] between 1968 and 1988, seven were due to white blood cell dyscrasias; none were attributed to red cell dyscrasias, although such reactions formed almost half of all serious reactions reported for dapsone.

Pure red cell aplasia has been reported in an elderly patient taking oral dapsone daily for granuloma annulare.[17]

Thrombocytosis was reported in a patient with AIDS receiving dapsone prophylactically.[18]

See also Hypoalbuminaemia, p. 285.2.

1. Jopling WH. Side-effects of antileprosy drugs in common use. *Lepr Rev* 1983; 54: 261–70.
2. Lachant NA, Tanaka KR. Case report: dapsone-associated Heinz body hemolytic anemia in a Cambodian woman with hemoglobin E trait. *Am J Med Sci* 1987; 294: 364–8.
3. Youngster I, *et al.* Medications and glucose-6-phosphate dehydrogenase deficiency: an evidence-based review. *Drug Safety* 2010; 33: 713–26.
4. Sanders SW, *et al.* Hemolytic anemia induced by dapsone transmitted through breast milk. *Ann Intern Med* 1982; 96: 465–6.
5. Piette WW, *et al.* Hematologic safety of dapsone gel, 5%, for topical treatment of acne vulgaris. *Arch Dermatol* 2008; 144: 1564–70.
6. Ashurst JV, *et al.* Pathophysiologic mechanisms, diagnosis, and management of dapsone-induced methemoglobinemia. *J Am Osteopath Assoc* 2010; 110: 16–20.
7. Seaton RA, *et al.* Blue and breathless. *Hosp Med* 1999; 60: 530.
8. Ward KE, McCarthy MW. Dapsone-induced methemoglobinemia. *Ann Pharmacother* 1998; 32: 549–53.
9. Coleman MD, *et al.* The use of cimetidine as a selective inhibitor of dapsone N-hydroxylation in man. *Br J Clin Pharmacol* 1990; 30: 761–7.
10. Rhodes LE, *et al.* Cimetidine improves the therapeutic/toxic ratio of dapsone in patients on chronic dapsone therapy. *Br J Dermatol* 1995; 132: 257–62.
11. Firkin FC, Mariani AF. Agranulocytosis due to dapsone. *Med J Aust* 1977; 2: 247–51.
12. Cockburn EM, *et al.* Dapsone-induced agranulocytosis: spontaneous reporting data. *Br J Dermatol* 1993; 128: 702–3.
13. Barss P. Fatal dapsone agranulocytosis in a Melanesian. *Lepr Rev* 1986; 57: 63–6.
14. Foucauld J, *et al.* Dapsone and aplastic anemia. *Ann Intern Med* 1985; 102: 139.
15. Meyerson MA, Cohen PR. Dapsone-induced aplastic anaemia in a woman with bullous systemic lupus erythematosus. *Mayo Clin Proc* 1994; 69: 1159–62.
16. Björkman A, Phillips-Howard PA. Adverse reactions to sulfa drugs: implications for malaria chemotherapy. *Bull WHO* 1991; 69: 297–304.
17. Borrás-Blasco J, *et al.* Pure red cell aplasia associated with dapsone therapy. *Ann Pharmacother* 2005; 39: 1137–8.
18. Wynn RF, *et al.* Case report of dapsone-related thrombocytosis in an AIDS patient. *Am J Med* 1995; 98: 602.

Effects on the eyes. There have been rare reports[1-4] of ocular toxicity, usually resulting in permanent loss of visual acuity, after overdoses with dapsone. Toxic effects included blurring of vision,[1,2] optic atrophy,[1] ischaemic retinopathy, ischaemic optic neuropathy,[3] and bilateral macular infarction.[4] These effects were thought to be due to acute hypoxia and obstruction with red cell fragments. A case of anterior ischaemic optic neuropathy[5] has also been reported in a patient taking usual doses of dapsone for dermatitis herpetiformis.

1. Daneshmend TK. The neurotoxicity of dapsone. *Adverse Drug React Acute Poisoning Rev* 1984; 3: 43–58.
2. Alexander TA, *et al.* Presumed DDS ocular toxicity. *Indian J Ophthalmol* 1989; 37: 150–1.
3. Seo M-S, *et al.* Dapsone maculopathy. *Korean J Ophthalmol* 1997; 11: 70–3.
4. Chakrabarti M, *et al.* Bilateral macular infarction due to diaminodiphenyl sulfone (4,4' DDS) toxicity. *Retina* 1999; 19: 83–4.
5. Chatioulias K, *et al.* Anterior ischaemic optic neuropathy associated with Dapsone. *Eye* 2006; 20: 943–5.

Effects on the liver. Toxic hepatitis and cholestatic jaundice have been reported by licensed product information to occur early in dapsone therapy. Jaundice may also form part of the dapsone syndrome (see Hypersensitivity, p. 285.1). Deterioration in liver function tests during dapsone treatment has been noted in a patient with dermatitis herpetiformis and primary sclerosing cholangitis.[1]

1. Kirby B, *et al.* Abnormal liver function tests induced by dapsone in a patient with dermatitis herpetiformis and primary sclerosing cholangitis. *Br J Dermatol* 1999; 141: 172–3.

Effects on the lungs. Hypersensitivity reactions to dapsone usually affect the skin, but there have been rare reports of dapsone hypersensitivity presenting with fever, wheezing, and pulmonary eosinophilia.[1-4] Pulmonary eosinophilia occurred in one patient taking dapsone for urticaria[1] and in another taking dapsone as part of the WHO multidrug treatment regimen for leprosy.[2] In both patient symptoms resolved when dapsone was stopped and occurred again on rechallenge. Another patient[3] known to develop fever and wheezing when taking dapsone for leprosy was given a dapsone challenge for 5 days. He became acutely ill and

had a high absolute eosinophil count; symptoms resolved 2 weeks after stopping dapsone.

1. Jaffuel D, *et al.* Eosinophilic pneumonia induced by dapsone. *BMJ* 1998; 317: 181.
2. Kaur J, *et al.* Dapsone-induced eosinophilic pneumonitis in a leprosy patient. *Indian J Lepr* 2005; 77: 267–71.
3. Arunthathi S, Raju S. Dapsone induced pulmonary eosinophilia without cutaneous allergic manifestations—an unusual encounter—a case report. *Acta Leprol* 1998; 11: 3–5.
4. Janier M, *et al.* Pulmonary eosinophilia associated with dapsone. *Lancet* 1994; 343: 860–1.

Effects on mental state. Psychiatric adverse effects have been reported in leprosy patients receiving dapsone, but the role of dapsone in this effect is poorly defined.[1–4] Manic-depressive reactions have been reported in 2 patients[2,3] with skin disorders and psychosis[4] was reported in a patient being treated for leprosy. These reactions appeared to be idiosyncratic reactions to dapsone. In all cases symptoms resolved when dapsone was stopped.

1. Daneshmend T. Idiosyncratic dapsone induced manic depression. *BMJ* 1989; 299: 324.
2. Carmichael AJ, Paul CJ. Idiosyncratic dapsone induced manic depression. *BMJ* 1989; 298: 1524. Correction. *ibid.*; 299: 56.
3. Gawkrodger D. Manic depression induced by dapsone in patient with dermatitis herpetiformis. *BMJ* 1989; 299: 860.
4. Balkrishna, Bhatia MS. Dapsone-induced psychosis. *J Indian Med Assoc* 1989; 87: 120–1.

Effects on the nervous system. A case review[1] of 21 patients who had dapsone-induced neuropathy reported that the median time to onset of symptoms was about 1 year; with a range of 11 days to 18 years. Symptoms occurred in patients taking doses varying from 25 to 800 mg/day and after a total cumulative dose of 4 to 1500 g. Most patients had either pure motor or mixed sensory-motor neuropathies, while pure sensory neuropathy was rarely reported. Patients generally recovered, either partially or completely, within one year of stopping dapsone. Progressive multifocal leukoencephalopathy has been reported in a patient with SLE treated with a dapsone-containing regimen, although it was unclear what role dapsone had played.[2]

1. Méry L, *et al.* Polynévrite sensitive induite par la dapsone (Disulone). *Ann Dermatol Venereol* 2003; 130: 447–9.
2. Stahl NI. Progressive multifocal leukoencephalopathy in a minimally immunosuppressed patient with systemic lupus erythematosus treated with dapsone. *J Rheumatol* 2008; 35: 725–7.

Effects on the pancreas. Acute pancreatitis has been associated with the use of dapsone to treat dermatitis herpetiformis in an 87-year-old man.[1] Symptoms resolved on stopping dapsone but recurred upon rechallenge.

1. Jha SH, *et al.* Dapsone-induced acute pancreatitis. *Ann Pharmacother* 2003; 37: 1438–40.

Effects on taste. A persistent sweet taste and tingling of the face and lips was described in a patient receiving dapsone for ocular cicatricial pemphigoid.[1] The symptoms resolved when dapsone was stopped.

1. Stafanous SN, Morgan SJ. A previously unrecognised side effect of dapsone. *Br J Ophthalmol* 1997; 81: 1113–14.

Hyperpigmentation. Hyperpigmented macules were reported in 32 of about 800 children given dapsone with pyrimethamine for 3 months or more for malaria prophylaxis.[1] The reaction was attributed to dapsone.

1. David KP, *et al.* Hyperpigmented dermal macules in children following the administration of Maloprim for malaria chemoprophylaxis. *Trans R Soc Trop Med Hyg* 1997; 91: 204–8.

Hypersensitivity. Dapsone syndrome is a rare idiosyncratic hypersensitivity reaction, although it has been suggested[1–3] that the incidence has increased since the introduction of multidrug therapy for leprosy. It usually occurs in the first 4 to 8 weeks of therapy, is not dose-related, and resolves within 14 days on stopping dapsone. Dapsone syndrome may also occur within 1 to 2 weeks of stopping the drug, due to its long elimination half-life and high protein binding.[4] Common clinical symptoms may include exanthematous rash, fever, hepatitis (cholestatic and hepatocellular injuries), eosinophilia, lymphadenopathy, and mononucleosis. The syndrome has occurred in leprosy patients,[5,6] in patients with skin disorders,[7] in patients with AIDS taking dapsone for prophylaxis of pneumocystis pneumonia,[4] and in patients taking weekly dapsone (with pyrimethamine) for malaria prophylaxis.[8] Fatalities have occurred.[9,10] Desensitisation has been successfully carried out in several patients with AIDS who had hypersensitivity to dapsone.[11,12]

1. Richardus JH, Smith TC. Increased incidence in leprosy of hypersensitivity reactions to dapsone after introduction of multidrug therapy. *Lepr Rev* 1989; 60: 267–73.
2. Kumar RH, *et al.* Dapsone syndrome—a five year retrospective analysis. *Indian J Lepr* 1998; 70: 271–6.
3. Rao PN, Lakshmi TSS. Increase in the incidence of dapsone hypersensitivity syndrome—an appraisal. *Lepr Rev* 2001; 72: 57–62.
4. Lee KB, Nashed TB. Dapsone-induced sulfone syndrome. *Ann Pharmacother* 2003; 37: 1044–6.
5. Alves-Rodrigues EN, *et al.* Dapsone syndrome with acute renal failure during leprosy treatment: case report. *Braz J Infect Dis* 2005; 9: 84–6.
6. Bucaretchi F, *et al.* Dapsone hypersensitivity syndrome in an adolescent during treatment during [sic] of leprosy. *Rev Inst Med Trop Sao Paulo* 2004; 46: 331–4.
7. Sener O, *et al.* Severe dapsone hypersensitivity syndrome. *J Investig Allergol Clin Immunol* 2006; 16: 268–70.
8. Tee AKH, *et al.* Dapsone hypersensitivity syndrome masquerading as a viral exanthem: three cases and a mini-review. *Ann Acad Med Singapore* 2004; 33: 375–8.
9. Frey HM, *et al.* Fatal reaction to dapsone during treatment of leprosy. *Ann Intern Med* 1981; 94: 777–9.
10. Agrawal S, Agarwalla A. Dapsone hypersensitivity syndrome: a clinico-epidemiological review. *J Dermatol* 2005; 32: 883–9.
11. Metroka CE, *et al.* Desensitization to dapsone in HIV-positive patients. *JAMA* 1992; 267: 512.
12. Cook DE, Kossey JL. Successful desensitization to dapsone for Pneumocystis carinii prophylaxis in an HIV-positive patient. *Ann Pharmacother* 1998; 32: 1302–5.

Hypoalbuminaemia. Severe and often life-threatening hypoalbuminaemia has been reported rarely in patients taking dapsone for long periods for dermatitis herpetiformis.[1–3] Hypoalbuminaemia usually resolves rapidly once dapsone is withdrawn.

1. Kingham JGC, *et al.* Dapsone and severe hypoalbuminaemia. *Lancet* 1979; ii: 662–4 and 1018.
2. Foster PN, Swan CHJ. Dapsone and fatal hypoalbuminaemia. *Lancet* 1981; ii: 806–7.
3. Sinclair SA, *et al.* Life threatening hypoalbuminaemia associated with dapsone therapy. *Br J Dermatol* 1996; 135 (suppl 47): 45.

Photosensitivity. Dapsone-induced photosensitivity is rare and has been reported mainly among patients being treated for leprosy.[1,2] Among 11 reported cases, skin lesions occurred after 5 to 34 weeks (mean 13 weeks) of dapsone therapy; in 8 cases, the severity required that dapsone be stopped. Systemic corticosteroids, antihistamines, and sunscreen lotions have typically been the mainstay of treatment.[1]

Dapsone-induced photosensitivity can be mimicked by polymorphous light eruption, chronic actinic dermatitis, pellagra, and rarely porphyria cutanea tarda or SLE; it may also occur as part of dapsone syndrome (see under Hypersensitivity, above).[1,2]

1. De D, *et al.* Dapsone induced acute photosensitivity dermatitis; a case report and review of literature. *Lepr Rev* 2007; 78: 401–4.
2. Kar BR. Dapsone-induced photosensitivity: a rare clinical presentation. *Photodermatol Photoimmunol Photomed* 2008; 24: 270–1.

Treatment of Adverse Effects

In severe overdosage, repeated oral doses of activated charcoal should be given with the aim of preventing absorption of dapsone but also to aid the elimination of dapsone and its monoacetyl metabolite. Methaemoglobinaemia has been treated with slow intravenous injections of methylthioninium chloride 1 to 2 mg/kg repeated after 30 to 60 minutes if necessary; due to the long half-life of dapsone and its metabolites, serious overdoses will usually require regular dosing every 6 to 8 hours for 2 to 3 days. Methylthioninium chloride should not be given to patients with G6PD deficiency since it will not be effective. Haemolysis has been treated by infusion of concentrated human red blood cells to replace the damaged cells. Supportive therapy includes giving oxygen and fluids.

Patients who develop dapsone syndrome (see Hypersensitivity, above) may require several weeks of corticosteroid therapy.

Overdosage. References.

1. Dawson AH, Whyte IM. Management of dapsone poisoning complicated by methaemoglobinaemia. *Med Toxicol Adverse Drug Exp* 1989; 4: 387–92.
2. Endre ZH, *et al.* Successful treatment of acute dapsone intoxication using charcoal hemoperfusion. *Aust N Z J Med* 1983; 13: 509–12.
3. Hoetelmans RMW, *et al.* Combined dapsone and clofazimine intoxication. *Hum Exp Toxicol* 1996; 15: 625–8.
4. Ferguson AJ, Lavery GG. Deliberate self-poisoning with dapsone: a case report and summary of relevant pharmacology and treatment. *Anaesthesia* 1997; 52: 359–63.
5. Southgate HJ, Masterson R. Lessons to be learned: a case study approach: prolonged methaemoglobinaemia due to inadvertent dapsone poisoning: treatment with methylene blue and exchange transfusion. *J R Soc Health* 1999; 119: 52–5.
6. Park KH, *et al.* Dapsone intoxication: clinical course and characteristics. *Clin Toxicol* 2010; 48: 516–21.

Precautions

Dapsone should not be used in patients with severe anaemia. It is recommended that regular blood counts be performed during treatment. Patients deficient in G6PD or methaemoglobin reductase, or with haemoglobin M are more susceptible to the haemolytic effects of dapsone. Dapsone contains the sulfa moiety ($-SO_2NH_2$) and the UK licensed product information states that it is contra-indicated in patients with a sulfonamide (sulfa) or sulfone allergy. For further information on cross-reactivity between sulfa-containing drugs see Hypersensitivity, under Sulfamethoxazole, p. 367.3.

Where possible, liver function should be monitored during treatment.

The benefits of dapsone in the treatment of leprosy during pregnancy are thought to outweigh any potential risks to the pregnant patient or fetus. Some recommend folic acid 5 mg daily for leprosy patients receiving dapsone during pregnancy.

Breast feeding. Dapsone is distributed into breast milk and the last available guidance from the American Academy of Pediatrics[1] stated that, although usually compatible with breast feeding, use of dapsone in a breast-feeding mother has resulted in sulfonamide detected in the infant's urine.[2] There has also been a report of haemolytic anaemia in a breast-fed infant (see Effects on the Blood, under Adverse Effects, p. 282.2). A study in 3 women who were given a single dose of dapsone 100 mg plus pyrimethamine and chloroquine estimated that if their infants were breast-fed they would receive 4.6, 10, or 14.3%, respectively, of the maternal dose in the 9-day period after it was given.[3]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 03/10/07)
2. Dreisbach JA. Sulphone levels in breast milk of mothers on sulphone therapy. *Lepr Rev* 1952; 23: 101–6.
3. Edstein MD, *et al.* Excretion of chloroquine, dapsone and pyrimethamine in human milk. *Br J Clin Pharmacol* 1986; 22: 733–5.

Porphyria. Although dapsone has not been classified in the Drug Database for Acute Porphyria compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden,[1] both Porphyria South Africa[2] and the European Porphyria Network[3] classify dapsone as unsafe and recommend it be avoided in patients with porphyria.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 12/10/11)
2. Porphyria South Africa. Available at: http://web.uct.ac.za/depts/porphyria/ (accessed 12/10/11)
3. European Porphyria Network. Available at: http://www.porphyria-europe.com (accessed 12/10/11)

Pregnancy. References.

1. Brabin BJ, *et al.* Dapsone therapy for malaria during pregnancy: maternal and fetal outcomes. *Drug Safety* 2004; 27: 633–48.

Interactions

Serum concentrations of dapsone are increased, with a consequent increased risk of adverse effects, when given with probenecid, probably as a result of reduced renal excretion of dapsone. Increased dapsone and trimethoprim concentrations have also been reported in patients receiving both drugs, who may similarly be at greater risk of dapsone toxicity. Rifampicin reduces serum concentrations of dapsone to a level that may compromise efficacy in infections other than leprosy. Rifampicin concentrations are generally unaffected. Dapsone may reduce the anti-inflammatory effects of clofazimine (p. 274.2).

Antibacterials. In a study of AIDS patients with pneumocystis pneumonia, the mean peak serum concentrations of dapsone after 7 days were 1.5 micrograms/mL after 100 mg daily and 2.1 micrograms/mL after the same dose with *trimethoprim* 20 mg/kg daily; concentrations of trimethoprim were also increased.[1] Elevated dapsone concentrations may contribute to the toxicity and the efficacy of this combination.

1. Lee BL, *et al.* Dapsone, trimethoprim, and sulfamethoxazole plasma levels during treatment of Pneumocystis pneumonia in patients with the acquired immunodeficiency syndrome (AIDS). *Ann Intern Med* 1989; 110: 606–11.

Antimalarials. Although some licensed product information has warned that dapsone-induced haematotoxicity could be potentiated by folic acid antagonists such as *pyrimethamine*, the tolerability of dapsone plus pyrimethamine was similar to dapsone alone when each treatment was given on a once-weekly basis to patients with HIV infection.[1] Dapsone concentrations were not significantly higher in patients receiving dapsone plus pyrimethamine than in those receiving dapsone alone.

1. Falloon J, *et al.* Pharmacokinetics and safety of weekly dapsone and dapsone plus pyrimethamine for prevention of pneumocystis pneumonia. *Antimicrob Agents Chemother* 1994; 38: 1580–7.

Gastrointestinal drugs. *Cimetidine* has been reported to increase the area under the curve for dapsone, but to decrease the area under the curve for the metabolite dapsone hydroxylamine. Haematotoxicity is thought to be related to production of this metabolite (see Effects on the Blood, p. 282.2).

Antimicrobial Action

Dapsone is a sulfone active against many bacteria and some protozoa, but it is mainly used for its action against *Mycobacterium leprae*. Like the sulfonamides it may inhibit folic acid synthesis in susceptible organisms although this is not considered to be the mechanism of action in *M. leprae*. It is usually considered to be bacteriostatic against *M. leprae*, although it may also possess weak bactericidal activity. As with the sulfonamides, antibacterial activity is inhibited by

p-aminobenzoic acid. Dapsone is also active against *Pneumocystis jirovecii*. *Plasmodium falciparum* is generally only moderately susceptible, but the drug's antiplasmodial activity is markedly increased when used with a dihydrofolate reductase inhibitor such as pyrimethamine (p. 662.3).

Secondary (acquired) dapsone resistance of *M. leprae* is mainly associated with dapsone being used on its own. Primary dapsone resistance has also been reported with increasing frequency in areas with secondary resistance. Resistance of *M. leprae* to dapsone should be suspected whenever a patient relapses clinically and bacteriologically.

Drug resistance. Monotherapy with dapsone was the standard of treatment for all forms of leprosy until the 1980's, when concerns about dapsone resistance led WHO to introduce a multidrug treatment (MDT) regimen consisting of dapsone, rifampicin, and clofazimine. Long-term follow-up studies[1,2] designed to evaluate the efficacy of WHO MDT regimen reported relapse rates of 1.1 to 9% after a minimum of 2 years treatment. Drug sensitivity analyses were reported for 15 of these patients; no resistance to clofazimine or rifampicin was reported, while isolates from 3 patients showed dapsone resistance.[1] An evaluation of drug resistance after the introduction of WHO MDT regimen in Nepal[3] concluded that secondary resistance to dapsone does not develop under this regimen. In a 25-year follow-up study,[4] re-treatment with an alternative dapsone-containing MDT (rifampicin 1.2 g plus clofazimine 1.2 g given *once a month*, plus dapsone 100 mg daily for 1 year) significantly reduced the rate of relapse among multibacillary leprosy patients previously treated with dapsone monotherapy. Strains of *Mycobacterium leprae* with multiple resistance to rifampicin, ofloxacin, and dapsone have been isolated from a patient who had previously received dapsone monotherapy followed by treatment with rifampicin plus ofloxacin for 28 days.[5]

1. Cellona RV, *et al.* Long-term efficacy of 2 year WHO multiple drug therapy (MDT) in multibacillary (MB) leprosy patients. *Int J Lepr Other Mycobact Dis* 2003; 71: 308–19.
2. Norman G, *et al.* Relapses in multibacillary patients treated with multidrug therapy until smear negativity: findings after twenty years. *Int J Lepr Other Mycobact Dis* 2004; 72: 1–7.
3. Roche PW, *et al.* Dapsone drug resistance in the MDT era. *Int J Lepr Other Mycobact Dis* 2000; 68: 323–5.
4. Jing Z, *et al.* Twenty five years follow up of MB leprosy patients retreated with a modified MDT regimen after a full course of dapsone monotherapy. *Lepr Rev* 2009; 80: 170–6.
5. Cambau E, *et al.* Multidrug-resistance to dapsone, rifampicin, and ofloxacin in Mycobacterium leprae. *Lancet* 1997; 349: 103–4.

Pharmacokinetics

Dapsone is almost completely absorbed from the gastrointestinal tract and peak plasma concentrations occur 2 to 8 hours after a dose. Steady-state concentrations are not attained until after at least 8 days of daily dosage; doses of 100 mg daily provide trough concentrations of 500 nanograms/mL, which are well in excess of the MIC for *M. leprae*. About 70 to 90% of dapsone in the circulation is bound to plasma proteins and nearly 100% of its monoacetylated metabolite is bound. Only very small amounts are absorbed after topical application.

Dapsone undergoes enterohepatic recycling. It is widely distributed; it is present in saliva and breast milk and crosses the placenta. The half-life ranges from 10 to 50 hours; with a mean of 20 to 30 hours.

Dapsone is acetylated to monoacetyldapsone, the major metabolite, and other mono and diacetyl derivatives. Acetylation shows genetic polymorphism. Hydroxylation is the other major metabolic pathway resulting in hydroxylamine dapsone, which may be responsible for dapsone-associated methaemoglobinaemia and haemolysis.

Dapsone is mainly excreted in the urine, only 20% of a dose as unchanged drug.

References.

1. Zuidema J, *et al.* Clinical pharmacokinetics of dapsone. *Clin Pharmacokinet* 1986; 11: 299–315.
2. May DG, *et al.* The disposition of dapsone in cirrhosis. *Clin Pharmacol Ther* 1992; 51: 689–700.
3. Mirochnick M, *et al.* Pharmacokinetics of dapsone in children. *J Pediatr* 1993; 122: 806–9.
4. Opravil M, *et al.* Levels of dapsone and pyrimethamine in serum during once-weekly dosing for prophylaxis of Pneumocystis carinii pneumonia and toxoplasmic encephalitis. *Antimicrob Agents Chemother* 1994; 38: 1197–9.
5. Gatti G, *et al.* Penetration of dapsone into cerebrospinal fluid of patients with AIDS. *J Antimicrob Chemother* 1997; 40: 113–15.
6. Mirochnick M, *et al.* Pharmacokinetics of dapsone administered daily and weekly in human immunodeficiency virus-infected children. *Antimicrob Agents Chemother* 1999; 43: 2586–91.
7. Mirochnick M, *et al.* Population pharmacokinetics of dapsone in children with human immunodeficiency virus infection. *Clin Pharmacol Ther* 2001; 70: 24–32.
8. Thiboutot DM, *et al.* Pharmacokinetics of dapsone gel, 5% for the treatment of acne vulgaris. *Clin Pharmacokinet* 2007; 46: 697–712.

Metabolism. Measurement of the relative activity of the two main routes of dapsone metabolism (acetylation and hydroxylation) suggests that the risk of adverse effects is greater in individuals in whom the *N*-hydroxylation route predominates.[1] This is consistent with the hypothesis that the toxicity of dapsone is related to production of an active metabolite. See also Effects on the Blood, p. 282.2.

1. Bluhm RE, *et al.* Development of dapsone toxicity in patients with inflammatory dermatoses: activity of acetylation and hydroxylation of dapsone as risk factors. *Clin Pharmacol Ther* 1999; 65: 598–605.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Dapsᵗ; *Canad.*: Aczone; *Gr.*: Sulfona; *India*: Acnesone; *Mex.*: Dapsoderm-X; *Philipp.*: Lepravir; *Port.*: Sulfona; *Spain*: Sulfonaᵗ; *Thai.*: Dopsan; *USA*: Aczone.

Multi-ingredient Preparations. *Austral.*: Maloprimᵗ; *Austria*: Isoprodianᵗ; *Fr.*: Disulone; *Singapore*: Pyrisone; *Thai.*: Lepromix MB; Lepromix PB.

Pharmacopoeial Preparations

BP 2014: Dapsone Tablets;
USP 36: Dapsone Oral Suspension; Dapsone Tablets.

Daptomycin *(BAN, USAN, rINN)*

Daptomicina; Daptomycine; Daptomycinum; LY-146032; Даптомицин.

N-Decanoyl-L-tryptophyl-L-asparaginyl-L-aspartyl-L-threonylglycyl-L-ornithyl-L-aspartyl-D-alanyl-L-aspartylglycyl-O-seryl-*threo*-3-methyl-L-glutamyl-3-anthraniloyl-L-alanine 1.13-3.4-lactone.

$C_{72}H_{101}N_{17}O_{26}$=1620.7

CAS — 103050-53-3.

ATC — J01XX09.

ATC Vet — QJ01XX09.

UNII — NWQ5N31VKK.

Uses and Administration

Daptomycin is given for the treatment of complicated Gram-positive infections of the skin and skin structures, and *Staphylococcus aureus* bacteraemia, including right-sided endocarditis, caused by meticillin-susceptible and meticillin-resistant strains.

For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

For the treatment of skin and soft-tissue infections, daptomycin is given by intravenous infusion over 30 minutes, or by intravenous injection over 2 minutes, in a dose of 4 mg/kg once daily for 7 to 14 days. A higher dose of 6 mg/kg once daily is given for 2 to 6 weeks in the treatment of bacteraemia.

For details of dosage modification in patients with renal impairment, see p. 286.2.

Daptomycin has also been investigated for use in other indications, including vancomycin-resistant enterococcal infections and complicated urinary-tract infections.

References.

1. Fenton C, *et al.* Daptomycin. *Drugs* 2004; 64: 445–55.
2. Steenbergen JN, *et al.* Daptomycin: a lipopeptide antibiotic for the treatment of serious Gram-positive infections. *J Antimicrob Chemother* 2005; 55: 283–8.
3. Schriever CA, *et al.* Daptomycin: a novel cyclic lipopeptide antimicrobial. *Am J Health-Syst Pharm* 2005; 62: 1145–58.
4. French GL. Bactericidal agents in the treatment of MRSA infections—the potential role of daptomycin. *J Antimicrob Chemother* 2006; 58: 1107–17.
5. Hair PI, Keam SJ. Daptomycin: a review of its use in the management of complicated skin and soft-tissue infections and *Staphylococcus aureus* bacteraemia. *Drugs* 2007; 67: 1483–1512.
6. Enoch DA, *et al.* Daptomycin. *J Infect* 2007; 55: 205–13.
7. Weis F, *et al.* Daptomycin, a lipopeptide antibiotic in clinical practice. *Curr Opin Investig Drugs* 2008; 9: 879–84.
8. Forrest GN, *et al.* Clinical experience with daptomycin for the treatment of patients with documented gram-positive septic arthritis. *Ann Pharmacother* 2008; 42: 213–17.
9. Levine DP. Clinical experience with daptomycin: bacteraemia and endocarditis. *J Antimicrob Chemother* 2008; 62 (suppl 3): iii35–iii39.
10. Warren RE. Daptomycin in endocarditis and bacteraemia: a British perspective. *J Antimicrob Chemother* 2008; 62 (suppl 3): iii25–iii33.
11. Gould IM. Who's winning the war? *J Antimicrob Chemother* 2008; 62 (suppl 3): iii3–iii6.
12. Sakoulas G. Clinical outcomes with daptomycin: a post-marketing, real-world evaluation. *Clin Microbiol Infect* 2009; 15 (suppl 6): 11–6.
13. Biziotis IA, *et al.* Daptomycin versus other antimicrobial agents for the treatment of skin and soft tissue infections: a meta-analysis. *Ann Pharmacother* 2010; 44: 97–106.
14. Kosmidis C, Levine DP. Daptomycin: pharmacology and clinical use. *Expert Opin Pharmacother* 2010; 11: 615–25.

Administration in renal impairment. Licensed product information recommends that in patients with a creatinine clearance of less than 30 mL/minute, including those receiving haemodialysis or peritoneal dialysis, the intravenous dosage of daptomycin should be modified to 4 mg/kg once every 48 hours in the treatment of skin and soft-tissue infections, and to 6 mg/kg once every 48 hours in the treatment of bacteraemia.

Alternatively, a review[1] has suggested that critically ill patients undergoing intermittent haemodialysis be given a dose of 4 to 6 mg/kg every 48 to 72 hours (after dialysis). For those undergoing continuous renal replacement therapy, 4 to 6 mg/kg every 48 hours is recommended, although a dose of 4 to 6 mg/kg every 24 hours or 8 mg/kg every 48 hours can be considered for patients with deep-seated infections or those who do not respond to standard doses; serum-drug concentration measurements and frequent monitoring of serum-creatinine kinase levels should be considered when these larger doses are used.

1. Heintz BH, *et al.* Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy* 2009; 29: 562–77.

High-dose therapy. Due to concerns regarding clinical failure and emergence of resistance, some have questioned whether the standard 4- to 6-mg/kg daily dose for daptomycin is sufficient,[1,2] particularly for deep-seated infections with heavy bacterial load.[3] In some case reports,[4] clinical success occurred after higher doses where standard doses had failed. In a retrospective study[6] of 61 patients treated with daptomycin, a mean dose of 8 mg/kg daily (range 7 to 11 mg/kg daily) for a median duration of 25 days was well tolerated; although 3 patients (4.9%) had symptomatic elevations in creatine phosphokinase, all cases resolved once the drug was stopped.

1. Cosgrove SE, Corey GR. A balancing act: microbe versus muscle. *Clin Infect Dis* 2009; 49: 181–3.
2. Moise PA, *et al.* Safety and clinical outcomes when utilizing high-dose (≥8 mg/kg) daptomycin therapy. *Ann Pharmacother* 2009; 43: 1211–9.
3. Livermore DM. Future directions with daptomycin. *J Antimicrob Chemother* 2008; 62 (suppl 3): iii41–iii49.
4. Cunha BA, *et al.* Pacemaker-induced Staphylococcus aureus mitral valve acute bacterial endocarditis complicated by persistent bacteremia from a coronary stent: cure with prolonged/high-dose daptomycin without toxicity. *Heart Lung* 2006; 35: 207–11.
5. Cunha BA, *et al.* Methicillin-resistant Staphylococcus aureus (MRSA) mitral valve acute bacterial endocarditis (ABE) in a patient with Job's syndrome (hyperimmunoglobulin E syndrome) successfully treated with linezolid and high-dose daptomycin. *Heart Lung* 2008; 37: 72–5.
6. Figueroa DA, *et al.* Safety of high-dose intravenous daptomycin treatment: three-year cumulative experience in a clinical program. *Clin Infect Dis* 2009; 49: 177–80.

Adverse Effects and Precautions

The most common adverse effects associated with daptomycin are gastrointestinal effects including nausea and vomiting, constipation, diarrhoea, and dyspepsia. Headache, insomnia, dizziness, and fever may occur. Injection site reactions have occurred. Effects on the skin have included rash and pruritus. Abnormal liver function tests and jaundice have been reported. Other reported adverse effects include hypertension or hypotension, renal failure, dyspnoea, and anaemia. There have been rare cases of hypersensitivity, anaphylaxis, infusion reactions, and eosinophilic pneumonia.

Elevated plasma creatine phosphokinase (CPK) concentrations during daptomycin therapy may be associated with muscle pain and/or weakness, myositis, myopathy, and rarely rhabdomyolysis; patients with renal impairment or taking other drugs known to cause myopathy (see Interactions, p. 287.1) may be at increased risk. All patients should be monitored for the development of muscle pain or weakness, and plasma CPK concentrations measured once weekly. More frequent measurements should be performed in those with an increased risk of myopathy, or with a baseline CPK concentration greater than 5 times the upper limit of normal (ULN), or who develop signs of myopathy. Daptomycin should be stopped in patients with signs of myopathy and CPK concentrations greater than 5 times the ULN, or in those without reported signs of myopathy but with CPK concentrations greater than 10 times the ULN.

Daptomycin should be given with caution and in reduced dosage to patients with renal impairment; clinical response and renal function should be monitored closely.

Consideration should be given to stopping daptomycin therapy in patients who develop signs or symptoms of peripheral neuropathy.

Effects on the lungs. Bronchiolitis obliterans organising pneumonia with eosinophilic infiltration has been reported in an 84-year-old man after 4 weeks of daptomycin therapy;[1] clinical improvement occurred after the drug was stopped. The mechanism of toxicity was unknown and the authors suggested that it might be associated with epithelial injury caused by daptomycin accumulating in the alveolar spaces.

A 60-year-old man receiving daptomycin developed eosinophilic pneumonia resulting in respiratory failure that required mechanical ventilation;[2] he improved after stopping the drug and starting corticosteroid therapy. Chronic corticosteroid-dependent pneumonitis has also been reported in two elderly patients after they developed eosinophilic pneumonia during daptomycin therapy.[3]

The FDA identified 7 cases of eosinophilic pneumonia between 2004 and 2010 that were most likely associated with daptomycin. The ages of the patients ranged from 60 to 87 years. Eosinophilic pneumonia generally developed 2 to 4 weeks after starting treatment and all patients reported improvement or resolution of symptoms when daptomycin

was stopped; 5 patients were also given systemic corticosteroid therapy. Two patients were rechallenged with daptomycin and eosinophilic pneumonia recurred.[4]

1. Cobb E, *et al.* Organizing pneumonia and pulmonary eosinophilic infiltration associated with daptomycin. *Ann Pharmacother* 2007; 41: 696–701.
2. Hayes D, *et al.* Eosinophilic pneumonia induced by daptomycin. *J Infect* 2007; 54: e211–e213.
3. Lal Y, Assimacopoulos AP. Two cases of daptomycin-induced eosinophilic pneumonia and chronic pneumonitis. *Clin Infect Dis* 2010; 50: 737–40.
4. FDA. FDA drug safety communication: eosinophilic pneumonia associated with the use of Cubicin (daptomycin) (issued 29th July, 2010). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm220273.htm (accessed 15/10/10)

Pregnancy. Intravenous daptomycin, 4 mg/kg daily for 14 days, was successfully used to treat pyelonephritis associated with vancomycin-resistant enterococci (VRE) in a 27-week pregnant woman; no neonatal abnormalities were reported.[1]

1. Shea K, *et al.* Successful treatment of vancomycin-resistant Enterococcus faecium pyelonephritis with daptomycin during pregnancy. *Ann Pharmacother* 2008; 42: 722–5.

Interactions

There may be an increased risk of myopathy if daptomycin is given with other drugs also known to have this adverse effect, such as statins, fibrates, and ciclosporin. Licensed product information recommends stopping the latter if possible; otherwise, plasma creatine phosphokinase concentrations should be measured more than once weekly in addition to the usual precautions (see Adverse Effects and Precautions, p. 284.3).

Daptomycin is mainly excreted by renal filtration and caution is advised if given with drugs that reduce renal filtration, such as NSAIDs and selective inhibitors of cyclooxygenase-2, since plasma concentrations of daptomycin may be increased.

Daptomycin has been reported to interact with a particular reagent used in some assays of PT-INR resulting in apparent prolongation of PT and elevation of INR.

Antimicrobial Action

Daptomycin is a lipopeptide antibacterial that is reported to have a spectrum of antibacterial activity similar to that of vancomycin (p. 389.1) and greater potency against most Gram-positive bacterial strains *in vitro*; it is inactive against Gram-negative bacteria. Daptomycin disrupts the bacterial cell membrane potential by binding to the cell membranes in a calcium-dependent process, but without entering the cytoplasm, thus inhibiting the synthesis of protein, DNA, and RNA.

Daptomycin has shown activity both *in vitro* and in clinical infection with both meticillin-susceptible and meticillin-resistant *Staphylococcus aureus*, vancomycin-susceptible *Enterococcus faecalis*, and some streptococci.

It is reported to show antimicrobial synergy *in vitro* with aminoglycosides, beta lactams, and rifampicin against *Staph. aureus* (including meticillin-resistant strains) and enterococci (including vancomycin-resistant strains).

Resistance to daptomycin has been shown in clinical studies but only rarely; the mechanism of resistance has not been identified.

Reviews.

1. Boucher HW, Sakoulas G. Perspectives on daptomycin resistance, with emphasis on resistance in Staphylococcus aureus. *Clin Infect Dis* 2007; 45: 601–8.

Pharmacokinetics

Daptomycin is not absorbed to any significant extent after oral doses. The pharmacokinetics of daptomycin are generally linear at intravenous doses ranging from 4 to 12 mg/kg once daily. Peak plasma concentrations occur within 0.5 to 0.8 hours. It is distributed mainly into the extracellular space with a volume of distribution of about 0.1 litres/kg. Daptomycin crosses the blood-brain barrier and the placenta. It is about 90% bound to plasma proteins, mainly serum albumin.

In-vitro studies indicate that daptomycin is not metabolised by, and does not affect, the cytochrome P450 isoenzyme system. Little or no metabolism is thought to take place although 4 minor metabolites have been detected in the urine.

Daptomycin is excreted mainly via renal filtration with about 78% and 6% of a dose recovered in the urine and faeces, respectively. It has an elimination half-life of about 8 hours after an intravenous dose of 4 mg/kg once daily for 7 days and is prolonged in patients with renal impairment; a two- to threefold increase has been reported in those with severe impairment or end-stage renal disease.

Daptomycin is removed by haemodialysis or peritoneal dialysis.

References.
1. Dvorchik B, *et al.* Population pharmacokinetics of daptomycin. *Antimicrob Agents Chemother* 2004; 48: 2799–2807.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cubicin; ***Austral.***: Cubicin; ***Austria***: Cubicin; ***Braz.***: Cubicin; ***Canad.***: Cubicin; ***China***: Cubicin (克必信); ***Cz.***: Cubicin; ***Denm.***: Cubicin; ***Fr.***: Cubicin; ***Ger.***: Cubicin; ***Gr.***: Cubicin; ***Hong Kong***: Cubicin; ***Irl.***: Cubicin; ***Israel***: Cubicin; ***Ital.***: Cubicin; ***Jpn***: Cubicin; ***Malaysia***: Cubicin; ***Neth.***: Cubicin; ***Norw.***: Cubicin; ***NZ***: Cubicin; ***Philipp.***: Cubicin; ***Pol.***: Cubicin; ***Port.***: Cubicin; ***Rus.***: Cubicin (Кубицин); ***Singapore***: Cubicin; ***Spain***: Cubicin; ***Swed.***: Cubicin; ***Switz.***: Cubicin; ***Thai.***: Cubicin; ***Turk.***: Cubicin; ***UK***: Cubicin; ***Ukr.***: Cubicin (Кубицин); ***USA***: Cubicin.

Delamanid *(USAN, rINN)*

Délamanid; Delamanidum; OPC-67683; Деламанид.

(2*R*)-2-Methyl-6-nitro-2-[(4-[4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl]phenoxy)methyl]-2,3-dihydroimidazo[2,1-*b*]oxazole.

$C_{25}H_{25}F_3N_4O_6$=534.5

CAS — 681492-22-8.

UNII — 8OOT6M1PC7.

Profile

Delamanid is an antimycobacterial under investigation for the treatment of multidrug-resistant tuberculosis. It is an orally active imidazole derivative that inhibits mycolic acid synthesis.

References.
1. Gler MT, *et al.* Delamanid for multidrug-resistant pulmonary tuberculosis. *N Engl J Med* 2012; 366: 2151–60.

Demeclocycline *(BAN, rINN)*

Demeclociclina; Demeclocyclin; Déméclocycline; Demeclocyclinum; Demeklocyklin; Demeklosiklin; Demeklosykliini; Demethylchlortetracycline; Демеклоциклин.

(4*S*,4a*S*,5a*S*,6*S*,12a*S*)-7-Chloro-4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-1,11-dioxonaphthacene-2-carboxamide; 7-Chloro-6-demethyltetracycline.

$C_{21}H_{21}ClN_2O_8$=464.9

CAS — 127-33-3 (demeclocycline); 13215-10-6 (demeclocycline sesquihydrate).

ATC — D06AA01; J01AA01.

ATC Vet — QD06AA01; QJ01AA01.

UNII — 5R5W9ICI6O.

Pharmacopoeias. In *US.*

USP 36: (Demeclocycline). A yellow, odourless crystalline powder. Sparingly soluble in water; soluble 1 in 200 of alcohol and 1 in 40 of methyl alcohol; dissolves readily in 3N hydrochloric acid and in alkaline solutions. pH of a 1% solution in water is between 4.0 and 5.5. Store in airtight containers. Protect from light.

Demeclocycline Hydrochloride *(BANM, rINNM)*

Demeclociclina, hidrocloruro de; Déméclocycline, Chlorhydrate de; Demeclocyclinhydrochlorid; Demeclocyclini hydrochloridum; Demeklociklin-hidroklorid; Demeklociklino hidrochloridas; Demeklocyklin-hydrochlorid; Demeklocyklin-hydroklorid; Demeklocykliny chlorowodorek; Demeklosiklin Hidroklorür; Demeklosykliinihydrokloridi; Demethylchlortetracycline Hydrochloride; Hidrocloruro de demeclociclina; Демеклоциклина Гидрохлорид.

$C_{21}H_{21}ClN_2O_8HCl$=501.3

CAS — 64-73-3.

ATC — D06AA01; J01AA01.

ATC Vet — QD06AA01; QJ01AA01.

UNII — 29O079NTYT.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Demeclocycline Hydrochloride). The hydrochloride of a substance produced by certain strains of *Streptomyces aureofaciens* or by any other means. A yellow powder. Soluble or sparingly soluble in water; slightly soluble in alcohol; very slightly soluble in acetone. It dissolves in solutions of alkali hydroxides and carbonates. A 1% solution in water has a pH of 2.0 to 3.0. Protect from light.

USP 36: (Demeclocycline Hydrochloride). A yellow, odourless, crystalline powder. Soluble 1 in 60 of water and 1 in 50 of methyl alcohol; slightly soluble in alcohol; practically insoluble in acetone and in chloroform; sparingly soluble in solutions of alkali hydroxides and carbonates. pH of a 1% solution in water is between 2.0 and 3.0. Store in airtight containers. Protect from light.

Uses and Administration

Demeclocycline is a tetracycline derivative with uses similar to those of tetracycline (p. 375.3). It is excreted more slowly and effective blood concentrations are maintained for a longer period.

Demeclocycline is given orally as the hydrochloride; the usual adult dose for susceptible **infections** is 600 mg daily in 2 or 4 divided doses, preferably 1 hour before or 2 hours after meals. For atypical pneumonia, 900 mg daily in 3 divided doses may be given. It has also sometimes been given orally with other tetracycline derivatives.

For details of doses in children, and in patients with hepatic impairment, see p. 287.3.

Demeclocycline may also be given to adults in the treatment of chronic **hyponatraemia** associated with the syndrome of inappropriate antidiuretic hormone secretion, when water restriction has proved ineffective. Initially 900 to 1200 mg is given daily in divided doses, reducing to maintenance doses of 600 to 900 mg daily. For further information see p. 287.3.

The calcium and magnesium salts of demeclocycline have also been used.

Administration in children. In children, the effects on teeth should be considered and tetracyclines only used when absolutely essential; demeclocycline (given as the hydrochloride) may be used for the treatment of susceptible infections. In the UK, it is licensed for use in children aged 12 years and over; the usual adult dose (see Uses and Administration, above) may be given orally. However, in the USA, it may be given to those over 8 years old in usual oral doses of 7 to 13 mg/kg (maximum 600 mg) daily in 2 or 4 divided doses.

Administration in hepatic impairment. UK licensed product information states that the oral dosage of demeclocycline should not exceed 1 g daily in patients with known liver disease.

Syndrome of inappropriate ADH secretion. Demeclocycline may be given to reduce hyponatraemia in the treatment of the syndrome of inappropriate ADH (antidiuretic hormone) secretion (SIADH—p. 2351.2) by antagonising the effect of ADH on the renal tubules; lithium has been given as an alternative. Both lithium and demeclocycline act by interfering with the cellular action of ADH to produce nephrogenic diabetes insipidus. Demeclocycline was reported to be superior to lithium[1] and may be better tolerated than urea for chronic SIADH, although fluid restriction is probably still the treatment of choice.[2] However, since nephrotoxicity has been reported in patients with cardiac or hepatic disease, the usefulness of demeclocycline in the treatment of hyponatraemic states might be limited; this view was supported by studies in patients with heart failure[3] and cirrhosis.[4]

1. Forrest JN, *et al.* Superiority of demeclocycline over lithium in the treatment of chronic syndrome of inappropriate secretion of antidiuretic hormone. *N Engl J Med* 1978; 298: 173–7.
2. Ellison DH, Berl T. Clinical practice. The syndrome of inappropriate antidiuresis. *N Engl J Med* 2007; 356: 2064–72.
3. Zegers de Beyl D, *et al.* Demeclocycline treatment of water retention in congestive heart failure. *BMJ* 1978; 1: 760.
4. Miller PD, *et al.* Plasma demeclocycline levels and nephrotoxicity: correlation in hyponatremic cirrhotic patients. *JAMA* 1980; 243: 2513–15.

Adverse Effects and Precautions

As for Tetracycline, p. 377.1.

Phototoxic reactions occur more frequently with demeclocycline than with other tetracyclines and patients should avoid direct exposure to sunlight or artificial ultraviolet light.

Reversible nephrogenic diabetes insipidus with polyuria, polydipsia, and weakness may occur in patients treated with demeclocycline, particularly with prolonged treatment and/or high doses. Plasma creatinine should be monitored in patients receiving demeclocycline for long periods for the treatment of inappropriate secretion of antidiuretic hormone, since tetracycline-induced renal impairment may not otherwise be apparent in the absence of oliguria. For a comment that the usefulness of demeclocycline for this indication may be limited by nephrotoxicity in patients with cardiac or hepatic disease, see Syndrome of Inappropriate ADH Secretion under Uses and Administration, above.

Interactions

As for Tetracycline, p. 377.3.

Antimicrobial Action

As for Tetracycline, p. 377.3.

Demeclocycline is stated to be somewhat more active against certain strains of some organisms including *Neisseria gonorrhoeae* and *Haemophilus influenzae*, as well as to being the most active of the tetracyclines *in vitro* against *Brucella* spp.

Pharmacokinetics

For the general pharmacokinetics of the tetracyclines, see Tetracycline, p. 378.2.

About 60 to 80% of a dose of demeclocycline is absorbed from the gastrointestinal tract. Peak plasma concentrations of about 1.5 to 1.7 micrograms/mL have been reported 3 to 4 hours after a single oral dose of 300 mg, but higher plasma concentrations may be achieved with repeated dosage. Its plasma elimination half-life is about 12 hours, although this may be prolonged in patients with renal impairment; values of 42 to 68 hours have been reported in severe impairment. The renal clearance of demeclocycline is about half that of tetracycline.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Alkonatrem; *Gr.*: Ledermycin; *India*: Ledermycin; *Neth.*: Ledermycin; *UK*: Ledermycin†; *USA*: Declomycin.

Multi-ingredient Preparations. *Ger.*: Ledermix; *Hong Kong*: Ledermix; *Irl.*: Ledermix; *Israel*: Ledermix; *S.Afr.*: Tritet†; *Switz.*: Ledermix; *UK*: Ledermix.

Pharmacopoeial Preparations

BP 2014: Demeclocycline Capsules;

USP 36: Demeclocycline Hydrochloride Capsules; Demeclocycline Hydrochloride Tablets; Demeclocycline Oral Suspension.

Dibekacin Sulfate *(BANM, rINNM)*

Dibekacin Sulphate; Dibekacina, sulfato de; Dibékacine, Sulfate de; Dibekacini Sulfas; Sulfato de dibekacina; Дибекацина Сульфат; 3',4'-Dideoxykanamycin B.

6-*O*-(3-Amino-3-deoxy-α-D-glucopyranosyl)-2-deoxy-4-*O*-(2,6-diamino-2,3,4,6-tetradeoxy-α-D-*erythro*-hexopyranosyl)-streptamine sulphate.

$C_{18}H_{37}N_5O_8xH_2SO_4$

CAS — 34493-98-6 (dibekacin); 58580-55-5 (dibekacin sulfate).

ATC — J01GB09.

ATC Vet — QJ01GB09.

UNII — A08691992Z.

Pharmacopoeias. In *Jpn.*

Profile

Dibekacin is an aminoglycoside antibacterial derived from kanamycin with actions and uses similar to those of gentamicin (p. 306.2). It has been given intramuscularly as the sulfate in doses equivalent to dibekacin 1 to 3 mg/kg daily in divided doses. It has also been given in similar doses by slow intravenous infusion. Dosage should be adjusted based on serum-dibekacin concentration monitoring. It has also been used topically for eye infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Pratonil; Rolimycin; *Jpn*: Panimycin; *Venez.*: Dibekan.

Dicloxacillin *(BAN, USAN, rINN)*

BRL-1702; Dicloxacilina; Dicloxacilline; Dicloxacillinum; Dikloksasilliini; Dikloxacillin; R-13423; Диклоксациллин.

(6*R*)-6-[3-(2,6-Dichlorophenyl)-5-methylisoxazole-4-carboxamido]penicillanic acid.

$C_{19}H_{17}Cl_2N_3O_5S$=470.3

CAS — 3116-76-5.

ATC — J01CF01.

ATC Vet — QJ01CF01; QJ51CF01.

UNII — COF19H7WBK.

Dicloxacillin Sodium *(BANM, USAN, rINNM)*

Dicloxacilina sódica; Dicloxacillin-Natrium; Dicloxacilline sodique; Dicloxacillinum natricum; Dicloxacillinum Natricum Monohydricum; Dikloksasilino natrio druska; Dikloksasilliini-natrium; Dikloxacilin sodná sůl monohydrát; Dikloxacillinnatrium; Dikloxacillin-nátrium; Natrii Dicloxacillinum; P-1011; Натрий Диклоксациллин.

Sodium dicloxacillin monohydrate.

$C_{19}H_{16}Cl_2N_3NaO_5S,H_2O$=510.3

CAS — 343-55-5 (anhydrous dicloxacillin sodium); 13412-64-1 (dicloxacillin sodium monohydrate).

ATC — J01CF01.

ATC Vet — QJ01CF01.

UNII — 4HZT2V9KX0.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Dicloxacillin Sodium). A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; soluble in alcohol and in methyl alcohol. A 10% solution in water has a pH of 5.0 to 7.0. Store at a temperature not exceeding 25 degrees in airtight containers.

USP 36: (Dicloxacillin Sodium). A white to off-white crystalline powder. Freely soluble in water. pH of a 1% solution in water is between 4.5 and 7.5. Store in airtight containers.

Uses and Administration

Dicloxacillin is an isoxazolyl penicillin used similarly to flucloxacillin (p. 301.2) in the treatment of infections due to staphylococci resistant to benzylpenicillin.

Dicloxacillin is given intravenously and orally as the sodium salt. All doses are expressed in terms of the equivalent amount of dicloxacillin; 1.09 g of dicloxacillin sodium is equivalent to about 1 g of dicloxacillin. Oral doses should be taken at least 1 hour before, or 2 hours after, meals since the presence of food in the stomach reduces absorption. The usual adult oral dose is 250 mg every 6 hours. Doses may be doubled in severe infections. Similar doses may be given by slow intravenous injection or, preferably, by intravenous infusion, although intravenous doses of up to 2 g every 4 or 6 hours, may be required for serious infections such as endocarditis or osteomyelitis.

Adverse Effects and Precautions

As for Flucloxacillin, p. 301.3.

Effects on the liver. References.

1. Kleinman MS, Presberg JE. Cholestatic hepatitis after dicloxacillin-sodium therapy. *J Clin Gastroenterol* 1986; 8: 77–8.

Phlebitis. Phlebitis has been associated with infusion of cloxacillin and dicloxacillin; a small study[1] in patients with peripheral venous catheters indicated that the incidence was higher with the latter drug (phlebitis occurred in 21% of cases with cloxacillin, and 38% with dicloxacillin). The risk was greater in catheters inserted in the forearm or antecubital fossa than those in the hand or wrist, but greater infusion time or concentration were not associated with increased risk.

1. Lanbeck P, *et al.* Dicloxacillin: a higher risk than cloxacillin for infusion phlebitis. *Scand J Infect Dis* 2003; 35: 397–400.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dicloxacillin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Sodium content. Each g of dicloxacillin sodium contains about 2 mmol of sodium.

Interactions

As for Benzylpenicillin, p. 230.1.

Antimicrobial Action

As for Flucloxacillin, p. 302.1.

Pharmacokinetics

Dicloxacillin is better absorbed from the gastrointestinal tract than cloxacillin but absorption is reduced by the presence of food in the stomach. Peak plasma concentrations of 10 to 18 micrograms/mL have been reported in fasting subjects 1 hour after a 500-mg oral dose. Doubling the dose can double the plasma concentration. About 97% of dicloxacillin in the circulation is bound to plasma proteins. Dicloxacillin has been reported to have a plasma half-life of 0.5 to 1 hour. The half-life is prolonged in neonates.

The distribution of dicloxacillin in body tissues and fluids is similar to that of cloxacillin (p. 275.2).

Dicloxacillin is metabolised to a limited extent and the unchanged drug and metabolites are excreted in the urine by glomerular filtration and renal tubular secretion. About 60% of an oral dose is excreted in the urine. Only small amounts are excreted in the bile. Dicloxacillin is not removed by haemodialysis.

Plasma concentrations are enhanced by probenecid. Reduced concentrations have been reported in patients with cystic fibrosis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Diclocil; Dicloxsig; Distaph; *Denm.*: Dicillin; Diclocil; *Fin.*: Diclocil; *Gr.*: Diclocil; *Hong Kong*: Odicoza; *India*: Klox-D; *Mex.*: Amifarin†; Antiben; Brispen; Butimaxil; Cilpen†; Clobioxal; Dic-FHI; Dicleophen; Dicle-Tecno; Dicloxaquim; Diluxina; Dimicin; Ditterolina; Dixen; Doxil†; Pardix; Penclox; Posipen; *Norw.*: Diclocil; *NZ*: Diclocil; *Port.*: Diclocil; *Swed.*: Diclocil†; *Thai.*: Amcidil†; Cloxydin†; D-K-Cil; Dicillin; Diclex; Diclocil†; Diclocillin; Diclohof; Diclonox; Dicloxon; Diclox; Dicloxa; Dicloxane; Dicloxcin; Dicloxgen; Dicloxia; Dicloxilin; Dicloxin†; Dicloxman; Dicloxno; Dicloxpac; Diloxin; Dixocillin; Dorox; U-Diclox; *Venez.*: Diclocil.

Multi-ingredient Preparations. *China*: Diclomox (泼尔); Kai Li Da (凯力达); Wei Jing (维净); *India*: ADC; Alcilox; Aldox-D; Alnaclox; Amdosym; Amclox DL; Amdiclox; Amklok; Amoclox-D; Amoxytek D; Ampoxin Plus; Amsat; Arimox-D; Baxin-D-LB+; Baxin-D-LB; Baxin-D; Betadac-DC; Bicil-P; Bicil; Blox-DC; Blumox-DXL; Calmox; Cefocef-DXL; Cefupop-XL; Checkmox-DX; Cinmox-DC; Clobimox; Clodax; Clos-DX; Clospen; Cloxinova; Clynox; Coax-DX; Combo-AD; Cosclox; D-Clox; Dicam; Dicloxa-MX; Dicmoxy; Dimotic Discloxy; Dixi; Ethiclox-LB; Flemiklox-DX; Formic-XL; Hclox; Hifen-LXX; Incef-CL; Intaclox-D; Intamox-D; Jinclox; Kemox Plus; Lexmox-DC; Lizamox-D; Lomox-D; Lupimox Forte; Monomox-DX; Moxifact Moxikind Plus; Moxipil-LB; Moxitrac-DX; Moxklok; Moxtid-D Moxyplus-DC; Napi-D; NBMox-DC; Nugen-XL; O-Moxy-DC Odimox-DL; *Mex.*: Ampiclox-D†; Anglotex†; Brucilina; Diamprex†; Doxapen†; Panac K†; Panac Pentidix.

Pharmacopoeial Preparations

USP 36: Dicloxacillin Sodium Capsules; Dicloxacillin Sodium for Oral Suspension.

Difloxacin Hydrochloride *(USAN, rINNM)*

A-56619; Abbott-56619; Difloxacine, Chlorhydrate de; Difloxacini hydrochloridum; Difloxacino, hidrocloruro de; Hidrocloruro de difloxacino; Дифлоксацина гидрохлорид.

6-Fluoro-1-(*p*-fluorophenyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid hydrochloride.

$C_{21}H_{19}F_2N_3O_3,HCl$=435.9

CAS — 98106-17-3 (difloxacin); 91296-86-5 (difloxacin hydrochloride).

UNII — XJ0260HJ0O.

Pharmacopoeias. In *Eur.* (see p. vii) as the trihydrate for veterinary use.

Ph. Eur. 8: (Difloxacin Hydrochloride Trihydrate for Veterinary Use). A white or light yellow, crystalline powder. It exhibits polymorphism. Slightly soluble in water and in methyl alcohol; very slightly soluble in dichloromethane.

Profile

Difloxacin is a fluoroquinolone antibacterial used as the hydrochloride in veterinary medicine for the treatment of susceptible infections in poultry. It was formerly used in humans but was associated with an unacceptable incidence of adverse CNS effects.

Dihydrostreptomycin Sulfate *(BANM, rINNM)*

Dihidroestreptomicina, sulfato de; Dihidrosztreptomicinszulfát; Dihydrostreptomycin sulfát; Dihydrostreptomycin Sulphate; Dihydrostreptomycine, Sulfate de; Dihydrostreptomycini Sulfas; Dihydrostreptomycinsulfat; Dihydrostreptomysiinisulfaatti; Sulfato de dihidroestreptomicina; Дигидрострептомицина Сульфат.

O-2-Deoxy-2-methylamino-α-L-glucopyranosyl-(1→2)-*O*-5-deoxy-3-*C*-hydroxymethyl-α-L-lyxofuranosyl-(1→4)-N^1,N^3-diamidino-D-streptamine sulphate.

$(C_{21}H_{41}N_7O_{12})_2,3H_2SO_4$=1461.4

CAS — 128-46-1 (dihydrostreptomycin); 5490-27-7 (dihydrostreptomycin sulfate).

ATC — S01AA15.

ATC Vet — QS01AA15.

UNII — T7D4876IUE.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*, both for veterinary use only.

Ph. Eur. 8: (Dihydrostreptomycin Sulfate for Veterinary Use; Dihydrostreptomycin Sulfate BP(Vet) 2014). The sulfate of a substance obtained by catalytic hydrogenation of streptomycin or by any other means. The semisynthetic product is derived from a fermentation product. Stabilisers may be added. A white or almost white, hygroscopic powder. It contains a maximum of 2.0% streptomycin sulfate calculated with reference to the dried drug. Freely soluble in water; practically insoluble in alcohol, in acetone, and in methyl alcohol. A 25% solution in water has a pH of 5.0 to 7.0. Store in airtight containers. Protect from light.

USP 36: (Dihydrostreptomycin Sulfate). A white or almost white amorphous or crystalline powder; the amorphous form is hygroscopic. Freely soluble in water; practically insoluble in acetone, in chloroform, and in methyl alcohol. pH of a solution in water containing the equivalent of dihydrostreptomycin 20% is between 4.5 and 7.0, except that if it is labelled as being solely for oral use, the pH is between 3.0 and 7.0. Store in airtight containers.

Profile

Dihydrostreptomycin is an aminoglycoside antibacterial with actions similar to those of streptomycin (p. 361.1). Since it is more likely than streptomycin to cause partial or complete loss of hearing it is not used parenterally in humans. It is not absorbed after oral doses, and has been given by this route for gastrointestinal infections. It is also used as the sulfate in veterinary medicine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Spain*: Citrocil.

Multi-ingredient Preparations. *Arg.*: Vagisan Compuesto; Vagisan; *Mex.*: Estrefen; *Spain*: Cilinafosal Dihidroestreptomicina†; Salitanol Estreptomicina†; Sulfintestin Neomicina.

Dirithromycin *(BAN, USAN, rINN)*

ASE-136BS; Dirithromycine; Dirithromycinum; Diritromicin; Diritromicina; Diritromicinas; Diritromisin; Diritromycin; Diritromysiini; LY-237216; Диритромицин.

(1*R*,2*R*,3*R*,6*R*,7*S*,8*S*,9*R*,10*R*,12*R*,13*S*,15*R*,17*S*)-7-(2,6-Dideoxy-3-*C*,3-*O*-dimethyl-α-L-*ribo*-hexopyranosyloxy)-3-ethyl-2,10-dihydroxy-15-(2-methoxyethoxymethyl)-2,6,8,10,12,17-hexamethyl-9-(3,4,6-trideoxy-3-dimethylamino-β-L-*xylo*-hexopyranosyloxy)-4,16-dioxa-14-azabicyclo[11.3.1]heptadecan-5-one; (9*S*)-9-Deoxo-11-deoxy-9,11-[imino[(1*R*)-2-(2-methoxyethoxy)-ethylidene]oxy]erythromycin.

$C_{42}H_{78}N_2O_{14}$=835.1

CAS — 62013-04-1.

ATC — J01FA13.

ATC Vet — QJ01FA13.

UNII — 1801D76STL.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Dirithromycin). A white or almost white powder. It exhibits polymorphism. Very slightly soluble in water; very soluble in dichloromethane and in methyl alcohol.

USP 36: (Dirithromycin). A white or practically white powder. Very slightly soluble in water; very soluble in dichloromethane and in methyl alcohol.

Uses and Administration

Dirithromycin is a prodrug of the macrolide antibacterial erythromycylamine, which has similar properties to those of erythromycin (p. 293.2) and is used in respiratory-tract, skin, and soft-tissue infections caused by susceptible organisms.

Dirithromycin is given orally as enteric-coated tablets in a usual dose of 500 mg once daily.

References.

1. Various. Dirithromycin: a new once-daily macrolide. *J Antimicrob Chemother* 1993; 31 (suppl C): 1–185.
2. Brogden RN, Peters DH. Dirithromycin: a review of its antimicrobial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1994; 48: 599–616.
3. Wintermeyer SM, *et al.* Dirithromycin: a new macrolide. *Ann Pharmacother* 1996; 30: 1141–9.
4. McConnell SA, Amsden GW. Review and comparison of advanced-generation macrolides clarithromycin and dirithromycin. *Pharmacotherapy* 1999; 19: 404–15.

Adverse Effects and Precautions

As for Erythromycin, p. 295.1.

The most frequent adverse effects of dirithromycin are gastrointestinal disturbances; headache has also occurred. Dirithromycin should be used with caution in patients with moderate to severe hepatic impairment since its active metabolite erythromycylamine is mainly eliminated in the bile. It should also be used with caution in those with severe renal impairment.

Interactions

For a discussion of drug interactions of macrolide antibacterials, see Erythromycin, p. 296.2.

Cytochrome P450 isoenzymes. Dirithromycin is reported to have little or no effect on hepatic cytochrome P450 isoenzymes and may therefore produce fewer interactions than erythromycin with other drugs metabolised by this enzyme system (see Mechanism, under Interactions of Erythromycin, p. 296.2). The lack of interactions between dirithromycin and theophylline, terfenadine, or warfarin would appear to support this.

Antimicrobial Action

As for Erythromycin, p. 297.1.

Dirithromycin is reported to be generally less active than erythromycin *in vitro*, but may show greater activity *in vivo* than is indicated by *in-vitro* studies and may exert a postantibiotic effect.

Pharmacokinetics

Dirithromycin is readily absorbed after oral doses and undergoes rapid non-enzymatic hydrolysis to its active metabolite erythromycylamine. Absorption is enhanced by food. Bioavailability is about 10%. Daily doses of dirithromycin 500 mg produce peak plasma concentrations of erythromycylamine of about 400 nanograms/mL.

Erythromycylamine is widely distributed and tissue concentrations exceed those in plasma. Protein binding is 15 to 30%. Erythromycylamine is mainly excreted unchanged in the bile with only about 2% in the urine. The mean plasma half-life is about 8 hours and the mean urinary terminal elimination half-life is about 44 hours.

Distribution into milk has been found in studies in *rodents*.

References.

1. Sides GD, *et al.* Pharmacokinetics of dirithromycin. *J Antimicrob Chemother* 1993; 31 (suppl C): 65–75.
2. LaBreque D, *et al.* Pharmacokinetics of dirithromycin in patients with impaired hepatic function. *J Antimicrob Chemother* 1993; 32: 741–50.
3. Mazzei T, *et al.* Pharmacokinetics of dirithromycin in patients with mild or moderate cirrhosis. *Antimicrob Agents Chemother* 1999; 43: 1556–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Bi Zheng (毕正); Di Hong (迪红); Di Mai Xin (迪迈欣); Hongjidi (红极第); Lu Di (路迪); Luo Ke Xin (罗可辛); Pai Sheng (派盛); Ping Li Da (平立达); Qi Li Tuo (奇立妥); Yan Jin (严尽); Yi Li Xin (怡力昕); Yu Da (域大); *Fr.*: Dynabac†; *Gr.*: Dynabac; *Turk.*: Dynabac.

Pharmacopoeial Preparations

USP 36: Dirithromycin Delayed-Release Tablets.

Doripenem *(USAN, rINN)*

Doripénem; Doripénème; Doripenemum; S-4661; Дорипенем.

(+)-(4*R*5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-7-oxo-3-[[(3*S*,5*S*)-5-[(sulfamoylamino)methyl]-3-pyrrolidinyl]thio)-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monohydrate.

$C_{15}H_{24}N_4O_6S_2$, H_2O=438.5

CAS — 148016-81-3 (doripenem); 364622-82-2 (doripenem monohydrate).

ATC — J01DH04.

ATC Vet — QJ01DH04.

UNII — BHV525JOBH (doripenem); 4B035T6NKT (doripenem monohydrate).

Uses and Administration

Doripenem is a carbapenem antibacterial similar to imipenem (p. 311.2). It is more stable to renal dehydropeptidase I than imipenem and need not be given with an enzyme inhibitor such as cilastatin. It is used in the treatment of susceptible infections such as hospital-acquired pneumonia, and complicated intra-abdominal or urinary-tract infections, including pyelonephritis. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Doripenem is given as the monohydrate, but doses are expressed in terms of the amount of anhydrous doripenem; 1.04 g of doripenem monohydrate is equivalent to about 1 g of anhydrous doripenem. In the treatment of susceptible infections, doripenem is given by intravenous infusion over 1 hour, in a usual dose of 500 mg every 8 hours. For some patients with hospital-acquired pneumonia, this dose may be insufficient and a dose of 1 g every 8 hours has been recommended (see p. 289.3 for further details). An extended infusion over 4 hours may be more suitable for very severe infections, or those caused by less susceptible organisms and UK licensed product information allows this as an option in the management of hospital-acquired pneumonia. Doripenem treatment is usually given for 5 to 14 days; all patients with hospital-acquired pneumonia should be treated for at least 10 days.

For details of reduced doses in renal impairment, see p. 289.3.

References.

1. Lister PD. Carbapenems in the USA: focus on doripenem. *Expert Rev Anti Infect Ther* 2007; 5: 793–809.
2. Poulakou G, Giamarellou H. Doripenem: an expected arrival in the treatment of infections caused by multidrug-resistant Gram-negative pathogens. *Expert Opin Invest Drugs* 2008; 17: 749–71.
3. Chastre J, *et al.* Efficacy and safety of intravenous infusion of doripenem versus imipenem in ventilator-associated pneumonia: a multicenter, randomized study. *Crit Care Med* 2008; 36: 1089–96.
4. Lucasti C, *et al.* Efficacy and tolerability of IV doripenem versus meropenem in adults with complicated intra-abdominal infection: a phase III, prospective, multicenter, randomized, double-blind, non-inferiority study. *Clin Ther* 2008; 30: 868–83.
5. Keam SJ. Doripenem: a review of its use in the treatment of bacterial infections. *Drugs* 2008; 68: 2021–57.
6. Paterson DL, Depestel DD. Doripenem. *Clin Infect Dis* 2009; 49: 291–8.
7. Naber KG, *et al.* Intravenous doripenem at 500 milligrams versus levofloxacin at 250 milligrams, with an option to switch to oral therapy, for treatment of complicated lower urinary tract infection and pyelonephritis. *Antimicrob Agents Chemother* 2009; 53: 3782–92.
8. Mandell L. Doripenem: a new carbapenem in the treatment of nosocomial infection. *Clin Infect Dis* 2009; 49 (suppl 1): S1–S3.
9. Chahine EB, *et al.* Doripenem: a new carbapenem antibiotic. *Am J Health-Syst Pharm* 2010; 67: 2015–24.
10. Overturf GD. Doripenem: an early look at a carbapenem not yet approved for pediatrics. *Pediatr Infect Dis J* 2010; 29: 163–5.

Administration in renal impairment. Doses of doripenem given by intravenous infusion should be reduced in patients with renal impairment according to creatinine clearance (CC):

- CC 30 to 50 mL/minute: 250 mg every 8 hours
- CC greater than 10 to less than 30 mL/minute: 250 mg every 12 hours

The pharmacokinetics of doripenem have been examined in a small study[1] in 11 dialysis-dependent patients with end-stage renal disease who were undergoing continuous renal replacement therapy (CRRT), either via 12-hour continuous venovenous haemofiltration (CVVH) or continuous venovenous haemodiafiltration (CVVHDF). The study found that despite significant removal of doripenem and the active metabolite (doripenem-M1) by CRRT, a single 500-mg doripenem dose infused over 1 hour produced significantly higher plasma concentrations of doripenem, higher systemic exposure, and longer half-life in those undergoing CRRT than in healthy subjects. During CVVH and CVVHDF, respectively, the percentages of administered doripenem dose removed were 38 and 29%, and clearances of doripenem were 22 and 25 mL/minute. It was recommended that dosage regimens for doripenem in patients receiving CRRT should be adjusted. The results of another small study[2] in patients with end-stage renal disease (CC less than 10 mL/minute) who were receiving 3-times weekly haemodialysis suggested that an intravenous dose of doripenem 500 mg once every 24 hours would provide adequate serum concentrations.

1. Cirillo I, *et al.* Influence of continuous venovenous hemofiltration and continuous venovenous hemodiafiltration on the disposition of doripenem. *Antimicrob Agents Chemother* 2011; 55: 1187–93.
2. Heil EL, *et al.* Validation of doripenem dosing in patients with end-stage renal disease receiving hemodialysis. *Ann Pharmacother* 2011; 45: 1455–6.

Pneumonia. Regulatory authorities in Europe[1] and the USA[2] have recently issued safety alerts after a study evaluating the use of doripenem in the treatment of ventilator-associated pneumonia was stopped early. Preliminary results had shown a lower cure rate and an excess mortality in patients receiving an unlicensed dose of doripenem (1 g every 8 hours for 7 days) when compared with treatment with imipenem-cilastatin for 10 days. Based on the available data, it was considered that the shorter duration of treatment, augmented renal clearance, and infection with some specific types of bacteria had all contributed to the outcome.

In view of these findings, the EMEA[1] has made the following recommendations when giving doripenem to patients with hospital-acquired pneumonia, which includes ventilator-associated pneumonia:

- The dose of doripenem should be increased to 1 g every 8 hours and infused over 4 hours for patients with augmented renal clearance or with infections by non-fermenting, Gram-negative pathogens such as *Pseudomonas* spp. and *Acinetobacter* spp..
- If non-fermenting Gram-negative pathogens are confirmed, concomitant treatment with an aminoglycoside should be considered.
- For all patients, treatment should be for 10 to 14 days and is usually in the upper range for infections with non-fermenting, Gram-negative pathogens.

In the USA, doripenem is not licensed for the treatment of pneumonia.

1. EMA. Questions and answers on the review of Doribax (doripenem) (issued 21st June, 2012). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2012/06/WC500129084.pdf (accessed 16/08/12)
2. Chang P. Doripenem dear healthcare professional letter (issued 3rd January, 2012). Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/UCM286277.pdf (accessed 16/08/12)

Adverse Effects and Precautions

As for Imipenem, p. 312.1.

Doripenem is more stable to renal dehydropeptidase I than imipenem and use with cilastatin, which inhibits the

enzyme, is not required. Excess mortality has been reported in patients with ventilator-associated pneumonia given inappropriate doses of doripenem; for further information, see under Uses and Administration, p. 287.2.

Effects on the nervous system. Doripenem appears to carry a relatively low risk of inducing seizures.[1]

1. Zhanel GG, *et al.* Overview of seizure-inducing potential of doripenem. *Drug Safety* 2009; 32: 709–16.

Interactions

Probenecid inhibits the renal excretion of doripenem thereby increasing its plasma concentrations and prolonging its elimination half-life; co-administration is not recommended.

Antiepileptics. For reports of decreased plasma-*valproate* concentrations (sometimes with loss of seizure control) attributed to carbapenem antibacterials, see p. 557.2.

Antimicrobial Action

Like other carbapenems (see Imipenem, p. 312.2), doripenem is active against most Gram-positive and Gram-negative bacteria (including aerobes and anaerobes) with the exception of *Stenotraphomonas maltophilia, Burkholderia cepacia, Enterococcus faecium,* and MRSA. It is reported to have good activity *in vitro* against a broader range of such organisms than other carbapenems.

Doripenem is a particularly potent inhibitor of Gram-negative bacteria that have a high potential for drug resistance, such as *Pseudomonas aeruginosa,* and the Enterobacteriaceae. Compared with other carbapenems, doripenem also appears to have a relatively weak ability to promote the emergence of antibacterial resistance *in vitro.*

References.

1. Sahm D. In vitro activity of doripenem. *Clin Infect Dis* 2009; 49 (suppl 1): S11–S16.

Pharmacokinetics

After intravenous infusion of doripenem 500 mg over 1 hour, a mean peak plasma concentration of 23 micrograms/mL is attained, falling to 10 micrograms/mL after 1.5 hours and 1 microgram/mL after 6 hours.

Doripenem is less than 10% bound to plasma proteins and is widely distributed into body tissues and fluids. It is metabolised via hydrolysis of its beta-lactam ring by dehydropeptidase I to an open-ringed metabolite (doripenem-M1). The plasma elimination half-life is about 1 hour in adults; the half-life may be prolonged in patients with renal impairment. Doripenem is mainly excreted in the urine by tubular secretion and glomerular filtration. About 70% and 15% of a dose is recovered as unchanged drug and metabolite, respectively, in the urine within 48 hours. Less than 1% is excreted in faeces.

Doripenem is removed by haemodialysis.

References.

1. Cirillo I, *et al.* Pharmacokinetics, safety, and tolerability of doripenem after 0.5-, 1-, and 4-hour infusions in healthy volunteers. *J Clin Pharmacol* 2009; 49: 798–806.
2. Nandy P, *et al.* Population pharmacokinetics of doripenem based on data from phase 1 studies with healthy volunteers and phase 2 and 3 studies with critically ill patients. *Antimicrob Agents Chemother* 2010; 54: 2354–9.
3. Samtani MN, *et al.* Pharmacokinetic-pharmacodynamic-model-guided doripenem dosing in critically ill patients. *Antimicrob Agents Chemother* 2010; 54: 2360–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Doribax; ***Austral.***: Doribax; ***Austria***: Doribax; ***Belg.***: Doribax; ***Canad.***: Doribax; ***Cz.***: Doribax; ***Denm.***: Doribax; ***Fr.***: Doribax; ***Ger.***: Doribax; ***Gr.***: Doribax; ***Hong Kong***: Doribax; ***Hung.***: Doribax; ***Irl.***: Doribax; ***Israel***: Doribax; ***Jpn***: Finibax; ***Malaysia***: Doribax; ***Neth.***: Doribax; ***Norw.***: Doribax; ***NZ***: Doribax; ***Philipp.***: Doribax; ***Pol.***: Doribax; ***Port.***: Doribax; ***Rus.***: Doriprex (Дорипрекс); ***Singapore***: Doribax; ***Spain***: Doribax; ***Swed.***: Doribax; ***Thai.***: Doribax; ***Turk.***: Doribax; ***UK***: Doribax; ***USA***: Doribax.

Doxycycline *(BAN, USAN, rINN)*

Doksiciklinas monohidratas; Doksisiklin; Doksisykliini; Doksisykliinimonohydraatti; Doksycyklina; Doxiciclina; Doxiciklin; Doxycyclin; Doxycyclin-Monohydrat; Doxycycline Monohydrate; Doxycycline monohydratée; Doxycyclinum; Doxycyclinum Monohydricum; Doxycyklin monohydrát; Doxycyklinmonohydrat; GS-3065; Доксициклин.

(4*S*,4a*R*,5*S*,5a*R*,6*S*,12a*S*)-4-Dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxonaphthacene-2-carboxamide monohydrate; 6-Deoxy-5β-hydroxytetracycline monohydrate.

$C_{22}H_{24}N_2O_8,H_2O$=462.5

CAS — 564-25-0 (anhydrous doxycycline); 17086-28-1 (doxycycline monohydrate).

ATC — A01AB22; J01AA02.

ATC Vet — QA01AB22; QJ01AA02.

UNII — N12000U13O (doxycycline monohydrate); 334895862 (anhydrous doxycycline).

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Doxycycline Monohydrate). A yellow crystalline powder. Very slightly soluble in water and in alcohol. It dissolves in dilute solutions of mineral acids and in solutions of alkali hydroxides and carbonates. A 1% suspension in water has a pH of 5.0 to 6.5. Store in airtight containers. Protect from light.

USP 36: (Doxycycline). A yellow crystalline powder. Very slightly soluble in water and in alcohol; practically insoluble in chloroform and in ether; freely soluble in dilute acid and in alkali hydroxide solutions. pH of a 1% suspension in water is between 5.0 and 6.5. Store in airtight containers. Protect from light.

Doxycycline Calcium *(BANM, rINNM)*

Calcii Doxycyclinum; Doxiciclina cálcica; Doxycycline Calcique; Кальций Доксициклин.

CAS — 94088-85-4.

ATC — A01AB22; J01AA02.

ATC Vet — QA01AB22; QJ01AA02.

UNII — 8ZL07I20SB.

Doxycycline Fosfatex *(BAN, USAN)*

AB-08; DMSC; Doxiciclina fosfatex.

6-Deoxy-5β-hydroxytetracycline—metaphosphoric acid—sodium metaphosphate in the ratio 3:3:1.

$(C_{22}H_{24}N_2O_8)_3(HPO_3)_3NaPO_3$=1675.2

CAS — 83038-87-3.

ATC — A01AB22; J01AA02.

ATC Vet — QA01AB22; QJ01AA02.

UNII — 2IQ26U2DZQ.

Doxycycline Hyclate *(BANM, rINNM)*

Doksiciklino hiklatas; Doksisykliinihyklaatti; Doksycykliny hyklan; Dossiciclina Iclato; Doxiciclina, hiclato de; Doxiciklin-hiklát; Doxycycline, Hyclate de; Doxycycline Hydrochloride; Doxycyclinhyclat; Doxycyclini Hyclas; Doxycyklinhyklat; Doxycyklin-hyklát; Hiclato de doxiciclina; Доксициклина Гиклат.

Doxycycline hydrochloride hemiethanolate hemihydrate.

$C_{22}H_{24}N_2O_8HCl,½C_2H_5OH,½H_2O$=512.9

CAS — 10592-13-9 (doxycycline hydrochloride); 24390-14-5 (doxycycline hyclate).

ATC — A01AB22; J01AA02.

ATC Vet — QA01AB22; QJ01AA02.

UNII — 19XT53T51U (doxycycline hyclate); 4182Z6T2ET (doxycycline hydrochloride).

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 8: (Doxycycline Hyclate). A yellow hygroscopic crystalline powder. Freely soluble in water and in methyl alcohol; sparingly soluble in alcohol. It dissolves in solutions of alkali hydroxides and of carbonates. A 1% solution in water has a pH of 2.0 to 3.0. Store in airtight containers. Protect from light.

USP 36: (Doxycycline Hyclate). A yellow crystalline powder. Soluble in water; slightly soluble in alcohol; practically insoluble in chloroform and in ether; soluble in solutions of alkali hydroxides and carbonates. pH of a solution in water containing the equivalent of doxycycline 1% is between 2.0 and 3.0. Store in airtight containers. Protect from light.

Incompatibility. Preparations of doxycycline hyclate have an acid pH and incompatibility may reasonably be expected with alkaline preparations or with drugs unstable at low pH.

Uses and Administration

Doxycycline is a tetracycline derivative with uses similar to those of tetracycline (p. 375.3). It is usually preferred to other tetracyclines in the treatment of susceptible infections because of its fairly reliable absorption and a long half-life that permits less frequent (often once daily) dosing. It also has the advantage that with care it can be given to patients with renal impairment. However, relatively high doses may need to be given for urinary-tract infections because of its low renal excretion.

Doxycycline has antiprotozoal actions and may be given with quinine in the management of falciparum malaria resistant to chloroquine (p. 644.1).

Solutions of doxycycline are also used for malignant effusions (p. 700.1).

Doxycycline is usually given orally as the base or its various salts, usually the hyclate. Doses are expressed in terms of doxycycline; doxycycline hyclate 115 mg is equivalent to about 100 mg of anhydrous doxycycline. Doxycycline capsules and tablets should be given with plenty of fluid, with the patient in an upright position, and well before going to bed. Doxycycline may be given with food or milk if gastric irritation occurs. Dispersible tablets or liquid formulations are advisable in elderly patients.

In patients in whom oral therapy is not feasible, doxycycline hyclate may be given by slow intravenous infusion of a solution containing 0.1 to 1 mg/mL, in equivalent doses. Infusions should be given over 1 to 4 hours.

The usual adult dose, either orally or intravenously, in susceptible **infections** is 200 mg of doxycycline on the first day (as a single dose or in divided doses), followed by 100 mg daily. In severe infections the initial dosage is maintained throughout the course of treatment. For details of doses in children and adolescents, see p. 291.1.

In patients with uncomplicated gonococcal infections (p. 204.2), doxycycline 100 mg twice daily for 7 days is given orally, although it has occasionally been given in a single dose of 300 mg followed by a second similar dose 1 hour later. For syphilis (p. 205.2) in penicillin-allergic patients, doxycycline 100 to 200 mg twice daily is given orally for at least 14 days; some authorities suggest giving the same dose for 28 to 30 days to patients with late latent disease and those with long-standing syphilis of more than a year should be given 100 mg twice daily for 28 days.

For relapsing fever (p. 202.2) and louse-borne typhus (p. 212.3), doxycycline 100 or 200 mg may be given as a single oral dose. For prophylaxis of scrub typhus, 200 mg may be taken as a single oral dose. For the prophylaxis of leptospirosis (p. 189.3), 200 mg may be given orally once a week throughout exposure for up to 21 days and 200 mg is also given when leaving the area of infection risk.

Doxycycline is used in non-endemic areas for the treatment of chloroquine-resistant falciparum malaria in an oral dose of 200 mg daily for at least 7 days with or after treatment with quinine. Doxycycline 100 mg daily may be used for prophylaxis in areas of high risk or where multidrug resistance exists, and can be used prophylactically for up to 2 years.

For treatment of inhalation anthrax (p. 173.2), a 60-day course of treatment with oral doses of 100 mg twice daily may be used; one or two other antibacterials should also be given. Although unlicensed, the same regimen is recommended by UK and US public health authorities for the treatment of gastrointestinal anthrax. In the treatment of cutaneous anthrax (also unlicensed), a 7- to 10-day course of treatment with an oral dose of doxycycline 100 mg twice daily is recommended; treatment may need to be extended to 60 days if infection is due to aerosol exposure. If there are signs of systemic involvement, extensive oedema, or lesions on the head and neck, intravenous therapy and a multidrug approach is recommended. For postexposure prophylaxis of inhalation anthrax, a 60-day course of treatment with oral doses of doxycycline 100 mg twice daily may be used. Alternatively prophylaxis may be started with oral ciprofloxacin for 5 days and then oral doxycycline (100 mg twice daily) may be substituted to complete the 60-day course.

In the treatment of acne vulgaris, an oral dose of 50 mg daily for 6 to 12 weeks may be adequate, although the *BNF* advocates a dose of 100 mg daily. It is also given in low doses of 40 mg once daily as a modified-release preparation for the treatment of inflammatory lesions associated with rosacea in adults.

Doxycycline may be given orally in low, **subantimicrobial doses** of 20 mg twice daily for 3 months as an adjunct to supragingival and subgingival scaling and root planing to adults with periodontitis. For chronic periodontitis, a modified-release subgingival gel containing doxycycline hyclate 10% (released over 7 days) has been inserted into the periodontal pocket.

For further information on the use of subantimicrobial doses of doxycycline for the treatment of acne, rosacea, and peridontal disease, see p. 290.3.

Administration. *SUBANTIMICROBIAL DOSES.* Doxycycline is given in doses of 20 mg orally twice daily, which are not sufficient to achieve antimicrobial concentrations in the body, as an adjunct in the treatment of periodontal disease (p. 192.3). The benefits of treatment are believed to be due to its ability to downregulate the actions of matrix metalloproteinases, enzymes involved in the breakdown of collagen and which play a key role in the inflammatory and destructive processes of periodontitis.[1-3]

Similar subantimicrobial doses have been investigated, and produced apparent benefit, in patients with acne (p. 1682.2) or rosacea (p. 1688.3);[4] there was no evidence that even quite prolonged therapy at these doses influenced the development of antibacterial resistance in bacterial flora. A low-dose modified-release preparation containing

doxycycline 40 mg is available in some countries for the treatment of inflammatory lesions associated with rosacea.

1. Preshaw PM, *et al.* Subantimicrobial dose doxycycline as adjunctive treatment for periodontitis: a review. *J Clin Periodontol* 2004; 31: 697–707.
2. Gapski R, *et al.* Systemic MMP inhibition for periodontal wound repair: results of a multi-centre randomized-controlled clinical trial. *J Clin Periodontol* 2009; 36: 149–56.
3. Caton J, Ryan ME. Clinical studies on the management of periodontal diseases utilizing subantimicrobial dose doxycycline (SDD). *Pharmacol Res* 2011; 63: 114–20.
4. Del Rosso JQ. A status report on the use of subantimicrobial-dose doxycycline: a review of the biologic and antimicrobial effects of the tetracyclines. *Cutis* 2004; 74: 118–122.

Administration in children. In children, the effects on teeth should be considered and tetracyclines only used when absolutely essential. In the UK, doxycycline is licensed for low-dose, **subantimicrobial**, and standard dose, **antibacterial** use in children aged 12 years and over only; the usual adult dose (see Uses and Administration, p. 288.2) may be given orally. However, in the USA, it may be given to children over 8 years old; those weighing 45 kg or less may be given usual oral or intravenous doses of 4.4 mg/kg on the first day (as a single dose or in divided doses), followed by 2.2 mg/kg daily and those weighing over 45 kg may be given the usual adult dose (see above).

In the USA, doxycycline is also licensed in children over 8 years old for prophylaxis of chloroquine-resistant falciparum **malaria** in areas of high risk or where multidrug resistance exists. The recommended oral dose is 2 mg/kg (to a maximum of 100 mg) once daily.

US public health authorities suggest that doxycycline may also be given to children under 8 years old for the treatment of inhalation, gastrointestinal, or cutaneous **anthrax**,[1] and for postexposure prophylaxis of inhalation anthrax.[2] For the treatment and postexposure prophylaxis of inhalation anthrax, a 60-day course of treatment with doses of 2.2 mg/kg (to a maximum of 100 mg) twice daily is suggested; the same regimen is also recommended for the treatment of gastrointestinal anthrax. As for adult treatment regimens, one or two other antibacterials should also be given when treating established infection. For treatment, antibacterials are initially given intravenously and then switched to oral therapy when clinically appropriate.[2,3] In the treatment of cutaneous anthrax, a 7-to 10-day course of treatment with an oral dose of 2.2 mg/kg twice daily is recommended; treatment may need to be extended to 60 days if infection is due to aerosol exposure.[2,3] In the UK[3] public health authorities only recommend doxycycline for those older than 8 years old and weighing over 45 kg who may be given the usual adult dose (see above).

Doxycycline can also be used to treat children with **Rocky Mountain spotted fever** (p. 208.1). US[4] public health authorities have suggested a dose of 2.2 mg/kg twice daily in children weighing less than about 45 kg, given either orally or intravenously.

1. CDC. Update: investigation of bioterrorism-related anthrax and interim guidelines for exposure management and antimicrobial therapy, October 2001. *MMWR* 2001; 50: 909–19. Correction. *ibid.*; 962. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5042a1.htm (accessed 02/02/11)
2. CDC. Update: Investigation of anthrax associated with intentional exposure and interim public health guidelines, October 2001. *MMWR* 2001; 50: 889–93. Also available at: http://www.cdc.gov/mmwr/PDF/wk/mm5041.pdf (accessed 02/02/11)
3. Health Protection Agency. *Anthrax: guidelines for action in the event of a deliberate release.* Version 6.2; issued 21/12/10. http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1194947401128 (accessed 02/02/11)
4. Chapman AS, *et al.* Tickborne Rickettsial Diseases Working Group. CDC. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever, ehrlichioses, and anaplasmosis—United States. A practical guide for physicians and other health-care and public health professionals. *MMWR* 2006; 55: 1–27. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5504.pdf (accessed 28/01/09)

Lymphatic filariasis. Filaria have been shown to contain *Wolbachia* endobacteria, which are essential for larval development and adult worm fertility and viability. This symbiotic dependency has provided a new approach in the treatment of individuals with lymphatic filariasis (p. 146.3). A double-blind, randomised, placebo-controlled study[1] of 72 patients infected with *Wuchereria bancrofti* found that those given oral doxycycline 200 mg daily for 8 weeks had a significant reduction in the number of adult worms at 14 months; ultrasonography detected adult worms in 22% of those given doxycycline and in 88% of those given placebo. Microfilaraemia was almost completely eliminated at 8 to 14 months follow-up. A small, double-blind, randomised, placebo-controlled study[2] also in patients infected with *W. bancrofti*, reported that a 3-week course of doxycycline 200 mg daily with a single dose of ivermectin (150 microgram/kg) plus albendazole (400 mg), given 4 months after starting treatment with doxycycline, is more effective in inducing long-term amicrofilaraemia than standard treatment with ivermectin plus albendazole, but is insufficient to kill adult worms. Similarly, courses of doxycycline for either 6 or 4 weeks (plus single doses of ivermectin with or without albendazole given 4 months after starting treatment) have been shown to decrease *Wolbachia* load and have strong microfilarial activity.[3,4] Another double-blind, randomised, placebo-controlled study[5] in persons infected with *Brugia malayi* found that doxycycline 100 mg daily for 6 weeks either alone or with a single dose of diethylcarbamazine (6 mg/kg) plus albendazole (400 mg), given 4 months after starting treatment with doxycycline, significantly reduced *Wolbachia* levels. Furthermore, after 1 year the prevalence of microfilaraemia was reduced by 77% in patients given doxycycline alone and by 87.5% in those given doxycycline and diethylcarbamazine plus albendazole; a 26.7% reduction of microfilaraemia was reported for those given placebo and diethylcarbamazine plus albendazole.

See also Onchocerciasis, p. 291.2.

1. Taylor MJ, *et al.* Macrofilaricidal activity after doxycycline treatment of Wuchereria bancrofti: a double-blind, randomised placebo-controlled trial. *Lancet* 2005; 365: 2116–21.
2. Turner JD, *et al.* A randomized, double-blind clinical trial of a 3-week course of doxycycline plus albendazole and ivermectin for the treatment of Wuchereria bancrofti infection. *Clin Infect Dis* 2006; 42: 1081–9.
3. Debrah AY, *et al.* Doxycycline reduces plasma VEGF-C/sVEGFR-3 and improves pathology in lymphatic filariasis. *PLoS Pathog* 2006; 2: e92.
4. Debrah AY, *et al.* Macrofilaricidal effect of 4 weeks of treatment with doxycycline on *Wuchereria bancrofti*. *Trop Med Int Health* 2007; 12: 1433–41.
5. Supali T, *et al.* Doxycycline treatment of Brugia malayi-infected persons reduces microfilaremia and adverse reactions after diethylcarbamazine and albendazole treatment. *Clin Infect Dis* 2008; 46: 1385–93.

For the use of doxycycline in the treatment of malaria see under Tetracycline, p. 376.1.

Mansonella infections. As with other filaria, *Mansonella perstans* have been shown to rely on a symbiotic relationship with *Wolbachia* endobacteria, leading to hopes that *M. perstans* infections (see p. 147.2) might be effectively treated with antibacterials. In a randomised open-label study[1] of patients with *M. perstans* microfilaraemia, [oral] doxycycline 200 mg daily given for 6 weeks led to significantly reduced levels of *M. perstans* at 12 months, and sustained suppression 36 months after treatment.

1. Coulibaly YI, *et al.* A randomized trial of doxycycline for *Mansonella perstans* infection. *N Engl J Med* 2009; 361: 1448–58.

Multiple sclerosis. Matrix metalloproteinases (MMPs) have been shown to play a role in the pathogenesis of multiple sclerosis and may also reduce the efficacy of therapy by degrading interferon beta. Tetracyclines have immunomodulatory and neuroprotective effects, and are also potent inhibitors of MMPs. Doxycycline has been evaluated in an open label study in a few patients with remitting-relapsing multiple sclerosis and breakthrough disease;[1] adding oral doxycycline to their intramuscular interferon beta-1a therapy was reported to be safe and associated with disease stabilisation in most.

1. Minagar A, *et al.* Combination therapy with interferon beta-1a and doxycycline in multiple sclerosis: an open-label trial. *Arch Neurol* 2008; 65: 199–204.

Musculoskeletal and joint disorders. For reference to the use of doxycycline in the management of various musculoskeletal and joint disorders, see under Tetracycline, p. 376.2.

Onchocerciasis. As in lymphatic filariasis (above), *Onchocerca volvulus* worms rely on a symbiotic relationship with *Wolbachia* endobacteria, and this has provided a new approach in the treatment of individuals with onchocerciasis (p. 147.2). A 4-month controlled clinical study[1] of 35 patients with onchocerciasis found that those given oral doxycycline 100 mg daily for 6 weeks showed a trend toward more frequent degeneration or death of adult worms and suppressed embryonic development at early stages for the duration of the study period. A subsequent study[2] of 88 patients found that embryogenesis was interrupted for at least 18 months in those given a single standard dose of ivermectin (150 micrograms/kg) plus oral doxycycline 100 mg daily for 6 weeks compared with those given only the standard dose of ivermectin.

1. Hoerauf A, *et al.* Endosymbiotic bacteria in worms as targets for a novel chemotherapy in filariasis. *Lancet* 2000; 355: 1242–3.
2. Hoerauf A, *et al.* Depletion of wolbachia endobacteria in Onchocerca volvulus by doxycycline and microfilaridermia after ivermectin treatment. *Lancet* 2001; 357: 1415–16.

Adverse Effects and Precautions

As for Tetracycline, p. 377.1.

Gastrointestinal disturbances with doxycycline are reported to be less frequent than with tetracycline and doxycycline may also cause less tooth discoloration.

Oesophageal ulceration or sometimes rupture may be a particular problem if capsules or tablets are taken with insufficient fluid or in a recumbent posture: doxycycline should be taken with at least half a glass of water, in an upright position, and well before going to bed. Dispersible tablets or liquid formulations should be used in elderly patients, who may be at greater risk of oesophageal injury.

Hypersensitivity reactions are uncommon with doxycycline, although the Jarisch-Herxheimer reaction may occur when it is used to treat spirochetal infections. Doxycycline is considered one of the most potent photosensitisers among the tetracyclines, and photosensitivity is common; photoonycholysis may rarely occur without an associated skin rash.

Unlike many tetracyclines, doxycycline does not appear to accumulate in patients with impaired renal function, and aggravation of impairment may be less likely. Similarly, there is also no evidence that doxycycline causes severe hepatitis.

Incidence of adverse effects. For the suggestion that doxycycline may cause fewer adverse effects than minocycline, see p. 327.2.

Anosmia. Anosmia or dysosmia (absent or impaired sense of smell) have occasionally been reported in patients receiving doxycycline, although the association has not been definitely established.[1]

1. Bleasel AF, *et al.* Anosmia after doxycycline use. *Med J Aust* 1990; 152: 440.

Breast feeding. See Pharmacokinetics, p. 291.3, for a suggestion that doxycycline has a greater potential for toxicity in breast-fed infants than other tetracyclines.

Effects on intracranial pressure. Doxycycline has been associated with benign intracranial hypertension; for further details, see under Tetracycline, p. 377.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies doxycycline as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 15/08/11)

Interactions

As for Tetracycline, p. 377.3.

Doxycycline has a lower affinity for binding with calcium than many tetracyclines. Consequently its absorption is less likely to be affected by milk or food, although it is still affected by calcium-containing antacids and other divalent and trivalent cations such as aluminium, bismuth, iron, magnesium, and zinc; even intravenous doxycycline may be affected, although less so than when given orally.

Doxycycline is a substrate of the cytochrome P450 isoenzyme CYP3A4 and a moderate inhibitor of the same cytochrome system. Its metabolism may therefore be accelerated by drugs that induce hepatic enzymes such as alcohol (chronic use), rifampicin, and antiepileptics including carbamazepine, phenobarbital, phenytoin, and primidone.

It has been suggested that doxycycline could increase ciclosporin concentrations, but evidence for this seems to be scant.

Antimicrobial Action

As for Tetracycline, p. 377.3.

Doxycycline is more active than tetracycline against many bacterial species including *Streptococcus pyogenes*, enterococci, *Nocardia* spp., *Yersinia pestis*, and various anaerobes. Cross-resistance is common although no resistance to doxycycline has been found in *Chlamydia* or *Rickettsia* spp.. Doxycycline is also more active against protozoa, particularly *Plasmodium* spp.

Pharmacokinetics

For the general pharmacokinetics of the tetracyclines, see Tetracycline, p. 378.2.

Doxycycline is readily and almost completely absorbed from the gastrointestinal tract and absorption is not significantly affected by the presence of milk or food in the stomach or duodenum. Mean peak plasma concentrations of 2.6 micrograms/mL have been reported 2 hours after a 200-mg oral dose, falling to 1.45 micrograms/mL at 24 hours. After intravenous infusion of the same dose peak plasma concentrations ranging from 5 to 10 micrograms/mL occur; these fall slowly and concentrations of 1 to 2 micrograms/mL persist for 24 hours.

Doxycycline is more lipid-soluble than tetracycline. It is widely distributed in body tissues and fluids, with excellent penetration into the liver, kidney, and sinuses. Penetration into CSF is only moderate, and CSF concentrations are not more than 1 microgram/mL in those with non-inflamed meninges. It crosses the placenta and is distributed into breast milk with concentrations of up to 40% of plasma. The potential for toxicity in a breast-fed infant may be greater than with the other tetracyclines because doxycycline is less bound to calcium. About 80 to 95% of doxycycline in the

circulation is reported to be bound to plasma proteins. Its biological half-life varies from about 12 to 24 hours.

In patients with normal renal function about 40% of a dose is slowly excreted in the urine, although more is excreted by this route if the urine is made alkaline. However, the majority of a dose of doxycycline is excreted in the faeces after chelation in the intestines. Although doxycycline has been reported to undergo partial inactivation in the liver, some sources consider this doubtful; however, the kinetics of doxycycline have been reportedly altered in patients receiving drugs that induce hepatic metabolism.

Doxycycline is stated not to accumulate significantly in patients with renal impairment, although excretion in the urine is reduced; increased amounts of doxycycline are excreted in the faeces in these patients. Nevertheless, there have been reports of some accumulation in renal failure. Removal of doxycycline by haemodialysis is insignificant.

Reviews.
1. Saivin S, Houin G. Clinical pharmacokinetics of doxycycline and minocycline. *Clin Pharmacokinet* 1988; **15**: 355–66.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Asolmicina dox; Atridox†; Ciclidoxan; Doxibiot†; Granudoxy; Verboril; Vibramicina; ***Austral.***: Doryx; Doxsig; Doxy; Doxyhexal; Doxylin; Frakas; Vibra-Tabs; Vibramycin; ***Austria***: Dotur; Doxybene; Doxyderm; Doxydyn; Doxyhexal†; Doxystad; Vibramycin; Vibravenos; ***Belg.***: Docdoxycy†; Doxylets; Doxytab; Vibratab; ***Braz.***: Ciclisan†; Clordox; Doxilegrand†; Neo Doxicilin; Protectina; Uni Doxiciclin; Vibradoxin; Vibramicina; ***Canad.***: Apo-Doxy; Atridox; Doxycin; Doxytab; Novo-Doxylin; Periostat; Vibra-Tabs; Vibramycin; ***Chile***: Abraxil; Dentarec; Doryx†; Doxithal; Sigadoxin; Tolexine; Vibramicina; ***China***: Ai Rui De An (艾瑞得安); Duo Di (多迪); Wan Shi Qi (万士奇); Yong Xi (永喜); ***Cz.***: Deoxymykoin; Doxybene; Doxyhexal; ***Denm.***: Dotur†; Oracea; Vibradox; ***Fin.***: Atridox†; Doximed; Doximycin; Doxitin; Oracea; ***Fr.***: Doxy; Doxylis; Doxypalu; Granudoxy; Spanor; Tolexine; Vibramycine N; Vibraveineuse; ***Ger.***: Aknefug Doxy†; Antodox†; Doxakne; Doxy Komb†; Doxy M; Doxy-HP†; Doxy-N-Tablinen†; Doxy-Wolff†; Doxy; Doxyderma; Doxydoc†; Doxyhexal†; Doxymono†; Ligosan; Oraycea; ***Gr.***: Anfadox†; Atridox; Combaforte; Impalamycin; Ivamycin; Lentomyk; Microvibrate; Novimax; Otosal; Relyomycin; Smilitene; Vibrabiotic; Vibramycin; Vibravenos; Vibravenosa; Visubiotic; ***Hong Kong***: Amermycin; Doxatt†; Doxitab†; Doxy; Doxycap†; Doxylin†; Doxymycin; Medomycin; Plemex†; Synvibra†; Vibramycin; Wanmycin; ***Hung.***: Doxitidin; Doxypharm; Doxyprotect; Huma-Doxylin; Tenutan; ***India***: Apidox; Bidox-DT; Biodoxi; Ceedox; Chemedox-HT; Codox; Dedoxyn; Dobid; Dox-M DT; Doxicip; Doxina; Doxipil; Doxitab; Doxodin-TR; Doxt; Doxy; Doxycap; Doxyleb; Doxylin-DT; Doxyn; Doxypal-DR; Doxyric; Doxytop; Duradox; DX-24; Emdox; Geeox; Ginadox; Idoxy; LAA; Lenteclin; Lupidox; M-Dox; Martidox-M; Microdox; Minicycline; Nab-DT; Nee; Novadox; Nudoxy; Solomycin; Vibazine; ***Indon.***: Dohixat; Dotur; Doxacin; Doxicor; Doxin†; Dumoxin; Interdoxin; Siclidon; Viadoxin; Vibramycin; ***Irl.***: Atridox†; By-Mycin; Efracea; Periostat; Vibramycin; ***Israel***: Doxibiotic†; Doxy; Doxylin; Periostat†; Vibramycin†; ***Ital.***: Atridox; Bassado; Miraclin; Periostat; ***Malaysia***: Doline†; Domycine; Doxycillin; Doxymycin; Medomycin; Vibramycin; ***Mex.***: Bioximicina; Domiken; Doranbax†; Doxinonflam; Kenciclen; Periosan; Roxidolin; Vibramicina; Vivradoxil; ***Neth.***: Atridox†; Doxy†; Efracea; Periostat; Unidox; Vibramycin; ***Norw.***: Doxylin; Vibramycin†; Vibranord; ***NZ***: Doxine; Doxy; ***Philipp.***: Bactidox; Comxin; Cytragen; Doxicon; Doxin; Doxylyn; Dyna; Harvellin; Quedox; Vibramycin; ***Pol.***: Dotur†; Doxicin; Doxyratio M; Supracyclin†; Unidox; ***Port.***: Actidox; Atridox†; Doxytrex; Periostat; Pluridoxina; Sigadoxin; Vibramicina; ***Rus.***: Doxal (Доксал); Medomycin (Медомицин)†; Unidox (Юнидокс); Vibramycin (Вибрамицин)†; Vidokcine (Видокцин); Xedocine (Кседоцин); ***S.Afr.***: Cyclidox; Doximal; Doxitab; Doxyclin†; Doxycyl; Doxyhexal†; Doxymycin†; Doxytet; Dumoxin; Noritet†; Vibramycin†; ***Singapore***: Apo-Doxy; Bronmycin; Domycine; Doryx†; Doxine†; Doxycap; Doxyline; Doxymycin; Medomycin; Microdox; Remycin; Tetradox; Vibramycin; Wanmycin†; ***Spain***: Atridox†; Dosil; Doxiclat; Doxicrisol†; Doxipil; Doxiten Bio; Mededoxi†; Peledox†; Proderma; Retens†; Rexilen; Vibracina; Vibravenosa; ***Swed.***: Atridox†; Doxyferm; Oracea; Vibramycin†; Vibranord; ***Switz.***: Doxycline; Doxylag; Doxysol; Oracea; Periostat†; Rudocyclin; Supracycline; Tasmacyclin Akne; Vibramycine; Vibraveineuse; Zadorin; ***Thai.***: Amermycin; Bronmycin†; Cin-Doxy; Docline; Docyl; Doxin; Doxine; Doxinin; Doxinpac; Doxxo†; Doxy-P; Doxy; Doxyclate; Doxycline; Doxycom; Doxyhol; Doxylcap; Doxylin; Doxyman; Doxymed; Madoxy; Medomycin; Medoxin†; Poli-Cycline; Pondoxcycline; Servidoxyne†; Siadocin; Tetradox; Torymycin; Veemycin; Vibramycin; Viprocin; ***Turk.***: Doksin; Monodoks; Tetradox; ***UAE***: DuraDox; ***UK***: Atridox; Doxylar; Efracea; Periostat; Vibramycin†; Vibramycin; ***Ukr.***: Doxy-M (Докси-М); Doxybene (Доксибене); Unidox (Юнидокс); ***USA***: Adoxa†; Alodox; Atridox; Avidoxy; Doryx; Monodox; Morgidox; NutriDox†; Ocudox; Oracea; Oraxyl†; Periostat; Vibra-Tabs†; Vibramycin; ***Venez.***: Doxidival; Tremesal; Vibramicina C.

Multi-ingredient Preparations. ***Cz.***: Doxycyclin Al Comp; ***Ger.***: Ambrodoxy†; Ambroxol AL comp†; Ambroxol comp; Doxy Comp†; Doxy Plus†; ***India***: Acnedox-LB; Avidox-LB; Avidox-OZ; Avidox-SP; Dox-M ST; Dox-M TZ; Dox-M-A; Dox-M-OZ; Doxy-1 L-DR Forte; Doxyguard; Doxylin-TZ; Emdox-TZ; Glodox-LB; Microdox; ***Spain***: Dosil Enzimatico; Doxiten Enzimatico; ***USA***: Avidoxy DK.

Pharmacopoeial Preparations

BP 2014: Dispersible Doxycycline Tablets; Doxycycline Capsules; **USP 36:** Doxycycline Calcium Oral Suspension; Doxycycline Capsules; Doxycycline for Injection; Doxycycline for Oral Suspension; Doxycycline Hyclate Capsules; Doxycycline Hyclate Delayed-release Capsules; Doxycycline Hyclate Delayed-Release Tablets; Doxycycline Hyclate Tablets; Doxycycline Tablets.

Enoxacin *(BAN, USAN, rINN)*

AT-2266; CI-919; Enoksasiini; Enoksasin; Énoxacine; Enoxacino; Enoxacinum; PD-107779; Эноксацин.

1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-1,8-naphthyridine-3-carboxylic acid.

$C_{15}H_{17}FN_4O_3$=320.3

CAS — 74011-58-8.

ATC — J01MA04.

ATC Vet — QJ01MA04.

UNII — 325OGW249P.

Pharmacopoeias. *Chin.* and *Jpn* include the sesquihydrate.

Uses and Administration

Enoxacin is a fluoroquinolone antibacterial with actions and uses similar to those of ciprofloxacin (p. 261.2). It is used mainly in the treatment of urinary-tract infections (p. 213.1) and gonorrhoea (p. 204.2).

For urinary-tract infections, enoxacin is given orally in doses of 200 or 400 mg twice daily.

For details of reduced doses in renal impairment, see p. 292.2.

A single 200-mg or 400-mg dose may be given for uncomplicated gonorrhoea.

References.
1. Patel SS, Spencer CM. Enoxacin: a reappraisal of its clinical efficacy in the treatment of genitourinary tract infections. *Drugs* 1996; **51**: 137–60.

Administration in renal impairment. When the creatinine clearance is 30 mL/minute or less urinary concentrations of enoxacin may be too low to have a therapeutic effect in urinary-tract infections. In other infections, half the usual oral dose of enoxacin is recommended.

Adverse Effects and Precautions

As for Ciprofloxacin, p. 262.2.

Reduced dosage may be needed in renal impairment—see Administration in Renal Impairment, under Uses and Administration, above.

Interactions

As for Ciprofloxacin, p. 264.3.

Of the fluoroquinolones, enoxacin has been reported to cause the most marked interaction with theophylline (p. 1234.2) and with caffeine (p. 1206.1).

Antimicrobial Action

As for Ciprofloxacin, p. 265.2, although enoxacin is generally less potent *in vitro*.

Pharmacokinetics

Peak plasma concentrations of 2 to 3 micrograms/mL occur 1 to 2 hours after a 400-mg oral dose of enoxacin. The plasma half-life is about 3 to 6 hours. Plasma protein binding ranges from 18 to 67%. Enoxacin appears to be widely distributed in the body and concentrations higher than those in plasma have been reported in tissues such as lung, kidney, and prostate. High concentrations occur in bile, but the extent of biliary excretion is not clear.

Enoxacin is eliminated from the body mainly by urinary excretion, but also by metabolism. The major metabolite, 3-oxo-enoxacin, has some antibacterial activity. Urinary excretion of enoxacin is by both tubular secretion and glomerular filtration and may be reduced by probenecid. High concentrations occur in the urine since about 60% of an oral dose of enoxacin appears unchanged in the urine within 24 hours; about 10% is recovered as 3-oxo-enoxacin. In renal impairment the half-life of enoxacin may be prolonged and the oxometabolite may accumulate.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Bi Cai Ni (必采尼); De Xing Li (的星力); Jiu Nuo (久诺); Kai Quan (凯全); Li De Jia (力得佳); Mei Feng (美风); Nuojia (诺佳); ***Fr.***: Enoxor; ***Ger.***: Enoxor; ***Gr.***: Enoxor; ***Ital.***: Enoxen; ***Jpn***: Flumark†; ***Turk.***: Enoksetin.

Enrofloxacin *(BAN, USAN, rINN)*

Bay-Vp-2674; Enrofloksasiini; Enrofloxacine; Enrofloxacino; Enrofloxacinum; Энрофлоксацин.

1-Cyclopropyl-7-(4-ethylpiperazin-1-yl)-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid.

$C_{19}H_{22}FN_3O_3$=359.4

CAS — 93106-60-6.

ATC Vet — QJ01MA90.

UNII — 3DX3XEK1BN.

Pharmacopoeias. In *Eur.* (see p. vii) and *US* for veterinary use only.

Ph. Eur. 8: (Enrofloxacin for Veterinary Use). A pale yellowish or light yellow, crystalline powder. Practically insoluble in water; slightly soluble in methyl alcohol; freely soluble in dichloromethane. Protect from light.

USP 36: (Enrofloxacin). A pale yellow to light yellow crystalline powder. Very slightly soluble in water at pH 7.0. Store in airtight containers. Protect from light.

Profile

Enrofloxacin is a fluoroquinolone antibacterial that is used in veterinary practice.

Ertapenem Sodium *(BANM, USAN, rINNM)*

Ertapenem sódico; Ertapénem Sodique; L-749345; MK-0826; MK-826; Natrii Ertapenemum; ZD-4433; Натрий Эртапенем.

Sodium (4*R*,5*S*,6*S*)-3-{{(3*S*,5*S*)-5-[(*m*-Carboxyphenyl)carbamoyl]-3-pyrrolidinyl}thio}-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

$C_{22}H_{24}N_3NaO_7S$=497.5

CAS — 153832-46-3 (ertapenem); 153832-38-3 (ertapenem disodium); 153773-82-1 (ertapenem sodium).

ATC — J01DH03.

ATC Vet — QJ01DH03.

UNII — 2T90KE67L0.

Incompatibility and stability. References.

1. McQuade MS, *et al.* Stability and compatibility of reconstituted ertapenem with commonly used iv infusion and coinfusion solutions. *Am J Health-Syst Pharm* 2004; **61**: 38–45.

Uses and Administration

Ertapenem is a carbapenem beta-lactam antibacterial with actions and uses similar to those of imipenem (p. 311.3). It is more stable to renal dehydropeptidase I than imipenem and need not be given with an enzyme inhibitor such as cilastatin. It is used in the treatment of infections due to susceptible Gram-positive and Gram-negative bacteria including intra-abdominal infections, acute gynaecological infections, complicated urinary-tract infections, skin and skin-structure infections (in particular, diabetic foot infections), and respiratory-tract infections. It is also used prophylactically in colorectal surgery. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Ertapenem is given as the sodium salt, but doses are expressed in terms of the base; 1.04 g of ertapenem sodium is equivalent to about 1 g of ertapenem. For treatment, it is given by intravenous infusion over 30 minutes or by intramuscular injection, in a usual dose of 1 g once daily. For prophylaxis, a single 1-g dose is given intravenously 1 hour before the start of surgery.

The dose of ertapenem may need to be reduced in renal impairment, see p. 292.3.

For details of doses in infants and children, see p. 292.3.

References.
1. Keating GM, Perry CM. Ertapenem: a review of its use in the treatment of bacterial infections. *Drugs* 2006; **65**: 2151–78.
2. Rogers LC, *et al.* Ertapenem for diabetic foot infections. *Drugs Today* 2006; **42**: 695–701.
3. Burkhardt O, *et al.* Ertapenem: the new carbapenem 5 years after first FDA licensing for clinical practice. *Expert Opin Pharmacother* 2007; **8**: 237–56.
4. Falagas ME, *et al.* Meta-analysis: ertapenem for complicated intra-abdominal infections. *Aliment Pharmacol Ther* 2008; **27**: 919–31.
5. Nielsen MD, *et al.* The use of ertapenem for the treatment of lower extremity infections. *J Foot Ankle Surg* 2009; **48**: 135–41.
6. Congeni BL. Ertapenem. *Expert Opin Pharmacother* 2010; **11**: 669–72.

Administration in children. Ertapenem may be given to children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria. It is given by intravenous infusion over 30 minutes or if appropriate by intramuscular injection. For children from 3 months of age the usual recommended dose is 15 mg/kg twice daily (up to a maximum of 1 g daily).

Administration in renal impairment. US licensed product information indicates that parenteral doses of ertapenem should be reduced in patients with renal impairment according to creatinine clearance (CC) as follows:

- CC 30 mL or less per minute per 1.73 m^2 (including end-stage disease where CC is 10 mL or less per minute per 1.73 m^2): 500 mg daily for adults
- haemodialysis: if the 500-mg dose is given in the 6-hour period before dialysis an additional 150 mg should be given after the dialysis session

The UK product information, however, states that in advanced renal insufficiency and haemodialysis there are inadequate data to make recommendations and that ertapenem should not be used in these patients.

Adverse Effects and Precautions

As for Imipenem, p. 312.1. There have been reports of DRESS syndrome (drug rash with eosinophilia and systemic symptoms) after the use of ertapenem.

Ertapenem is more stable to renal dehydropeptidase I than imipenem and use with cilastatin, which inhibits the enzyme, is not required.

Effects on the nervous system. Unusual mental status changes were reported in 2 elderly men after 5 to 7 days of treatment with ertapenem.[1] The first, a 79-year-old man, developed garbled speech and miosis that resolved after ertapenem was stopped but recurred upon rechallenge. The second patient, a 70-year-old man with cachexia and acute renal insufficiency, developed delirium that resolved the day after ertapenem was stopped. There have also been postmarketing reports of aggression, hallucinations, dyskinesia, myoclonus, and tremor after the use of ertapenem.

1. Duquaine S, *et al.* Central nervous system toxicity associated with ertapenem use. Abstract: *Ann Pharmacother* 2011; **45**: 127. Full version: http://www.theannals.com/cgi/reprint/45/1/e6 (accessed 24/06/11)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ertapenem as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/09/11)

Interactions

Probenecid inhibits the renal excretion of ertapenem thereby increasing its plasma concentrations and prolonging its elimination half-life.

Antiepileptics. For reports of decreased plasma-*valproate* concentrations (sometimes with loss of seizure control) attributed to ertapenem, and the view that carbapenems should not be used with valproates, see p. 557.2.

Antimicrobial Action

As for Imipenem, p. 312.2.

Ertapenem is reported to be slightly more active overall *in vitro* than imipenem but is less active against Gram-positive bacteria and has a narrower spectrum of activity. It is generally not active against *Acinetobacter* spp., *Pseudomonas aeruginosa*, MRSA, or enterococci.

Pharmacokinetics

After intravenous infusion of ertapenem 1 g over 30 minutes, a mean plasma concentration of 155 micrograms/mL is attained, falling to 9 micrograms/mL after 12 hours and 1 microgram/mL after 24 hours. After the same dose intramuscularly, a plasma concentration of 67 micrograms/mL is achieved after 2 hours. Bioavailability after intramuscular injection is about 90%.

Ertapenem is more than 90% bound to plasma proteins. It is distributed into breast milk. The plasma half-life is about 4 hours in adults and 2.5 hours in infants and in children aged 3 months to 12 years; the half-life may be prolonged in patients with renal impairment.

Ertapenem is partially metabolised via hydrolysis of its beta-lactam ring by dehydropeptidase I to an open-ringed metabolite. About 80% of a dose is excreted in the urine as both unchanged drug and metabolite. About 10% is excreted in faeces.

Ertapenem is removed by haemodialysis.

References.

1. Mistry GC, *et al.* Pharmacokinetics of ertapenem in patients with varying degrees of renal insufficiency and in patients on hemodialysis. *J Clin Pharmacol* 2006; **46**: 1128–38.
2. Brink AJ, *et al.* Pharmacokinetics of once-daily dosing of ertapenem in critically ill patients with severe sepsis. *Int J Antimicrob Agents* 2009; **33**: 432–6.
3. Frasca D, *et al.* Pharmacokinetics of ertapenem following intravenous and subcutaneous infusions in patients. *Antimicrob Agents Chemother* 2010; **54**: 924–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Invanz; *Austral.*: Invanz; *Austria*: Invanz; *Braz.*: Invanz; *Canad.*: Invanz; *Chile*: Invanz; *China*: Invanz (怡万之); *Cz.*: Invanz; *Denm.*: Invanz; *Fin.*: Invanz; *Fr.*: Invanz; *Ger.*: Invanz; *Gr.*: Invanz; *Hong Kong*: Invanz; *Hung.*: Invanz; *India*: Invanz; *Indon.*: Invanz; *Irl.*: Invanz; *Israel*: Invanz; *Ital.*: Invanz; *Malaysia*: Invanz; *Neth.*: Invanz; *Norw.*: Invanz; *NZ*: Invanz; *Philipp.*: Invanz; *Pol.*: Invanz; *Port.*: Invanz; *Rus.*: Invanz (Инванз); *S.Afr.*: Invanz; *Singapore*: Invanz; *Spain*: Invanz; *Swed.*: Invanz; *Switz.*: Invanz; *Thai.*: Invanz; *Turk.*: Invanz; *UK*: Invanz; *Ukr.*: Invanz (Инванз); *USA*: Invanz; *Venez.*: Invanz.

Erythromycin *(BAN, rINN)*

Eritromicin; Eritromicina; Eritromicinas; Eritromisin; Érythromycine; Erythromycinum; Erytromycin; Erytromycyna; Erytromysiini; Эритромицин.

Erythromycin A is (*2R,3S,4S,5R,6R,8R,10R,11R,12S,13R*)-5-(3-amino-3,4,6-trideoxy-*N,N*-dimethyl-β-D-*xylo*-hexopyranosyloxy)-3-(2,6-dideoxy-3-*C*,3-*O*-dimethyl-α-L-*ribo*-hexopyranosyloxy)-13-ethyl-6,11,12-trihydroxy-2,4,6,8,10,12-hexamethyl-9-oxotridecan-13-olide.

$C_{37}H_{67}NO_{13}$=733.9

CAS — 114-07-8.

ATC — D10AF02; J01FA01; S01AA17.

ATC Vet — QD10AF02; QJ01FA01; QJ51FA01; QS01AA17.

UNII — 63937KV33D.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Erythromycin). It is produced by the growth of a strain of *Streptomyces erythreus* and is a mixture of macrolide antibiotics consisting largely of erythromycin A. It occurs as a white or slightly yellow powder or colourless or slightly yellow crystals; slightly hygroscopic. Slightly soluble in water but less soluble at higher temperatures; freely soluble in alcohol; soluble in methyl alcohol. Protect from light.

USP 36: (Erythromycin). It consists primarily of erythromycin A. A white or slightly yellow, odourless or practically odourless, crystalline powder. Soluble 1 in 1000 of water; soluble in alcohol, in chloroform, and in ether. Store in airtight containers.

Erythromycin Estolate *(BAN, USAN, rINNM)*

Eritromicina, estolato de; Eritromicin-esztolát; Eritromicino estolatas; Erythromycin Propionate Lauryl Sulfate; Erythromycin Propionate Lauryl Sulphate; Érythromycine, Estolate d'; Erythromycinestolat; Erythromycin-estolát; Erytromycini Estolas; Erytromycinestolat; Erytromycyny estolan; Erytromysiiniestolaatti; Estolato de eritromicina; Propionylerythromycin Lauryl Sulphate; Эритромицина Эстолат.

Erythromycin 2′-propionate dodecyl sulphate.

$C_{40}H_{71}NO_{14}C_{12}H_{26}O_4S$=1056.4

CAS — 3521-62-8.

ATC — D10AF02; J01FA01; S01AA17.

ATC Vet — QD10AF02; QJ01FA01; QS01AA17.

UNII — XRJ2P631HP.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Erythromycin Estolate). A white or almost white, crystalline powder. Practically insoluble in water; freely soluble in alcohol; soluble in acetone; practically insoluble in dilute hydrochloric acid. Protect from light.

USP 36: (Erythromycin Estolate). A white, odourless or practically odourless, crystalline powder. It has a potency equivalent to not less than 600 micrograms of erythromycin per mg, calculated on the anhydrous basis. Practically insoluble in water; soluble 1 in 20 of alcohol, 1 in 15 of acetone, and 1 in 10 of chloroform. Store in airtight containers.

Erythromycin Ethyl Succinate *(BANM)*

Eritromicina, etilsuccinato de; Eritromicin-etilszukcinát; Eritromicino etilsukcinatas; Erythromycin Ethylsuccinate; Érythromycine, éthylsuccinate d'; Erythromycinethylsuccinat; Erythromycin-ethylsukcinát; Erythromycini ethylsuccinas; Erytromycinetylsuccinat; Erytromycyny etylobursztynian; Erytromysiinietyylisuksinaatti; Эритромицина этилсукцинат.

Erythromycin 2′-(ethylsuccinate).

$C_{43}H_{75}NO_{16}$=862.1

CAS — 41342-53-4.

ATC — D10AF02; J01FA01; S01AA17.

ATC Vet — QD10AF02; QJ01FA01; QS01AA17.

UNII — 1014KSJ86F.

NOTE. Compounded preparations of erythromycin ethyl succinate may be represented by the following names:

- Co-erynsulfisox (*PEN*)—erythromycin ethyl succinate and acetyl sulfafurazole.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Erythromycin Ethylsuccinate; Erythromycin Ethyl Succinate BP 2014). A white or almost white, hygroscopic crystalline powder. Practically insoluble in water; freely soluble in dehydrated alcohol, in acetone, and in methyl alcohol. Store in airtight containers. Protect from light.

USP 36: (Erythromycin Ethylsuccinate). A white or slightly yellow, odourless or practically odourless, crystalline powder. It has a potency equivalent to not less than 765 micrograms of erythromycin per mg, calculated on the anhydrous basis. Very slightly soluble in water; freely soluble in alcohol, in chloroform, and in macrogol 400. Store in airtight containers.

Erythromycin Gluceptate *(BANM, rINNM)*

Eritromicina, gluceptato de; Érythromycine, Gluceptate d'; Erythromycini Gluceptas; Gluceptato de eritromicina; Эритромицина глюцептат.

Erythromycin glucoheptonate.

$C_{37}H_{67}NO_{13}C_7H_{14}O_8$=960.1

CAS — 304-63-2; 23067-13-2.

ATC — D10AF02; J01FA01; S01AA17.

ATC Vet — QD10AF02; QJ01FA01; QS01AA17.

UNII — 2AY21R0U64.

Pharmacopoeias. In *US*.

USP 36: (Sterile Erythromycin Gluceptate). It is erythromycin gluceptate suitable for parenteral use. It has a potency equivalent to not less than 600 micrograms of erythromycin per mg, calculated on the anhydrous basis. pH of a 2.5% solution in water is between 6.0 and 8.0.

Erythromycin Lactobionate *(BANM, rINNM)*

Eritromicina, lactobionato de; Eritromicin-laktobionát; Eritromicino laktobionatas; Érythromycine, Lactobionate d'; Erythromycini Lactobionas; Erythromycinlactobionat; Erythromycin-laktobionát; Erytromycinlaktobionat; Erytromycyny laktobionian; Erytromysiinilaktov; Éthyleneglycol, monostéarate d', Lactobionato de eritromicina; Эритромицина лактобионат.

Erythromycin mono(4-O-β-D-galactopyranosyl-D-gluconate).

$C_{37}H_{67}NO_{13}C_{12}H_{22}O_{12}$=1092.2

CAS — 3847-29-8.

ATC — D10AF02; J01FA01; S01AA17.

ATC Vet — QD10AF02; QJ01FA01; QS01AA17.

UNII — 33H58I7GLQ.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Erythromycin Lactobionate). Salt of a product obtained by fermentation using a strain of *Streptomyces erythreus*. White or slightly yellow, hygroscopic powder. Soluble in water; freely soluble in dehydrated alcohol and in methyl alcohol; very slightly soluble in acetone and in dichloromethane. A 2% solution in water has a pH of 6.5 to 7.5. Store in airtight containers.

USP 36: (Sterile Erythromycin Lactobionate). It has a potency equivalent to not less than 525 micrograms of erythromycin per mg, calculated on the anhydrous basis. pH of a solution in water containing the equivalent of erythromycin 5% is between 6.5 and 7.5.

Erythromycin Propionate *(BANM, USAN, rINNM)*

Eritromicina, propionato de; Erythromycin Propanoate; Érythromycine, Propionate d'; Erythromycini Propionas; Propionato de eritromicina; Propionylerythromycin; Эритромицина пропионат.

Erythromycin 2′-propionate.

$C_{40}H_{71}NO_{14}$=790.0

CAS — 134-36-1.

ATC — D10AF02; J01FA01; S01AA17.

ATC Vet — QD10AF02; QJ01FA01; QS01AA17.

UNII — HB75CIT999.

Pharmacopoeias. In *Fr*.

Erythromycin Stearate *(BANM, rINNM)*

Eritromicina, estearato de; Eritromicino stearatas; Eritromicin-sztearát; Eritromisin Stearat; Érythromycine, Stéarate d'; Erythromycini Stearas; Erythromycinstearat; Erythromycin-stearát; Erytromycinstearat; Erytromycyny stearynian; Erytromysiinistearaatti; Estearato de eritromicina; Эритромицина стеарат.

Erythromycin octadecanoate.

$C_{37}H_{67}NO_{13}C_{18}H_{36}O_2$=1018.4

CAS — 643-22-1.

ATC — D10AF02; J01FA01; S01AA17.

ATC Vet — QD10AF02; QJ01FA01; QS01AA17.

UNII — LXW024X05M.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet*.

Ph. Eur. 8: (Erythromycin Stearate). A mixture of the stearates of erythromycin and stearic acid. A white or almost white crystalline powder. Practically insoluble in water;

soluble in acetone and in methyl alcohol. Solutions may be opalescent.

USP 36: (Erythromycin Stearate). The stearic acid salt of erythromycin with an excess of stearic acid. White or slightly yellow crystals or powder, odourless or may have a slight, earthy odour. Practically insoluble in water; soluble in alcohol, in chloroform, in ether, and in methyl alcohol. Store in airtight containers.

Incompatibility and stability. The stability of erythromycin derivatives is dependent upon pH, with particularly rapid degradation occurring at a pH greater than 10 or less than 5.5. Incompatibility might reasonably be expected, therefore, when erythromycin preparations are mixed with drugs or preparations that have a highly acidic or alkaline pH. In practice, reports of incompatibility are not always consistent, and other factors such as the temperature and concentration of solutions, and the diluents used, may play a role.

Solutions for infusion. For the preparation of solutions of erythromycin lactobionate for infusion, a primary solution containing not more than 5% of erythromycin should be prepared first; only water for injection should be used in preparing the primary solution. It should be further diluted with sodium chloride 0.9% or other suitable intravenous fluid before use. Acidic solutions, such as glucose, should only be used if neutralised with sodium bicarbonate.

Uses and Administration

Erythromycin is a macrolide antibacterial with a wide spectrum of activity, that is used in the treatment of infections caused by susceptible organisms.

Its uses have included the treatment of severe campylobacter enteritis, chancroid, diphtheria, legionnaires' disease and other *Legionella* infections, neonatal conjunctivitis, pertussis, respiratory-tract infections including bronchitis, pneumonia (mycoplasmal and other atypical pneumonias as well as streptococcal), and sinusitis, and trench fever, and, combined with neomycin, for the prophylaxis of surgical infection in patients undergoing bowel surgery. It may be used as part of a multidrug regimen for the treatment of inhalation and gastrointestinal anthrax. It is also used in the prevention of diphtheria in non-immune patients and of pertussis in non- or partially immune patients.

Erythromycin is used as an alternative to penicillin in penicillin-allergic patients with various conditions including actinomycosis, leptospirosis, listeriosis, mouth infections, otitis media (usually with a sulfonamide such as sulfafurazole), pelvic inflammatory disease caused by *Neisseria gonorrhoeae*, pharyngitis, and staphylococcal and streptococcal skin infections. It has been used in the treatment of penicillin-allergic patients with syphilis, but there are doubts about its efficacy. It is also used in the prevention of perinatal or Group A streptococcal infections, rheumatic fever, and infections in splenectomised patients. In penicillin-allergic patients in the early stages of Lyme disease, erythromycin may be used as an alternative to a tetracycline; this use is generally restricted to pregnant women and young children, since it is less effective than other drugs. It is also used as an alternative to the tetracyclines in patients with cholera, *Chlamydia* or *Chlamydophila* infections (such as epididymitis, lymphogranuloma venereum, nongonococcal urethritis, pneumonia, psittacosis, and trachoma), Q fever, and spotted fevers.

For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Both oral and topical erythromycin may be used in acne (see Skin Disorders, p. 295.1) and rosacea (p. 1688.3).

Erythromycin may be given as the base or its salts or esters; doses are expressed in terms of the base. Each 1 g of erythromycin is equivalent to about the following amounts of each salt or ester:

- erythromycin estolate 1.44 g
- erythromycin ethyl succinate 1.17 g
- erythromycin gluceptate 1.31 g
- erythromycin lactobionate 1.49 g
- erythromycin propionate 1.08 g
- erythromycin stearate 1.39 g

The usual oral adult dose is the equivalent of erythromycin 1 to 2 g daily in 2 to 4 divided doses; for severe infections this may be increased to up to 4 g daily in divided doses. Daily doses higher than 1 g should be given in more than 2 divided doses.

For the prevention of streptococcal infections in patients with evidence of rheumatic fever or heart disease, who are unable to take penicillin or sulfonamides, a dose of 250 mg twice daily may be given.

For the management of acne, maintenance doses as low as 250 mg daily have been used but resistant strains of propionibacteria are widespread; the *BNF* recommends a dose of 500 mg twice daily.

In patients who are unable to take erythromycin orally and in those who are severely ill, in whom it is necessary to attain an immediate high blood concentration, erythromycin may be given intravenously as the lactobionate, in doses equivalent to those given orally. The gluceptate has also been used intravenously. To reduce the risk of venous irritation it should be given only by continuous or intermittent intravenous infusion of a solution containing not more than 0.5% of erythromycin. Intermittent infusions should be given every 6 hours over 20 to 60 minutes.

Doses may need to be limited in patients with renal impairment (see p. 294.3).

For details of doses in children, see p. 294.2.

Erythromycin was formerly given by intramuscular injection, but such injections are painful and are no longer generally recommended. Erythromycin is used as a 0.5% eye ointment for the treatment of superficial ocular infections, including neonatal conjunctivitis, caused by susceptible strains of bacteria and for the prophylaxis of neonatal conjunctivitis caused by *N. gonorrhoeae* or *C. trachomatis*. It may also be applied topically as a 2 to 4% gel or solution for the treatment of acne vulgaris and is also available in combination preparations with benzoyl peroxide, ichthammol, isotretinoin, tretinoin, and zinc acetate.

Erythromycin acistrate, erythromycin cyclocarbonate, and propionyl erythromycin mercaptosuccinate have also been used. Erythromycin thiocyanate and erythromycin phosphate are used in veterinary medicine.

Reviews.

1. Zhanel GG, *et al.* Review of macrolides and ketolides: focus on respiratory tract infections. *Drugs* 2001; 61: 443–98.

Administration. A discussion of the significance of different formulations and salts used for oral preparations of erythromycin concluded that there was no clear evidence that any was superior in terms of clinical effect.[1]

1. Anonymous. Giving erythromycin by mouth. *Drug Ther Bull* 1995; 33: 77–9.

Administration in children. Erythromycin may be given orally or by continuous or intermittent intravenous infusion for the treatment of **infections** caused by susceptible organisms. The usual dose for infants and children is the equivalent of about 30 to 50 mg/kg of erythromycin daily in 2 to 4 divided doses although it may be doubled in severe infections. Based on age, the usual dose in children 2 to 8 years old is 1 g daily and in infants and children up to 2 years old 500 mg daily. Those over 8 years of age may be given the usual adult dose (see Uses and Administration, above).

The following doses have been suggested for use in neonates:

- In the UK, the *BNFC* suggests an oral dose of 12.5 mg/kg, or an intravenous dose of 10 to 12.5 mg/kg, every 6 hours
- In the USA, the American Academy of Pediatrics[1] suggests that neonates of 1 week of age or less may be given 10 mg/kg orally or intravenously every 12 hours. All neonates more than 1 week of age may be given the same dose every 8 hours; a dosing interval of 12 hours may be used until 2 weeks of life in extremely low birthweight neonates (weighing less than 1 kg)

For the **prevention of recurrence of rheumatic fever** the *BNFC* suggests that erythromycin may be given orally in penicillin allergic children in the following doses:

- children 1 month to 2 years of age: 125 mg twice daily
- children from 2 years of age: 250 mg twice daily

For the **prevention of secondary cases of group A streptococcal infection** the *BNFC* suggests that erythromycin may be given orally for 10 days in penicillin allergic children in the following doses:

- children 1 month to 2 years of age: 125 mg every 6 hours
- children 2 to 8 years of age: 250 mg every 6 hours
- children from 8 years of age: 250 to 500 mg every 6 hours

For the **prevention of secondary cases of diphtheria** in non-immune patients the *BNFC* suggests that erythromycin may be given orally for 7 days:

- children 1 month to 2 years of age: 125 mg every 6 hours
- children 2 to 8 years of age: 250 mg every 6 hours
- children from 8 years of age: 500 mg every 6 hours

If nasopharyngeal swabs for *Corynebacterium diphtheriae* are positive after the first 7 days, treatment should be continued for a further 10 days.

For the management of **acne**, oral maintenance doses as low as 250 mg daily have been used but resistant strains of propionibacteria are widespread; the *BNFC* recommends a dose of 500 mg twice daily in those over 12 years of age. It also suggests a dose of 250 mg daily in 1 or 2 divided doses for infants with acne.

Although unlicensed in the UK for use in **gastrointestinal stasis**, the *BNFC* suggests a dose of 3 mg/kg given orally or by intravenous infusion, 4 times daily for neonates and children up to 18 years of age (see also p. 294.3).

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Administration in renal impairment. A maximum dose of erythromycin 1.5 g daily has been suggested by the *BNF* for adult patients with severe renal impairment.

Decreased gastrointestinal motility. Erythromycin stimulates gut motility, apparently by acting as a motilin receptor agonist, although it has been suggested that it may have other actions as well.[1] It has been tried, with some success, for its prokinetic action in a small number of patients with decreased gastrointestinal motility (p. 1808.2) including those with functional dyspepsia,[2] gastroparesis,[3] reflux ileus,[4] acute colonic pseudo-obstruction (Ogilvie's syndrome),[4,5] delayed gastric emptying after pancreatic-duodenal surgery,[6] and neonatal postoperative intestinal dysmotility.[7] It has also been used to increase gastrointestinal motility in critically ill, mechanically ventilated patients[8,9] and in preterm very low birth-weight infants.[10,11] However, the prophylactic or routine use of erythromycin in such circumstances has been cautioned against,[9,10] and a systematic review[12] of neonatal use also suggested that erythromycin should be reserved for a very small subset of high-risk preterm neonates with persistent or severe feed intolerance. Although another systematic review[13] reported more positive effects on feeding tolerance when erythromycin was given at higher doses (40 to 50 mg/kg daily) or to infants more than 32 weeks of gestational age, it concluded that there was insufficient evidence to recommend the use of erythromycin (at low or high doses) for preterm infants with or at risk of feeding intolerance. Adverse effects associated with the long-term use of erythromycin that is necessary in, for example, diabetic gastroparesis, may also be problematic.[14]

For suggested doses in the treatment of children with gastrointestinal stasis, see Administration in Children, above.

1. Catnach SM, Fairclough PD. Erythromycin and the gut. *Gut* 1992; 33: 397–401.
2. Arts J, *et al.* Influence of erythromycin on gastric emptying and meal related symptoms in functional dyspepsia with delayed gastric emptying. *Gut* 2005; 54: 455–60.
3. Maganti K, *et al.* Oral erythromycin and symptomatic relief of gastroparesis: a systematic review. *Am J Gastroenterol* 2003; 98: 259–63.
4. Armstrong DN, *et al.* Erythromycin for reflux ileus in Ogilvie's syndrome. *Lancet* 1991; 337: 378.
5. Bonacioli M, *et al.* Erythromycin as therapy for acute colonic pseudo-obstruction (Ogilvie's syndrome). *J Clin Gastroenterol* 1991; 13: 475–6.
6. Yeo CJ, *et al.* Erythromycin accelerates gastric emptying after pancreaticoduodenectomy: a prospective, randomized, placebo-controlled trial. *Ann Surg* 1993; 218: 229–38.
7. Simkiss DE, *et al.* Erythromycin in neonatal postoperative intestinal dysmotility. *Arch Dis Child* 1994; 71: F128–9.
8. Chapman MJ, *et al.* Erythromycin improves gastric emptying in critically ill patients intolerant of nasogastric feeding. *Crit Care Med* 2000; 28: 2334–7.
9. Hawkyard CV, Koerner RJ. The use of erythromycin as a gastrointestinal prokinetic agent in adult critical care: benefits versus risks. *J Antimicrob Chemother* 2007; 59: 347–58.
10. Ng PC, *et al.* Randomised controlled study of oral erythromycin for treatment of gastrointestinal dysmotility in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2001; 84: F177–F182.
11. Nuntnarumit P, *et al.* Efficacy of oral erythromycin for treatment of feeding intolerance in preterm infants. *J Pediatr* 2006; 148: 600–605.
12. Patole S, *et al.* Erythromycin as a prokinetic agent in preterm neonates: a systematic review. *Arch Dis Child Fetal Neonatal Ed* 2005; 90: F301–F306.
13. Ng E, Shah VS. Erythromycin for the prevention and treatment of feeding intolerance in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 14/07/09).
14. Tanis AA, *et al.* Side-effects of oral erythromycin for treatment of diabetic gastroparesis. *Lancet* 1993; 342: 1431.

Respiratory disorders. As well as their established antibacterial effect, it has been suggested that the 14-membered ring macrolides (such as clarithromycin, erythromycin, and roxithromycin) and the 15-membered ring macrolides (such as azithromycin) also have immunomodulatory and anti-inflammatory effects that could be useful in the management of respiratory diseases including asthma (p. 1195.2), bronchiectasis, chronic obstructive pulmonary disease (p. 1199.1), cystic fibrosis (p. 177.2), desquamative interstitial pneumonia, diffuse panbronchiolitis, and sinusitis (p. 206.2).[1-6] However, a systematic review[7] found insufficient evidence to support or refute the use of macrolides in chronic asthma although some clinical data indicated a positive effect; routine use was not recommended and further studies were warranted. A systematic review[8] on the use of macrolides in cystic fibrosis found evidence of a small but significant improvement in respiratory function at 6 months with azithromycin compared with placebo; the role of other macrolides was unclear and further studies were needed. A randomised, double-blind, placebo-controlled study[9] to evaluate the use of oral azithromycin given three times a week for 12 months for the treatment of cystic fibrosis in children, reported a significant reduction in the number of pulmonary exacerbations needing treatment with antibacterials,

even in the absence of infection with *Pseudomonas aeruginosa*. In another study, in patients with chronic obstructive pulmonary disease, oral azithromycin 250 mg taken daily for 12 months, in addition to their usual treatment, decreased the frequency of exacerbations and improved quality of life;[10] a reduction in hearing was noted in a small percentage of patients. Azithromycin has also been investigated[11-13] in the management of bronchiolitis obliterans in patients who have undergone lung transplantation (p. 1941.3), although its role has yet to be defined.

1. Gotfried MH. Macrolides for the treatment of chronic sinusitis, asthma, and COPD. *Chest* 2004; 125 (suppl 2): 52S–61S.
2. Rubin BK, Henke MO. Immunomodulatory activity and effectiveness of macrolides in chronic airway disease. *Chest* 2004; 125 (suppl 2): 70S–78S.
3. Schultz MJ. Macrolide activities beyond their antimicrobial effects: macrolides in diffuse panbronchiolitis and cystic fibrosis. *J Antimicrob Chemother* 2004; 54: 21–8.
4. King P. Is there a role for inhaled corticosteroids and macrolide therapy in bronchiectasis? *Drugs* 2007; 67: 965–74.
5. Knyazhitskiy A, *et al.* Beneficial response to macrolide antibiotic in a patient with desquamative interstitial pneumonia refractory to corticosteroid therapy. *Chest* 2008; 134: 185–7.
6. Giamarellos-Bourboulis EJ. Macrolides beyond the conventional antimicrobials: a class of potent immunomodulators. *Int J Antimicrob Agents* 2008; 31: 12–20.
7. Richeldi L, *et al.* Macrolides for chronic asthma. Available in the Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 02/03/07).
8. Southern KW, *et al.* Macrolide antibiotics for cystic fibrosis. Available in the Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 02/03/07).
9. Clement A, *et al.* Long term effects of azithromycin in patients with cystic fibrosis: a double blind, placebo controlled trial. *Thorax* 2006; 61: 895–902.
10. Albert RK, *et al.* Azithromycin for prevention of exacerbations of COPD. *N Engl J Med* 2011; 365: 689–98.
11. Gottlieb J, *et al.* Long-term azithromycin for bronchiolitis obliterans syndrome after lung transplantation. *Transplantation* 2008; 85: 36–41.
12. Porhownik NR, *et al.* Effect of maintenance azithromycin on established bronchiolitis obliterans syndrome in lung transplant patients. *Can Respir J* 2008; 15: 199–202.
13. Fietta AM, Meloni F. Lung transplantation: the role of azithromycin in the management of patients with bronchiolitis obliterans syndrome. *Curr Med Chem* 2008; 15: 716–23.

Skin disorders. *ACNE.* Erythromycin may be used topically or orally in the treatment of acne (p. 1682.2). Topical erythromycin may be used for mild inflammatory acne if benzoyl peroxide is ineffective or poorly tolerated. It is also used as adjunctive treatment in more severe acne. Erythromycin is also available as a complex with zinc acetate that has been reported to be more effective than topical erythromycin alone[1] or oral minocycline.[2] However, development of resistance by the skin flora is an increasing problem. Combination therapy with benzoyl peroxide and erythromycin has been reported to be helpful in preventing the selection of resistant mutants[3,4] and to be more effective than topical clindamycin alone.[5] Combination with azelaic acid has also been tried.[6] Alternatively, short intervening courses of benzoyl peroxide during antibacterial therapy may help to eliminate any resistant bacteria that have been selected.[7] It has also been recommended that courses of topical antibacterials be continued for no longer than necessary (although treatment should be used for at least 6 months), that the same drug be used if further treatment is required, and that treatment with different oral and topical antibacterials or antibacterial rotation be avoided.[7]

Oral erythromycin has been used as an alternative to a tetracycline in moderate acne. However, resistance to erythromycin is becoming widespread among propionibacteria, and response may be poor, although it may perhaps be an option for those patients in whom other antibacterials are unsuitable.

1. Habbema L, *et al.* A 4% erythromycin and zinc combination (Zineryt) versus 2% erythromycin (Eryderm) in acne vulgaris: a randomized, double-blind comparative study. *Br J Dermatol* 1989; 121: 497–502.
2. Stainforth J, *et al.* A single-blind comparison of topical erythromycin/zinc lotion and oral minocycline in the treatment of acne vulgaris. *J Dermatol Treat* 1993; 4: 119–22.
3. Eady EA, *et al.* Effects of benzoyl peroxide and erythromycin alone and in combination against antibiotic-sensitive and -resistant skin bacteria from acne patients. *Br J Dermatol* 1994; 131: 331–6.
4. Eady EA, *et al.* The effects of acne treatment with a combination of benzoyl peroxide and erythromycin on skin carriage of erythromycin-resistant propionibacteria. *Br J Dermatol* 1996; 134: 107–13.
5. Packman AM, *et al.* Treatment of acne vulgaris: combination of 3% erythromycin and 5% benzoyl peroxide in a gel compared to clindamycin phosphate lotion. *Int J Dermatol* 1996; 35: 209–11.
6. Pazoki-Toroudi H, *et al.* Combination of azelaic acid 5% and erythromycin 2% in the treatment of acne vulgaris. *J Dermatolog Treat* 2010; 21: 212–16.
7. Eady EA, *et al.* Antibiotic resistant propionibacteria in acne: need for policies to modify antibiotic usage. *BMJ* 1993; 306: 555–6.

Adverse Effects

Erythromycin and its salts and esters are generally well tolerated and serious adverse effects are rare. Gastrointestinal disturbances such as abdominal discomfort and cramp, nausea, vomiting, and diarrhoea are fairly common after both oral and parenteral use, probably because of the stimulant activity of erythromycin on the gut. Gastrointestinal effects are dose related and appear to be more common in young than in older patients. Superinfection with resistant organisms may occur and pseudomembranous colitis has been reported.

Hypersensitivity reactions appear to be uncommon, having been reported in about 0.5% of patients, and include pruritus, urticaria, and skin rash as well as occasional cases of anaphylaxis. Stevens-Johnson syndrome and toxic epidermal necrolysis have also been reported very rarely. Hypersensitivity or irritation may occur after topical application of erythromycin.

A hypersensitivity reaction is thought to be responsible for the hepatotoxicity sometimes reported in patients receiving erythromycin or its derivatives but this has been disputed by some. Most reports of cholestatic hepatitis have been in patients receiving the estolate, and it has been suggested that the propionyl ester linkage is particularly associated with hepatotoxicity, but symptoms have also been reported in patients given the base and most of the other derivatives, both orally and parenterally. Symptoms indicative of cholestasis, including upper abdominal pain (sometimes very severe), nausea and vomiting, abnormal liver function values, raised serum bilirubin, and usually jaundice, may be accompanied by rash, fever, and eosinophilia. Symptoms usually occur in patients who have been taking the drug for more than 10 days, although they may develop more quickly in patients given the drug previously. Hepatic dysfunction seems to be rare in children under 12 years of age. The effects of erythromycin on the liver are generally reversible on stopping treatment. Erythromycin may interfere with tests for serum aspartate aminotransferase, which might make diagnosis of hepatotoxicity more difficult.

A generally reversible sensorineural deafness, sometimes with tinnitus, has been reported in patients given erythromycin and appears to be related to serum concentration, with an increased likelihood of such effects in patients given doses of 4 g or more daily of base or its equivalent, in those given intravenous therapy, and in those with renal or hepatic impairment.

Other adverse effects that have been reported in patients given erythromycin include agranulocytosis, aggravation of muscular weakness in myasthenia gravis patients, and pancreatitis. Prolongation of the QT interval and other arrhythmias, sometimes fatal, including torsade de pointes have been reported particularly with intravenous use. There have also been isolated reports of transient CNS adverse effects including confusion, hallucinations, seizures, and vertigo.

Parenteral formulations of erythromycin are irritant and intravenous dosage may produce thrombophlebitis, particularly at high doses. Intramuscular injection is generally avoided as it may produce severe pain.

General reviews.

1. Periti P, *et al.* Adverse effects of macrolide antibacterials. *Drug Safety* 1993; 9: 346–64.
2. Principi N, Esposito S. Comparative tolerability of erythromycin and newer macrolide antibacterials in paediatric patients. *Drug Safety* 1999; 20: 25–41.
3. Rubinstein E. Comparative safety of the different macrolides. *Int J Antimicrob Agents* 2001; 18 (suppl 1): S71–S76.

Effects on body temperature. A report of hypothermia associated with oral erythromycin in 2 children.[1] Symptoms resolved on stopping the drug. The children were cousins, perhaps indicating a genetic predisposition to the effect. There has also been a similar report of hypothermia in 3 children given azithromycin orally.[2]

1. Hassel B. Hypothermia from erythromycin. *Ann Intern Med* 1991; 115: 69–70.
2. Kavukçu S, *et al.* Hypothermia from azithromycin. *J Toxicol Clin Toxicol* 1997; 35: 225 6.

Effects on the cardiovascular system. There have been several reports[1-6] of QT prolongation or torsade de pointes associated with erythromycin, particularly with intravenous use.

A review[7] of reports of torsade de pointes received by the FDA Adverse Event Reporting System between 1987 and December 2000 identified 156 cases associated with use of azithromycin, clarithromycin, dirithromycin, or erythromycin. Of these reports, half involved the use of other drugs known to prolong the QT interval; comorbid diseases and physiological abnormalities, including cardiac abnormalities, were also commonly reported. A retrospective analysis[8] of a cohort of patients who suffered sudden death from cardiac causes found that the rate of sudden cardiac death was twice as high among current users of erythromycin as in those not using antibacterials; there was no such increase among former users, nor among current users of amoxicillin. The greatest increase in risk was seen in patients using erythromycin with inhibitors of the cytochrome P450 isoenzyme subfamily CYP3A; such patients had more than 5 times the risk of sudden cardiac death of patients who took neither. Findings from an observational population-based case-control study[9] in patients who had had ventricular arrhythmia or cardiac arrest supported the association between recent use of macrolides and increased risk of these events. Another observational study[10] of data from a US cohort reported that treatment with oral azithromycin for 5 days was associated with a small absolute increase in deaths from cardiovascular causes; this was most pronounced among patients with a high baseline risk of cardiovascular disease. The risk of death was significantly greater with azithromycin than with amoxicillin or ciprofloxacin but did not differ significantly from the risk with levofloxacin.

1. McComb JM, *et al.* Recurrent ventricular tachycardia associated with QT prolongation after mitral valve replacement and its association with intravenous administration of erythromycin. *Am J Cardiol* 1984; 54: 922–3.
2. Schoenenberger RA, *et al.* Association of intravenous erythromycin and potentially fatal ventricular tachycardia with Q-T prolongation (torsades de pointes). *BMJ* 1990; 330: 1375–6.
3. Nattel S, *et al.* Erythromycin-induced long QT syndrome: concordance with quinidine and underlying cellular electrophysiologic mechanism. *Am J Med* 1990; 89: 235–8.
4. Gitler B, *et al.* Torsades de pointes induced by erythromycin. *Chest* 1994; 105: 368–72.
5. Gouyon JB, *et al.* Cardiac toxicity of intravenous erythromycin lactobionate in preterm infants. *Pediatr Infect Dis J* 1994; 13: 840–1.
6. Drici M-D, *et al.* Cardiac actions of erythromycin: influence of female sex. *JAMA* 1998; 280: 1774–6.
7. Shaffer D, *et al.* Concomitant risk factors in reports of torsades de pointes associated with macrolide use: review of the United States Food and Drug Administration Adverse Event Reporting System. *Clin Infect Dis* 2002; 35: 197–200.
8. Ray WA, *et al.* Oral erythromycin and the risk of sudden death from cardiac causes. *N Engl J Med* 2004; 351: 1089–96.
9. Zambon A, *et al.* Effect of macrolide and fluoroquinolone antibacterials on the risk of ventricular arrhythmia and cardiac arrest: an observational study in Italy using case-control, case-crossover and case-time-control designs. *Drug Safety* 2009; 32: 159–67.
10. Ray WA, *et al.* Azithromycin and the risk of cardiovascular death. *N Engl J Med* 2012; 366: 1881–90.

Effects on the gastrointestinal tract. Comparison in patients with upper respiratory-tract infections has suggested that erythromycin ethyl succinate may be associated with less **abdominal pain** than an equivalent dosage of erythromycin base.[1] Another study has indicated that there was no significant difference in gastrointestinal symptoms between plain and enteric-coated formulations of erythromycin base.[2] Severe **nausea and vomiting** after rapid intravenous infusion of erythromycin lactobionate stopped in 2 patients who transferred to oral erythromycin base or ethyl succinate.[3] However, the adverse effects may have been due to the rate of infusion, since in 2 further patients symptoms resolved when the lactobionate was given more slowly as a more dilute solution.[3]

Studies have suggested an association between erythromycin and infantile **hypertrophic pyloric stenosis.**[4-6] A retrospective cohort study of 469 infants who had received erythromycin found that 43 were diagnosed with the condition including 36 male infants, although erythromycin had been prescribed almost equally for males and females.[5] All the infants in whom stenosis developed were given erythromycin in the first 2 weeks of life. In another study,[4] involving 7138 infants given erythromycin between 3 and 90 days of life, use of the drug between 3 and 13 days of life was associated with an almost eightfold increased risk of infantile hypertrophic pyloric stenosis. However, it was believed that the evidence did not support a generalisation of this association to the whole class of macrolides[7] although pyloric stenosis has been reported in breast-fed infants associated with the use of erythromycin or several other macrolides in their mothers (see under Precautions, p. 296.1). Hypertrophic pyloric stenosis has also been reported in 2 of 3 premature triplets treated with azithromycin.[8]

A case of black **hairy tongue** has been reported[9] associated with long-term erythromycin treatment.

For reference to the stimulant effects of erythromycin on the gastrointestinal tract, see Decreased Gastrointestinal Motility under Uses and Administration, p. 292.3.

1. Saloranta P, *et al.* Erythromycin ethylsuccinate, base and acistrate in the treatment of upper respiratory tract infection: two comparative studies of tolerability. *J Antimicrob Chemother* 1989; 24: 455–62.
2. Ellsworth AJ, *et al.* Prospective comparison of patient tolerance to enteric-coated vs non-enteric-coated erythromycin. *J Fam Pract* 1990; 31: 265–70.
3. Seifert CF, *et al.* Intravenous erythromycin lactobionate-induced severe nausea and vomiting. *DICP Ann Pharmacother* 1989; 23: 40–4.
4. Honein MA, *et al.* Infantile hypertrophic pyloric stenosis after pertussis prophylaxis with erythromycin: a case review and cohort study. *Lancet* 1999; 354: 2101–5. Correction. *Ibid.* 2000; 355: 758.
5. Mahon BE, *et al.* Maternal and infant use of erythromycin and other macrolide antibiotics as risk factors for infantile hypertrophic pyloric stenosis. *J Pediatr* 2001; 139: 380–4.
6. Cooper WO, *et al.* Very early exposure to erythromycin and infantile hypertrophic pyloric stenosis. *Arch Pediatr Adolesc Med* 2002; 156: 647–50.
7. Hauben M, Amsden GW. The association of erythromycin and infantile hypertrophic pyloric stenosis: causal or coincidental? *Drug Safety* 2002; 25: 929–42.
8. Morrison W. Infantile hypertrophic pyloric stenosis in infants treated with azithromycin. *Pediatr Infect Dis J* 2007; 26: 186–8.
9. Pigatto PD, *et al.* Black hairy tongue associated with long-term oral erythromycin use. *J Eur Acad Dermatol Venereol* 2008; 22: 1269–70.

Effects on the neonate. For a suggestion that erythromycin or other macrolides might be associated with an increased risk of infantile hypertrophic pyloric stenosis in

neonates, see under Effects on the Gastrointestinal Tract, p. 293.3.

Effects on the skin. Skin reactions ranging from mild eruptions to erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have rarely been reported with macrolides.[1,2]

1. Lesjco MR, Smith AD. Stevens-Johnson syndrome following erythromycin administration. *Am J Health-Syst Pharm* 1995; 52: 1805–7.
2. Sullivan S, *et al.* Stevens-Johnson syndrome secondary to erythromycin. *Ann Pharmacother* 1999; 33: 1369.

Overdosage. Acute pancreatitis was reported in a 12-year-old girl after ingestion of about 5 g of erythromycin base.[1] Transient pancreatitis has also been reported in another 15-year-old girl who took 5.328 g of erythromycin base.[2] Erythromycin produces contraction of the sphincter of Oddi resulting in reflux of bile into the pancreas but the resulting pancreatitis is self-limited and remits when sphincter tone returns to normal after the erythromycin is eliminated from the body.

1. Berger TM, *et al.* Acute pancreatitis in a 12-year-old girl after an erythromycin overdose. *Pediatrics* 1992; 90: 624–6.
2. Tenenbein MS. Tenenbein M. Acute pancreatitis due to erythromycin overdose. *Pediatr Emerg Care* 2005; 21: 675–6.

Precautions

Erythromycin and its derivatives should be avoided in those known to be hypersensitive to it, or in those who have previously developed jaundice. All forms of erythromycin should be used with care in patients with existing liver disease or hepatic impairment, and the estolate is best avoided in such patients; liver function should be monitored. Repeated courses of the estolate or use for longer than 10 days increases the risk of hepatotoxicity.

The lactobionate should be used with caution in patients with severe renal impairment; dosage reduction may be necessary particularly in those who develop toxicity. A reduced dose of the estolate has also been recommended in severe renal impairment.

Erythromycin may aggravate muscle weakness in patients with myasthenia gravis.

Erythromycin should be used with care in patients with a history of arrhythmias or a predisposition to QT interval prolongation. Certain medications may also increase the risk of arrhythmias (see Interactions, p. 296.2).

Erythromycin may interfere with some diagnostic tests including measurements of urinary catecholamines and 17-hydroxycorticosteroids. It has also been associated with falsely-elevated serum aspartate aminotransferase values when measured colorimetrically, although genuine elevations of this enzyme, due to hepatotoxicity, also occur, particularly with the estolate.

Erythromycin is irritant; solutions for parenteral use should be suitably diluted and given by intravenous infusion over 20 to 60 minutes to reduce the incidence of thrombophlebitis. Rapid infusion is also more likely to be associated with arrhythmias or hypotension.

Breast feeding. There has been a report[1] of a breast-fed infant who developed pyloric stenosis thought to be associated with use of erythromycin by the mother. However, the American Academy of Pediatrics[2] states that, although erythromycin is concentrated in human breast milk, no adverse effects have been seen in breast-fed infants whose mothers were receiving erythromycin and it is therefore usually compatible with breast feeding. A large Danish population-based cohort study[3] later concluded that the use of macrolides (azithromycin, clarithromycin, erythromycin, roxithromycin, or spiramycin) during breast feeding increased the risk of infantile hypertrophic pyloric stenosis. (See also Effects on the Gastrointestinal Tract, p. 293.3.) A milk-to-plasma ratio of 0.5 has been reported for erythromycin.[4]

1. Stang H. Pyloric stenosis associated with erythromycin ingested through breastmilk. *Mimn Med* 1986; 69: 669–70, 682.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/04/07)
3. Sørensen HT, *et al.* Risk of infantile hypertrophic pyloric stenosis after maternal postnatal use of macrolides. *Scand J Infect Dis* 2003; 35: 104–106.
4. *et al. Drugs in pregnancy and lactation.* 8th ed. Philadelphia, USA: Lippincott Williams and Wilkins, 2008.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies erythromycin as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Pregnancy. Of 298 pregnant women who took erythromycin estolate, clindamycin, or placebo for 3 weeks or longer, about 14, 4, and 3% respectively had abnormally high serum aspartate aminotransferase values.[1] Erythromycin estolate should probably not be given to pregnant women.

A study[2] of data from the Swedish Medical Birth Registry of infants born between July 1995 and December 2002 examined details of infants exposed to erythromycin or phenoxymethylpenicillin during early pregnancy. Of 1844 exposed to erythromycin, 103 (5.6%) had congenital malformations compared with 420 of 9110 (4.7%) for phenoxymethylpenicillin. Of these, 34 (1.8%) and 86 (0.9%) respectively had a cardiovascular malformation, the rate being considered high for erythromycin. This contrasted with a previous study based on a 1980–96 dataset of the Hungarian Case-Control Surveillance of Congenital Abnormalities which found no signs of teratogenicity for erythromycin.[3] Although an increased risk for cardiovascular abnormalities was initially apparent when analysing erythromycin usage throughout pregnancy as reported by the mother, this was not confirmed when assessing usage only in the second or third month nor in the entire pregnancy for medically documented intake. The Swedish data also revealed a possible association between infant pyloric stenosis and early prenatal exposure to erythromycin[2] although others had previously failed to confirm such a risk[4] (see also Effects on the Gastrointestinal Tract, p. 293.3).

For information on the use of antibacterials, including erythromycin, as adjuncts in the management of premature labour, see p. 201.3.

1. McCormack WM, *et al.* Hepatotoxicity of erythromycin estolate during pregnancy. *Antimicrob Agents Chemother* 1977; 12: 630–5.
2. Källén BAJ, *et al.* Is erythromycin therapy teratogenic in humans? *Reprod Toxicol* 2005; 20: 209–14.
3. Czeizel AE, *et al.* A population-based case-control teratologic study of oral erythromycin treatment during pregnancy. *Reprod Toxicol* 1999; 13: 531–6.
4. Hussain N, Herson VC. Erythromycin use during pregnancy in relation to pyloric stenosis. *Am J Obstet Gynecol* 2002; 187: 821–2.

Interactions

Erythromycin and other macrolides have the potential to interact with many drugs through their action on hepatic cytochrome P450 isoenzymes, particularly CYP1A2 and CYP3A4. Macrolides competitively inhibit drug metabolism by these microsomal cytochromes, and also form inactive complexes with them. Enzyme inhibition is reported to be particularly pronounced with macrolides such as erythromycin and troleandomycin. Other macrolides such as azithromycin and dirithromycin are reported to have little or no effect on hepatic cytochromes, and consequently may produce fewer interactions (see also Mechanism, p. 296.2).

Macrolide-induced inhibition of metabolism can result in severe adverse effects, including ventricular arrhythmias with astemizole, cisapride, and terfenadine. Macrolides themselves have been reported rarely to prolong the QT interval and should in any case be used with caution with other drugs known to also have this effect.

Other mechanisms by which macrolides cause interactions include suppression of the gastrointestinal flora responsible for the intraluminal metabolism of digoxin and possibly oral contraceptives, and the stimulant effect of macrolides on gastrointestinal motility which is believed to be responsible for the interaction between spiramycin and levodopa. An alternative mechanism by which macrolides increase serum concentrations of digoxin is thought to be via the inhibition of intestinal or renal P-glycoprotein transport of digoxin.

Few drugs are reported to affect erythromycin but cimetidine may increase and theophylline may decrease erythromycin concentrations (see p. 296.3).

The effect on antimicrobial action when erythromycin is given with other antimicrobials is discussed under Antimicrobial Action, p. 297.1.

General references[1-4] to interactions associated with macrolide antibacterials.

1. von Rosenstiel N-A, Adam D. Macrolide antibacterials: drug interactions of clinical significance. *Drug Safety* 1995; 13: 105–22.
2. Westphal JF. Macrolide-induced clinically relevant drug interactions with cytochrome P-450A (CYP) 3A4: an update focused on clarithromycin, azithromycin and dirithromycin. *Br J Clin Pharmacol* 2000; 50: 285–95.
3. Pai MP, *et al.* Macrolide drug interactions: an update. *Ann Pharmacother* 2000; 34: 495–513.
4. Shakeri-Nejad K, Stahlmann R. Drug interactions during therapy with three major groups of antimicrobial agents. *Expert Opin Pharmacother* 2006; 7: 639–51.

Mechanism

In *rats* and humans, troleandomycin, and erythromycin and some of its derivatives, induce microsomal enzymes; the nitrosoalkane metabolites so formed produce stable inactive complexes with the iron of cytochrome P450. Eventually the oxidative metabolism of other drugs may be decreased. These effects are marked after troleandomycin, moderate after erythromycin, small after oleandomycin, and absent or negligible after josamycin, midecamycin, or spiramycin.[1,2]

1. Pessayre D, *et al.* Drug interactions and hepatitis produced by some macrolide antibiotics. *J Antimicrob Chemother* 1985; 16 (suppl A): 181–94.
2. Periti P, *et al.* Pharmacokinetic drug interactions of macrolides. *Clin Pharmacokinet* 1992; 23: 106–31.

Drugs

For reference to the effects of erythromycin and other macrolides on other drugs, see

- alfentanil (p. 19.3)
- bromocriptine (p. 900.1)
- carbamazepine (p. 516.2)
- ciclosporin (p. 1956.1)
- clozapine (p. 1061.2)
- colchicine (p. 606.3)
- conivaptan (p. 2486.2)
- digoxin (p. 1356.3)
- dihydroergotamine and ergotamine (p. 675.2)
- disopyramide (p. 1365.2)
- levodopa (p. 908.1)
- midazolam and triazolam (p. 1068.2)
- oxycodone (p. 113.3)
- phenytoin (p. 542.3)
- pimozide (p. 1052.1)
- quetiapine (p. 1102.2)
- quinidine (p. 1483.1)
- repaglinide (p. 498.1)
- rifabutin (p. 351.3)
- sertraline (see under Fluoxetine, p. 426.1)
- sildenafil (p. 2366.3)
- simvastatin and other statins (p. 1494.3)
- tacrolimus (p. 1977.3)
- terfenadine (p. 641.2)
- theophylline (p. 1234.1)
- tolvaptan (p. 2633.1)
- valproate (p. 557.2)
- verapamil (p. 1525.1)
- vinblastine (p. 882.3)
- warfarin (p. 1531.1)
- zopiclone (p. 1118.3)

In the case of astemizole, cisapride, and terfenadine the UK CSM has warned that there is a risk of inducing ventricular arrhythmias if erythromycin, or possibly other macrolides, are also given,[1,2] and that, in particular, cisapride should not be used with macrolides.[3] The CHM[4] later advised that amisulpride, ergotamine, dihydroergotamine, mizolastine, pimozide, simvastatin, and tolterodine should not be given with erythromycin. A warning was also issued that increased erythromycin concentrations may occur when used with other inhibitors of the cytochrome P450 CYP3A isoenzymes such as the azole antifungals, some calcium-channel blockers including diltiazem and verapamil, and HIV-protease inhibitors. For a report of an increased risk of sudden cardiac death associated with such combinations see Effects on the Cardiovascular System, p. 293.2.

1. CSM. Ventricular arrhythmias due to terfenadine and astemizole. *Current Problems* 35 1992. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024453&RevisionSelectionMethod=LatestReleased (accessed 27/04/07)
2. CSM/MCA. Cisapride (Prepulsid, Alimax): interactions with antifungals and antibiotics can lead to ventricular arrhythmias. *Current Problems* 1996; 22: 1. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024458&RevisionSelectionMethod=LatestReleased (accessed 27/04/07)
3. CSM/MCA. Cisapride (Prepulsid): risk of arrhythmias. *Current Problems* 1998; 24: 11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023231&RevisionSelectionMethod=LatestReleased (accessed 27/04/07)
4. CHM/MHRA. Erythromycin and other macrolides: focus on interactions. *Current Problems* 2006; 31: 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023860&RevisionSelectionMethod=LatestReleased (accessed 08/01/07)

Bronchodilators. Intravenous *theophylline* has been reported[1,2] to decrease serum concentrations of oral erythromycin although other studies[3,4] using intravenous or oral theophylline with intravenous erythromycin did not show any significant pharmacokinetic changes.

For reference to the effects of erythromycin on theophylline, see Macrolides, under Interactions of Theophylline, p. 1234.1.

1. Iliopoulou A, *et al.* Pharmacokinetic interaction between theophylline and erythromycin. *Br J Clin Pharmacol* 1982; 14: 495–9.
2. Paulsen O, *et al.* The interaction of erythromycin with theophylline. *Eur J Clin Pharmacol* 1987; 32: 493–8.
3. Hildebrandt R, *et al.* Influence of theophylline on the renal clearance of erythromycin. *Int J Clin Pharmacol Ther Toxicol* 1987; 25: 601–4.
4. Pasic J, *et al.* The interaction between chronic oral slow-release theophylline and single-dose intravenous erythromycin. *Xenobiotica* 1987; 17: 493–7.

Gastrointestinal drugs. *Cimetidine* may increase plasma concentrations of erythromycin and deafness occurred in a patient taking both drugs.[1]

1. Mogford N, *et al.* Erythromycin deafness and cimetidine treatment. *BMJ* 1994; 309: 1620.

Antimicrobial Action

Erythromycin is a macrolide antibacterial with a broad and essentially bacteriostatic action against many Gram-positive and to a lesser extent some Gram-negative bacteria, as well as other organisms including some *Mycoplasma* spp., Chlamydiaceae, *Rickettsia* spp., and spirochaetes.

Mechanism of action. Erythromycin and other macrolides bind reversibly to the 50S subunit of the ribosome, resulting in blockage of the transpeptidation or translocation reactions, inhibition of protein synthesis, and hence inhibition of cell growth. Its action is mainly bacteriostatic, but high concentrations are slowly bactericidal against the more sensitive strains. Because macrolides penetrate readily into white blood cells and macrophages there has been some interest in their potential synergy with host defence mechanisms *in vivo*. The actions of erythromycin are increased at moderately alkaline pH (up to about 8.5), particularly in Gram-negative species, probably because of the improved cellular penetration of the nonionised form of the drug.

Spectrum of activity. Erythromycin has a broad spectrum of activity. The following pathogenic organisms are usually sensitive to erythromycin:

- Gram-positive cocci, particularly streptococci such as *Streptococcus pneumoniae* and *Str. pyogenes*. However, resistance has been increasingly reported in both organisms, particularly in penicillin-resistant *Str. pneumoniae*.
  Most strains of *Staphylococcus aureus* remain susceptible, although resistance can emerge rapidly, and some enterococcal strains are also susceptible.
- Other Gram-positive organisms including *Bacillus anthracis, Corynebacterium diphtheriae, Erysipelothrix rhusiopathiae,* and *Listeria monocytogenes*. Anaerobic *Clostridium* spp. are also usually susceptible, as is *Propionibacterium acnes*. *Nocardia* spp. vary in their susceptibility.
- Gram-negative cocci including *Neisseria meningitidis* and *N. gonorrhoeae,* and *Moraxella catarrhalis* (*Branhamella catarrhalis*) are usually sensitive.
- Other Gram-negative organisms vary in their susceptibility, but *Bordetella* spp., some *Brucella* strains, and *Flavobacterium* and *Legionella* spp. are usually susceptible. *Haemophilus ducreyi* is reportedly susceptible, but *H. influenzae* is somewhat less so. The Enterobacteriaceae are usually resistant, although some strains may respond at alkaline pH. *Helicobacter pylori* and most strains of *Campylobacter jejuni* are sensitive (about 1% of the latter are reported to be resistant in the USA).
- Among the Gram-negative anaerobes most strains of *Bacteroides fragilis* and many *Fusobacterium* strains are resistant.
- Other organisms usually sensitive to erythromycin include *Actinomyces,* Chlamydiaceae, rickettsias, spirochaetes such as *Treponema pallidum* and *Borrelia burgdorferi,* some mycoplasmas (notably *Mycoplasma pneumoniae*), and some of the opportunistic mycobacteria: *Mycobacterium scrofulaceum* and *M. kansasii* are usually susceptible, but *M. intracellulare* is often resistant and *M. fortuitum* usually so.

Fungi, yeasts, and viruses are not susceptible to erythromycin.

Activity with other antimicrobials. As with other bacteriostatic antimicrobials, the possibility of an antagonistic effect if erythromycin is given with a bactericide exists, and some antagonism has been shown *in vitro* between erythromycin and various penicillins and cephalosporins or gentamicin. However, in practice the results of such concurrent use are complex, and depend on the organism; in some cases synergy has been seen. Because of the adjacency of their binding sites on the ribosome, erythromycin may competitively inhibit the effects of chloramphenicol or lincosamides such as clindamycin or lincomycin.

Resistance. Several mechanisms of acquired resistance to erythromycin have been reported of which the most common is a plasmid-mediated ability to methylate ribosomal RNA, resulting in decreased binding of the antimicrobial drug. This can result in cross-resistance between erythromycin, other macrolides, lincosamides, and streptogramin B, because they share a common binding site on the ribosome and this pattern of resistance is referred to as the MLS_B phenotype. It is seen in staphylococci, and to a somewhat lesser extent in streptococci, as well as in a variety of other species including *B. fragilis, Clostridium perfringens, Corynebacterium diphtheriae,* and *Listeria* and *Legionella* spp.

Decreased binding of antimicrobial to the ribosome may also occur as a result of a chromosomal mutation, resulting in an alteration of the ribosomal proteins in the 50S subunit, which conveys one-step high-level erythromycin resistance. This form of resistance has been found in some strains of *Str. pneumoniae, H. pylori, M. pneumoniae, Escherichia coli, Str. pyogenes, Staph. aureus,* and *Campylobacter* spp.

Other forms of erythromycin resistance may be due to the production of a plasmid-determined erythromycin esterase that can inactivate the drug, or to decreased drug penetration. The latter may be partly responsible for the intrinsic resistance of Gram-negative bacteria like the Enterobacteriaceae, but has also been shown to be acquired as a plasmid-mediated determinant in some organisms; production of a protein which increases drug efflux from the cell is thought to explain the M phenotype resistance, in which organisms are resistant to 14-and 15-carbon ring macrolides, but retain sensitivity to 16-carbon ring macrolides, lincosamides, and streptogramins.

The incidence of resistance varies greatly with the area and the organism concerned and, although the emergence of resistance is rarely a problem in the short-term treatment of infection, it is quite common in conditions requiring prolonged treatment such as endocarditis due to *Staph. aureus*. The incidence of resistance in streptococci is generally lower than in *Staph. aureus* but shows geographical variation and may be increasing in some countries, including the UK. In addition, localised outbreaks of resistant strains may occur and produce a much higher incidence of resistance.

Antipseudomonal activity. Although macrolides have limited direct antibacterial activity against *Pseudomonas aeruginosa,* prolonged exposure at sub-MICs has produced antipseudomonal effects *in vitro*[1-3] and synergy has been shown with other antipseudomonals.[4] Erythromycin and clarithromycin appear to have the greatest activity. This action has been partly attributed to the ability of macrolides to reduce the protective biofilm produced by some strains of *P. aeruginosa*.[3,5] Other proposed mechanisms of action include modification of the inflammatory response to infection and direct inhibition of other virulence factors such as twitching motility.[3]

1. Tateda K. *et al.* Effects of sub-MICs of erythromycin and other macrolide antibiotics on serum sensitivity of Pseudomonas aeruginosa. *Antimicrob Agents Chemother* 1993; 37: 675–80.
2. Tateda K. *et al.* Direct evidence of antipseudomonal activity of macrolides: exposure-dependent bactericidal activity and inhibition of protein synthesis by erythromycin, clarithromycin, and azithromycin. *Antimicrob Agents Chemother* 1996; 40: 2271–5.
3. Wozniak DJ, Keyser R. Effects of subinhibitory concentrations of macrolide antibiotics on Pseudomonas aeruginosa. *Chest* 2004; 125 (suppl 2): 62S–69S.
4. Bui KQ. *et al.* In vitro and in vivo influence of adjunct clarithromycin on the treatment of mucoid Pseudomonas aeruginosa. *J Antimicrob Chemother* 2000; 45: 57–62.
5. Yasuda H. *et al.* Interaction between biofilms formed by Pseudomonas aeruginosa and clarithromycin. *Antimicrob Agents Chemother* 1993; 37: 1749–55.

Resistance. A meta-analysis[1] found that reported macrolide resistance in *Streptococcus pneumoniae* varied greatly from country to country. The percentage of erythromycin-resistant *Str. pneumoniae* in the USA (20.7%) was less than that in Europe (32.0%) although this difference was not considered statistically significant, and higher levels of resistance were found in Asia (57.3%). In Europe, *Str. pyogenes* showed greater resistance to erythromycin (36.8%) than *Str. pneumoniae*. However, across all regions, the mean resistance of *Str. pneumoniae* was statistically equivalent (30.4%) and also similar to that of *Str. pyogenes* (30.0%).

1. Halpern MT. *et al.* Meta-analysis of bacterial resistance to macrolides. *J Antimicrob Chemother* 2005; 55: 748–57.

Pharmacokinetics

Erythromycin base is unstable in gastric acid, and absorption is therefore variable and unreliable. Consequently, the base is usually given in film- or enteric-coated preparations, or one of the more acid-stable salts or esters is used. Food may reduce absorption of the base or the stearate, although this depends to some extent on the formulation; the esters are generally more reliably and quickly absorbed and their absorption is little affected by food, so that the timing of doses in relation to food intake is unimportant.

Peak plasma concentrations generally occur between 1 and 4 hours after a dose and have been reported to range from about 0.3 to 1.0 micrograms/mL after 250 mg of erythromycin base, and from 0.3 to 1.9 micrograms/mL after 500 mg. Similar concentrations have been seen after equivalent doses of the stearate. Peak concentrations may be somewhat higher after repeated use 4 times daily. Higher total concentrations occur after oral doses of the estolate or ethyl succinate, but only about 20 to 30% of estolate or 55% of ethyl succinate is present as the active base, the rest being present as the inactive ester (in the case of the estolate as the propionate). Peak concentrations of about 500 nanograms/mL of erythromycin base have been reported after 250 mg of the estolate or 500 mg of the ethyl succinate. A peak of 3 to 4 micrograms/mL results after 200 mg of gluceptate or lactobionate intravenously.

Erythromycin is widely distributed throughout body tissues and fluids, although it does not cross the blood-brain barrier well and concentrations in CSF are low. Relatively high concentrations are found in the liver and spleen, and some is taken up into polymorphonuclear lymphocytes and macrophages. Around 70 to 75% of the base is protein bound, but after doses as the estolate the propionate ester is stated to be about 95% protein bound. Erythromycin crosses the placenta: fetal plasma concentrations are variously stated to be 5 to 20% of those in the mother. It is distributed into breast milk.

Erythromycin is partly metabolised in the liver by the cytochrome P450 isoenzyme CYP3A4 via *N*-demethylation to inactive, unidentified metabolites. It is excreted in high concentrations in the bile and undergoes intestinal reabsorption. About 2 to 5% of an oral dose is excreted unchanged in the urine and as much as 12 to 15% of an intravenous dose may be excreted unchanged by the urinary route. The half-life of erythromycin is usually reported to be about 1.5 to 2.5 hours, although this may be slightly longer in patients with renal impairment and has been reported to be between 4 to 7 hours in severe impairment.

Erythromycin is not removed by haemodialysis or peritoneal dialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Algiderm; Ambamida; Atlamicin; Clarex; Cuartal; Eri; Erigrand; Erisine; Erisol; Erit; Eritroderm; Eritrofarm; Eritromed; Eritrovis; Eryacne; Eryfluid; Etisux; Iloticina; Ingelets†; Kitacne; Oftalmolets; Pantomicina; Pentoclave; Stiemycin; Toperit; Trixne; Wemid; ***Austral.***: E-Mycin; EES; Eryacne; Eryc; Eryhexal†; Erythrocin; ***Austria***: Akne Cordes†; Eryaknen; Erystad†; Erythrocin; Meromycin; Stiemycine†; ***Belg.***: Acneryne; Aknemycin; Erythrocine; Erythroforte; Indern; Stimycine; ***Braz.***: Eribiotic; Eritrex; Eryacnen; Ilosone; Kanazimas†; Pantomicina; Stiemycin; Valmicin; ***Canad.***: Ak Mycin; Apo-Erythro; Diomycin; EES; Erybid; Eryc; Erysol; Erythro; Erythrocin; Novo-Rythro; PCE; ***Chile***: Cinactiv; Eryacnen; Erypark†; Gelerit; Labocne†; Mercina; Pantomicina; ***China***: Ai Jia Xing (艾加星); AoShuDa (澳抒达); AoShuXin (澳抒欣); Davercin (达发新); Guansha (冠沙); Ke Te Jia (科特加); Lijunsha (利君沙); Mei Hong (美红); San Jiu Jun Bi Sha (三九君必沙); Xin Hong Kang (新红康); Yi Hu Wei Mei Su Chong Ji (乙琥威); ***Cz.***: Aknefug-EL†; Aknemycin; Bryfluid; Erythrocin†; ***Denm.***: Abboticin; Erycin; Escumycin; Hexabotin; ***Fin.***: Abboticin; Ermysin; ***Fr.***: Abboticine; Egery; Ery; Eryacne; Eryfluid; Erythrocine; Erythrogel; Stimycine; ***Ger.***: Aknederm Ery†; Aknefug-EL; Aknemycin; Ery-Diolan†; Ery†; Eryaknen; Erybeta†; Erycinum; Erydermec; Eryhexal†; Erythro; Erythrocin; Inderm; InfectoMycin; Paediathrocin†; Sanasepton; Stiemycine; ***Gr.***: Acne Hermal; Dankit; Eryacne; Erycream; Erygel; Erymyk; Erythrocin; Erythrogel; Erythropen; Erythroskin; Lederpax; Rotacin; Roug-Mycin; ***Hong Kong***: Aknemycin; E-Mycin†; EES†; Erismycine†; Erogran†; Erotab†; Erymycin†; Erythro; Erythrocin†; Oracin†; Rycin†; Stiemycin; ***Hung.***: Aknefug-EL; Aknemycin; Davercin; Eryc†; Erythrotrop; Meromycin; ***India***: Acnederm; Acnelak; Acnesol; Acnet; Althrocin; Aritomycin; Calthrox; Citamycin; E-Mycin; EES; Eltocin; Eludin; Erase; Eroate; Erocyn; Erolcid; Eroma; Eromed; Ery; Eryacne; Erycin; Erycip; Erypal; Erysafe†; Erysoft; Eryspans; Eryster; Erythrocin; Erythrokem; Erythrolar; Erytop; Etomin; Floramycin; Gery; Inderyth; Okamycin; ***Indon.***: Cetathrocin†; Corsatrocin; Dothrocyn; Duramycin†; EES†; Erphathrocin; Eryceat; Eryderm; Erymed; Erysanbe; Erythrin; Erythrocin; Jeracin; Narlecin; Opithrocin; Pharothrocin; ***Irl.***: Erymax; Erythrocin; Erythroped; Primacine; Stiemycin; ***Israel***: Acnetrim; Aknemycin; Erythro-Teva; Erythrocin; ***Ital.***: Eritrocina; Eryacne; Lauromicina; ***Malaysia***: Aknemycin†; EES; Erycin; Eryderm; Eryped†; Eryson; Erythrocin†; Oftalmolosa Cusi; Sathrocin; Stiemycin; ***Mex.***: Apo-Trina; Benitrom†; Bestocin; Biotril; Eribec†; Eriber; Erisuspen; Eritrolat; Eritropharma; Eritrosol; Eritrovier; Eritrowel†; Eryacnen; Eryderm; Erylar; Iliocin†; Ilosin†; Ilosone; Iqfamicina; Lantrom; Latotryd; Lauricin; Laurimicina†; Lauritran; Optomicin; Pantomicina; Pertrosom; Procephal†; Promicin; Quimolauril; Sansacne; Stiemycin; T-Stat; Tropharma; Witromin†; ***Neth.***: Aknemycin†; Eryacne; Eryderm; Eryfluid†; Erythrocine; Erytrolyve†; Inderm; Stiemycin†; ***Norw.***: Abboticin; Ery-Max; ***NZ***: E-Mycin; EES; Era; Eryacne; Erythrocin; Stiemycin; ***Philipp.***: Aldricin; Ery-Max†; Ery-V; Erycar; Erylide; Erythrocin; Fildrocin; Ilosone; Medripol; Optryl; Pertustat; Romaxin; Sansacne; Sorestin; Stiemycin; Upperzin; ***Pol.***: Aknemycin; Davercin; ***Port.***: Akne-Mycin; Clinac; Eritrazon; Eritrocel; Eritrocina; Eryfluid; ESE; ***S. Afr.***: Acu-Erylate S†; Betamycin; Erycette†; Eryderm; Eryko†; Erymycin; Erystat†; Erythrocin; Estomycin†; Ilosone; Ilotycin TS; Purmycin; Rubimycin†; Spectrasone; Stiemycin; Xeramel; ***Singapore***: Akne-Mycin; EES; Ermycin; Erogran; Erotab; Eryacne; Eryc; Erycyn; Eryderm; Eryped; Erysol; Eryson; Erythro; Ranthrocin; Stiemycin; ***Spain***: Bronsema†; Deripil; Eridosis; Eritrogobens; Eritroveinte; Euskin; Lagarmicin; Loderm; Pantomicina; ***Swed.***: Abboticin; Ery-Max; ***Switz.***: Akne-Mycin; Aknilox; Eriost†; Eryaknen; Eryderm†; Erythrocine; ***Thai.***: E S; Erathrom; Ericin; Erimit; Erimycin; Ery-Tab†; Eryacne; Erycin; Erycon; Erymin; Eryo; Erypac; Erysate; Erysil; Eryth-mycin; Erythorate; Erythrocin†; Erythromed; Erytomin; Etrola†; Etrolate†; Ilosone†; Malocin; Medthrocin; Pocin; Redrocin†; Rintacap; Rintacin; Rytho-Cap; Rythocin†; Servitrocin†; Stacin; Stiemycin; Suthrocin; Tomcin; ***Turk.***: Aknilox; Erimicin; Eritro; Eritrosif; Eryacne; Erythrocin; ***UAE***: Eromycin; ***UK***: Eryacne; Erymax; Erythrocin; Erythroped; Stiemycin; Tiloryth; ***USA***: Akne-Mycin; ATS; Del-Mycin; E-Base; E-Mycin; EES; Eramy-

cin; Ery-Tab; Eryc; Erycette; Eryderm; Erygel; Eryped; Erythrocin; Ilotycin; PCE; Robimycin Robitabs; *Venez.*: Eryacne; Ilosone; Inderm; Leda-Rix; Pantomicina; Yisadin.

Multi-ingredient Preparations. *Arg.*: Acneout; Acnepas E; Clarex Compuesto; Ecnagel E; Erimicin; Eristin; Eritrobron; Pentoclave Combi; Peroximicina; Stievamycin; Tratacne; Zineryt; *Austria*: Aknemycin compositum; Isotrexin; *Belg.*: Benzadermine; Benzamycin†; Zineryt; *Braz.*: Eritrex A; Isotrexin; *Canad.*: Benzamycin; Pediazole; Stievamycin; *Chile*: Benzac Plus; Bioquin; Dermodan Plus; Erimicin; Erylik; Stievamycin; *China*: Benzamycin (必麦森); Fuqing (芙晴); *Cz.*: Aknemycin Plus; Isotrexin; Zineryt; *Fr.*: Antibiotrex; Erylik; Pediazole; *Ger.*: Aknemycin Plus; Aknemycin†; Ecolicin; Isotrexin; Zineryt; *Gr.*: Benzamycin; Erybenz; Pediazole; Zarcad; *Hong Kong*: Aknemycin Plus; Erylik; *Hung.*: Isotrexin; Zineryt; *India*: Acnebenz; Acnelak-Z; Acrub; Aknemycin Plus; Calthrox; Eltocin-BR; Ero-B; Erysia; *Indon.*: Erymed Plus; *Irl.*: Benzamycin†; Isotrexin; Zineryt; *Israel*: Aknemycin Plus; Aknemycin; Benzamycin; Pediazole†; *Ital.*: Isotrexin; Lauromicina; Zineryt; *Malaysia*: Aknemycin Plus; Efasol; *Mex.*: Benzac Plus†; Benzamycin†; Bisolvon E; Eriwest; Pantobron; Pediazole; Quimobrom; Stievamycin; *Neth.*: Zineryt; *NZ*: Antibiotic Simplex; *Philipp.*: Elicocin; *Pol.*: Aknemycin Plus; Isotrexin; Zineryt; *Port.*: Isotrexin; Zineryt; *Rus.*: Isotrexin (Изотрексин); Zineryt (Зинерит); *S.Afr.*: Zineryt; *Singapore*: Aknemycin Plus; Benzamycin†; Isotrexin; *Spain*: Isotrex Eritromicina; Loderm Retinoico†; Zineryt; *Switz.*: AknеMycin†; *Thai.*: Isotrexin; *Turk.*: Benzamycin; Eritretin; Isotrexin; *UK*: Aknemycin Plus; Isotrexin; Zineryt; *Ukr.*: Isotrexin (Изотрексин); Macrotussin (Макротуссин); Zineryt (Зинерит); *USA*: Benzamycin; Pediazole†.

Pharmacopoeial Preparations

BP 2014: Erythromycin and Zinc Acetate Lotion; Erythromycin Estolate Capsules; Erythromycin Ethyl Succinate Oral Suspension; Erythromycin Ethyl Succinate Tablets; Erythromycin Lactobionate Infusion; Erythromycin Stearate Tablets; Gastro-resistant Erythromycin Capsules; Gastro-resistant Erythromycin Tablets;

USP 36: Erythromycin and Benzoyl Peroxide Topical Gel; Erythromycin Delayed-release Capsules; Erythromycin Delayed-release Tablets; Erythromycin Estolate and Sulfisoxazole Acetyl Oral Suspension; Erythromycin Estolate Capsules; Erythromycin Estolate for Oral Suspension; Erythromycin Estolate Oral Suspension; Erythromycin Estolate Tablets; Erythromycin Ethylsuccinate and Sulfisoxazole Acetyl for Oral Suspension; Erythromycin Ethylsuccinate for Oral Suspension; Erythromycin Ethylsuccinate Injection; Erythromycin Ethylsuccinate Oral Suspension; Erythromycin Ethylsuccinate Tablets; Erythromycin Lactobionate for Injection; Erythromycin Ointment; Erythromycin Ophthalmic Ointment; Erythromycin Pledgets; Erythromycin Stearate Tablets; Erythromycin Tablets; Erythromycin Topical Gel; Erythromycin Topical Solution; Sterile Erythromycin Ethylsuccinate; Sterile Erythromycin Gluceptate; Sterile Erythromycin Lactobionate.

Ethambutol Hydrochloride

(BANM, USAN, rINNM)

CL-40881; Etambutol, hidrocloruro de; Etambutol Hidroklorür; Etambutol-hidroklorid; Etambutolhydroklorid; Etambutolihydrokloridi; Etambutolio hidrochloridas; Etambutolo; Etambutolu chlorowodorek; Éthambutol, Chlorhydrate d'; Ethambutol-dihydrochlorid; Ethambutoldihydrochlorid; Ethambutoli Dihydrochloridum; Ethambutoli Hydrochloridum; Ethambutolo; Hidrocloruro de etambutol; Этамбутола Гидрохлорид.

(S,S)-N,N'-Ethylenebis(2-aminobutan-1-ol) dihydrochloride.

$C_{10}H_{24}N_2O_2.2HCl$=277.2

CAS — 74-55-5 (ethambutol); 1070-11-7 (ethambutol hydrochloride).

ATC — J04AK02.

ATC Vet — QJ04AK02.

UNII — QE4VW5FO07.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Ethambutol Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water; soluble in alcohol. A 2% solution in water has a pH of 3.7 to 4.0. Store in airtight containers.

USP 36: (Ethambutol Hydrochloride). A white crystalline powder. Freely soluble in water; soluble in alcohol and in methyl alcohol; slightly soluble in chloroform and in ether.

Uses and Administration

Ethambutol is used with other antituberculous drugs in the primary treatment of pulmonary and extrapulmonary tuberculosis (p. 210.2) to suppress emergence of resistance to the other drugs used in the regimens. It is also used as a component of regimens for the treatment of nontuberculous mycobacterial infections (p. 194.1).

In the treatment of tuberculosis, ethambutol is given, as the hydrochloride, usually with isoniazid, rifampicin, and pyrazinamide in the initial 8-week phase and sometimes in the continuation phase. It is given orally in a single daily dose of 15 mg/kg, or 30 mg/kg three times weekly. Initial doses of ethambutol 25 mg/kg daily for 60 days may be given to patients who have previously had antimycobacterial therapy, reduced to 15 mg/kg daily thereafter.

For details of doses in children, see p. 298.2.

Doses may require adjustment in patients with renal impairment, for details see p. 298.2.

Fixed-dose combination products have been developed in order to improve patient compliance and avoid monotherapy, thereby decreasing the risk of acquired drug resistance. Combination products containing ethambutol with isoniazid, isoniazid and rifampicin, or isoniazid, rifampicin, and pyrazinamide are available in some countries.

References.

1. Anonymous. Ethambutol. *Tuberculosis (Edinb)* 2008; **88**: 102–5.

Administration in children. For the treatment of tuberculosis in infants, children, and adolescents the American Academy of Pediatrics[1] suggests an oral dose of ethambutol of 20 mg/kg daily or 50 mg/kg (to a maximum of 2.5 g) twice weekly.

For *congenitally acquired* tuberculosis in neonates the *BNFC* suggests a dose of 20 mg/kg once daily. For the treatment of children 1 month and older a dose of 20 mg/kg once daily or 30 mg/kg three times a week for the 2 month initial treatment phase is suggested.

See also Children, under Precautions p. 299.1

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics. 2012.

Administration in renal impairment. Licensed product information advises that ethambutol doses be adjusted based on serum concentrations (see Precautions, p. 299.1) for patients with renal impairment.

Alternatively, for patients with severe renal impairment (creatinine clearance < 30 mL/minute) an empirical dose adjustment may be considered; WHO guidelines for the treatment of tuberculosis[1] recommend a dose of 15 mg/kg orally 3 times weekly, while the *BNF* recommends a dose of 15 to 25 mg/kg depending on serum-ethambutol concentrations (to a maximum of 2.5 g) orally 3 times weekly.

1. WHO. *Treatment of tuberculosis: guidelines—4th edition*. Geneva: WHO, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf (accessed 02/12/10)

Adverse Effects and Treatment

The most important adverse effect of ethambutol is retrobulbar neuritis with a reduction in visual acuity, constriction of visual field, central or peripheral scotoma, and green-red colour blindness. One or both eyes may be affected. The degree of visual impairment appears to depend on the dose and duration of therapy; toxicity occurs most frequently at daily doses of 25 mg/kg or more and after at least 2 months of therapy. Recovery of vision usually takes place over a period of a few weeks or months, but in rare cases it may take up to a year or more or the effect may be permanent. Retinal haemorrhage has occurred rarely.

Renal clearance of urate may be reduced and acute gout has been precipitated rarely.

Hypersensitivity reactions including rashes, pruritus, leucopenia, fever, and joint pains have occurred but appear to be rare with ethambutol. Other adverse effects which have been reported include confusion, disorientation, hallucinations, headache, dizziness, malaise, jaundice or transient liver dysfunction, peripheral neuropathy, thrombocytopenia, pulmonary infiltrates, eosinophilia, and gastrointestinal disturbances such as nausea, vomiting, anorexia, and abdominal pain.

Teratogenicity has been seen in *animals* (but see also Precautions, p. 299.1).

Blood concentrations of ethambutol after overdosage may be reduced by haemodialysis or peritoneal dialysis.

Effects on the blood. Neutropenia has been reported in a patient on ethambutol, isoniazid, and rifampicin.[1] Each drug induced neutropenia individually on rechallenge. In another patient also receiving mixed antituberculous therapy, eosinophilia and neutropenia were associated with ethambutol; the effects recurred only on rechallenge with this drug.[2] Rash, blood eosinophilia, and pulmonary infiltrates occurred in a patient after 8 weeks of multidrug therapy for miliary tuberculosis. Rechallenge again attributed the adverse event to ethambutol.[3] Thrombocytopenia attributable to ethambutol has been reported in 2 patients.[4,5]

1. Jenkins PF, *et al.* Neutropenia with each standard antituberculosis drug in the same patients. *BMJ* 1980; **280**: 1069–70.
2. Wong CF, Yew WW. Ethambutol-induced neutropenia and eosinophilia. *Chest* 1994; **106**: 1638–9.
3. Wong PC, *et al.* Ethambutol-induced pulmonary infiltrates with eosinophilia and skin involvement. *Eur Respir J* 1995; **8**: 866–8.
4. Rabinovitz M, *et al.* Ethambutol-induced thrombocytopenia. *Chest* 1982; **81**: 765–6.
5. Prasad R, Mukerji PK. Ethambutol-induced thrombocytopaenia. *Tubercle* 1989; **70**: 211–12.

Effects on the CNS. A 40-year-old man with advanced HIV infection had rapid cognitive decline, hallucinations, and delusions within 2 weeks of starting oral ethambutol treatment for *Mycobacterium avium* complex infection; symptoms resolved on stopping treatment.[1]

1. Martin SJ, Bowden FJ. Ethambutol toxicity manifesting as acute onset psychosis. *Int J STD AIDS* 2007; **18**: 287–8.

Effects on the eyes. The ocular toxicity of ethambutol has been reviewed.[1-3] One such review[1] reported that when ethambutol is taken for more than 2 months the incidence of retrobulbar neuritis is about 18% in patients receiving a daily dose of more than 35 mg/kg, reducing to 5 to 6% with a daily dose of 25 mg/kg, and less than 1% with a daily dose of 15 mg/kg. An earlier study reported ophthalmic effects in 10 of 2184 patients taking ethambutol in doses of 25 mg/kg or less daily, although few of the 10 patients complained of symptoms.[4] In 9 of the 10 patients, ocular changes occurred after the second month of treatment. In the 928 patients who only had 2 months of ethambutol therapy, ocular toxicity was not reported. A prospective study[5] of 229 patients taking ethambutol for *Mycobacterium avium* complex lung disease reported that ocular toxicity was more common in patients given daily doses rather than intermittent (3 times a week) therapy.

While short-term use of ethambutol is usually safe, deterioration of vision leading to long-term blindness has been reported after only a few doses;[6] it was suspected that this was an idiosyncratic reaction. Rapid onset reversible ocular toxicity has also occurred.[7]

Visual defects occurring with ethambutol generally resolve when the drug is stopped.

1. Chan RYC, Kwok AKH. Ocular toxicity of ethambutol. *Hong Kong Med J* 2006; **12**: 56–60.
2. Fraunfelder FW, *et al.* Update on ethambutol optic neuropathy. *Expert Opin Drug Safety* 2006; **5**: 615–8.
3. Vistamehr S, *et al.* Ethambutol neuroretinopathy. *Semin Ophthalmol* 2007; **22**: 141–6.
4. Citron KM, Thomas GO. Ocular toxicity from ethambutol. *Thorax* 1986; **41**: 737–9.
5. Griffith DE, *et al.* Ethambutol ocular toxicity in treatment regimens for Mycobacterium avium complex lung disease. *Am J Respir Crit Care Med* 2005; **172**: 250–3.
6. Kamik AM, *et al.* A case of ocular toxicity to ethambutol—an idiosyncratic reaction? *Postgrad Med J* 1985; **61**: 811–13.
7. Schild HS, Fox BC. Rapid-onset reversible ocular toxicity from ethambutol therapy. *Am J Med* 1991; **90**: 404–6.

Effects on the kidneys. Interstitial nephritis has been reported[1,2] in 5 patients receiving ethambutol and isoniazid; 3 were also receiving other antimycobacterials. In another patient, acute renal failure occurred secondary to interstitial nephritis, which was thought to have been induced by ethambutol.[3]

1. Collier J, *et al.* Two cases of ethambutol nephrotoxicity. *BMJ* 1976; **2**: 1105–6.
2. Stone WJ, *et al.* Acute diffuse interstitial nephritis related to chemotherapy of tuberculosis. *Antimicrob Agents Chemother* 1976; **10**: 164–72.
3. García-Martín F, *et al.* Acute interstitial nephritis induced by ethambutol. *Nephron* 1991; **59**: 679–80.

Effects on the liver. Although transient abnormalities in liver function commonly occur during the early stages of antituberculosis treatment, drugs other than ethambutol are generally considered responsible. Ethambutol has generated fewer reports of hepatotoxicity to the UK CSM than rifampicin, isoniazid, or pyrazinamide,[1] and the use of regimens containing ethambutol has been recommended for patients unable to tolerate standard regimens due to hepatotoxicity.[1-3]

1. Ormerod LP, *et al.* Hepatotoxicity of antituberculosis drugs. *Thorax* 1996; **51**: 111–13.
2. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; **53**: 536–48.[Although these guidelines were replaced by ones issued by NICE in 2006 the latter do not *"explain tuberculosis or its treatment in detail"* and therefore reference to the earlier guidelines has been retained] Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Tuberculosis/Guidelines/Chemotherapy.pdf (accessed 29/07/08)
3. American Thoracic Society, CDC, and the Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; **52** (RR-11): 1–77. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf (accessed 03/10/07) Correction. *ibid.* 2005; **53**: 1203. [dose]

Effects on the skin. Toxic epidermal necrolysis[1] and lichenoid[2] and erythema multiforme-type drug eruptions[3] have been associated with the use of ethambutol. Delayed hypersensitivity reactions have also been reported.[4] Licensed product information notes that Stevens-Johnson syndrome and dermatitis have also occurred.

1. Pegram PS, *et al.* Ethambutol-induced toxic epidermal necrolysis. *Arch Intern Med* 1981; **141**: 1677–8.
2. Grossman ME, *et al.* Lichenoid eruption associated with ethambutol. *J Am Acad Dermatol* 1995; **33**: 675–6.
3. Kurokawa I, *et al.* Erythema multiforme-type drug eruption due to ethambutol with eosinophilia and liver dysfunction. *Int J Antimicrob Agents* 2003; **21**: 596–7.
4. Bakkum RSLA, *et al.* Delayed-type hypersensitivity reaction to ethambutol and isoniazid. *Contact Dermatitis* 2002; **46**: 359.

Hyperuricaemia. In a controlled study of 71 patients taking ethambutol 20 mg/kg daily orally with other antimycobacterials, serum-uric acid concentrations increased in 66, mainly in the first 2 weeks of treatment.[1] One patient developed arthralgia and another acute gouty arthritis. Serum-uric acid concentrations did not change in 60 control patients receiving other antimycobacterials.

1. Khanna BK, Gupta VP. Ethambutol-induced hyperuricaemia. *Tubercle* 1984; 65: 195–9.

Precautions

Ethambutol is generally contra-indicated in patients with optic neuritis. It should be used with great care in patients with visual defects, the elderly, and in children in whom evaluation of changes in visual acuity may be difficult (see also Children, p. 299.1). Ocular examination is recommended before treatment with ethambutol and some consider that regular examinations are necessary during treatment, especially in children. Patients should be advised to report visual disturbances immediately and to stop ethambutol pending visual evaluation.

Ethambutol should be given in reduced dosage to patients with renal impairment and dosage adjustments may need to be made according to serum concentrations (but see also Administration in Renal Impairment, p. 296.2). *BNF* recommends peak concentrations of 2 to 6 mg/litre and trough concentrations of less than 1 mg/litre.

Ethambutol may precipitate attacks of gout.

Although ethambutol crosses the placenta and may be teratogenic in *animals*, problems in humans have not been documented. The benefits of ethambutol in the treatment of tuberculosis are thought to outweigh any potential risks in pregnancy.

Breast feeding. Ethambutol distributes into breast milk to produce concentrations similar to those in plasma. However, no adverse effects have been seen in breast-fed infants whose mothers were receiving ethambutol, and the last available guidance from the American Academy of Pediatrics considered[1] that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *Ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 03/10/07)

Children. Due to the possible difficulty of evaluating changes in visual acuity that may be induced in children receiving ethambutol, the *BNFC* advises that it should be used with caution in children under 5 years of age and unable to report visual changes accurately, whereas in the USA licensed product information has advised against use in those under 13 years of age.

The authors of a review of the use of ethambutol in children concluded that no extra precautions were necessary in children aged 5 years or more, and that it could also be used in younger children without undue fear of adverse effects.[1] Another review suggested that visual toxicity is not a particular problem except perhaps when CNS infection is involved.[2] A literature review[3] on the use of ethambutol in children reported almost no ocular toxicity at daily doses of 15 to 30 mg/kg. Ethambutol is therefore considered safe in children of all ages at a daily dose of 20 mg/kg (range 15 to 25 mg/kg) or a three times weekly dose of 30 mg/kg.

1. Trébucq A. Should ethambutol be recommended for routine treatment of tuberculosis in children? A review of the literature. *Int J Tubere Lung Dis* 1997; 1: 12–15.
2. Graham SM, *et al.* Ethambutol in tuberculosis: time to reconsider? *Arch Dis Child* 1998; 78: 274–8.
3. WHO. *Ethambutol efficacy and toxicity: literature review and recommendations for daily and intermittent dosage in children.* Geneva: WHO, 2006. Available at: http://whqlibdoc.who.int/hq/2006/WHO_HTM_TB_2006.365_eng.pdf (accessed 03/10/07)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ethambutol as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/07/11)

Antimicrobial Action

Ethambutol is active against *Mycobacterium tuberculosis* and some other mycobacteria, including some strains of *M. avium* complex, *M. kansasii*, *M. fortuitum*, and *M. intracellulare*. Activity seems to be limited against many isolates of *Mycobacterium avium* complex, but, synergistic activity occurs when used with clarithromycin, azithromycin, rifampicin, rifabutin, ciprofloxacin, amikacin, or streptomycin in 2- (or preferably) 3-drug regimens. Resistant strains of *M. tuberculosis* are readily produced if ethambutol is used alone.

Pharmacokinetics

About 80% of an oral dose of ethambutol is absorbed from the gastrointestinal tract. Absorption is not significantly impaired by food (but see also Bioavailability, p. 299.2). After a single dose of 25 mg/kg peak plasma concentrations of up to 5 mg/L occur within 4 hours, and are less than 1 mg/L by 24 hours.

Ethambutol is distributed to most tissues, including the lungs, kidneys, and erythrocytes. About 10 to 50% may diffuse into the CSF when the meninges are inflamed. It has been reported to cross the placenta and is distributed into breast milk. The elimination half-life after oral doses is about 3 to 4 hours.

Ethambutol is partially metabolised in the liver to the aldehyde and dicarboxylic acid derivatives, which are inactive. Most of a dose appears in the urine within 24 hours as unchanged drug and 8 to 15% as the inactive metabolites. About 20% of the dose is excreted unchanged in the faeces.

Bioavailability. Although the absorption of ethambutol is not generally regarded as being impaired by food, a study in 14 healthy subjects[1] suggested that giving it with a high-fat meal or an antacid could delay absorption and reduce the peak plasma concentration.

1. Peloquin CA, *et al.* Pharmacokinetics of ethambutol under fasting conditions, with food, and with antacids. *Antimicrob Agents Chemother* 1999; 43: 568–72.

HIV-infected patients. Malabsorption of ethambutol and other antituberculous drugs may occur in patients with HIV infection and tuberculosis, and may contribute to acquired drug resistance and reduced efficacy of tuberculosis treatment. For further information on the absorption of antituberculous drugs in HIV-infected patients see under Rifampicin, p. 356.1.

Pregnancy and breast feeding. Ethambutol crosses the placenta and is present in fetal tissue in amounts of at least 74.5% of the maternal serum concentration.[1] Ethambutol distributes into breast milk to produce concentrations similar to those in plasma.[2]

1. Holdiness MR. Transplacental pharmacokinetics of the antituberculosis drugs. *Clin Pharmacokinet* 1987; 13: 125–9.
2. Snider DE, Powell KE. Should women taking antituberculosis drugs breast-feed? *Arch Intern Med* 1984; 144: 589–90.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Myambutol; *Austria*: Etibi; Myambutol; *Belg.*: Myambutol; *Canad.*: Etibi; *Cz.*: Sural; *Denm.*: Myambutol; *Fin.*: Oributol; *Fr.*: Myambutol; *Ger.*: EMB-Fatol; Myambutol; *Gr.*: Althocin; Blomison; Dexambutol; Myambutol; *Hong Kong*: EMB; *Hung.*: Sural; *India*: Albutol; Anbutol; Colbutol; Combutol; Ebutol; Ecox; EMTB; Etibi; Isotol; Koxi; Myambutol; Mycoback; Mycobact; Mycobutol; Mycostat; Rifacom-EZ; Themibutol; Tibitol; *Indon.*: Arsitam; Bacbutol; Cetabutol†; Corsabutol; ETH Ciba†; Parabutol†; Santibi; Tibigon†; Tibitol; *Ital.*: Etapiam; Miambutol; *Mex.*: Dovalem; Etadotbal; Tambutec; *Mon.*: Dexambutol; *Neth.*: Myambutol; *NZ*: Myambutol; *Philipp.*: Danbutol; E-tol; Holtresis; Odetol; Triambutol; *Port.*: Turresis; *Rus.*: Combutol (Комбутол); Ebutol (Эбутол); EMB (ЕМБ); Ly-Butol (Лы-Бутол); Upbutol (Апбутол)†; *S.Afr.*: Purderal†; *Singapore*: E-Butol; Ebutol; *Spain*: Myambutol; *Switz.*: Myambutol; *Thai.*: ATB; Etham; Ethbutol; Lambutol; Myrin-P†; Servambutol†; Tibitab; Tobutol; *Turk.*: Dimbutol; Miambutol; *Ukr.*: Inbutol (Инбутол); *USA*: Myambutol.

Multi-ingredient Preparations. *China*: An Si Nuo Kang (安斯诺康); Ke Lao Er Kang (克劳尔康); Yi Nuo Ni Kang (怡诺尼康); *Denm.*: Rimstar; *Fin.*: Rimstar; *Gr.*: Myambutol-INH; *India*: AFB3; AFB4; Akt-3; Akt-4; Akt-FD; Akurit-3; Akurit-4; Becox Forte Kit; Bicox-E; Binex DT; Binex E; Binex ZE; Cavitar RHE; Caviter FD; Combunex; Confez-3; Coxina-3; Coxina-4; Coxkit-3; Coxrid; Coxter-4; Cx-4; Cx-5; Emrif Kit; Eufacin Plus; Forecox; Inabutol Forte†; Infez-4; Isokoxi; Lifebutol-H; Monto-3; Monto-4; Mycocox-4; Mycocox-E; Mycodot-4; Mycodot-E; Myconex; Mycurit-3; Mycurit-4; RHZ Plus; Rifa E; Wokex-3; Wokex-4; Xeed 3E; Xeed 4; *Indon.*: bacbutINH; Erabutol Plus; Meditam-6†; Metham; Mycothambin-INH†; Niaztol; Pulna; Rimstar; Santibi Plus; *Irl.*: Rimstar; *Ital.*: Etanicozid B6; Rimstar; *Mex.*: Dotbal; *Mon.*: Dexambutol-INH†; *Neth.*: Rimstar†; *Norw.*: Rimstar; *Philipp.*: 4D; AKuriT-4; Continukit Plus†; Continukit; Ebutol; Econofix; Econokit-MDR; Econokit; Ethamizid; Ethi 400; Fixcom 3; Fixcom 4; Myrin-P; Myrin; Quadmax; Quadtab; Rimstar; Sthamizide; SVM-Polypac-A†; Tres; Tritab; Viper†; *Rus.*: Combitub (Комбитуб); Combitub-Neo (Комбитуб-Нео); Forecox (Форкокс); Isocomb (Изокомб); Laslonvita (Ласлонвита); Lomecomb (Ломекомб); Phthizoetham (Фтизоэтам); Protiocomb (Протиокомб); Protub-4 (Протуб-4); Protub-5 (Протуб-5); Protub-Lome (Протуб-Ломе); Protubetham (Протубэтам); Repin B_6 (Репин B_6); Rimstar 4-FDC (Римстар 4-ФДС)†; *S.Afr.*: Rifafour; Rimstar; *Singapore*: Merip; *Spain*: Rimstar; *Swed.*: Rimstar; *Switz.*: Rimstar; *Thai.*: Rifafour; Rimstar†; *UK*: Rimstar; Voractiv.

Pharmacopoeial Preparations
BP 2014: Ethambutol Tablets;
USP 36: Ethambutol Hydrochloride Tablets; Rifampin, Isoniazid, Pyrazinamide, and Ethambutol Hydrochloride Tablets.

Ethionamide *(BAN, USAN, rINN)*

Ethionamid; Ethionamide; Ethionamidum; 2-Ethylthioisonicotinamide; Etionamid; Etionamida; Etionamidas; Etionamide; Etionamidi; 1314-TH; Этионамид.

2-Ethylpyridine-4-carbothioamide.

$C_8H_{10}N_2S$=166.2

CAS — 536-33-4.

ATC — J04AD03.

ATC Vet — QJ04AD03.

UNII — CAY8ORS3CQ.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Ethionamide). Small yellow crystals or a yellow crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; soluble in methyl alcohol.

USP 36: (Ethionamide). A bright yellow powder having a faint to moderate sulfide-like odour. Slightly soluble in water, in chloroform, and in ether; sparingly soluble in alcohol and in propylene glycol; soluble in methyl alcohol. pH of a 1% slurry in water is between 6.0 and 7.0. Store in airtight containers.

Uses and Administration

Ethionamide is a thioamide derivative considered to be interchangeable with protionamide. It is used with other antituberculous drugs for the treatment of tuberculosis (p. 210.2) when resistance to primary drugs has developed. It has also been used, as a substitute for clofazimine, in regimens for the treatment of leprosy (p. 188.3) but less toxic alternatives are now preferred.

In the treatment of resistant tuberculosis, adults may be given 15 to 20 mg/kg daily (maximum 1 g daily) orally. Ethionamide may be given in divided doses with meals, or as a single daily dose after the evening meal, or at bedtime, to minimise gastrointestinal adverse effects. For details of doses in infants, children, and adolescents, see p. 299.3.

Similar doses were used for the treatment of leprosy.

Ethionamide has also been used as rectal suppositories; the hydrochloride has been given intravenously.

References.

1. Anonymous. Ethionamide. *Tuberculosis (Edinb)* 2008; 88: 106–8.

Administration in children. For the treatment of drug-resistant tuberculosis in infants, children, and adolescents the American Academy of Pediatrics[1] suggests an oral dose of ethionamide 15 to 20 mg/kg (to a maximum of 1 g) daily, given in 2 to 3 divided doses.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Adverse Effects and Treatment

Many patients cannot tolerate therapeutic doses of ethionamide and have to stop treatment. The most common adverse effects are dose-related gastrointestinal disturbances, including nausea, vomiting, diarrhoea, anorexia, excessive salivation, a metallic taste, stomatitis, and abdominal pain. Tolerance may be improved by reducing the dose, adjusting the timing of dosage, or giving an antiemetic.

Mental disturbances including depression, anxiety, and psychosis have been provoked. Dizziness, drowsiness, headache, orthostatic hypotension, and asthenia may also occur occasionally. Peripheral and optic neuropathy, diplopia and blurred vision, and a pellagra-like syndrome have occurred. Pyridoxine or nicotinamide have been suggested for the treatment or prevention of neurotoxic effects.

Hepatitis may occur occasionally, with or without jaundice. The incidence of hepatotoxicity is increased when ethionamide is given with rifampicin.

Other adverse effects reported include hypersensitivity reactions, thrombocytopenia and purpura, alopecia, dermatitis (including photodermatitis), endocrine disturbances, hypoglycaemia, and hypothyroidism with or without goitre.

Teratogenic effects have been reported in *animals*.

Effects on the liver. Use of ethionamide or protionamide with rifampicin for the treatment of multibacillary leprosy has been associated with a high incidence of hepatotoxicity. A hepatitis incidence of 4.5 to 5% has been reported for patients on ethionamide or protionamide, rifampicin, and either dapsone or clofazimine.[1,2] In these studies, diagnosis of hepatitis was based on clinical assessment. When laboratory monitoring was used, an incidence of 13% was reported with a regimen of ethionamide or pro-

tionamide with rifampicin and dapsone.[3] A regimen of protionamide, dapsone, rifampicin, and clofazimine has been associated with a 22% incidence based on laboratory monitoring.[4] Use of ethionamide with pyrazinamide has also resulted in a high incidence of abnormal liver function tests.[5]

In the above studies rifampicin was given daily during part or all of the regimens. The incidence of hepatotoxicity when ethionamide or protionamide is used with once-monthly rifampicin may be lower; hepatotoxicity was not reported in patients receiving monthly rifampicin and daily protionamide, isoniazid, and dapsone.[6]

1. Pattyn SR, *et al.* Hepatotoxicity of the combination of rifampin-ethionamide in the treatment of multibacillary leprosy. *Int J Lepr* 1984; 52: 1–6.
2. Pattyn SR, *et al.* Combined regimens of one year duration in the treatment of multibacillary leprosy—II: combined regimens with rifampicin administered during 6 months. *Lepr Rev* 1989; 60: 118–23.
3. Cartel J-L, *et al.* Hepatitis in leprosy patients treated by a daily combination of dapsone, rifampin, and a thioamide. *Int J Lepr* 1983; 51: 461–5.
4. Ji B, *et al.* Hepatotoxicity of combined therapy with rifampicin and daily prothionamide for leprosy. *Lepr Rev* 1984; 55: 283–9.
5. Schless JM, *et al.* The use of ethionamide in combined drug regimens in the re-treatment of isoniazid-resistant pulmonary tuberculosis. *Am Rev Respir Dis* 1965; 91: 728–37.
6. Ellard GA, *et al.* Long-term prothionamide compliance: a study carried out in India using a combined formulation containing prothionamide, dapsone and isoniazid. *Lepr Rev* 1988; 59: 163–75.

Precautions

Ethionamide should not be used in severe hepatic impairment. Liver function tests should be carried out before, and regularly during, treatment with ethionamide.

Caution is necessary in patients with depression or other psychiatric illness. Difficulty may occur in the management of diabetes mellitus. Periodic monitoring of blood glucose, thyroid function, and visual function is desirable.

Ethionamide is teratogenic in *animals*.

Interactions

The adverse effects of other antimycobacterials may be increased when ethionamide is used (see Effects on the Liver, p. 297.3, and under Cycloserine, Interactions, p. 281.1).

Alcohol. A psychotic reaction has been reported in a patient receiving ethionamide after excessive intake of alcohol.[1]

1. Lansdown PS, *et al.* Psychotoxic reaction during ethionamide therapy. *Am Rev Respir Dis* 1967; 95: 1053–5.

Antimicrobial Action

Ethionamide is active only against mycobacteria including *Mycobacterium tuberculosis*, *M. kansasii*, *M. leprae*, *M. malmoense*, and some strains of *M. avium* complex.

Resistance develops rapidly if used alone and there is complete cross-resistance between ethionamide and protionamide. Cross-resistance has also been reported with isoniazid and with *in vitro* thioacetazone.

Cross-resistance. References.

1. Schaaf HS, *et al.* Ethionamide cross- and co-resistance in children with isoniazid-resistant tuberculosis. *Int J Tuberc Lung Dis* 2009; 13: 1355–9.

Pharmacokinetics

Ethionamide has been given as a sugar-coated tablet or more recently as a more stable film-coated tablet. Both formulations are readily absorbed from the gastrointestinal tract: after an oral dose of 250 mg, sugar-coated tablets produce a peak plasma concentration of about 1.5 micrograms/mL after 1.5 hours, while film-coated tablets give a peak plasma concentration of 2.16 micrograms/mL after about 1 hour. Distribution of ethionamide from the film-coated tablet into body tissues and fluids was expected to be similar to that of the sugar-coated tablets. Ethionamide from sugar-coated tablets is widely distributed throughout body tissues and fluids. It crosses the placenta and penetrates the uninflamed meninges, appearing in the CSF in concentrations equivalent to those in serum. It is about 30% bound to plasma proteins. The half-life for the sugar-coated tablet is reported to be 2 to 3 hours and 1.92 hours for the film-coated tablet. Ethionamide is extensively metabolised, probably in the liver, to the active sulfoxide and other inactive metabolites and less than 1% of a dose appears in the urine as unchanged drug.

Distribution. After single doses of ethionamide 15 or 20 mg/kg as an oral suspension in children with tuberculous meningitis, the peak spinal fluid concentration was reached in 1½ to 2½ hours.[1] A wide range of concentrations was reported but doses of 20 mg/kg were more likely to produce spinal fluid concentrations above 2.5 micrograms/mL, the concentration considered by the authors to be essential for therapeutic success.

1. Donald PR, Seifart HI. Cerebrospinal fluid concentrations of ethionamide in children with tuberculous meningitis. *J Pediatr* 1989; 115: 483–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Trecator; *India*: E-Thio; Enamide; Ethide; Ethimax; Ethiobin; Ethiocid; Ethiokox; Ethionam; Ethomid; Etomide; Etumide; MDThide; Mycotuf; Myobid; *Rus.*: Ethide (Этид); Ethomid (Этомид); Myobid (Миобид); Reginicid (Регинид); *S.Afr.*: Ethatyl; *Thai.*: Eton; *Turk.*: Etyomid; *USA*: Trecator.

Pharmacopoeial Preparations
USP 36: Ethionamide Tablets.

Etimicin Sulfate

Antibiotic 89-07; E-402.
1-*N*-Ethyl gentamicin C_{1a} sulfate.
$(C_{21}H_{43}N_5O_7)_2.5H_2SO_4$=1445.6
CAS — 59711-96-5 (etimicin); 362045-44-1 (etimicin sulfate).

Pharmacopoeias. In *Chin.*

Profile

Etimicin, a derivative of gentamicin C_{1a}, is an aminoglycoside antibacterial with actions similar to those of gentamicin (p. 306.2). It is given intravenously as the sulfate.

References.

1. Zhao C, *et al.* A randomized controlled clinical trial on etimicin, a new aminoglycoside antibiotic, versus netilmicin in the treatment of bacterial infections. *Chin Med J (Engl)* 2000; 113: 1026–30.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Ai Yi (爱益); Aida (爱大); Chuang Cheng (创成); Ge Mei Da (格美达); Pan Nuo (潘诺); XiNeng (悉能); Yi Qing (亦清).

Faropenem Sodium *(rINNM)*

ALP-201; Faropenem sódico; Faropénem Sodique; Fropenem Sodium; Furopenem; Natrii Faropenemum; SUN-5555; SY-5555; Wy-49605; YM-044; Натрий Фаропенем.
Sodium (+)-(5*R*,6*S*)-6-[(1*R*)-1-hydroxyethyl]-7-oxo-3-[(2*R*)-tetrahydro-2-furyl]-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.
$C_{12}H_{14}NaNO_5S$=307.3
CAS — 106560-14-9 (faropenem); 141702-36-5 (faropenem medoxomil); 122547-49-3 (faropenem sodium).
ATC — J01DI03.
ATC Vet — QJ01DI03.
UNII — 7O46G914RQ.

Pharmacopoeias. *Jpn* includes the hemipentahydrate.

Profile

Faropenem is a penem antibacterial that is given orally as the sodium salt for the treatment of susceptible infections.

Faropenem medoxomil (*USAN*) (A-0026; Bay-56-6854; SUN-A0026; SUN-208) has been investigated for the treatment of respiratory-tract infections and uncomplicated skin and skin-structure infections. NOTE. Faropenem medoxomil has also been referred to as faropenem daloxate although such use of the term daloxate is not in keeping with *INN* nomenclature conventions.

References.

1. Critchley IA, *et al.* Activities of faropenem, an oral β-lactam, against recent US isolates of Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis. *Antimicrob Agents Chemother* 2002; 46: 550–5.
2. von Eiff C, *et al.* Comparative in vitro activity of faropenem against staphylococci. *J Antimicrob Chemother* 2002; 50: 277–80.
3. Milatovic D, *et al.* In vitro activity of faropenem against 5460 clinical bacterial isolates from Europe. *J Antimicrob Chemother* 2002; 50: 293–9.
4. Wexler HM, *et al.* In vitro activities of faropenem against 579 strains of anaerobic bacteria. *Antimicrob Agents Chemother* 2002; 46: 3669–75.
5. Jones ME, *et al.* Activity of faropenem, a new furanem, against European respiratory pathogens collected during 2000-2001: a comparison with other beta-lactam agents. *J Antimicrob Chemother* 2003; 51: 196–9.
6. Gettig JP, *et al.* Faropenem medoxomil. *Ann Pharmacother* 2008; 42: 80–90.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Di Pai (迪哌); Gaoyi (高益); Jun Di (君迪); Peifu (蓓芙); *India*: Duonem; Faronem; Farozet; *Jpn*: Farom.

Fidaxomicin *(USAN, rINN)*

Fidaxomicina; Fidaxomicine; Fidaxomicinum; Lipiarmycin; OPT-80; PAR-101; Tiacumicin B; Фидаксомицин.
(3*E*,5*E*,8*S*,9*E*,11*S*,12*R*,13*E*,15*E*,18*S*)-3-({[6-Deoxy-4-*O*-(3,5-dichloro-2-ethyl-4,6-dihydroxybenzoyl)-2-*O*-methyl-β-D-mannopyranosyl]oxy}methyl)-12-{[6-deoxy-5-*C*-methyl-4-*O*-(2-methylpropanoyl)-β-D-*lyxo*-hexopyranosyl]oxy}-11-ethyl-8-hydroxy-18-[(1*R*)-1-hydroxyethyl]-9,13,15-trimethyloxacyclooctadeca-3,5,9,13,15-pentaen-2-one.
$C_{52}H_{74}Cl_2O_{18}$=1058
CAS — 873857-62-6.
ATC — A07AA12.
ATC Vet — QA07AA12.
UNII — Z5N076G8YQ.

Uses and Administration

Fidaxomicin is a nonabsorbed, narrow-spectrum macrocyclic antibacterial used in the treatment of *Clostridium difficile*-associated diarrhoea (see Antibiotic-associated Colitis, p. 183.1). It is given orally in a dose of 200 mg twice daily for 10 days.

References.

1. Sullivan KM, Spooner LM. Fidaxomicin: a macrocyclic antibiotic for the management of *Clostridium difficile* infection. *Ann Pharmacother* 2010; 44: 352–9.
2. Miller M. Fidaxomicin (OPT-80) for the treatment of *Clostridium difficile* infection. *Expert Opin Pharmacother* 2010; 11: 1569–78.
3. Louie TJ, *et al.* Fidaxomicin versus vancomycin for *Clostridium difficile* infection. *N Engl J Med* 2011; 364: 422–31.
4. Mullane KM, Gorbach S. Fidaxomicin: first-in-class macrocyclic antibiotic. *Expert Rev Anti Infect Ther* 2011; 9: 767–77.
5. Mullane KM, *et al.* Efficacy of fidaxomicin versus vancomycin as therapy for *Clostridium difficile* infection in individuals taking concomitant antibiotics for other concurrent infections. *Clin Infect Dis* 2011; 53: 440–7.

Adverse Effects and Precautions

Adverse effects occurring with oral use of fidaxomicin are mainly gastrointestinal in nature and include nausea, vomiting, and abdominal pain. Anaemia, neutropenia, and gastrointestinal haemorrhage may also occur.

Since there is only minimal systemic absorption, oral fidaxomicin should not be used for the treatment of systemic infections. Use of oral fidaxomicin in the absence of a proven or strongly suspected *Clostridium difficile* infection is unlikely to provide benefit and may lead to the development of drug resistant bacteria.

Antimicrobial Action

Fidaxomicin has potent bactericidal activity against *Clostridium difficile in vitro* through its inhibition of RNA synthesis by RNA polymerases. It has more limited activity against other Gram-positive bacteria, and no activity against Gram-negative bacteria.

Pharmacokinetics

Fidaxomicin is essentially nonabsorbed from the gastrointestinal tract after an oral dose. It undergoes hydrolysis in the gut to form the main metabolite, OP-1118, which is microbiologically active. Over 92% of a dose is excreted in the faeces as either fidaxomicin or OP-118, although very small amounts of OP-118 have been recovered in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Dificid; *Denm.*: Dificlir; *Irl.*: Dificlir; *Norw.*: Dificlir; *Spain*: Dificlir; *Swed.*: Dificlir; *UK*: Dificlir; *USA*: Dificid.

Fleroxacin *(BAN, USAN, rINN)*

AM-833; Fleroksasiini; Fléroxacine; Fleroxacino; Fleroxacinum; Ro-23-6240; Ro-23-6240/000; Флероксацин.
6,8-Difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid.
$C_{17}H_{18}F_3N_3O_3$=369.3
CAS — 79660-72-3.
ATC — J01MA08.
ATC Vet — QJ01MA08.
UNII — NB04LDH51K.

Pharmacopoeias. In *Chin.*

Profile

Fleroxacin is a fluoroquinolone antibacterial with actions and uses similar to those of ciprofloxacin (p. 261.1), but is reported to have greater systemic bioavailability and a longer half-life. It is given orally for the treatment of susceptible infections in usual doses of 200 to 300 mg once daily. It has also been given by intravenous infusion.

The incidence of adverse effects associated with fleroxacin has been relatively high.

General references.

1. Balfour JA, *et al.* Fleroxacin: a review of its pharmacology and therapeutic efficacy in various infections. *Drugs* 1995; 49: 794–850.

Adverse effects. References[1-3] to adverse effects associated with fleroxacin.

1. Bowie WR, *et al.* Adverse reactions in a dose-ranging study with a new long-acting fluoroquinolone, fleroxacin. *Antimicrob Agents Chemother* 1989; 33: 1778–82.
2. Geddes AM. Safety of fleroxacin in clinical trials. *Am J Med* 1993; 94 (suppl 3A): 201S–203S.
3. Kimura M, *et al.* Photosensitivity induced by fleroxacin. *Clin Exp Dermatol* 1996; 21: 46–7.

Breast feeding. The American Academy of Pediatrics[1] states that fleroxacin is usually compatible with breast feeding. However, in a study,[2] in which women were given a single 400-mg dose and breast feeding was withheld for 48 hours, it was concluded that although a breast-fed infant would only receive a moderate amount (maximum 10 mg daily), fleroxacin should not be used in breast-feeding mothers due to the potential for adverse effects such as arthropathy in the infant.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/05/04)
2. Dan M, *et al.* Penetration of fleroxacin into breast milk and pharmacokinetics in lactating women. *Antimicrob Agents Chemother* 1993; 37: 293–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Bang Lai Li Xin (邦来立欣); Chen Long Luo Xin (辰龙罗欣); Ding Ke Si (定克斯); Duo Mi Te Ding (多米特定); Fu Lu Xin (福路新); Fu Luo Ke (富络克); Fu Nuo Ding (复诺定); Fuluxing (芙璐星); Hu Kang (护康); Jimin FuXin (济民福欣); Luo Fei (洛菲); Nuo Er (诺尔); Nuo Tong (诺同); Qian Le An (千乐安); Si Tong Tuo Luo (四通佗罗); Wo Er De (沃尔得); Yan Li Da (严力达); *Jpn*: Megalocin†.

Flomoxef Sodium *(rINNM)*

Flomoxef sódico; Flomoxef Sodique; Natrii Flomoxefum; 6315-S; Натрий Фломоксеф.

7R-7-[2-(Difluoromethylthio)acetamido]-3-[1-(2-hydroxyethyl)-1*H*-tetrazol-5-ylthiomethyl]-7-methoxy-1-oxa-3-cephem-4-carboxylic acid sodium.

$C_{15}H_{17}F_2N_6NaO_7S_2$=518.4

CAS — 99665-00-6 (flomoxef); 92823-03-5 (flomoxef sodium).

UNII — 445HIB8XNF.

Pharmacopoeias. In *Jpn*.

Profile

Flomoxef is an oxacephalosporin or oxacephem antibacterial with properties similar to latamoxef (p. 317.2). It is given intravenously as the sodium salt and doses are expressed in terms of flomoxef; 1.04 g of flomoxef sodium is equivalent to about 1 g of flomoxef. The usual dose is 1 to 2 g daily in two divided doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Flumarin (氟吗宁); *Jpn*: Flumarin.

Florfenicol *(BAN, USAN, rINN)*

Florfénicol; Florfenicolum; Florfenikol; Florfeniköl; Sch-25298; Флорфеникол.

2,2-Dichloro-*N*-[(α*S*,β-α*R*)-(fluoromethyl)-β-hydroxy-4-methanesulfonylphenethyl]acetamide.

$C_{12}H_{14}Cl_2FNO_4S$=358.2

CAS — 76639-94-6.

ATC Vet — QJ01BA90; QJ51BA90.

UNII — 9J97307Y1H.

Profile

Florfenicol, a fluorinated analogue of chloramphenicol, is an antibacterial used in veterinary medicine.

Flucloxacillin *(BAN, rINN)*

BRL-2039; Floxacillin (USAN); Flucloxacilina; Flucloxacilline; Flucloxacillinum; Flukloksasilin; Flukloksasiliini; Flukloxacillin; Флуклоксациллин.

(6*R*)-6-[3-(2-Chloro-6-fluorophenyl)-5-methylisoxazole-4-carboxamido]penicillanic acid.

$C_{19}H_{17}ClFN_3O_5S$=453.9

CAS — 5250-39-5.

ATC — J01CF05.

ATC Vet — QJ01CF05; QJ51CF05.

UNII — 43B2M34G2V.

NOTE. Compounded preparations of flucloxacillin may be represented by the following names:

- Co-fluampicil (*BAN*)—flucloxacillin 1 part and ampicillin 1 part (w/w).

Flucloxacillin Magnesium *(BANM, rINNM)*

Flucloxacilina magnésica; Flucloxacilline Magnesique; Flucloxacilline-magnésium; Flucloxacillinum magnesicum; Magnesii Flucloxacillinum; Магния Флуклоксациллин.

$(C_{19}H_{16}ClFN_3O_5S)_2Mg.8H_2O$=1074.1

CAS — 58486-36-5.

ATC — J01CF05.

ATC Vet — QJ01CF05.

UNII — 4Z8782KMVT.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Flucloxacillin Magnesium Octahydrate). A white or almost white, crystalline powder. Slightly soluble in water; freely soluble in methyl alcohol. A 0.5% solution in water has a pH of 4.5 to 6.5.

Flucloxacillin Sodium *(BANM, rINNM)*

Flucloxacilina sódica; Flucloxacillin-Natrium; Flucloxacilline Sodique; Flucloxacillinum natricum; Flucloxacillinum Natricum Monohydricum; Flukloksacilino natrio druska; Flukloksasilin Sodyum; Flukloksasilliininatrium; Flukloxacilin sodná sůl monohydrát; Flukloxacillinnatrium; Flukloxacillin-nátrium; Natrii Flucloxacillinum; Натрий Флуклоксациллин.

$C_{19}H_{16}ClFN_3NaO_5S.H_2O$=493.9

CAS — 1847-24-1 (anhydrous flucloxacillin sodium); 34214-51-2 (flucloxacillin sodium monohydrate).

ATC — J01CF05.

ATC Vet — QJ01CF05.

UNII — 05F65O42VK (anhydrous flucloxacillin sodium); LMG7C674WJ (flucloxacillin sodium monohydrate).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Flucloxacillin Sodium). A white or almost white, crystalline hygroscopic, powder. Freely soluble in water and in methyl alcohol; soluble in alcohol. A 10% solution in water has a pH of 5.0 to 7.0. Store at a temperature not exceeding 25 degrees in airtight containers.

Incompatibility. As with other penicillins, flucloxacillin sodium is incompatible with aminoglycosides. Incompatibility has also been reported with many other drugs given parenterally including antibacterials such as ciprofloxacin, erythromycin lactobionate, and ofloxacin, cardiac drugs such as amiodarone, atropine sulfate, dobutamine hydrochloride, and verapamil hydrochloride, and others including buprenorphine, calcium gluconate, chlorpromazine hydrochloride, diazepam, metoclopramide hydrochloride, morphine sulfate, papaveretum, pethidine hydrochloride, prochlorperazine edisilate, and promethazine hydrochloride.

Flucloxacillin should not be mixed with blood products or other proteinaceous fluids, or with intravenous lipid emulsions.

Uses and Administration

Flucloxacillin is an isoxazolyl penicillin used primarily for the treatment of infections due to staphylococci resistant to benzylpenicillin. These include bone and joint infections, endocarditis, pneumonia, skin infections (including soft-tissue infections), and toxic shock syndrome. For discussions of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Flucloxacillin is given parenterally and orally as the sodium or magnesium salt. All doses are expressed as flucloxacillin; 1.18 g of flucloxacillin magnesium and 1.09 g of flucloxacillin sodium are each equivalent to about 1 g of flucloxacillin.

The usual adult dose orally or by intramuscular injection is 250 mg four times daily. Oral doses should be taken at least 30 minutes before meals as the presence of food in the stomach reduces absorption. Flucloxacillin is given intravenously in a dose of 0.25 to 1 g four times daily by slow injection over 3 to 4 minutes or by intravenous infusion. All systemic doses may be doubled in severe infections. Up to 8 g daily in 3 or 4 divided doses may be given for osteomyelitis; in endocarditis a dose of 8 g daily in 4 divided doses may be given to patients weighing up to 85 kg, and 12 g daily in 6 divided doses may be used in those weighing more. In severe renal impairment a reduction in dosage may be necessary.

Flucloxacillin has been given by other routes in conjunction with systemic therapy. It has been given in a dose of 250 to 500 mg daily by intra-articular injection, dissolved if necessary in a 0.5% solution of lidocaine hydrochloride, or by intrapleural injection in a dose of 250 mg daily. Using powder for injection, 125 to 250 mg has been dissolved in 3 mL of sterile water and inhaled by nebuliser 4 times daily.

For details of doses in children, see p. 301.3.

Flucloxacillin may be used with other antibacterials, including ampicillin (known as co-fluampicil), to produce a wider spectrum of activity. If flucloxacillin is given with an aminoglycoside the two drugs should not be mixed.

Administration in children. Flucloxacillin may be given to neonates and children for the treatment of infections caused by susceptible organisms and may be given orally, by intramuscular or slow intravenous injection, or by intermittent intravenous infusion over 30 to 60 minutes.

In the UK, the *BNFC* suggests the following:

For infections due to beta-lactamase-producing staphylococci including in **otitis externa, pneumonia, impetigo, and cellulitis:**

- neonates: 25 mg/kg *orally* or *intravenously*, given twice daily for those under 7 days of age, 3 times daily for those 7 to 21 days of age, and 4 times daily for those 21 to 28 days of age; intravenous doses may be doubled for severe infection
- children from 1 month to 2 years of age: 62.5 to 125 mg; 2 to 10 years, 125 to 250 mg; 10 years and older, 250 to 500 mg; all doses to be given *orally* 4 times daily
  or
  children from 1 month of age: 12.5 to 25 mg/kg *intramuscularly* (to a maximum of 500 mg) or *intravenously* (to a maximum of 1 g) every 6 hours; intravenous dose may be doubled for severe infection

For **osteomyelitis, cerebral abscess, and staphylococcal meningitis:**

- neonates: 50 to 100 mg/kg *intravenously*, given every 12 hours for those under 7 days of age, every 8 hours for those 7 to 21 days of age, and every 6 hours for those 21 to 28 days of age
- children from 1 month of age: 50 mg/kg (maximum 2 g) *intravenously* every 6 hours

For **endocarditis:**

- children from 1 month of age: 50 mg/kg (maximum 2 g) *intravenously* every 6 hours

For *prevention* of **staphylococcal lung infection in cystic fibrosis:**

- for the primary prevention, flucloxacillin is given orally to neonates and children in a dose of 125 mg twice daily
- for secondary prevention in children from 1 month of age an oral dose of 50 mg/kg (to a maximum of 1 g) twice daily is given

For the *treatment* of staphylococcal lung infection, infants and children from 1 month of age may be given an oral dose of 25 mg/kg (to a maximum dose of 1 g) in 3 or 4 divided doses; alternatively, it may be given intravenously in a dose of 50 mg/kg (to a maximum of 2 g) every 6 hours.

In children with severe renal impairment (creatinine clearance less than 10 mL/min), the normal dose should be given no more frequently than every 8 hours.

Adverse Effects and Precautions

As for Benzylpenicillin p. 229.2.

Hepatitis and cholestatic jaundice have been reported occasionally with flucloxacillin and may be delayed in onset for up to 2 months after treatment has been stopped; older patients and those receiving flucloxacillin for more than 2 weeks are at greater risk. Fatalities have occurred, usually in patients with serious underlying hepatic disease. There have been rare reports of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis associated with flucloxacillin. Agranulocytosis and neutropenia have been associated rarely with isoxazolyl penicillins such as flucloxacillin. Haemolytic anaemia has also been reported. Phlebitis has followed intravenous infusion.

Effects on the liver. In October 2004, the UK CSM issued a reminder[1] that flucloxacillin is associated rarely with an increased risk of hepatitis and cholestatic jaundice. In some patients, almost always those with serious underlying hepatic disease, fatalities have occurred. The onset of hepatic adverse effects may be delayed for up to 2 months after stopping treatment, and is not related to the dose or to the route. Older patients and those receiving flucloxacillin for more than 2 weeks are at increased risk. Flucloxacillin should not be used in patients with a history of hepatic dysfunction related to its use, and should be used only with caution in patients with evidence of other hepatic impairment. Careful enquiry should be made concerning previous hypersensitivity to beta lactams. A cohort study[2] using UK prescription data found that the risk of developing cholestatic liver disease in the 45 days after

starting flucloxacillin was 6.1 per 100 000. In contrast to other countries, flucloxacillin continued to be seen as a first-line drug in the UK. The potential genetic mechanisms of flucloxacillin-induced liver injury have been reviewed.[3]

1. CSM. Reminder: flucloxacillin and serious hepatic disorders. *Current Problems* 2004; 30: 9. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007448&RevisionSelectionMethod=LatestReleased (accessed 11/07/06)
2. Li L, *et al.* Updated study on risk of cholestatic liver disease and flucloxacillin. *Br J Clin Pharmacol* 2009; 68: 269–70.
3. Andrews E, Daly AK. Flucloxacillin-induced liver injury. *Toxicology* 2008; 254: 158–63.

Effects on metabolism. Use of flucloxacillin, often with paracetamol, has been associated with accumulation of pyroglutamic acid resulting in pyroglutamic aciduria (5-oxoprolinuria) and high-anion gap metabolic acidosis.[1-3]

1. Croal BL, *et al.* Transient 5-oxoprolinuria (pyroglutamic aciduria) with systemic acidosis in an adult receiving antibiotic therapy. *Clin Chem* 1998; 44: 336–40.
2. Peter JV, *et al.* An unusual cause of severe metabolic acidosis. *Med J Aust* 2006; 185: 223–5. Correction. *ibid.*: 528.
3. Rolleman EJ, *et al.* Guilty as charged: unmeasured urinary anions in a case of pyroglutamic acidosis. *Neth J Med* 2008; 66: 351–3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies flucloxacillin as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Sodium content. Each g of flucloxacillin sodium contains about 2 mmol of sodium.

Interactions

As for Benzylpenicillin, p. 230.1.

Antibacterials. In a small randomised study in healthy subjects,[1] *piperacillin* was found to decrease both renal and non-renal clearance of flucloxacillin to 45 and 66% respectively. The extent of the interaction was larger at higher doses, and considered clinically significant by the authors. The pharmacokinetics of piperacillin were not significantly affected by flucloxacillin.

1. Landersdorfer CB, *et al.* Inhibition of flucloxacillin tubular renal secretion by piperacillin. *Br J Clin Pharmacol* 2008; 66: 648–59.

Antimicrobial Action

Flucloxacillin is bactericidal with a mode of action similar to that of benzylpenicillin, but is resistant to staphylococcal penicillinase. It is active therefore against penicillinase-producing and non-penicillinase-producing staphylococci. Its activity against streptococci such as *Streptococcus pneumoniae* and *Str. pyogenes* is less than that of benzylpenicillin, but sufficient to be useful when these organisms are present with penicillin-resistant staphylococci. Flucloxacillin is virtually ineffective against *Enterococcus faecalis*.

Resistance. The resistance of staphylococci to flucloxacillin and other penicillinase-resistant penicillins is described under meticillin (p. 325.3).

Pharmacokinetics

Flucloxacillin is better absorbed from the gastrointestinal tract than cloxacillin, but absorption is reduced by the presence of food in the stomach. After an oral dose of 0.25 to 1 g, in fasting subjects, peak plasma concentrations in about 1 hour are usually in the range of 5 to 15 micrograms/mL. Plasma concentrations after intramuscular injection of flucloxacillin sodium are similar, but peak concentrations occur after about 30 minutes. Doubling the dose can double the plasma concentration. About 95% of flucloxacillin in the circulation is bound to plasma proteins. Flucloxacillin has been reported to have a plasma half-life of about 1 hour. The half-life is prolonged in neonates.

The distribution of flucloxacillin into body tissues and fluids is similar to that of cloxacillin (p. 275.2).

Flucloxacillin is metabolised to a limited extent and the unchanged drug and metabolites are excreted in the urine by glomerular filtration and renal tubular secretion. About 66% of an oral dose and 76% of a parenteral dose is excreted in the urine within 8 hours. Only small amounts are excreted in the bile. Flucloxacillin is not removed by haemodialysis or peritoneal dialysis.

Plasma concentrations are enhanced by probenecid.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Flopen; Floxapen†; Floxsig; Flubiclox; Flucil; Staphylex; *Austria*: Floxapen; *Belg.*: Floxapen; Staphycid; *Chile*: Fluxacina†; Vitalpen; *China*: Aofolin (奥佛林); Kun Te (昆特); Yifen (伊芬); *Denm.*: Heracillin; *Ger.*: Fluclox; Staphylex; *Gr.*: Floxapen; Itaclox; *Hong Kong*: Floxapen†; Fluclоxil†; *India*: Neoflox; *Indon.*: Floxapen†; *Irl.*: Floxapen; Flucillin; Fluclon; Geriflox; *Ital.*: Cloxillin; Evercid; Faifloc; Fareclox; Flucacid; Flucef; Flucinal; Fluclox; Fluxacil; Liderclox; Nepenic; Pantaflux; Recaflux; *Malaysia*: Flucloxil; Staphlex†; *Mex.*: Floxapen†; *Neth.*: Floxapen; *NZ*: Floxapen; Flucloxin; Staphlex†; *Philipp.*: Fluclox; Fluxin; Stafloxin; *Port.*: Floxapen; *S.Afr.*: Floxapen†; Flupen; *Singapore*: Staphlex†; *Swed.*: Heracillin; *Switz.*: Floxapen; *Thai.*: Staphycid†; *Turk.*: Flix; Floksin; *UK*: Floxapen; Fluclomix; Ladropen; *Venez.*: Floxapen.

Multi-ingredient Preparations. *China*: Pu Wei (苏威); Kun Bai (昆柏); *Ger.*: Flanamox; *S.Afr.*: Macropen; Megapen; Suprapen; *UK*: Magnapen†; Magnapen; Magnapen.

Pharmacopoeial Preparations

BP 2014: Co-fluampicil Capsules; Co-fluampicil Oral Suspension; Flucloxacillin Capsules; Flucloxacillin Injection; Flucloxacillin Oral Solution; Flucloxacillin Oral Suspension.

Flumequine *(BAN, USAN, rINN)*

Flumechin; Flumekiini; Flumekin; Flumekvinas; Flumequin; Flumequina; Flumequine; Flumequinum; R-802; Флумехин.

9-Fluoro-6,7-dihydro-5-methyl-1-oxo-1*H*,5*H*-pyrido[3,2,1-*ij*]quinoline-2-carboxylic acid.

$C_{14}H_{12}FNO_3$=261.3

CAS — 42835-25-6.

ATC — J01MB07.

ATC Vet — QJ01MB07.

UNII — UVG8VSP2SJ.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Flumequine). A white or almost white microcrystalline powder. Practically insoluble in water; sparingly soluble in dichloromethane; very slightly soluble in methyl alcohol; freely soluble in dilute solutions of alkali hydroxides.

Profile

Flumequine is a 4-quinolone antibacterial with actions and uses similar to those of nalidixic acid (p. 330.3). It may be more active *in vitro* against some Enterobacteriaceae. In the treatment of urinary-tract infections doses of 400 mg are given orally 3 times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Apurone.

Flurithromycin Ethyl Succinate *(rINNM)*

Etilsuccinato de fluritromicina; Flurithromycin Ethylsuccinate; Flurithromycine, Éthylsuccinate de; Flurithromycini Ethylsuccinas; Fluritromicina, etilsuccinato de [erINNM]; Флуритромицина Этилсукцинат.

(8*S*)-8-Fluoroerythromycin mono(ethyl butanedioate) ester.

$C_{43}H_{74}FNO_{16}$=880.1

CAS — 82664-20-8 (flurithromycin); 82730-23-2 (flurithromycin ethyl succinate).

ATC — J01FA14.

ATC Vet — QJ01FA14.

Profile

Flurithromycin is a fluorinated macrolide antibacterial derived from erythromycin (p. 291.2). It is given orally as the ethyl succinate but doses are expressed in terms of the base. The usual dose in the treatment of susceptible infections is the equivalent of 375 mg of flurithromycin twice daily, after meals.

References.

1. Saverino D, *et al.* Antibacterial profile of flurithromycin, a new macrolide. *J Antimicrob Chemother* 1992; 30: 261–72.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Flurizic; Mizar; Ritro.

Formosulfathiazole

Formaldehyde-sulphathiazole; Formosulfatiazol; Formosulphathiazole; Methylenesulfathiazole.

$(C_9H_9N_3O_2S_2.CH_2O)_x$

CAS — 12041-72-4; 13968-86-0.

ATC Vet — QA07AB90; QD06BA90; QG51AA09.

Profile

Formosulfathiazole, a condensation product of sulfathiazole with formaldehyde, has properties similar to those of sulfamethoxazole (p. 367.2). It is poorly absorbed and has been given for its antibacterial action in the gastrointestinal tract, often with other antibacterials.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Pol.*: Sterovag†; *Spain*: Sulfintestin Neomicina.

Fosfomycin *(BAN, USAN, rINN)*

Fosfomicina; Fosfomycine; Fosfomycinum; Fosfomysiini; MK-955; Phosphomycin; Phosphonomycin; Фосфомицин.

(1*R*,2*S*)-1,2-Epoxypropylphosphonic acid.

$C_3H_7O_4P$=138.1

CAS — 23155-02-4.

ATC — J01XX01.

ATC Vet — QJ01XX01.

UNII — 2N81MY12TE.

Description. Fosfomycin is an antibacterial isolated from *Streptomyces fradiae* and other *Streptomyces* spp. or produced synthetically.

Fosfomycin Calcium *(BANM, rINNM)*

Calcii Fosfomycinum; Fosfomicina cálcica; Fosfomicina cálcical; Fosfomicino kalcio druska; Fosfomycin-Calcium; Fosfomycin vápenatá sůl monohydrát; Fosfomycine Calcique; Fosfomycinkalcium; Fosfomycinum Calcicum; Fosfomycinum Calcicum Monohydricum; Fosfomysiinikalsium; Foszfomicin-kalcium; Кальций Фосфомицин.

$C_3H_5CaO_4P.H_2O$=194.1

CAS — 26016-98-8; 26469-67-0.

ATC — J01XX01.

ATC Vet — QJ01XX01.

UNII — 76EIK6888N (fosfomycin calcium); T330QG2NYS (fosfomycin calcium hydrate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn.*

Ph. Eur. 8: (Fosfomycin Calcium). A white or almost white powder. Slightly soluble in water; practically insoluble in acetone, in dichloromethane, and in methyl alcohol. A 0.1% solution in water has a pH of 8.1 to 9.6. Store in airtight containers. Protect from light.

Fosfomycin Sodium *(BANM, rINNM)*

Fosfomicina sódica; Fosfomicino natrio druska; Fosfomycin disodná sůl; Fosfomycin-Natrium; Fosfomycine Sodique; Fosfomycinnatrium; Fosfomycinum Dinatricum; Fosfomycinum Natricum; Fosfomysiininatrium; Foszfomicin-nátrium; Natrii Fosfomycinum; Натрий Фосфомицин.

$C_3H_5Na_2O_4P$=182.0

CAS — 26016-99-9.

ATC — J01XX01.

ATC Vet — QJ01XX01.

UNII — 97MMO19FNO.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn.*

Ph. Eur. 8: (Fosfomycin Sodium). A white or almost white, very hygroscopic powder. Very soluble in water; practically insoluble in dehydrated alcohol and in dichloromethane; sparingly soluble in methyl alcohol. A 5% solution in water has a pH of 9.0 to 10.5. Store in airtight containers. Protect from light.

Fosfomycin Trometamol *(BANM, rINNM)*

Fosfomicina trometamol; Fosfomicinas trometamolis; Fosfomisin Trometamol; Fosfomycin Tromethamine (USAN); Fosfomycine Trométamol; Fosfomycintrometamol; Fosfomycin-trometamol; Fosfomycinum Trometamol; Fosfomycinum Trometamoli; Fosfomycinum Trometamolum; Fosfomycyna z trometamolem; Fosfomysiinitrometamoli; Foszfomicin-trometamol; FZ-588; Z-1282; Фосфомицин Трометамол.

$C_3H_7O_4P.C_4H_{11}NO_3$=259.2

CAS — 78964-85-9.

ATC — J01XX01.

ATC Vet — QJ01XX01.

UNII — 7FXW6U30GY.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Fosfomycin Trometamol). A white or almost white, hygroscopic powder. Very soluble in water; slightly soluble in alcohol and in methyl alcohol; practically insoluble in acetone. A 5% solution in water has a pH of 3.5 to 5.5. Store in airtight containers.

USP 36: (Fosfomycin Tromethamine). pH of a 5% solution in carbon dioxide-free water is 3.5 to 5.5. Store in airtight containers at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Fosfomycin is a phosphonic acid antibacterial given orally as the trometamol or calcium salt and intramuscularly or intravenously as the disodium salt in the treatment of a variety of bacterial infections due to susceptible organisms. Doses are expressed in terms of the base; fosfomycin calcium 1.4 g, fosfomycin sodium 1.3 g, and fosfomycin trometamol 1.9 g are each equivalent to about 1 g of fosfomycin.

In the treatment of acute uncomplicated infections of the urinary tract (p. 213.1), fosfomycin trometamol is given orally as a single dose equivalent to 3 g of fosfomycin. Fosfomycin trometamol has also been used for the prophylaxis of infection in transurethral surgical procedures. For a discussion of surgical infections and their prophylaxis and treatment, see p. 209.1.

The usual oral dose of fosfomycin calcium is the equivalent of 0.5 to 1 g of fosfomycin every 8 hours. Higher doses have been given parenterally as the sodium salt, with up to 20 g daily having been given intravenously in severe infection.

Fosfomycin has also been used with beta lactam antibacterials.

References.

1. Reeves DS. Fosfomycin trometamol. *J Antimicrob Chemother* 1994; **34:** 853–8.
2. Patel SS, *et al.* Fosfomycin tromethamine: a review of its antibacterial activity, pharmacokinetic properties and therapeutic efficacy as a single-dose oral treatment for acute uncomplicated lower urinary tract infections. *Drugs* 1997; **53:** 637–56.
3. Stein GE. Single-dose treatment of acute cystitis with fosfomycin tromethamine. *Ann Pharmacother* 1998; **32:** 215–19.
4. Schito GC. Why fosfomycin trometamol as first line therapy for uncomplicated UTI? *Int J Antimicrob Agents* 2003; **22** (suppl 2): 79–83.
5. Rudenko N, Dorofeyev A. Prevention of recurrent lower urinary tract infections by long-term administration of fosfomycin trometamol: double blind, randomized, parallel group, placebo controlled study. *Arzneimittelforschung* 2005; **55:** 420–7.
6. Sádaba-Díaz de Rada B, *et al.* Fosfomicina trometamol: dosis múltiples como pauta larga en el tratamiento de las infecciones urinarias bajas. *Enferm Infecc Microbiol Clin* 2006; **24:** 546–50.
7. Pullukcu H, *et al.* Fosfomycin in the treatment of extended spectrum beta-lactamase-producing Escherichia coli-related lower urinary tract infections. *Int J Antimicrob Agents* 2007; **29:** 62–5.
8. Falagas ME, *et al.* Fosfomycin: use beyond urinary tract and gastrointestinal infections. *Clin Infect Dis* 2008; **46:** 1069–77.
9. Falagas ME, *et al.* Fosfomycin for the treatment of infections caused by multidrug-resistant non-fermenting Gram-negative bacilli: a systematic review of microbiological, animal and clinical studies. *Int J Antimicrob Agents* 2009; **34:** 111–20.
10. Falagas ME, *et al.* Fosfomycin for the treatment of infections caused by Gram-positive cocci with advanced antimicrobial drug resistance: a review of microbiological, animal and clinical studies. *Expert Opin Invest Drugs* 2009; **18:** 921–44.
11. Falagas ME, *et al.* Fosfomycin for the treatment of multidrug-resistant, including extended-spectrum beta-lactamase producing, Enterobacteriaceae infections: a systematic review. *Lancet Infect Dis* 2010; **10:** 43–50.
12. Popovic M, *et al.* Fosfomycin: an old, new friend? *Eur J Clin Microbiol Infect Dis* 2010; **29:** 127–42.

Adverse Effects and Precautions

Gastrointestinal disturbances including nausea and diarrhoea, transient increases in serum concentrations of aminotransferases, headache, visual disturbances, and skin rashes have been reported after use of fosfomycin. Eosinophilia and, rarely, angioedema, aplastic anaemia, exacerbation of asthma, cholestatic jaundice, hepatic necrosis, and toxic megacolon, have also occurred.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fosfomycin as probably not porphyrinogenic; it may be used as a drug of first-choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Antimicrobial Action

Fosfomycin is a bactericidal antibacterial. After active uptake into the cell it is reported to interfere with the first step in the synthesis of bacterial cell walls. It is active *in vitro* against a range of Gram-positive and Gram-negative bacteria including *Staphylococcus aureus*, some streptococci, most Enterobacteriaceae, *Haemophilus influenzae*, *Neisseria* spp., and some strains of *Pseudomonas aeruginosa* although some are resistant. *Bacteroides* spp. are not sensitive.

Bacterial resistance to fosfomycin has been reported and can be chromosomal or, in some organisms, transferred by plasmids encoding multiple resistance (for example in *Serratia marcescens*). However, there appears to be little cross-resistance with other antibacterials.

Fosfomycin has been reported to show antimicrobial synergy with many antibacterials against organisms such as enterococci, meticillin-resistant *Staph. aureus*, and the enterobacteria. Such synergistic effects have been reported particularly with the beta lactams, but also with aminoglycosides, macrolides, tetracyclines, chloramphenicol, rifamycin, and lincomycin. Antimicrobial antagonism with a beta lactam has also been reported.

There is some suggestion that use of fosfomycin with an aminoglycoside may also reduce the nephrotoxicity of the latter *in vivo*.

References.

1. Barry AL, Brown SD. Antibacterial spectrum of fosfomycin trometamol. *J Antimicrob Chemother* 1995; **35:** 228–30.

Pharmacokinetics

Fosfomycin or fosfomycin calcium are poorly absorbed from the gastrointestinal tract. Peak plasma concentrations 4 hours after a 1-g dose of fosfomycin calcium are about 7 micrograms/mL, and bioavailability has been calculated at about 30 to 40%. Similar bioavailability has been reported for the trometamol salt, and plasma concentrations of about 22 to 32 micrograms/mL have been reported 2 hours after an oral dose equivalent to 3 g fosfomycin. Fosfomycin disodium is given intramuscularly or intravenously: intravenous infusion of a 4-g dose results in peak plasma concentrations of around 120 micrograms/mL. The plasma half-life is about 2 hours. Fosfomycin does not appear to be bound to plasma proteins. It crosses the placenta and is widely distributed in body fluids including the CSF; small amounts have been found in breast milk and bile. The majority of a parenteral dose is excreted unchanged in the urine, by glomerular filtration, within 24 hours.

Urinary concentrations of up to 3 mg/mL have been reported within 2 to 4 hours of an oral dose of fosfomycin trometamol equivalent to 3 g of fosfomycin; therapeutic concentrations of 200 to 300 micrograms/mL remained in urine after 48 hours.

References.

1. Bergan T, *et al.* Pharmacokinetic profile of fosfomycin trometamol. *Chemotherapy* 1993; **39:** 297–301.
2. Roussos N, *et al.* Clinical significance of the pharmacokinetic and pharmacodynamic characteristics of fosfomycin for the treatment of patients with systemic infections. *Int J Antimicrob Agents* 2009; **34:** 506–15.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Veramina; *Austria*: Monuril; *Belg.*: Monuril; *Braz.*: Monuril; *Canad.*: Monurol; *Chile*: Monurol†; *China*: Fu An Xin (复安欣); Fumeixin (复美欣); Monurol (美乐力); Vnikon (维尼康); *Fin.*: Monurol†; *Fr.*: Fosfocine; Monuril; Uridoz; *Ger.*: InfectoFos; Monuril; *Gr.*: Monurol; *Hong Kong*: Monurol; *Hung.*: Monural; *Indon.*: Fosmicin; Fosmidex; Monuril; *Irl.*: Monuril; *Israel*: Monurol; *Ital.*: Fosfocin; Monuril; *Jpn*: Fosmicin-S; Fosmicin; *Malaysia*: Monurol; *Mex.*: Fosfocil; Monurol; *Neth.*: Monuril; *Philipp.*: Monurol; *Pol.*: Monural; *Port.*: Monuril; *Rus.*: Monural (Монурал); Urofosfabol (Урофосфабол); *S.Afr.*: Urizone; *Singapore*: Monurol; *Spain*: Fosfocina; Monurol; Solufos; Uroseptic; *Switz.*: Monuril; *Thai.*: Fosfomin; Fosmicin; Monurol; *Turk.*: Monurol; Urocare; Uromisin; *Ukr.*: Monural (Монурал); *USA*: Monurol.

Framycetin Sulfate *(BANM, rINNM)*

Framicetina, sulfato de; Framicetino sulfatas; Framicetinszulfát; Framycetin Sulphate; Framycétine, Sulfate de; Framycetini Sulfas; Framycetinsulfat; Framycetin-sulfát; Framysetiinisulfaatti; Neomycin B Sulphate; Sulfato de framicetina; Sulfato de neomicina B; Фрамицетина Сульфат.

2-Deoxy-4-*O*-(2,6-diamino-2,6-dideoxy-α-D-glucopyranosyl)-5-*O*-[3-*O*-(2,6-diamino-2,6-dideoxy-β-L-idopyranosyl)-β-D-ribofuranosyl]streptamine sulphate.

$C_{23}H_{46}N_6O_{13}xH_2SO_4$

CAS — 119-04-0 (framycetin); 4146-30-9 (framycetin sulfate).

ATC — D09AA01; R01AX08; S01AA07.

ATC Vet — QD09AA01; QJ01GB91; QR01AX08; QS01AA07.

UNII — Y3720KZ4TQ.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Framycetin Sulfate). A substance produced by growth of selected strains of *Streptomyces fradiae* or *S. decaris* or obtained by any other means. It contains not more than 3% of neomycin C (p. 331.3) and loses not more than 8% of its weight on drying. A white or yellowish-white, hygroscopic powder. The potency is not less than 630 units of neomycin B per mg, calculated with reference to the dried substance. Freely soluble in water; very slightly soluble in alcohol; practically insoluble in acetone. A 1% solution in water has a pH of 6.0 to 7.0. Store in airtight containers. Protect from light.

Profile

Framycetin is an aminoglycoside antibacterial that forms the major component of neomycin (p. 331.3) and has similar actions and uses. Framycetin sulfate is used topically in usual concentrations of 1% for the treatment of infections of the skin, and in concentrations of 0.5% for infections of the eye and ear. It is often used with other antibacterials and corticosteroids in topical preparations.

Framycetin sulfate is poorly absorbed from the gastrointestinal tract and has been given orally for the treatment of gastrointestinal infections and pre-operatively for bowel preparation. It has sometimes been given prophylactically as part of regimens for the selective decontamination of the digestive tract in patients in intensive care.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Sofra-Tulle†; Soframycin; *Belg.*: Soframycine; *Canad.*: Sofra-Tulle; Soframycin; *Ger.*: Leukase N; *India*: Frade; Sofra-Tulle; Soframycin; *Indon.*: Daryant-Tulle; Sofra-Tulle; *Irl.*: Soframycin†; *NZ*: Soframycin; *Philipp.*: Steri-Tin; *Rus.*: Isofra (Изофра); *S.Afr.*: Sofra-Tulle†; Soframycin†; *Singapore*: Fractin; Soframycin; *Switz.*: Soframycin†; *Thai.*: Sofra-Tulle; *UK*: Sofra-Tulle†; *Ukr.*: Isofra (Изофра).

Multi-ingredient Preparations. *Arg.*: Biotaer Nasal†; *Austral.*: Otodex; Sofradex; Soframycin†; *Austria*: Leukase†; *Belg.*: Frakidex; Sofraline; Sofrasolone; *Braz.*: Fonergin; *Canad.*: Opticort; Proctol; Proctomyxin HC; Proctosedyl; ratio-Proctosone; Sofracort; Soframycin; Soframycin; *Cz.*: Pulpomixine†; Septomixine; *Denm.*: Proctosedyl; Sofradex; *Fin.*: Proctosedyl; *Fr.*: Arthrisone†; Cortexan Framycetine; Corticetine†; Frakidex; Framyxone; Polyfra†; Pulpomixine; Septomixine; *Ger.*: Leukase N; *Gr.*: Sofradex; *Hong Kong*: Frakidex; Frazoline†; Sofradex; *India*: Proctosedyl; Sofracort; Sofradex-F; Sofradex; *Indon.*: Blecidex; Sofradex; *Irl.*: Proctosedyl; Sofradex; *Malaysia*: Proctosedyl; Sofradex; *Neth.*: Proctosedyl; Sofradex; *Norw.*: Proctosedyl; Sofradex; *NZ*: Sofradex; Soframycin†; *Philipp.*: Proctosedyl; *Pol.*: Carident; Dexadent; *Port.*: Frakidex; *Rus.*: Proctosedyl (Проктоседил); Proctosedyl M (Проктоседил М); Sofradex (Софрадекс); *S.Afr.*: Proctosedyl; Sofradex; *Singapore*: Frakidex; Proctosedyl; Sofradex; *Spain*: Abrasone; Aldoderma; Nesfare; Otomidrin; *Swed.*: Proctosedyl†; *Switz.*: Dexalocal-F; Frakidex; Septomixine; Sofradex†; *Thai.*: Proctosedyl; Sofradex; Topifram; *UK*: Sofradex; *Ukr.*: Proctosedyl (Проктоседил); Sofradex (Софрадекс)†.

Ftivazide *(rINN)*

Ftivazida; Ftivazidum; Phthivazid; Phthivazidum; Фтивазид.

2′-Vanillylideneisonicotinohydrazide monohydrate.

$C_{14}H_{13}N_3O_3.H_2O$=289.3

CAS — 149-17-7 (anhydrous ftivazide).

UNII — 40Q4C3O4V0.

Pharmacopoeias. In *Chin.* and *Int.*

Profile

Ftivazide is an antimycobacterial given orally in the treatment of tuberculosis. It is a derivative of isoniazid.

Furaltadone Hydrochloride *(BANM, rINNM)*

Furaltadone, Chlorhydrate de; Furaltadoni Hydrochloridum; Hidrocloruro de furaltadona; Фуральтадона Гидрохлорид.

(±)-5-Morpholinomethyl-3-(5-nitrofurfurylideneamino)oxazolidin-2-one hydrochloride.

$C_{13}H_{18}N_4O_6.HCl$=360.8

CAS — 139-91-3 (furaltadone); 59302-14-6 (±-furaltadone).

UNII — 37Q02H7JT2.

Pharmacopoeias. *Fr.* includes Furaltadone for veterinary use.

Profile

Furaltadone was formerly given orally as an antibacterial but was later withdrawn owing to its toxic effects. Furaltadone hydrochloride is still used topically in preparations for ear disorders.

Furaltadone has been used in veterinary medicine.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Thai.*: Otosamthong†; SM Oto.

Furazidin

Akritoin; Furagin; Furazidine; Фуразидин.

1-{[3-(5-Nitro-2-furyl)allylidene]amino}hydantoin.

$C_{10}H_8N_4O_5$=264.2

CAS — 1672-88-4.

UNII — K2R4N34Y9I.

Profile

Furazidin is a nitrofuran antibacterial with properties similar to those of nitrofurantoin. It is used in the treatment of urinary-tract infections. A usual oral dose is 100 mg given

four times daily for one day followed by 100 mg given three times daily for 7 to 8 days.

It has been used similarly as the potassium salt.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Pol.*: Furaginum; *Rus.*: Furamag (Фурамаг); Furasol (Фурасол); *Ukr.*: Furamag (Фурамаг); Furasol (Фурасол).

Fusafungine *(BAN, rINN)*

Fusafungin; Fusafungina; Fusafunginum; Фузафунгин.

CAS — 1393-87-9.

ATC — R02AB03.

ATC Vet — QR02AB03.

UNII — 65DD690W0C.

Profile

Fusafungine is a depsipeptide antibacterial produced by *Fusarium lateritium* strain 437. It is active against some Gram-positive and Gram-negative organisms, *Candida albicans*, and *Mycoplasma pneumoniae*. It has also been stated to possess anti-inflammatory activity.

It is used in the form of an aerosol spray in the treatment of infections of the upper respiratory tract, inhaled in usual doses of 500 micrograms every 4 hours into each nostril or via the mouth. These routes may be used simultaneously if necessary.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Locabiosol; *Belg.*: Locabiotal; *Braz.*: Locabiotal; *Cz.*: Bioparox; *Ger.*: Locabiosol; *Gr.*: Locabiotal; *Hung.*: Bioparox; *Irl.*: Locabiotal; *Ital.*: Locabiotal; *Malaysia*: Locabiotal; *Philipp.*: Locabiotal†; *Pol.*: Bioparox; *Port.*: Locabiosol; *Rus.*: Bioparox (Биопарокс); *S.Afr.*: Locabiotal†; *Spain*: Fusaloyos; *Switz.*: Locabiotal; *Turk.*: Locabiotal; *Ukr.*: Bioparox (Биопарокс).

Fusidic Acid *(BAN, USAN, rINN)*

Acide Fusidique; Ácido fusídico; Acidum Fusidicum; Acidum Fusidicum Hemihydricum; Fucidinsyra; Fusidico, ácido; Fusidiinihappo; Fusidik Asit; Fusidinsyra; Fuzidinsav; Fuzido rūgštis; Kyselina fusidová hemihydrát; SQ-16603; Фэузидовая Кислота.

ent-16α-Acetoxy-3β-dihydroxy-4β,8β,14α-trimethyl-18-nor-5β,10α-cholesta-(17Z)-17(20),24-dien-21-oic acid hemihydrate.

$C_{31}H_{48}O_6,½H_2O$=525.7

CAS — 6990-06-3 (anhydrous fusidic acid); 172343-30-5 (fusidic acid hemihydrate).

ATC — D06AX01; D09AA02; J01XC01; S01AA13.

ATC Vet — QD06AX01; QD09AA02; QJ01XC01; QS01AA13.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Fusidic Acid). An antimicrobial substance produced by the fermentation of certain strains of *Fusidium coccineum* or by any other means. A white or almost white crystalline powder. Practically insoluble in water; freely soluble in alcohol. Store at a temperature of 2 degrees to 8 degrees. Protect from light.

Sodium Fusidate *(BANM, rINNM)*

Fusidate de Sodium; Fusidate Sodium (USAN); Fusidato sódico; Natrii Fusidas; Natrio fuzidatas; Natriumfusidaatti; Natriumfusidat; Natrium-fusidát; Nátrium-fuzidát; Sodium, fusidate de; Sodyum Fusidat; SQ-16360; Натрий Фэузидат.

$C_{31}H_{47}NaO_6$=538.7

CAS — 751-94-0.

ATC — D06AX01; D09AA02; J01XC01; S01AA13.

ATC Vet — QD06AX01; QD09AA02; QJ01XC01; QS01AA13.

UNII — J7P3696BCQ.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.*

Ph. Eur. 8: (Sodium Fusidate). An antimicrobial substance produced by the fermentation of certain strains of *Fusidium coccineum* or by any other means. A white or almost white, slightly hygroscopic, crystalline powder. Freely soluble in water and in alcohol. A 1.25% solution in water has a pH of 7.5 to 9.0. Store in airtight containers at a temperature of 2 degrees to 8 degrees. Protect from light.

Incompatibility. UK licensed product information states that reconstituted sodium fusidate injection is incompatible with infusion solutions containing glucose 20% or more, lipid infusions, and peritoneal dialysis fluids; precipitation may occur in solutions with a pH of less than 7.4.

Uses and Administration

Fusidic acid and its salts are antibacterials used mainly in the treatment of susceptible staphylococcal infections, often with other anti-staphylococcal antibacterials to prevent the emergence of resistance (see Resistance, under Antimicrobial Action, p. 305.1). They have been used systemically mainly in infections caused by penicillin-resistant strains, including in osteomyelitis and endocarditis, and topically in eye infections and superficial infections of the skin. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

The fusidates are given orally or topically as fusidic acid or sodium fusidate, or intravenously as sodium fusidate. Sodium fusidate 1 g is equivalent to about 980 mg of fusidic acid. Because of differences in absorption (see Pharmacokinetics, p. 305.1) 250 mg of fusidic acid is therapeutically equivalent to only 175 mg of the sodium salt, so doses of fusidic acid suspension (commonly used in children) appear relatively higher (see p. 304.2). The diolamine salt was formerly used intravenously in humans but is still used in topical preparations in veterinary medicine.

Sodium fusidate is given as tablets in a usual oral adult dose of 500 mg every 8 hours, although this dose may be doubled in severe infection. For cutaneous staphylococcal infections, a dose of 250 mg twice daily is suitable. When given orally as the suspension the usual adult dose is 750 mg of fusidic acid three times daily.

In severe infections in adults weighing over 50 kg, sodium fusidate 500 mg is given three times daily by slow intravenous infusion. Each 500-mg dose is usually given as a buffered solution (pH 7.4 to 7.6) diluted to 500 mL with sodium chloride or other suitable intravenous solution. For those weighing less than 50 kg, a dose of 6 to 7 mg/kg three times daily is used. For details of doses in children, see p. 304.2.

Sodium fusidate as a 2% ointment or medicated dressing, or fusidic acid as a 2% cream or gel, are used in the local treatment of skin infections. Eye drops containing fusidic acid 1% are used in eye infections. Topical use may lead to problems of resistance (see Antimicrobial Action, p. 304.3).

References.
1. García-Rodríguez JA, *et al.* Acido fusidico. *Rev Esp Quimioter* 2003; 16: 161–71.
2. Doughty MJ, Dutton GN. Fusidic acid viscous eyedrops—an evaluation of pharmacodynamics, pharmacokinetics and clinical use for UK optometrists. *Ophthalmic Physiol Opt* 2006; 26: 343–61.
3. Schöfer H, Simonsen L. Fusidic acid in dermatology: an updated review. *Eur J Dermatol* 2010; 20: 6–15.

Administration in children. Fusidic acid and its salt may be used in neonates and children for the treatment of susceptible staphylococcal infections, particularly those due to penicillin-resistant strains. *Oral* doses of **fusidic acid suspension**, given three times daily, are:

- up to 1 year old: about 16 mg/kg
- 1 to 5 years: 250 mg
- 5 to 12 years: 500 mg
- over 12 years: usual adult doses (see above)

Suggested doses of **sodium fusidate** by *intravenous* infusion are:

- 1 month and above: if weighing less than 50 kg, 6 to 7 mg/kg three times daily; heavier children may be given usual adult doses (see Uses and Administration, above)

Adverse Effects and Precautions

Apart from mild gastrointestinal upsets, fusidic acid or sodium fusidate appear to be well tolerated when given orally. Treatment with fusidates, orally or especially by the intravenous route, has been associated with jaundice and changes in liver function; normal liver function is usually restored when treatment is stopped. Therefore, fusidates should be given with caution to patients with hepatic impairment, and periodic monitoring of hepatic function is recommended in these patients and in those receiving high or prolonged oral doses. Caution is also required in biliary disease or biliary obstruction.

Venospasm, thrombophlebitis, and haemolysis have occurred in patients given fusidates intravenously. To reduce this it is recommended that solutions be buffered and that the solution should be given as a slow infusion into a large vein where there is a good blood flow. Hypocalcaemia has occurred after use of intravenous doses above those recommended, and has been attributed to the phosphate-citrate buffer in the preparation. Intramuscular or subcutaneous use may lead to tissue necrosis and is contra-indicated.

Hypersensitivity reactions in the form of rashes and irritation may occur with topical fusidates; rash is rare after systemic use.

Fusidic acid competes with bilirubin for binding to albumin *in vitro* and caution has been advised if it is given to premature, jaundiced, acidotic, or seriously-ill neonates because of the risk of kernicterus.

Effects on the blood. There have been occasional reports of granulocytopenia[1-3] and thrombocytopenia[3] after the use of fusidic acid systemically. Sideroblastic anaemia has also been reported.[4] UK licensed product information also states that there have been isolated cases of neutropenia, agranulocytosis, and pancytopenia.

1. Revell P, *et al.* Granulocytopenia due to fusidic acid. *Lancet* 1988; ii: 454–5.
2. Evans DIK. Granulocytopenia due to fusidic acid. *Lancet* 1988; ii: 851.
3. Leibowitz G, *et al.* Leukopenia and thrombocytopenia due to fusidic acid. *Postgrad Med J* 1991; 67: 591–2.
4. Vial T, *et al.* Sideroblastic anaemia during fusidic acid treatment. *Eur J Haematol* 2004; 72: 358–60.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fusidic acid as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

Although the exact metabolic pathways of fusidic acid are not known, an interaction has been suspected with drugs metabolised by the hepatic cytochrome P450 isoenzyme CYP3A4, and UK licensed product information suggests avoiding their use with fusidic acid.

Antivirals. An HIV-infected patient had fusidic acid toxicity after taking fusidic acid orally for one week with his usual antiretroviral treatment of *ritonavir*, *saquinavir*, and stavudine.[1] The plasma-fusidic acid concentration was about twice that expected and the ritonavir and saquinavir concentrations were also elevated. Fusidic acid was stopped and the patient initially improved. However, 4 days later he presented with jaundice, nausea, weakness, and further increases in liver function tests and hence all medications were stopped. The fusidic acid concentration, as well as those of ritonavir and saquinavir, were found to be still significantly elevated 6 days after fusidic acid had been stopped. The patient was able to restart his antiretroviral therapy later with no problems. The authors suggested that this interaction may be due to mutual inhibition of metabolism between the HIV-protease inhibitors and fusidic acid, and recommended that use of fusidic acid with either saquinavir or ritonavir should be avoided.

1. Khaliq Y, *et al.* A drug interaction between fusidic acid and a combination of ritonavir and saquinavir. *Br J Clin Pharmacol* 2000; 50: 82–3.

Lipid regulating drugs. For reference to the effect of fusidic acid in patients receiving *statins*, see p. 1494.3.

Antimicrobial Action

Fusidic acid is a steroidal antibacterial with a bacteriostatic or bactericidal activity, mainly against Gram-positive bacteria.

Fusidic acid inhibits bacterial protein synthesis although, in contrast to drugs such as the macrolides or tetracyclines, it does not bind to the bacterial ribosome, but inhibits a factor necessary for translocation of peptide subunits and elongation of the peptide chain. It is capable of inhibiting protein synthesis in mammalian cells but exerts a selective action against susceptible infecting organisms because of poor penetration into the host cell.

- Fusidic acid is very active against staphylococci, notably *Staph. aureus* and *Staph. epidermidis* (including meticillin-resistant strains). *Nocardia asteroides* and many clostridial strains are also highly susceptible. The streptococci and enterococci are less susceptible.
- Most Gram-negative bacteria are intrinsically resistant but fusidic acid is active against *Neisseria* spp. and *Bacteroides fragilis*.
- It has some activity against strains of *Mycobacterium tuberculosis* and is highly active against *M. leprae*.
- Fungi are resistant, but fusidic acid has some activity against a range of protozoa including *Giardia lamblia* and *Plasmodium falciparum*.
- High concentrations of fusidate are reported to inhibit viral growth *in vitro*, including that of HIV, although it is unclear whether this represents a surfactant effect, a general cytotoxic effect, or a genuine antiviral action.

No synergy has been shown *in vitro* in most studies between fusidic acid and rifampicin or vancomycin, and antagonism of the effects of ciprofloxacin has been reported. Interactions with the penicillins are complex, with either antagonism of the effect of one or both drugs, or no interaction. However, use of an antistaphylococcal penicillin with fusidic acid may prevent the emergence of fusidic acid-resistant staphylococcal mutants, and such combinations may be clinically effective.

Resistance. Resistance may be chromosomally mediated, representing altered protein synthesis, or plasmid-mediated, which appears to be due to reduced penetration of active

drug into the cell. For further details on the increase of resistance to fusidic acid, see p. 305.1.

Resistance. There has been an increase in the number of reports of fusidic acid resistance in *Staphylococcus aureus* particularly in dermatological isolates. The number of clinical isolates of initially resistant staphylococci has historically been low at about 1 to 2% overall.[1-3] However, in the UK the rate of fusidic acid resistance in staphylococcal isolates increased by up to 200% during the 1990s, and over half of all isolates are resistant in some samples.[3] This has been attributed to the widespread topical use of fusidic acid.[1-3] Resistance may remain high for some time, even where use of fusidates has been restricted to preserve activity.[4]

The rate of resistance to short courses of fusidic acid used in systemic monotherapy is reported to be about 5%. In contrast, when given systemically with other antibacterials, the rate of resistance remains low at 0.8%.[5] Therefore, it has been suggested that systemic fusidic acid should be restricted to use with other antibacterial agents where clinically indicated in order to reduce the rate of resistance.[3,5]

1. Livermore D, *et al.* Fusidic-acid use and resistance. *Lancet* 2002; 360: 806.
2. Mason BW, *et al.* Fusidic acid resistance in community isolates of methicillin-susceptible Staphylococcus aureus and fusidic acid prescribing. *J Antimicrob Chemother* 2003; 51: 1033–6.
3. Dobie D, Gray J. Fusidic acid resistance in Staphylococcus aureus. *Arch Dis Child* 2004; 89: 74–7.
4. Mitra A, *et al.* High levels of fusidic acid-resistant Staphylococcus aureus despite restrictions on antibiotic use. *Clin Exp Dermatol* 2009; 34: 136–9.
5. Howden BP, Grayson ML. Dumb and dumber—the potential waste of a useful antistaphylococcal agent: emerging fusidic acid resistance in Staphylococcus aureus. *Clin Infect Dis* 2006; 42: 394–400.

Pharmacokinetics

Sodium fusidate is well absorbed from the gastrointestinal tract, and a single oral 500-mg dose is reported to produce mean plasma concentrations of about 30 micrograms/mL within 2 to 4 hours, although there is considerable interindividual variation. Oral suspensions of fusidic acid are less well absorbed, with a bioavailability reported to be about 70% of that for sodium fusidate. Absorption may be delayed by food and may be more rapid in children than adults. Some accumulation occurs with repeated dosage and plasma concentrations of 100 micrograms/mL or more have been reported after 500 mg of sodium fusidate given three times daily for 4 days.

Fusidate is widely distributed into tissues and body fluids, including bone, pus, and synovial fluid; it penetrates cerebral abscesses but does not enter CSF in appreciable amounts. It has been found in the fetal circulation and in breast milk. About 95% or more of fusidate in the circulation is bound to plasma proteins.

Fusidate has a plasma half-life of about 10 to 15 hours. It is excreted in the bile, almost entirely as metabolites, some of which have weak antimicrobial activity. About 2% appears unchanged in the faeces. Little is excreted in the urine or removed by haemodialysis.

References.

1. Reeves DS. The pharmacokinetics of fusidic acid. *J Antimicrob Chemother* 1987; 20: 467–76.
2. Peter J-D, *et al.* Pharmacokinetics of intravenous fusidic acid in patients with cholestasis. *Antimicrob Agents Chemother* 1993; 37: 501–6.
3. Brown NM, *et al.* The pharmacokinetics and protein-binding of fusidic acid in patients with severe renal failure requiring either haemodialysis or continuous ambulatory peritoneal dialysis. *J Antimicrob Chemother* 1997; 39: 803–9.
4. Turnidge J. Fusidic acid pharmacology, pharmacokinetics and pharmacodynamics. *Int J Antimicrob Agents* 1999; 12 (suppl 2): S23–S34.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Acifusin; Arzimol; Biofucid; Drum; Fucidin; Fucithalmic; Fusitop; Gelbiotic; ***Austral.***: Fucidin; ***Austria***: Fucidin; Fucithalmic; ***Belg.***: Affusine; Fucidin; Fucithalmic; ***Braz.***: Verutex; ***Canad.***: Fucidin; Fucithalmic; ***Chile***: Fucidin; Fucithalmic; ***China***: Fucidin (立思丁); Fucithalmic (夫司名); Phudicin (奥络); ***Cz.***: Fucidin; Fucithalmic; ***Denm.***: Fucidin; Fucidine; Fucithalmic; ***Fin.***: Fucidin; Fucithalmic; ***Fr.***: Diacutis†; Fucidine; Fucithalmic; ***Ger.***: Fucidine; Fucithalmic; Fusicutan; ***Gr.***: Flusterix; Fucidin; Fusindac; ***Hong Kong***: Foban; Fucidin; Fucithalmic; Fusidate; Qualifutin; ***Hung.***: Fucidin; Fucithalmic†; ***India***: Fucidin; Fucin; Fucinex; Fucithalmic; Fudec; Fudic; Fusa; Fusibact; Fusid; Fusiderm; Fusigen; Fusital; Fusiwal; Fuson; Futop; Noboyle; ***Indon.***: Afucid; Fucidin; Fucilex; Fucithalmic; Fuladic; Fuson; Fusycom; Futaderm; ***Irl.***: Fucidin; Fucithalmic; ***Israel***: Fucidin; Fucithalmic; Staphiderm; ***Ital.***: Dermomycin; Fucidin; Fucithalmic; ***Malaysia***: Foban; Fucidin Intertulle; Fucidin; Fucithalmic; ***Mex.***: Aceler; Fucidin; Uniderm; ***Neth.***: Affusine; Fucidin; Fucidine; Fucithalmic; ***Norw.***: Fucidin; Fucithalmic; ***NZ***: Foban; Fucidin; Fucithalmic; ***Philipp.***: Flexid; Fucidin; Fucithalmic; Fusigen; Fuson; Hoebenate; Hopaq; Woncare; ***Pol.***: Fucidin; Fusacid; ***Port.***: Fucidine; Fucithalmic; Fusextrine; Infloc; Nadiclox; ***Rus.***: Fucidin (Фуцидин); Fucithalmic (Фуцисталмик); ***S.Afr.***: Fucidin; Fucithalmic; ***Singapore***: Duzen; Foban; Forsuderm; Fucidin; Fucithalmic†; Fudikin; ***Spain***: Fucidine; Fucithalmic; ***Swed.***: Fucidin; Fucithalmic; ***Switz.***: Fucidin; Fucithalmic; Fusicutan; ***Thai.***: Difusin; Foban; Fucidin; Fucithalmic; Fusid; ***Turk.***: Fucidin; Fucithalmic; Robisid; Stafeks; Stafine; ***UAE***: Futasole; ***UK***: Fucidin; Fucithalmic; ***Ukr.***: Fusiderm (Фузидерм).

Multi-ingredient Preparations. ***Arg.***: Acifusin B; Arzimol B; Drum B; Fucicort; Fucidin H; Fusimed B; Fusimed; Gelbiotic Plus; ***Belg.***: Fucicort; Fucidin Hydrocortisone; ***Braz.***: Veruderm B; Verutex B; ***Canad.***: Fucidin H; ***Chile***: Fucicort; Fucidin H; ***Cz.***: Fucicort; Fucidin H; ***Denm.***: Fucibet; Fucicort; Fucidin-Hydrocortison; ***Fin.***: Fucicort; Fucidin-Hydrocortison; ***Ger.***: Fucicort; Fucidine H; ***Gr.***: Alpider; Befucil; Betacort; Betafusin; Betasid; Betfu; Pubecot; Fucicort; Fucicream; Fucidin H; Fusibet; Fusindac-H; Hydrofusin; Roseti; Sensibio; Staficort; ***Hong Kong***: Fobancort; Fucicort; Fucidin H; ***Hung.***: Fucicort; Fucidin H; ***India***: Clonate-F; Fucibet; Fucidin H; Fucin-B; Fudec-B; Fudec-M; Fusacort; Fusibact-B; Fusiderm B; Fusigen-B; Fusiwal-B; Fuson-B; Fuson-H; Halostrol-F; Halovate-F; Mecloma-F; Momoz-F; ***Indon.***: Fucicort; ***Irl.***: Fucibet; Fucidin H; ***Israel***: Fucicort; Fucidin H; ***Ital.***: Dermomycin Cort; Fucicort; Fucidin H; Piodermina; ***Malaysia***: Axcel Fusi-Corte†; Foban-Hydro; Fobancort; Fucicort; Fucidin H; Fusidic B; ***Mex.***: Aceler-Co; Fucicort; ***Neth.***: Fucidin + Hydrocortisone†; ***Norw.***: Fucidin-Hydrocortison; ***NZ***: Fucicort; ***Philipp.***: Fucicort; Fucidin H; Hoebedic; ***Port.***: Fucicort; Fucidine H; ***Rus.***: Fucicort (Фуцикорт); Fucidin H (Фуцидин Г); Fugentin (Фугентин); ***S.Afr.***: Fucidin H; ***Singapore***: Fobancort; Fucicort; Fucidin H; ***Spain***: Fucibet; Fucidine H; ***Swed.***: Fucidin-Hydrocortison; ***Switz.***: Fucicort; Fucidin H; ***Thai.***: Fobancort; Fucicort; Fucidin H; ***Turk.***: Fucicort; Fucidin H; ***UAE***: Futasone; ***UK***: Fucibet; Fucidin H; ***Ukr.***: Fusiderm B (Фузидерм Б).

Pharmacopoeial Preparations

BP 2014: Fusidic Acid Cream; Fusidic Acid Eye Drops; Fusidic Acid Oral Suspension; Sodium Fusidate Ointment.

Garenoxacin Mesilate *(BANM, rINNM)*

BMS-284756-01; Garenoxacin Mesylate (USAN); Garénoxacine, Mésilate de; Garenoxacini Mesilas; Mesilato de garenoxacino; T-3811ME; Гареноксацина Мезилат.

1-Cyclopropyl-8-(difluoromethoxy)-7-[(1*R*)-1-methyl-2,3-dihydro-1*H*-isoindol-5-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid methanesulfonate monohydrate.

$C_{23}H_{20}F_2N_2O_4.CH_4O_3S.H_2O$=540.5

CAS — 194804-75-6 (garenoxacin); 223652-82-2 (garenoxacin mesilate); 223652-90-2 (garenoxacin mesilate monohydrate).

ATC — J01MA19.

ATC Vet — QJ01MA19.

UNII — OXI6EF55FR.

Profile

Garenoxacin is a fluoroquinolone antibacterial with properties similar to those of ciprofloxacin (p. 261.2). Garenoxacin is used as the mesilate but doses are given in terms of the base: about 507 mg of the mesilate is equivalent to 400 mg of garenoxacin. It is given orally in the treatment of susceptible infections in usual doses equivalent to 400 mg of garenoxacin daily.

Reviews.

1. Takagi H, *et al.* Clinical studies of garenoxacin. *Int J Antimicrob Agents* 2008; 32: 468–74.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Geninax.

Gatifloxacin *(USAN, rINN)*

AM-1155; BMS-206584-01; CG-5501; Gatifloxacine; Gatifloxacino; Gatifloxacinum; Гатифлоксацин.

(±)-1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid sesquihydrate.

$C_{19}H_{22}FN_3O_4.1½H_2O$=402.4

CAS — 160738-57-8 (anhydrous gatifloxacin); 180200-66-2 (gatifloxacin sesquihydrate).

ATC — J01MA16; S01AE06.

ATC Vet — QJ01MA16; QS01AE06.

UNII — L46188D7KJ (gatifloxacin sesquihydrate); 81485Y3A9A (anhydrous gatifloxacin).

Uses and Administration

Gatifloxacin is a fluoroquinolone antibacterial with actions and uses similar to those of ciprofloxacin (p. 261.2).

It has been given orally, or by intravenous infusion as a 2 mg/mL solution over 60 minutes, for the treatment of susceptible infections, in a usual adult dose of 400 mg once daily. However, systemic products have now been withdrawn in most countries due to safety concerns.

For details of reduced doses to be used in renal impairment, see p. 305.3.

Gatifloxacin is also used as either a 0.3 or 0.5% eye drop for the treatment of bacterial conjunctivitis.

Reviews.

1. Keam SJ, *et al.* Gatifloxacin: a review of its use in the treatment of bacterial infections in the US. *Drugs* 2005; 65: 695–724.
2. Gatifloxacin. *Tuberculosis (Edinb)* 2008; 88: 109–11.

Administration in renal impairment. Oral and intravenous doses of gatifloxacin should be reduced in patients with renal impairment; the usual initial dose of 400 mg should be followed by reduced maintenance doses of 200 mg daily in those with a creatinine clearance of less than 40 mL/minute and in those on haemodialysis or continuous peritoneal dialysis.

Adverse Effects and Precautions

As for Ciprofloxacin, p. 262.2.

Symptomatic hyperglycaemia and/or hypoglycaemia have been reported in patients (usually diabetics) taking gatifloxacin. However, hypoglycaemia, and particularly hyperglycaemia, have occurred in non-diabetic patients. Severe life-threatening events, including hyperosmolar nonketotic hyperglycaemic coma, diabetic ketoacidosis, hypoglycaemic coma, convulsions, and mental status changes have been reported very rarely. Although in most cases the blood-glucose disturbance was reversible, fatalities have been reported. Gatifloxacin should not be given to diabetic patients. Other risk factors for developing blood-glucose disturbances include older age (patients 65 years of age or over), renal impairment, or use of other drugs that alter blood-glucose concentrations, particularly hypoglycaemics. Patients with risk factors should have their blood-glucose concentrations closely monitored and if signs or symptoms of glucose disturbances develop, gatifloxacin should be stopped.

Effects on glucose metabolism. Hypoglycaemia and hyperglycaemia have been associated with gatifloxacin in both diabetic and non-diabetic patients.[1-6] A review[7] of spontaneous adverse effects reported to the FDA in the USA between November 1997 and September 2003 found the rate of blood-glucose disturbances with gatifloxacin to be tenfold higher when compared with ciprofloxacin, levofloxacin, and moxifloxacin. Subsequent population-based case-control studies[8] in elderly patients given fluoroquinolones (ciprofloxacin, gatifloxacin, levofloxacin, or moxifloxacin), second-generation cephalosporins, or macrolides also found an increased risk of blood-glucose disturbances with gatifloxacin.

While blood-glucose disturbances appear to be mainly associated with gatifloxacin, the possibility that they may also be a class effect of fluoroquinolones cannot be excluded; patients most at risk are the elderly, those with diabetes and/or those taking hypoglycaemic drugs, and patients with impaired renal function.[9] Twenty two case reports of dysglycaemia associated with the use of levofloxacin were received by Health Canada between January 1997 and June 2006; reported cases included 15 diabetic patients.[10] In a retrospective cohort study,[11] the odds of severe hypo- or hyperglycaemia among diabetics treated with levofloxacin was significantly higher than in those treated with azithromycin, although the risk from gatifloxacin was found to be greater still.

In contrast, the same study[11] found no significant difference in the odds of severe dysglycaemia between ciprofloxacin and azithromycin, or for non-diabetic patients, between any of the antibacterials studied. A review of the effects of moxifloxacin on blood glucose, including data from large postmarketing studies, suggests it also has no significant effect.[12]

1. Baker SE, Hangii MC. Possible gatifloxacin-induced hypoglycemia. *Ann Pharmacother* 2002; 36: 1722–6.
2. Donaldson AR, *et al.* Possible gatifloxacin-induced hyperglycemia. *Ann Pharmacother* 2004; 38: 602–5.
3. Happe MR, *et al.* Gatifloxacin-induced hyperglycemia. *Ann Intern Med* 2004; 141: 968–9.
4. Khovidhunkit W, Sunthornyothin S. Hypoglycemia, hyperglycemia, and gatifloxacin. *Ann Intern Med* 2004; 141: 969.
5. Greenberg AL, *et al.* Gatifloxacin therapy associated with hypoglycemia. *Clin Infect Dis* 2005; 40: 1210–11.
6. Blommel AL, Lutes RA. Severe hyperglycemia during renally adjusted gatifloxacin therapy. *Ann Pharmacother* 2005; 39: 1349–52.
7. Frothingham R. Glucose homeostasis abnormalities associated with use of gatifloxacin. *Clin Infect Dis* 2005; 41: 1269–76.
8. Park-Wyllie LY, *et al.* Outpatient gatifloxacin therapy and dysglycemia in older adults. *N Engl J Med* 2006; 354: 1352–61.
9. Lewis RJ, Mohr JF. Dysglycaemias and fluoroquinolones. *Drug Safety* 2008; 31: 283–92.
10. Health Canada. Levofloxacin: dysglycemia and liver disorders. *Can Adverse React News* 2007; 17: 1–2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v17n1-eng.pdf (accessed 17/06/08)
11. Aspinall SL, *et al.* Severe dysglycemia with the fluoroquinolones: a class effect? *Clin Infect Dis* 2009; 49: 402–8.
12. Gavin JR, *et al.* Moxifloxacin and glucose homeostasis: a pooled-analysis of the evidence from clinical and postmarketing studies. *Drug Safety* 2004; 27: 671–86.

Interactions

As for Ciprofloxacin, p. 264.3.

Use of gatifloxacin with drugs that alter blood-glucose concentrations increases the risk of blood-glucose disturbances.

Antidiabetics. Given the adverse effects of gatifloxacin, pharmacodynamic interactions with antidiabetics might reasonably be anticipated. Severe and persistent hypoglycaemia occurred in 3 patients taking oral hypoglycaemics (*repaglinide, glibenclamide* and *pioglitazone*, and *glimepiride*) when gatifloxacin was added to their therapy.[1]

1. Menzies DJ, *et al.* Severe and persistent hypoglycemia due to gatifloxacin interaction with oral hypoglycemic agents. *Am J Med* 2002; 113: 232–4.

Antimicrobial Action

As for Ciprofloxacin, p. 265.2.

Gatifloxacin is reported to have greater activity against Gram-positive bacteria, including pneumococci, than ciprofloxacin.

References.

1. Stein GE, *et al.* Bactericidal activities of methoxyfluoroquinolones gatifloxacin and moxifloxacin against aerobic and anaerobic respiratory pathogens in serum. *Antimicrob Agents Chemother* 2003; 47: 1308–12.

Pharmacokinetics

Gatifloxacin is readily absorbed from the gastrointestinal tract with an absolute bioavailability of 96%. Peak plasma concentrations occur within 1 to 2 hours of an oral dose. Gatifloxacin is widely distributed into body tissues and is about 20% bound to plasma proteins. It undergoes limited metabolism and has an elimination half-life of 7 to 14 hours. Gatifloxacin is excreted mainly unchanged in the urine with less than 1% as metabolites. About 5% is also excreted unchanged in the faeces. Distribution into milk occurs in *animals*.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Gatif; Zymaran: *Braz.*: Zymar; *Canad.*: Zymar; *Chile*: Gatif; Zymar; *China*: Ai Er Jia (艾尔嘉); Ao Lai Ke (澳莱克); Ba Ti (巴替); Bai Ke Sha (百科沙); Bi Zhi (必致); Chen Li (辰立); Chen Zheng (辰正); Di Na Ke (地纳克); Diyou (迪友); Fudixing (芙蒂星); Fuqi (福奇); Gan Nuo Xin (敢诺新); Gatilox (加西); Haichao (海超); Heng Sen (恒森); Jia Di Pu (嘉迪福); Jia Heng Xing (加恒兴); Jia Kui Long (加葵龙); Jia Li (加力); Jia Luo Ling (佳洛灵); Jia Mai Xin (加迈欣); Jia Tai (加泰); Jia Yi Xin (加益新); Kai Ze (凯泽); Kui Er Tai (奎尔泰); Kui Tai (奎泰); Kui Yan (葵严); Lai Di (莱迪); Lai Fu Le Xin (来福乐欣); Lai Mei Qing (莱美清); Laijia (来佳); Le Pai (乐派); Li Ou (利欧); Lin Ke Jia (林可佳); Luo Ka Nuo (洛卡诺); Luoxin Yanda (罗欣严达); Nuo Li Er (诺丽尔); Ou Nuo (欧诺); Ou Te Luo Kang (欧特罗康); Pa Te La (帕特拉); Qian Yi (千意); Shang Bang (尚邦); Sheng Di Feng (圣迪锋); Shu Pu Ren (舒普仁); Tequin (天坤); Tong Bo (同博); Tong Nuo Xin (同诺欣); Wan Yue (万悦); Xian Kui Sha (先奎莎); Xindite (欣迪特); Yan Ke Xian (严克仙); Yan Li Fei (严立菲); Yu Kuai (誉快); Yue Bo (悦博); Zhe Peng (哲朋); Zhu Ning; *India*: Adiflox; Adgat; Alex; Algat; Arigat; Arnflox; Avigat; Biogat; Comigat; Cugat; Dasikon; E-Gati; Ecogat BCD; Engatt; Exagt; Fatiflox; Floxigat; Fugat; Fydogat; G-Cebran; G-Flox; G-Quin; G2K; Gabact; Gabee; Gabir; Gaity; Gale; Gate; Gateme; Gatex; Gad-OD; Gatiba; Gatibenz; Gaticad; Gaticare; Gaticas; Gaticin; Gatifect; Gatigo; Gatigram; Gatik; Gatikind; Gatilab; Gatilex; Gatilink; Gatilox; Gatimac; Gatimore; Gatin; Gatina; Gatinex; Gatinova; Gatiom; Gatiospi; Gatipan; Gatiquin; Gatisia; Gatispan; Gatistac; Gatistal; Gatitoon; Gativar; Gatix; Gatiz; Gatizen; Gatlak; Garme; Gatmor; Gatnic; Gatomed; Gator; Gatox; Gatri; Gatrid; Gatrital; Gatt; Gatven; Gatymal; Gatz; Getflox; Getoli; Getready; GP; Giflexcin; Giftum; Glyph; Gofel; Granaz; Gres; Gulf; Guts; Gutts; Intragat; K-Gat; KGT; Lyflox; Mach-X; Meris; Microgat; Multigat; Oxigat; Zyquin; *Indon.*: Gaticin†; Gatimax†; *Israel*: Zymar; Zymaxid; *Jpn*: Gatiflo; *Malaysia*: Zymar; *Mex.*: Zymar; *NZ*: Tequin†; *Philipp.*: Itiflox; Zymar; *Rus.*: Gatispan (Гатиспан); Zarquin (Зарквин); *S.Afr.*: Zymar; *Singapore*: Zymar; *Thai.*: Zymar; *Turk.*: Zymar; *Ukr.*: Bigaflon (Бигафлон); Dasikon (Дасикон)†; Gatibact (Гатибакт); Gatijem (Гатиджем)†; Gatonova (Гатинова)†; *USA*: Zymar; Zymaxid.

Multi-ingredient Preparations. *Braz.*: Zypred; *India*: Amgat; Diragyl; Ecogat A; Engatt-DX; Fatiflox-OZ; Floxigat M; Garnid; Gate-DX; Gatigram-OZ; Gatikind-AM; Gatikind-OZ; Gatilox-DM; Gatimore-OZ; Gatiquin Oz Kit; Gatri-OZ; Gatrich; Gatrid-OZ; Gatrix; Gatus; Getoli D; Inogat-O; Intragat-AM; Intragat-O; Meris-D; Microgat-DX.

Gemifloxacin Mesilate *(INNM)*

Gemifloxacin Mesylate (USAN); Gémifloxacine, Mésilate de; Gemifloxacini Mesilas; Gemifloxacino, mesilato de; LB-20304 (gemifloxacin); LB-20304a; Mesilato de gemifloxacino; SB-265805 (gemifloxacin); SB-265805S; Гемифлоксацина Мезилат.

(±)-7-[3-(Aminomethyl)-4-oxo-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid 7⁴-(*Z*)-(*O*-methyloxime) methanesulfonate.

$C_{18}H_{20}FN_5O_4.CH_4O_3S$=485.5

CAS — 204519-64-2 (gemifloxacin); 204519-65-3 (gemifloxacin mesilate).

ATC — J01MA15.

ATC Vet — QJ01MA15.

UNII — X459F8RL01.

Uses and Administration

Gemifloxacin is a fluoroquinolone antibacterial with actions and uses similar to those of ciprofloxacin (p. 261.2).

It is given orally, as the mesilate, for the treatment of community-acquired pneumonia and acute bacterial exacerbations of chronic bronchitis. Doses are expressed in terms of the base; 399 mg of gemifloxacin mesilate is equivalent to about 320 mg of gemifloxacin. The usual dose is 320 mg once daily for 5 days in patients with bronchitis or for 7 days in those with pneumonia.

For details of reduced doses in patients with renal impairment, see p. 306.2.

Reviews.

1. Lowe MN, Lamb HM. Gemifloxacin. *Drugs* 2000; 59: 1137–47.
2. Yoo BK, *et al.* Gemifloxacin: a new fluoroquinolone approved for treatment of respiratory infections. *Ann Pharmacother* 2004; 38: 1226–35.
3. File TM, Tillotson GS. Gemifloxacin: a new, potent fluoroquinolone for the therapy of lower respiratory tract infections. *Expert Rev Anti Infect Ther* 2004; 2: 831–43.
4. Bhavnani SM, Andes DR. Gemifloxacin for the treatment of respiratory tract infections: in vitro susceptibility, pharmacokinetics and pharmacodynamics, clinical efficacy, and safety. *Pharmacotherapy* 2005; 25: 717–40.
5. Blondeau JM, Tillotson G. Role of gemifloxacin in the management of community-acquired lower respiratory tract infections. *Int J Antimicrob Agents* 2008; 31: 299–306.
6. Lode HM, *et al.* Gemifloxacin for community-acquired pneumonia. *Expert Opin Invest Drugs* 2008; 17: 779–86.
7. Tillotson GS. Role of gemifloxacin in community-acquired pneumonia. *Expert Rev Anti Infect Ther* 2008; 6: 405–18.
8. Jivcu C, Gotfried M. Gemifloxacin use in the treatment of acute bacterial exacerbation of chronic bronchitis. *Int J Chron Obstruct Pulmon Dis* 2009; 4: 291–300.

Administration in renal impairment. Oral doses of gemifloxacin should be halved in patients with a creatinine clearance of 40 mL/minute or less, including those receiving haemodialysis or continuous peritoneal dialysis.

Adverse Effects and Precautions

As for Ciprofloxacin, p. 262.2.

Rashes may be more common with gemifloxacin and treatment should be stopped if they occur.

Interactions

As for Ciprofloxacin, p. 264.3.

Antimicrobial Action

As for Ciprofloxacin, p. 265.2.

Gemifloxacin is reported to have greater activity against Gram-positive bacteria, including pneumococci, than ciprofloxacin.

References.

1. Morrissey I, Tillotson G. Activity of gemifloxacin against Streptococcus pneumoniae and Haemophilus influenzae. *J Antimicrob Chemother* 2004; 53: 144–8.

Pharmacokinetics

Gemifloxacin is rapidly absorbed from the gastrointestinal tract with an absolute bioavailability of about 71%. Peak plasma concentrations occur 0.5 to 2 hours after an oral dose. Gemifloxacin is widely distributed into body tissues including the bronchial mucosa and lungs, and is about 55 to 73% bound to plasma proteins. It undergoes limited hepatic metabolism and has an elimination half-life of about 7 hours. It is excreted as unchanged drug and metabolites in the faeces and urine. Urinary excretion is by active tubular secretion and is reduced by probenecid. Distribution into milk has been found in *rats*.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Factive; *Canad.*: Factive†; *China*: Factive (吉速星); *India*: Floxigem; G-Floren; Gembax; Gemistar; Gemitab; Graptor; *Mex.*: Factive-5; *Rus.*: Factiv (Фактив); *S.Afr.*: Factive; *Turk.*: Factive; *USA*: Factive.

Gentamicin Sulfate *(BANM, USAN, pINNM)*

Gentamicin sulfát; Gentamicin Sulphate; Gentamicina, sulfato de; Gentamicine, Sulfate de; Gentamicini sulfas; Gentamicino sulfatas; Gentamicinsulfat; Gentamicin-szulfát; Gentamisiinisulfaatti; Gentamisin Sülfat; Gentamycyny siarczan; NSC-82261; Sch-9724; Sch-13706 (gentamicin C_1); Sulfato de gentamicina; Гентамицина Сульфат.

CAS — 1403-66-3 (gentamicin); 1405-41-0 (gentamicin sulfate).

ATC — D06AX07; J01GB03; S01AA11; S02AA14; S03AA06.

ATC Vet — QD06AX07; QJ01GB03; QS01AA11; QS02AA14; QS03AA06.

UNII — 8X7386QRLV (gentamicin sulfate); 1904Y9FPPV (gentamicin C_1).

NOTE. GNT is a code approved by the BP 2014 for use on single unit doses of eye drops containing gentamicin sulfate where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Gentamicin Sulfate). A mixture of the sulfates of antimicrobial substances produced by *Micromonospora purpurea*, the main components being gentamicins C1, C1a, C2, C2a, and C2b. It contains 20 to 40% of gentamicin C1, 10 to 30% of gentamicin C1a; the sum of gentamicins C2, C2a, and C2b is 40 to 60%. The potency is not less than 590 units/mg, calculated with reference to the anhydrous substance. A white or almost white hygroscopic powder. Freely soluble in water; practically insoluble in alcohol. A 4% solution in water has a pH of 3.5 to 5.5. Store in airtight containers.

USP 36: (Gentamicin Sulfate). The sulfate salt, or a mixture of such salts, of antibiotic substances produced by the growth of *Micromonospora purpurea*. The content of gentamicin C1 is between 25 and 50%, the content of gentamicin C1a is between 10 and 35%, and the sum of the contents of gentamicin C2a and gentamicin C2 is between 25 and 55%. It has a potency equivalent to not less than 590 micrograms of gentamicin per mg, calculated on the dried basis. A white to buff powder. Freely soluble in water; insoluble in alcohol, in acetone, in chloroform, in ether, and in benzene. pH of a 4% solution in water is between 3.5 and 5.5. Store in airtight containers.

Incompatibility. The aminoglycosides are inactivated *in vitro* by various penicillins and cephalosporins via an interaction with the beta-lactam ring, the extent of inactivation depending on temperature, concentration, and duration of contact. The different aminoglycosides vary in their stability, with amikacin apparently the most resistant and tobramycin the most susceptible to inactivation; gentamicin and netilmicin are of intermediate stability. The beta lactams also vary in their ability to produce inactivation, with ampicillin, benzylpenicillin, and antipseudomonal penicillins such as carbenicillin and ticarcillin producing marked inactivation. Inactivation has also been reported with clavulanic acid.

Gentamicin is also incompatible with furosemide, heparin, sodium bicarbonate (the acid pH of gentamicin solutions may liberate carbon dioxide), and some solutions for parenteral nutrition. Interactions with preparations having an alkaline pH (such as aciclovir or sulfadiazine sodium), or drugs unstable at acid pH (for example erythromycin salts), might reasonably be expected.

Given their potential for incompatibility, gentamicin and other aminoglycosides should not generally be mixed with other drugs in syringes or infusion solutions nor given through the same intravenous line. When aminoglycosides are given with a beta lactam, they should generally be given at separate sites.

General references.

1. Henderson JL, *et al.* In vitro inactivation of gentamicin, tobramycin, and netilmicin by carbenicillin, azlocillin, or mezlocillin. *Am J Hosp Pharm* 1981; 38: 1167–70.
2. Tindula RJ, *et al.* Aminoglycoside inactivation by penicillins and cephalosporins and its impact on drug-level monitoring. *Drug Intell Clin Pharm* 1983; 17: 906–8.
3. Navarro AS, *et al.* In-vitro interaction between dibekacin and penicillins. *J Antimicrob Chemother* 1986; 17: 83–9.
4. Courcol RJ, Martin GR. Comparative aminoglycoside inactivation by potassium clavulanate. *J Antimicrob Chemother* 1986; 17: 682–4.
5. Canann D, *et al.* Visual compatibility of i.v. medications routinely used in bone marrow transplant recipients. *Am J Health-Syst Pharm* 2009; 66: 727–9. Correction. *ibid.*: 1431.

Stability. There was an average 16% potency loss of gentamicin sulfate from solutions containing 10 and 40 mg/mL when stored at 4 degrees or 25 degrees in plastic disposable syringes for 30 days, and a brown precipitate formed in several. Storage in glass disposable syringes for 30 days produced an average 7% potency loss, which was considered acceptable, but storage for longer resulted in precipitate formation in some cases and was not recommended.[1]

1. Weiner B, *et al.* Stability of gentamicin sulfate injection following unit dose repackaging. *Am J Hosp Pharm* 1976; 33: 1254–9.

Uses and Administration

Gentamicin is an aminoglycoside antibacterial used, often with other antibacterials, to treat severe systemic infections due to sensitive Gram-negative and other organisms (see

Antimicrobial Action, p. 309.2). Such infections include abscesses, biliary-tract infections (acute cholecystitis or cholangitis), brucellosis, cat scratch disease, cystic fibrosis, endocarditis (in the treatment and prophylaxis of endocarditis due to streptococci, enterococci, or staphylococci), endometritis, gastro-enteritis, granuloma inguinale, listeriosis, meningitis, otitis externa, otitis media, pelvic inflammatory disease, peritonitis, plague, pneumonia, septicaemia, skin infections such as in burns or ulcers (given systemically for pseudomonal and other Gram-negative infections), trench fever, tularaemia, and urinary-tract infections (acute pyelonephritis), as well as in the prophylaxis of surgical infection and the treatment of immunocompromised patients and those in intensive care. It may be used as part of a multidrug regimen for the treatment of inhalation and gastrointestinal anthrax. Gentamicin is also applied topically for localised infections. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Gentamicin is often used with other antibacterials to extend its spectrum of activity or increase its efficacy, e.g. with a penicillin for enterococcal and streptococcal infections, or an antipseudomonal beta lactam for pseudomonal infections, or with metronidazole or clindamycin for mixed aerobic-anaerobic infections.

Administration and dosage. Gentamicin is used as the sulfate but doses are expressed in terms of gentamicin base. For many of the infections above it is given *intramuscularly* every 8 hours to provide a total daily dose of 3 to 5 mg/kg. Intramuscular (or intravenous—see below) doses have traditionally played an important role in regimens for the treatment and prophylaxis of bacterial endocarditis, although the need for prophylaxis has largely been re-evaluated in recent years (see Endocarditis, p. 179.2, for details and doses). For urinary-tract infections, if renal function is not impaired, 160 mg once daily may be used.

Gentamicin sulfate may also be given *intravenously* in similar doses to those used intramuscularly, but there is some disagreement as to the appropriate method, since intravenous infusion has been associated with both subtherapeutic and excessive trough concentrations of gentamicin, while bolus intravenous injection may increase the risk of neuromuscular blockade. In the USA, intravenous infusion of the recommended dose diluted in 50 to 200 mL and given over 30 minutes to 2 hours is favoured, while UK licensed product information recommends infusion over no more than 20 to 30 minutes, in a limited fluid volume (100 mL), or slow bolus injection over at least 2 to 3 minutes.

The course of treatment should generally be limited to 7 to 10 days. As gentamicin is poorly distributed into fatty tissue it has been suggested that dosage calculations should be based on an estimate of lean body-weight.

For details of use in children, see p. 307.3.

Dose adjustment and monitoring. Dosage should be adjusted in all patients according to plasma-gentamicin concentrations, and this is discussed in more detail under Administration and Dosage, p. 307.2.

Once-daily dosage. The total daily requirement may be given as a single dose (see Once-daily Dosage, p. 307.2). In suitable patients this appears to be as safe and effective as conventional regimens, and is more convenient. However, it is not suitable for all patients, especially those with endocarditis, extensive burns, or renal impairment (creatinine clearance less than 20 mL/minute). The *BNF* recommends a once-daily dose regimen for gentamicin, of 5 to 7 mg/kg by intravenous infusion and then adjusted according to serum-gentamicin concentration. With once-daily dosage, traditional methods of monitoring peak and trough plasma concentrations may not be applicable and local guidelines on dosage and plasma concentrations should be consulted.

Other routes. Gentamicin has sometimes been given orally for enteric infections and to suppress intestinal flora and has occasionally been given by inhalation of nebulised solution in cystic fibrosis. In meningitis it has been given intrathecally or intraventricularly usually in doses of 1 to 5 mg daily with intramuscular therapy. Gentamicin has also been given by subconjunctival injection.

A bone cement impregnated with gentamicin is used in orthopaedic surgery. Acrylic beads containing gentamicin and threaded on to surgical wire are implanted in the management of bone infections.

Gentamicin has also been applied topically for skin infections in concentrations of 0.1%, but such use may lead to the emergence of resistance and is considered inadvisable. Concentrations of 0.3% are used in preparations for topical application to the eyes and ears.

A liposomal formulation of gentamicin is under investigation.

Reviews.

1. Edson RS, Terrell CL. The aminoglycosides. *Mayo Clin Proc* 1999; 74: 519–28.

Administration and dosage. *CONCENTRATION MONITORING.* Measurements of aminoglycoside plasma concentrations are routinely performed to individualise dosage regimens, both in terms of dose given and dosing interval, in order to attain the desired therapeutic range as quickly as possible.[1] This entails measurement of both peak concentrations to monitor efficacy and trough concentrations to avoid accumulation and thereby prevent toxicity. Dosage should be adjusted in all patients according to these concentrations, but this is of particular importance where factors such as age, renal impairment, or high dosage may predispose to toxicity. Although there has been some dispute about the relationship between plasma concentrations and toxicity it is generally recommended that, for multiple daily dosing with gentamicin, trough plasma concentrations (measured just before the next dose) should be less than 2 micrograms/mL, and peak concentrations should reach at least 4 micrograms/mL but not exceed 10 micrograms/mL. In the UK, peak concentrations are generally measured 1 hour after intramuscular and intravenous doses, but practice has varied between centres and countries and this may lead to difficulties when comparing figures.

Methods exist for calculating aminoglycoside dosage requirements, though none has been universally accepted. Simple pharmacokinetic methods involve linear dosage adjustment based on peak or trough concentrations or area under the concentration-time curve, or the use of predictive nomograms.[1] For most patients receiving once-daily dosage (see p. 307.2), the nomogram is the method of choice, mainly because of its simplicity. However, it has not been validated for children and does not work in patients with either a very high clearance of aminoglycosides or a high volume of distribution, such as those with ascites, burns, or cystic fibrosis, or in other conditions such as pregnancy where the fixed dose assumed in the construction of the nomogram is irrelevant. When a nomogram cannot be applied, a more sophisticated pharmacokinetic method is required, using either Bayesian statistics or non-Bayesian methods such as that of Sawchuk and Zaske.[2,3] Bayesian methods are favoured when the patient population's pharmacokinetic parameters are well known because of their good predictive performance. Otherwise, the Sawchuk and Zaske method is the method of choice because of its robustness and the lack of requirement for prior information about the distribution of parameters within the population.[1]

1. Tod MM, *et al.* Individualising aminoglycoside dosage regimens after therapeutic drug monitoring: simple or complex pharmacokinetic methods? *Clin Pharmacokinet* 2001; 40: 803–14.
2. Sawchuk RJ, Zaske DE. Pharmacokinetics of dosing regimens which utilize multiple intravenous infusions: gentamicin in burn patients. *J Pharmacokinet Biopharm* 1976; 4: 183–95.
3. Sawchuk RJ, *et al.* Kinetic model for gentamicin dosing with the use of individual patient parameters. *Clin Pharmacol Ther* 1977; 21: 362–9.

IN PATIENTS WITH NON-IDEAL BODY-WEIGHT. **References.**

1. Traynor AM, *et al.* Aminoglycoside dosing weight correction factors for patients of various body sizes. *Antimicrob Agents Chemother* 1995; 39: 545–8.

ONCE-DAILY AND EXTENDED-INTERVAL DOSE REGIMENS. Parenteral aminoglycosides have been given in multiple daily dose regimens (usually 2 or 3 doses daily); these are usually the dose regimens included in most licensed product information. However, current practice is to give the same total daily dose of the aminoglycosides once-daily in selected patients. The rationale for preferring single daily dose regimens and therefore higher intermittent plasma concentrations includes the prolonged postantibiotic effect of aminoglycosides (persistent antibacterial activity after plasma concentrations have fallen below the MIC), potentially higher antibacterial concentrations at the site of infection, and theoretical reductions in the incidence of adaptive resistance, with no apparent increase in oto- or nephrotoxicity. Such regimens are also attractive on the grounds of convenience and economy. Clinical studies have generally included small numbers of patients with uncomplicated infections and have excluded patients with altered pharmacokinetic profiles, but several meta-analyses have been published which have concluded that once-daily administration appears to be at least as effective as, and no more toxic than, multiple daily dosing in such patient populations.[1-7] Similar results have been seen in children and neonates;[8] once-daily and extended-interval dose regimens respectively have been suggested for amikacin, gentamicin, and tobramycin.

Several methods for calculating doses and monitoring treatment have been proposed.[9-11] There is insufficient information for pregnant or breast-feeding women, or patients with burns or impaired renal or hepatic function.[11-13] However, preliminary reports suggest that once-daily use may be practical in trauma patients[14] and children with neutropenia.[15] A systematic review[16] also concluded that once-daily tobramycin was as effective in the treatment of patients with cystic fibrosis as the multiple dose regimens. Once-daily dosage may, though, be inappropriate for elderly patients[17] (due to an increased incidence of nephrotoxicity), patients in whom the volume of drug distribution or clearance is difficult to predict or markedly abnormal,[18] and in the treatment of enterococcal endocarditis.[11] In the UK, the *BNF* states that a once-daily high dose regimen should be avoided in patients with endocarditis, extensive burns, or creatinine clearance less than 20 mL/minute. For mention of an increase in endotoxin reactions associated with the use of single daily doses see under Adverse Effects, p. 308.3.

1. Barza M, *et al.* Single or multiple daily doses of aminoglycosides: a meta-analysis. *BMJ* 1996; 312: 338–45.
2. Hatala R, *et al.* Once-daily aminoglycoside dosing in immunocompetent adults: a meta-analysis. *Ann Intern Med* 1996; 124: 717–25.
3. Ferriols-Lisart R, Alos-Almiñana M. Effectiveness and safety of once-daily aminoglycosides: a meta-analysis. *Am J Health-Syst Pharm* 1996; 53: 1141–50.
4. Munckhof WJ, *et al.* A meta-analysis of studies on the safety and efficacy of aminoglycosides given either once daily or as divided doses. *J Antimicrob Chemother* 1996; 37: 645–63.
5. Bailey TC, *et al.* A meta-analysis of extended-interval dosing versus multiple daily dosing of aminoglycosides. *Clin Infect Dis* 1997; 24: 786–95.
6. Ali MZ, Goetz MB. A meta-analysis of the relative efficacy and toxicity of single daily dosing versus multiple daily dosing of aminoglycosides. *Clin Infect Dis* 1997; 24: 796–809.
7. Hatala R, *et al.* Single daily dosing of aminoglycosides in immunocompromised adults: a systematic review. *Clin Infect Dis* 1997; 24: 810–15.
8. Rao SC, *et al.* One dose per day compared to multiple doses per day of gentamicin for treatment of suspected or proven sepsis in neonates. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 19/12/08).
9. Begg EJ, *et al.* A suggested approach to once-daily aminoglycoside dosing. *Br J Clin Pharmacol* 1995; 39: 605–9.
10. Prins JM, *et al.* Validation and nephrotoxicity of a simplified once-daily aminoglycoside dosing schedule and guidelines for monitoring therapy. *Antimicrob Agents Chemother* 1996; 40: 2494–9.
11. Freeman CD, *et al.* Once-daily dosing of aminoglycosides: review and recommendations for clinical practice. *J Antimicrob Chemother* 1997; 39: 677–86.
12. Rodvold KA, *et al.* Single daily doses of aminoglycosides. *Lancet* 1997; 350: 1412.
13. Anonymous. Aminoglycosides once daily? *Drug Ther Bull* 1997; 35: 36–7.
14. Finnell DL, *et al.* Validation of the Hartford nomogram in trauma surgery patients. *Ann Pharmacother* 1998; 32: 417–21.
15. Tomlinson RJ, *et al.* Once daily ceftriaxone and gentamicin for the treatment of febrile neutropenia. *Arch Dis Child* 1999; 80: 125–31.
16. Smyth AR, Bhatt J. Once-daily versus multiple-daily dosing with intravenous aminoglycosides for cystic fibrosis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 16/07/10).
17. Koo J, *et al.* Comparison of once-daily versus pharmacokinetic dosing of aminoglycosides in elderly patients. *Am J Med* 1996; 101: 177–83.
18. Gerberding JL. Aminoglycoside dosing: timing is of the essence. *Am J Med* 1998; 105: 256–8.

Administration in children. For severe infections caused by susceptible bacteria in children beyond the newborn period the American Academy of Pediatrics (AAP)[1] suggests an intravenous or intramuscular dose equivalent to 3 to 7.5 mg/kg daily of gentamicin, in 3 divided doses.

For *septicaemia, CNS infections and meningitis, biliary-tract infection, acute pyelonephritis, endocarditis, and pneumonia* in infants and children the *BNFC* suggests:

- **a once-daily** dose regimen (not for endocarditis or meningitis) by intravenous infusion of 7 mg/kg and then adjusted according to serum-gentamicin concentration in those from 1 month of age, *or*
- **a multiple daily dose regimen** by intramuscular or by slow intravenous injection over at least 3 minutes
  - those 1 month to 12 years of age: 2.5 mg/kg every 8 hours
  - children from 12 years of age: 2 mg/kg every 8 hours

For the treatment of pseudomonal lung infection in *cystic fibrosis* the *BNFC* suggests:

- **a multiple daily dose regimen** of gentamicin given by slow intravenous injection or by intravenous infusion of 3 mg/kg every 8 hours in those from 1 month of age

For the treatment of *bacterial ventriculitis* and *CNS infection* the *BNFC* suggests that in addition to systemic treatment an **intrathecal** or **intraventricular** injection of a suitable preparation of gentamicin in a dose of 1 mg daily (increasing to 5 mg daily if necessary) may be given in those from 1 month of age.

For *neonatal sepsis* the *BNFC* suggests an **extended-interval dose regimen** of gentamicin by slow intravenous injection or intravenous infusion as follows:

- for neonates aged ⩽ 7 days: 5 mg/kg every 36 hours
- for neonates aged > 7 days: 5 mg/kg every 24 hours

An alternative regimen also based on the age and birth-weight of the neonate is suggested by the AAP;[1] doses should be given by intramuscular or intravenous injection:

- for neonates aged ⩽ 7 days and weighing ⩽ 2 kg: 5 mg/kg every 48 hours
- for neonates aged ⩽ 7 days and weighing > 2 kg: 4 mg/kg every 24 hours
- for neonates aged 8 to 28 days and weighing ⩽ 2 kg: 4 to 5 mg/kg every 24 to 48 hours; a dosing interval of 48 hours may be used until 2 weeks of life in extremely low birth-weight neonates (those weighing less than 1 kg)
- for neonates aged 8 to 28 days and weighing > 2 kg: 4 mg/kg every 12 to 24 hours

Many studies have been carried out in neonates and infants to evaluate the use and determine the dose of aminoglycosides when used in once-daily or in extended-interval dosing regimens.[2-17]

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.
2. Isemann BT, *et al.* Optimal gentamicin therapy in preterm neonates includes loading doses and early monitoring. *Ther Drug Monit* 1996; **18**: 549–55.
3. Logsdon BA, Phelps SJ. Routine monitoring of gentamicin serum concentrations in pediatric patients with normal renal function is unnecessary. *Ann Pharmacother* 1997; **31**: 1514–18.
4. Murphy JE, *et al.* Evaluation of gentamicin pharmacokinetics and dosing protocols in 195 neonates. *Am J Health-Syst Pharm* 1998; **55**: 2280–9.
5. Yeung MY, Smyth JP. Targeting gentamicin concentrations in babies: the younger the baby, the larger the loading dose and the longer the dose interval. *Aust J Hosp Pharm* 2000; **30**: 98–101.
6. Stickland MD, *et al.* An extended interval dosing method for gentamicin in neonates. *J Antimicrob Chemother* 2001; **48**: 887–93.
7. Rastogi A, *et al.* Comparison of two gentamicin dosing schedules in very low birth weight infants. *Pediatr Infect Dis J* 2002; **21**: 234–40.
8. Chattopadhyay B. Newborns and gentamicin—how much and how often? *J Antimicrob Chemother* 2002; **49**: 13–16.
9. English M, *et al.* A randomised, controlled trial of once daily and multi-dose daily gentamicin in young Kenyan infants. *Arch Dis Child* 2004; **89**: 665–9.
10. Lanao JM, *et al.* Pharmacokinetic basis for the use of extended interval dosage regimens of gentamicin in neonates. *J Antimicrob Chemother* 2004; **54**: 193–8.
11. Contopoulos-Ioannidis DG, *et al.* Extended-interval aminoglycoside administration for children: a meta-analysis. Abstract: *Pediatrics* 2004; **114**: 248. Full version: http://pediatrics.aappublications.org/cgi/reprint/114/1/e111 (accessed 23/03/09)
12. Smyth A, *et al.* Once versus three-times daily regimens of tobramycin treatment for pulmonary exacerbations of cystic fibrosis—the TOPIC study: a randomised controlled trial. *Lancet* 2005; **365**: 573–8.
13. Nestaas E, *et al.* Aminoglycoside extended interval dosing in neonates is safe and effective: a meta-analysis. *Arch Dis Child Fetal Neonatal Ed* 2005; **90**: F294–300.
14. Murphy JE. Prediction of gentamicin peak and trough concentrations from six extended-interval dosing protocols for neonates. *Am J Health-Syst Pharm* 2005; **62**: 823–7.
15. Hale LS, Durham CR. A simple, weight-based, extended-interval gentamicin dosage protocol for neonates. *Am J Health-Syst Pharm* 2005; **62**: 1613–16.
16. Khan AM, *et al.* Extended-interval gentamicin administration in malnourished children. *J Trop Pediatr* 2006; **52**: 179–84.
17. Hennig S, *et al.* Target concentration intervention is needed for tobramycin dosing in paediatric patients with cystic fibrosis–a population pharmacokinetic study. *Br J Clin Pharmacol* 2008; **65**: 502–10.

Administration in renal impairment. Although many nomograms, schedules, and rules have been devised for the calculation of aminoglycoside dosage in renal impairment, where possible dosage modification should be based on the monitoring of individual pharmacokinetic parameters. Standard dosage calculation methods should not be used for patients undergoing dialysis as they may require supplementary post-dialysis doses.

A review[1] of antimicrobial dosing in critically ill patient undergoing renal replacement therapy, suggests that such patients should receive a loading dose of 2 to 3 mg/kg (except for synergy dosing in those on intermittent haemodialysis), with the following empirical maintenance doses, dependent on the clinical indication, type of renal replacement therapy, and serum-gentamicin concentrations:

- intermittent haemodialysis: 1 mg/kg (for synergy or mild urinary-tract infections), 1 to 1.5 mg/kg (for moderate to severe urinary-tract infections), or 1.5 to 2 mg/kg (for systemic Gram-negative infections) every 48 to 72 hours
- continuous renal replacement therapy: 1 mg/kg (for synergy or mild urinary-tract infections) or 1 to 1.5 mg/kg (for moderate to severe urinary-tract infections) every 24 to 36 hours, or 1.5 to 2.5 mg/kg every 24 to 48 hours (for systemic Gram-negative infections)

Serum-gentamicin concentration measurements (drawn before the run for those on haemodialysis) should be used to further adjust the dosing interval. The next maintenance dose should be given when serum-gentamicin concentrations are within the following ranges:[1]

- for synergy or mild urinary-tract infections: < 1 mg/litre
- for moderate to severe urinary-tract infections: < 1.5 to 2 mg/litre
- for systemic Gram-negative bacterial infections: < 3 to 5 mg/litre

1. Heintz BH, *et al.* Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy* 2009; **29**: 562–77.

Ménière's disease. Gentamicin and streptomycin have been used for medical ablation in advanced Ménière's disease (p. 611.2). Although gentamicin given systemically is considered to be more ototoxic than streptomycin, evidence from *animal* studies suggests that intratympanic use may be less ototoxic. This, and a higher incidence of adverse effects with streptomycin, has meant that intratympanic gentamicin is now preferred. Intratympanic gentamicin has been reported to control vertigo symptoms in the majority of patients, although some have a worsening of their hearing loss immediately after treatment.[1-9] However, the ideal regimen for intratympanic gentamicin has yet to be defined.

1. Nedzelski JM, *et al.* Chemical labyrinthectomy: local application of gentamicin for the treatment of unilateral Meniere's disease. *Am J Otol* 1992; **13**: 18–22.
2. Pyykkö I, *et al.* Intratympanic gentamicin in bilateral Meniere's disease. *Otolaryngol Head Neck Surg* 1994; **110**: 162–7.
3. Quaranta A, *et al.* Intratympanic therapy for Ménière's disease: high-concentration gentamicin with round-window protection. *Ann N Y Acad Sci* 1999; **884**: 410–24.
4. Longridge NS, Mallinson AL. Low-dose intratympanic gentamicin treatment for dizziness in Meniere's disease. *J Otolaryngol* 2000; **29**: 35–9.
5. Quaranta A, *et al.* Intratympanic therapy for Ménière's disease: effect of administration of low concentration of gentamicin. *Acta Otolaryngol* 2001; **121**: 387–92.
6. Marzo SJ, Leonetti JP. Intratympanic gentamicin therapy for persistent vertigo after endolymphatic sac surgery. *Otolaryngol Head Neck Surg* 2002; **126**: 31–3.
7. Cohen-Kerem R, *et al.* Intratympanic gentamicin for Menière's disease: a meta-analysis. *Laryngoscope* 2004; **114**: 2085–91.
8. Postema RJ, *et al.* Intratympanic gentamicin therapy for control of vertigo in unilateral Menière's disease: a prospective, double-blind, randomized, placebo-controlled trial. *Acta Otolaryngol* 2008; **128**: 876–80.
9. Pullens B, van Benthem PP. Intratympanic gentamicin for Ménière's disease or syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester, John Wiley; 2011 (accessed 17/06/13).

Adverse Effects

The aminoglycosides can produce irreversible, cumulative ototoxicity. This affects both the cochlea (manifest as hearing loss, initially of higher tones, and which, because speech recognition relies greatly on lower frequencies, may not be at first apparent) and the vestibular system (manifest as dizziness or vertigo). The incidence and relative toxicity with different aminoglycosides is a matter of some dispute, but netilmicin is probably less cochleotoxic than gentamicin or tobramycin, and amikacin more so. Netilmicin also exhibits less vestibular toxicity than gentamicin, tobramycin, or amikacin, while streptomycin produces a high incidence of vestibular damage. Vestibular damage is more common than hearing loss in patients receiving gentamicin.

Reversible nephrotoxicity may occur and acute renal failure has been reported, often in association with the use of other nephrotoxic drugs. Renal impairment is usually mild, although acute tubular necrosis and interstitial nephritis have occurred. Decreased glomerular filtration rate is usually seen only after several days, and may even occur after therapy has stopped. Electrolyte disturbances (notably hypomagnesaemia, but also hypocalcaemia and hypokalaemia) have occurred. The nephrotoxicity of gentamicin is reported to be largely due to the gentamicin C_2 component.

Although particularly associated with high plasma concentrations, many risk factors have been suggested for ototoxicity and nephrotoxicity in patients receiving aminoglycosides—see Precautions p. 308.3.

Aminoglycosides possess a neuromuscular-blocking action and respiratory depression and muscular paralysis have been reported, notably after absorption from serous surfaces. Neomycin has the most potent action and deaths have been associated with its use.

Hypersensitivity reactions have occurred, especially after local use, and cross-sensitivity between aminoglycosides may occur. Very rarely, anaphylactic reactions to gentamicin have occurred. Some hypersensitivity reactions have been attributed to the presence of sulfites in parenteral formulations, and endotoxic shock has also been reported.

Infrequent effects reported for gentamicin include blood dyscrasias, purpura, nausea and vomiting, stomatitis, and signs of liver dysfunction such as increased serum-aminotransferase values and increased serum-bilirubin concentrations. Neurotoxicity has occurred, with both peripheral neuropathies and central symptoms being reported including encephalopathy, confusion, lethargy, hallucinations, convulsions, and mental depression.

Atrophy or fat necrosis has been reported at injection sites. There have been isolated reports of meningeal irritation, arachnoiditis, polyradiculitis, and ventriculitis after intrathecal, intracisternal, or intraventricular use of aminoglycosides. Subconjunctival injection of gentamicin may lead to pain, hyperaemia, and conjunctival oedema, while severe retinal ischaemia has followed intra-ocular injection.

Effects on the ears. Reviews and references to aminoglycoside-induced ototoxicity.

1. Cone LA. A survey of prospective, controlled clinical trials of gentamicin, tobramycin, amikacin, and netilmicin. *Clin Ther* 1982; **5**: 155–62.
2. Kahlmeter G, Dahlager JI. Aminoglycoside toxicity—a review of clinical studies published between 1975 and 1982. *J Antimicrob Chemother* 1984; **13** (suppl A): 9–22.
3. Brummett RE, Fox KE. Aminoglycoside-induced hearing loss in humans. *Antimicrob Agents Chemother* 1989; **33**: 797–800.
4. Mattie H, *et al.* Determinants of efficacy and toxicity of aminoglycosides. *J Antimicrob Chemother* 1989; **24**: 281–93.
5. Schacht J. Aminoglycoside ototoxicity: prevention in sight? *Otolaryngol Head Neck Surg* 1998; **118**: 674–7.
6. Nakashima T, *et al.* Vestibular and cochlear toxicity of aminoglycosides—a review. *Acta Otolaryngol* 2000; **120**: 904–11.
7. Darlington CL, Smith PF. Vestibulotoxicity following aminoglycoside antibiotics and its prevention. *Curr Opin Investig Drugs* 2003; **4**: 841–6.
8. Rizzi MD, Hirose K. Aminoglycoside ototoxicity. *Curr Opin Otolaryngol Head Neck Surg* 2007; **15**: 352–7.
9. Ariano RE, *et al.* Aminoglycoside-induced vestibular injury: maintaining a sense of balance. *Ann Pharmacother* 2008; **42**: 1282–9.
10. Mulrennan SA, *et al.* Aminoglycoside ototoxicity susceptibility in cystic fibrosis. *Thorax* 2009; **64**: 271–2.
11. Bitner-Glindzicz M, *et al.* Aminoglycoside-induced deafness during treatment of acute leukaemia. *Arch Dis Child* 2010; **95**: 153–5.

Effects on the kidneys. Reviews and references to aminoglycoside-induced nephrotoxicity.

1. Cone LA. A survey of prospective, controlled clinical trials of gentamicin, tobramycin, amikacin, and netilmicin. *Clin Ther* 1982; **5**: 155–62.
2. Lieuman PS, Smith CR. Aminoglycoside nephrotoxicity in humans. *Rev Infect Dis* 1983; **5** (suppl 2): S284–93.
3. Kahlmeter G, Dahlager JI. Aminoglycoside toxicity—a review of clinical studies published between 1975 and 1982. *J Antimicrob Chemother* 1984; **13** (suppl A): 9–22.
4. Kohlhepp SJ, *et al.* Nephrotoxicity of the constituents of the gentamicin complex. *J Infect Dis* 1984; **149**: 605–14.
5. Mattie H, *et al.* Determinants of efficacy and toxicity of aminoglycosides. *J Antimicrob Chemother* 1989; **24**: 281–93.
6. Appel GB. Aminoglycoside nephrotoxicity. *Am J Med* 1990; **88** (suppl 3C): 16S–20S.
7. Berrino JS, *et al.* Incidence of and significant risk factors for aminoglycoside-associated nephrotoxicity in patients dosed by using individualized pharmacokinetic monitoring. *J Infect Dis* 1993; **167**: 173–9.
8. Swan SK. Aminoglycoside nephrotoxicity. *Semin Nephrol* 1997; **17**: 27–33.
9. Baciewicz AM, *et al.* Aminoglycoside-associated nephrotoxicity in the elderly. *Ann Pharmacother* 2003; **37**: 182–6.
10. Rougier F, *et al.* Aminoglycoside nephrotoxicity. *Curr Drug Targets Infect Disord* 2004; **4**: 153–62.
11. Martínez-Salgado C, *et al.* Glomerular nephrotoxicity of aminoglycosides. *Toxicol Appl Pharmacol* 2007; **223**: 86–98.
12. Oliveira JFP, *et al.* Prevalence and risk factors for aminoglycoside nephrotoxicity in intensive care units. *Antimicrob Agents Chemother* 2009; **53**: 2887–91.

Effects on the skin. Periocular ulcerative dermatitis has been reported in some newborn infants following the routine use of gentamicin ointment for ocular infection prophylaxis. The dermatitis was thought to be due to a direct vaso-occlusive effect of gentamicin on the blood vessels of the eyelid; however, the possibility of a hypersensitivity reaction or the synergistic action of gentamicin and the preservative could not be excluded.[1]

1. Binenbaum G, *et al.* Periocular ulcerative dermatitis associated with gentamicin ointment prophylaxis in newborns. *J Pediatr* 2010; **156**: 320–1.

Endotoxin reactions. Reports of endotoxin reactions associated with intravenous gentamicin have been received by the CDC and the FDA in the USA.[1] Although endotoxin concentrations in the injections used were within USP limits, giving a single daily dose rather than divided doses was thought to have resulted in toxic serum concentrations of endotoxins.[1,2]

1. CDC. Endotoxin-like reactions associated with intravenous gentamicin—California, 1998. *MMWR* 1998; **47**: 877–80.
2. Krieger JA, Duncan L. Gentamicin contaminated with endotoxin. *N Engl J Med* 1999; **340**: 1122.

Treatment of Adverse Effects

Aminoglycosides may be removed by haemodialysis or to a much lesser extent by peritoneal dialysis. Calcium salts given intravenously have been used to counter neuromuscular blockade; the efficacy of neostigmine has been variable.

For reference to the potential for calcium-channel blockers to reduce aminoglycoside-related nephrotoxicity see Kidney Disorders, under Uses of Verapamil, p. 1523.1.

Precautions

Gentamicin is contra-indicated in patients with a history of hypersensitivity to it, and probably in those hypersensitive to other aminoglycosides. It should be avoided in patients with myasthenia gravis, and great care is required in patients with parkinsonism and other conditions characterised by muscular weakness.

The risk of ototoxicity and nephrotoxicity from aminoglycosides is increased at high plasma concentrations and it is therefore generally desirable to determine dosage requirements by individual monitoring. In patients receiving standard multiple daily dose regimens of gentamicin, dosage should be adjusted to avoid peak plasma concentrations above 10 micrograms/mL, or trough concentrations (immediately before next dose) exceeding 2 micrograms/mL. Local guidelines on serum concentration should be consulted where once-daily dosage regimens are used. Monitoring is particularly important in patients receiving high doses or prolonged courses, in infants and the elderly, and in patients with renal impairment, who generally require reduced doses. It is also important in patients with cystic fibrosis or significant obesity; again, altered doses may be required. See Pharmacokinetics p. 309.3 for other patient groups in whom pharmacokinetics may be altered. Impaired hepatic function or auditory function, bacteraemia, fever, and perhaps exposure to loud

noises have also been reported to increase the risk of ototoxicity, while circulatory volume depletion or hypotension, liver disease, or female sex have been reported as additional risk factors for nephrotoxicity. Regular assessment of auditory and renal function is particularly necessary in patients with additional risk factors.

Topical application of gentamicin into the ear is contra-indicated in patients with known or suspected perforation of the ear drum.

Use of aminoglycosides during pregnancy may damage the eighth cranial nerve of the fetus.

Breast feeding. A study[1] involving 10 mothers given gentamicin and their breast-fed infants found measurable gentamicin concentrations in the serum of 5 of the 10 neonates, indicating that appreciable gastrointestinal absorption had occurred. It was, however, considered that these low concentrations would not cause clinical effects and the American Academy of Pediatrics[2] also considers that the use of gentamicin is usually compatible with breast feeding.

1. Celiloglu M, *et al.* Gentamicin excretion and uptake from breast milk by nursing infants. *Obstet Gynecol* 1994; 84: 263–5.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/05/04)

Interference with assay procedures. The implications of drug interference with assays for aminoglycosides have been reviewed.[1] Other antimicrobials and antineoplastics may alter the results of microbiological assays but this can be overcome by selection of an appropriate assay organism.

Microbiological assays for aminoglycosides in samples also containing *imipenem* could be accomplished by using cysteine hydrochloride to inactivate imipenem, which is stable to most beta-lactamases.[2] Because aminoglycosides may be inactivated by *penicillins* and *cephalosporins*, it has been recommended that aminoglycoside sampling times should be chosen to coincide with a trough plasma concentration for the beta lactam. Samples should be frozen if there is to be a delay before they are assayed[3] or a penicillinase added. However, one group of workers have reported loss of gentamicin activity after storage at -60 degrees before assay.[4] Furthermore, there have been reports that concentrations of aminoglycosides in patients also given beta lactams have been overestimated using a homogeneous enzyme immunoassay, probably because of an inability to differentiate between active drug and inactivated products.[5,6]

The radionuclide *gallium-67* interferes with radioenzymatic assays, and it has been suggested that an agar diffusion method should be used in patients who have received a gallium scan.[7,8]

Heparin has been shown to produce underestimation of aminoglycoside concentrations when using microbiological, enzymatic, or immunoassays.[9-11] It has been recommended either that serum should be used or that blood samples should not be collected in heparinised tubes or from indwelling catheter lines. Some consider that concentrations of heparin in the blood of patients receiving heparin are too low to affect gentamicin.[12]

Falsely low concentrations of aminoglycoside have also been reported in microbiological assays in the presence of *zinc* salts.[13]

Heat treatment of whole *blood* to inactivate human immunodeficiency virus leads to an increase in the concentration of gentamicin subsequently found on assay.[14]

1. Yosselson-Superstine S. Drug interferences with plasma assays in therapeutic drug monitoring. *Clin Pharmacokinet* 1984; 9: 67–87.
2. McLeod KM, *et al.* Gentamicin assay in the presence of imipenem. *J Antimicrob Chemother* 1986; 17: 828–9.
3. Tindula RJ, *et al.* Aminoglycoside inactivation by penicillins and cephalosporins and its impact on drug-level monitoring. *Drug Intell Clin Pharm* 1983; 17: 906–8.
4. Carlson LG, *et al.* Potential liabilities of gentamicin homogeneous enzyme immunoassay. *Antimicrob Agents Chemother* 1982; 21: 192–4.
5. Ebert SC, Clementi WA. In vitro inactivation of gentamicin by carbenicillin, compared by Emit and microbiological assays. *Drug Intell Clin Pharm* 1983; 17: 451.
6. Dalmady-Israel C, *et al.* Ticarcillin and assay of tobramycin. *Ann Intern Med* 1984; 100: 460.
7. Bhattacharya I, *et al.* Effects of radiopharmaceuticals on radioenzymatic assays of aminoglycoside antibiotics: interference by gallium-67 and its elimination. *Antimicrob Agents Chemother* 1978; 14: 448–53.
8. Shannon K, *et al.* Interference with gentamicin assays by gallium-67. *J Antimicrob Chemother* 1980; 6: 285–300.
9. Nilsson L. Factors affecting gentamicin assay. *Antimicrob Agents Chemother* 1980; 17: 918–21. Correction. *ibid.*; 18: 839.
10. Nilsson L, *et al.* Inhibition of aminoglycoside activity by heparin. *Antimicrob Agents Chemother* 1981; 20: 155–8.
11. O'Connell MB, *et al.* Heparin interference with tobramycin, netilmicin, and gentamicin concentrations determined by Emit. *Drug Intell Clin Pharm* 1984; 18: 503–4.
12. Regamey C, *et al.* Inhibitory effect of heparin on gentamicin concentrations in blood. *Antimicrob Agents Chemother* 1972; 1: 329–32.
13. George RH, Healing DE. The effect of zinc on aminoglycoside assay. *J Antimicrob Chemother* 1978; 4: 186.
14. Eley A, *et al.* Effect of heat on gentamicin assays. *Lancet* 1987; ii: 335–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies gentamicin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

Use of other nephrotoxic drugs (including other aminoglycosides, vancomycin, some cephalosporins, ciclosporin, cisplatin, and fludarabine), or of potentially ototoxic drugs such as etacrynic acid and perhaps furosemide, may increase the risk of aminoglycoside toxicity. It has been suggested that use of an antiemetic such as dimenhydrinate may mask the early symptoms of vestibular ototoxicity. Care is also required if other drugs with a neuromuscular-blocking action are used (see Atracurium, p. 2032.1). The neuromuscular-blocking properties of aminoglycosides may be sufficient to provoke severe respiratory depression in patients given general anaesthetics or opioids.

There is a theoretical possibility that the antibacterial effects of aminoglycosides could be reduced by bacteriostatic antibacterials, but such combinations have been used successfully in practice.

Since aminoglycosides have been shown to be incompatible with some beta lactams *in vitro* (see Incompatibility, p. 304.3), these antibacterials should be given separately if both are required; antagonism *in vivo* has been reported only in a few patients with severe renal impairment, in whom aminoglycoside activity was diminished. Aminoglycosides have synergistic activity with some beta lactams *in vivo* (see Antimicrobial Action, p. 309.2).

Renal excretion of zalcitabine may be reduced by aminoglycosides.

For reports of severe hypocalcaemia in patients treated with aminoglycosides and bisphosphonates, see p. 1177.2.

Gentamicin may inhibit α-galactosidase activity and should not be used with agalsidase alfa or beta.

Antimicrobial Action

Gentamicin is an aminoglycoside antibiotic and has a bactericidal action against many Gram-negative aerobes and against some strains of staphylococci.

Mechanism of action. Aminoglycosides are taken up into sensitive bacterial cells by an active transport process which is inhibited in anaerobic, acidic, or hyperosmolar environments. Within the cell they bind to the 30S, and to some extent to the 50S, subunits of the bacterial ribosome, inhibiting protein synthesis and generating errors in the transcription of the genetic code. The manner in which cell death is brought about is imperfectly understood, and other mechanisms may contribute, including effects on membrane permeability.

Spectrum of activity. The following pathogenic organisms are usually sensitive to gentamicin (but see also Resistance, below).

- Many strains of Gram-negative bacteria including species of *Brucella, Calymmatobacterium, Campylobacter, Citrobacter, Escherichia, Enterobacter, Francisella, Klebsiella, Proteus, Providencia, Pseudomonas, Serratia, Vibrio,* and *Yersinia.* Some activity has been reported against isolates of *Neisseria,* although aminoglycosides are rarely used clinically in neisserial infections.
- Among the Gram-positive organisms many strains of *Staphylococcus aureus* are highly sensitive to gentamicin. *Listeria monocytogenes* and some strains of *Staph. epidermidis* may also be sensitive to gentamicin, but enterococci and streptococci are usually insensitive to gentamicin.
- Some actinomycetes and mycoplasmas have been reported to be sensitive to gentamicin, but mycobacteria are insensitive at clinically achievable concentrations.
- Anaerobic organisms, yeasts, and fungi are resistant.

Activity with other antimicrobials. Gentamicin has synergy with beta lactams, probably because the effects of the latter on bacterial cell walls enhance aminoglycoside penetration. Enhanced activity has been shown with a penicillin (such as ampicillin or benzylpenicillin) and gentamicin against the enterococci, and gentamicin has been combined with an antipseudomonal penicillin such as ticarcillin for enhanced activity against *Pseudomonas* spp., and with vancomycin for enhanced activity against staphylococci and streptococci.

Resistance to the aminoglycosides may be acquired by three main mechanisms. The first is by mutation of ribosomal target sites leading to reduced affinity for binding; this type of resistance is generally only relevant for streptomycin and, even then, it appears to be rare in Gram-negative bacteria. Secondly, penetration of aminoglycosides into bacterial cells is by an oxygen-dependent active transport process and resistance may occur because of elimination or reduction of this uptake; when it occurs this generally results in cross-resistance to all aminoglycosides. Thirdly, and by far the most important cause of resistance to the aminoglycosides, is inactivation by enzymatic modification.

Three main classes of enzyme conferring resistance have been found, operating by phosphorylation, acetylation, or addition of a nucleotide group, usually adenyl. Enzyme production is usually plasmid-determined and resistance can therefore be transferred between bacteria, even of different species. Resistance to other antibacterials may be transferred at the same time. In *Staph. aureus,* transfer of resistance is more likely when these drugs are used topically.

Each type of enzyme produces characteristic patterns of resistance, but their overlapping and variable affinities for their substrates result in many permutations of cross-resistance to the different aminoglycosides. The different enzymes vary in their distribution and prevalence in different locations, and at different times, presumably with variations in antibacterial usage, but relationships to the use of specific aminoglycosides are difficult to establish. These variations in drug sensitivity require local testing to determine resistance and establish susceptibility of bacteria to the aminoglycoside being used, but such local variations mean that estimates of the incidence of resistance are of limited value.

In general, the occurrence of resistant pathogens seems to have been greater in southern than in northern Europe, and perhaps greater in the USA than in Europe. There has been particular concern over the increasing incidence of high-level gentamicin resistance among enterococci (in up to 50% of isolates from some centres), since they already possess inherent or acquired resistance to many drugs, including vancomycin in some cases. A similar problem exists with gentamicin resistance in meticillin-resistant strains of *Staph. aureus.* Such multiply-resistant strains pose a major therapeutic problem in those centres where they occur, since the usual synergistic combinations with other antibacterials are ineffective. However, results from some centres indicate that rational use of a wider range of aminoglycosides (including amikacin which is not affected by most of the aminoglycoside-degrading enzymes) has resulted in a modest decline in overall aminoglycoside resistance.

References.

1. Mingeot-Leclercq M-P, *et al.* Aminoglycosides: activity and resistance. *Antimicrob Agents Chemother* 1999; 43: 727–37.
2. Kotra LP, *et al.* Aminoglycosides: perspectives on mechanisms of action and resistance and strategies to counter resistance. *Antimicrob Agents Chemother* 2000; 44: 3249–56.
3. Barclay ML, Begg EJ. Aminoglycoside adaptive resistance: importance for effective dosage regimens. *Drugs* 2001; 61: 713–21.
4. Magnet S, Blanchard JS. Molecular insights into aminoglycoside action and resistance. *Chem Rev* 2005; 105: 477–98.

Pharmacokinetics

Gentamicin and other aminoglycosides are poorly absorbed from the gastrointestinal tract but are rapidly absorbed after intramuscular injection. Average peak plasma concentrations of about 4 micrograms/mL have been attained in patients with normal renal function 30 to 60 minutes after an intramuscular dose equivalent to gentamicin 1 mg/kg, which is similar to concentrations achieved after intravenous infusion. There may be considerable individual variation. Several doses are required before plasma equilibrium concentrations occur and this may represent the saturation of binding sites in body tissues such as the kidney. Binding of gentamicin to plasma proteins is usually low.

On parenteral use, gentamicin and other aminoglycosides diffuse mainly into extracellular fluids. However, there is little diffusion into the CSF and even when the meninges are inflamed effective concentrations may not be achieved; diffusion into the eye is also poor. Aminoglycosides diffuse readily into the perilymph of the inner ear. They cross the placenta but only small amounts have been reported in breast milk.

Systemic absorption of gentamicin and other aminoglycosides has been reported after topical use on denuded skin and burns and on instillation into, and irrigation of, wounds, body-cavities (except the urinary bladder), and joints.

The plasma elimination half-life for gentamicin has been reported to be 2 to 3 hours though it may be considerably longer in neonates and patients with renal impairment. Gentamicin and other aminoglycosides do not appear to be metabolised and are excreted virtually unchanged in the urine by glomerular filtration. At steady state at least 70% of a dose may be recovered in the urine in 24 hours and urine concentrations in excess of 100 micrograms/mL may be achieved. However, gentamicin and the other aminoglycosides appear to accumulate in body tissues to some extent, mainly in the kidney, although the relative degree to which this occurs may vary with different aminoglycosides. Release from these sites is slow and small amounts of aminoglycosides may be detected in the urine for up to 20

days or more after treatment stops. Small amounts of gentamicin appear in the bile.

The pharmacokinetics of the aminoglycosides are affected by many factors, which may become significant because of the relatively small difference between therapeutic and toxic concentrations, reinforcing the need for monitoring.

- Absorption from intramuscular sites may be reduced in critically ill patients, especially in conditions that reduce perfusion such as shock, resulting in **reduced plasma concentrations**. Plasma concentrations may also be reduced in patients with conditions which expand extracellular fluid volume or increase renal clearance including ascites, cirrhosis, heart failure, malnutrition, spinal cord injury, burns, cystic fibrosis, and possibly leukaemia. Clearance is also reportedly increased in intravenous drug abusers, and in patients who are febrile.
- In contrast, renal impairment or reduced renal clearance for any reason (for example in neonates with immature renal function, or in the elderly in whom glomerular function tends to decline with age) can result in markedly **increased plasma concentrations** and/or prolonged half-lives. However, in neonates initial plasma concentrations may actually be reduced, due to a larger volume of distribution. Plasma concentrations may also be higher than expected for a given dose in obese patients (in whom extracellular volume is low relative to weight), and in patients with anaemia.

Renal clearance, and hence plasma concentrations, of aminoglycosides may vary according to a circadian cycle, and it has been suggested that this should be taken into account when determining and comparing plasma aminoglycoside concentrations.

References.

1. Young P, Ensom MHH. Pharmacokinetics of aminoglycosides in patients with chronic spinal cord injury. *Am J Health-Syst Pharm* 2011; **68**: 1607–14.
2. Hilmer SN, *et al.* Gentamicin pharmacokinetics in old age and frailty. *Br J Clin Pharmacol* 2011; **71**: 224–31.

Pharmacokinetics in neonates. References

1. Lingvall M, *et al.* The effect of sepsis upon gentamicin pharmacokinetics in neonates. *Br J Clin Pharmacol* 2005; **59**: 54–61.
2. Hale LS, Durham CR. A simple, weight-based, extended-interval gentamicin dosage protocol for neonates. *Am J Health-Syst Pharm* 2005; **62**: 1613–16.
3. García B, *et al.* Population pharmacokinetics of gentamicin in premature newborns. *J Antimicrob Chemother* 2006; **58**: 372–9.
4. Murphy JE, Roether AM. Two nomograms for determining extended-dosing intervals for gentamicin in neonates. *Am J Health-Syst Pharm* 2008; **65**: 624–30. Correction. *ibid.*; 795.
5. Touw DJ, *et al.* Therapeutic drug monitoring of aminoglycosides in neonates. *Clin Pharmacokinet* 2009; **48**: 71–88. Correction. *ibid.*; 209–10. [dose]
6. Nielsen EI, *et al.* Developmental pharmacokinetics of gentamicin in preterm and term neonates: population modelling of a prospective study. *Clin Pharmacokinet* 2009; **48**: 253–63.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Gentaderm; Gentamina; Gentapharma; Gentaren; Gentoler†; Glevomicina; Plurisemina; Provisual; Rupegen; Sintepul†; ***Austral.***: Genoptic ***Austria***: Gentax; Refobacin; Sulmycin; ***Belg.***: Geomycine; ***Braz.***: Emisgenta; Garacin; Garamicina; Garamin†; Gentagran; Gentamicil; Gentamil; Gentamisan; Gentaron; Vitamicin†; ***Canad.***: Diogent; Garamycin; Gentak; ***Chile***: Gentalyn; Gentisal; Oftagen; ***China***: Jie Li Tai (杰力泰); Rui Bei Ke (瑞贝克); Wei Lun (维伦); ***Cz.***: Garamycin; ***Denm.***: Garamycin†; Gentacoll; Hexamycin; ***Fin.***: Gensumycin; Gentacoll; ***Fr.***: Gentalline; ***Ger.***: Gencin; Gent-Ophtal; Genta†; Gentamytrex†; InfectoGenta; Refobacin; Sulmycin; Terramycin N†; ***Gr.***: Anfomilan; Centaurin; Cortolexan; Dabroson; Diakarmon; Epabe; Fripeintil; Garamycin; Garbilocin; Gentagen; Gentamedin; Octoret; Septospes; Yedoc ***Hong Kong***: Garamycin; Genoptic†; Miramycin; ***Hung.***: Garamycin†; ***India***: Andregen†; Bactigen; Biogaracin; Emugent; G Mycin; G-Mycin; G20/80; Garamax; Garamycin; Genka; Genkind; Genmycin; Gensat; Genster; Gentacip; Gentact; Gentalab; Gentam; Gentaril; Gentasia; Gentasporin; Gentate; Genticyn Eye/Ear; Genticyn; Gentina; Genty; Gentyric; Gerocin; Indogenta; Ingen; Intagenta; Intragen; Ketajet; Lyramycin; Mycin; Mygenta; Optocin; ***Indon.***: Balticin; Bioderm†; Dermabiotik†; Dermagen; Ethigent; Garabiotic†; Garamycin; Garapon; Garexin; Gentacyl†; Gentamerck; Gentamisin†; Ikagen; Isotic Timact; Konigen†; Licogenta; Nichogencin; Ottogenta; Sagestam; Salgen; Salticin; Timact; Ximex Konigen; ***Irl.***: Cidomycin; Genoptic†; Genticin; ***Israel***: Gentatrim; Lacromycin; Opti-Genta; ***Ital.***: Ciclozinil; Eutopic; Gentacream; Gentalyn; Genticol; Gentomil; Nemalin; Ribomicin; Tacigen; ***Malaysia***: Beagenta; Garamycin; Garasent; Miramycin; ***Mex.***: Beramicina; Fustermicina†; G-I†; Garacoll†; Garakacin; Garalen†; Garamicina; Geclicin; Genemicin; Genkova; Genrex; Genser; Genta-Micron; Genta; Gentamil; Gentapat; Gentazaf Z; Gentazol; Gentialoquin†; Geracin; Ikatin; Lifegram; Progen†; Quilagen; Servigenta; Tamicin-G; Tamigen; Tondex; Tremax; Yectamicina; ***Neth.***: Garacol; Gentamytrex†; ***Norw.***: Garamycin†; Gensumycin; ***NZ***: Genoptic; ***Philipp.***: Agentam; Bellagen; Garamycin; Garazin; Gecitam; Genom; Gentamytrex†; Gentaxin; Gentrobex; Klontar; Migentax; Minoglen†; Mycin; Obogen; Opthagen; Orimed; Rocygen; Servigenta; Tangyn; Topigen; ***Pol.***: Garamycin; ***Port.***: Cronocol; Garalone; Genta Gobens; Gentalin; Gentocil; Ophtagram; Septopal; ***S.Afr.***: Cidomycin†; Garamycin; Sabax Gentamix; Sterisol Fermentmycin†; ***Singapore***: Colircusi; Dermogen; Garasent; Genoptic†; Gentamytrex; Gentapro; Gentasol; Miramycin; Optigen; ***Spain***: Genta Gobens; Gevramycin†; Rexgenta; ***Swed.***: Garamycin; Gensumycin; ***Switz.***: Garamycin; Ophtagram; ***Thai.***: Garamycin; Gencidal; Genta-Oph; Genta; Gentacin; Gentaderm; Gental; Gentawin; Gentrex; Grammicin; Grammixin; Miramycin; Skinfect; Versigen; ***Turk.***: Genmisin; Genta†; Gentagut; Gentamed; Genthaver; Gentreks; Getamisin; Getasin†; ***UAE***: Gental; ***UK***: Cidomycin; Genticin; ***USA***: Garamycin; Genoptic; Gentacidin†; Gentak; Gentasol; Ocu-Mycin; ***Venez.***: Gentalyn; Gentamilan; Gentisul; Solgenta.

Multi-ingredient Preparations. ***Arg.***: Adenil; Anginotrat; Bacticort Complex; Bacticort; Bactisona†; Becortin; Betacort Plus; Blamy; Butimerin Complex; Calmurid; Cevaderm; Cicatrizol; Ciprocort; Cuta Crema; Denvercrem; Dercotex; Dermizol G; Dermizol Trio; Dermoperative; Dermosona; Dexamytrex; Dicasone Complex; Diprogenta; Factor Dermico; Filoderma Plus; Filoderma; Genamic†; Gentacler; Gentacort Plus; Gentasol; Griseocrem; Hifamonil Crema; Lazar-Cort Complex; Lichensa; Linfol Dermico; Lisoderma; Macril; Magicrem; Microsona C; Miklogen; Monizol Cort Crema; Otalex G; Otonorthia; Pancutan; Provisual Compuesto; Quadriderm; Quiacort G Plus; Quiacort G; Sirotamicin BG; Tribiocort; Tricifa; Tricur; Tridermal; Triliver; Triplex; Vitacortil: ***Austral.***: Palacos E with Garamycin†; Palacos R with Garamycin†; Septopal†; ***Austria***: Decoderm Compositum; Decoderm trivalent†; Dexagenta; Diprogenta; Septopal; Voltamicin†; ***Belg.***: Decoderm Compositum†; Dexagenta-POS; Duracoll; Infectoflam†; Septopal; ***Braz.***: Betogenta; Cauterex; Crememderme; Diprogenta; Diprozil; Duotrat; Garasone; Gentacort; Gino Cauterex; Permut; Poliderms; Quadribeta; Quadriderm; Quadrihexal; Quadrikin†; Quadrilon; Quadriplus†; Qualiderm; Septopal; Tetraderm; ***Canad.***: Diprogen; Garasone; Pentasone; Valisone-G; ***Chile***: Diprospan G; Gentasone; Labosona G; Mixgen; Oftagen Compuesto; Palacos E con Gentamicina†; Palacos R con Gentamicina†; Perlas De PMMA con Gentamicina†; ***China***: Chanyanling (肠炎灵); Guan Xin Ke (贯新克); Infectoflam (易妥芬); Jinquan (金泉); Muli (目力); Qiyu (奇钰); Septopal (塞透派勒); Voltamicin (复美新); ***Cz.***: Belogent; Dexa-Gentamicin; Garasone; ***Denm.***: Septopal†; ***Fin.***: Celestoderm cum Garamycin; Septopal; ***Fr.***: Indobiotic; Septopal†; ***Ger.***: Cibaflam†; Decoderm Comp; Dexa-Gentamicin; Dexagent-Ophtal; Dexamytrex; Diprogenta; Heraeus PMMA Kette G; Inflanegent; Palasepti G†; Refobacin Bone Cement R; Refobacin Plus Bone Cement; Refobacin Revision; Septocoll; Septopal; Smart-Mix Cemvac GHV; SmartSet GHV; Sulmycin mit Celestan-V; Terracortril Dexagenta†; ***Gr.***: BV 17G; Celestoderm-V with Garamycin; Dermobeta; Dexamytrex; Garamat; Gentadex; Helpogen; Luzin; Palacos R with Gentamycin; Propiogenta; Septopal; Upanil; ***Hong Kong***: Beta-Genta†; Clobert-G†; Clobeta-G; Clotrim-B†; Cobetsol†; Conazole; Dermacloſ†; Dermafacte†; Dermal G; Diprogenta; Garasone; Lycobeta-G; Quadriderm; Septopal†; Triderm; Tridewel†; Triditol-G; ***Hung.***: Garasone; Gentasont; Septopal†; ***India***: ABC Derm; Aiclos-GM; Alcoderm; Aliderma; Aloederm-G; Atderm; Baclasia-CG; Balderm; BC-Zole; Beclasone-GM; Beclex-GM; Beclocid-G; Beclolab-CG; Beclotis-CG; Beclozen; Becmet-CG; Becmet-CG; Becmet-G; Becmet-GM; Belar-G; Benda; Bestopic; Betagel-G; Betamil-GM; Betanate G; Betanate GM; Betaspi-GM; Betnederm GM; Betnovate-GM; Betzee-G; Betzee-GM; Caltec; Candiderma; Candigen-BG; Canoderma; CGM; Clobaderm-GM; Clobasia-GM; Clobecos-GM; Clobequad; Cloberis-GM; Clobesym-GM; Clobeta-CF; Clobetamil-G; Clobquad; Cloby; Cloderm-GM; Clodip-GM; Clofung GM; Clofung-G; Clogem; Clomax-BG; Clomycin†; Clonate-G; Clonate-GM; Clop-G; Clop-MG; Clos-GM; Clotof-G; Clotof-GM; Corge-C; Cortiderm-G; Cortiderm-GM; Cortisol-G; Cosvate-G; Cosvate-GM; Cutasol-GM; Cuticare; Cutivate-GT; Darederm; Decand BG; Dermaspan; Derminol; Dermitop; Dermocrat Plus; Dermonit; Dermotriad; Dermowin-GM; Diclogenta; Dipgenta; Diprogen; Diprovate-G; Drep; E-Derm; Ecodax-G; Ecziclo-G; Ecziclo-GM; Ecziclo-M; Enderm-GM; Epicort-GC; Esgiderm; Etan-G; Etan-GM; Eumosone-G; Flunec; Fourderm AF; Fourderm; Fubac; GCB; Gem; Genta Cort B; Genta Cort D; Genta Swift-D; Genta Swift; Gentacip D; Gentacort-FC; Gentacort-MF; Gentalene-C; Gentasia-D; Gentasporin-HC; Gentate-B; Genticyn B; Genticyn HC; Gentopic; Gentyl-DM; Gerocin-BM; GMF; Hyton; IFB; Ifyclo-G; Imidil Plus; Intragen-D; Kloryl-G; Labosol-GM; Lamonte-BG; Leobet-GM; Leobet-GZ; Leta-GM; Lobate-G; Lotril-BG; Lupiderm-G; Lupiderm-GM; Magclo-G; Mediron; Miclogenta; Micocort-G; Nuforce-GM; Quiss; Septopal†; Sigmaderm; Tenovate G; Translipo-Triple; ***Indon.***: Benoson G; Betagentam; Betasin; Biocort†; Celestoderm-V with Garamycin; Cinogenta; Digenta; Diprogenta; Diprosta†; Garasone; Genolon; Gentacortin†; Gentasolon; Isotic Betaracin; Mastroson†; Salgen Plus; Sinobiotik†; Skilone; Skinal†; Sonigen; Synalten; Zensoderm; ***Irl.***: Gentisone HC; ***Israel***: Allumycin; Betacorten-G; Cicloderm-C; Diprogenta; Triderm; ***Ital.***: Betacream; Citrizan Antibiotico; Dermabiolene; Egerian; Fidagenbeta; Genalfa†; Gentacort†; Gentalyn Beta; Kamelyn; Sterozinil; Vasosterone Oto†; ***Malaysia***: B-Mycin; Beprogent; Betagen; Betamethasone G; Diprogenta; Garasone; Genta-Dex; Gentadexa; Joysun; ***Mex.***: Barnicil Compuesto; Beclogen; Beclotrin; Betrigen; Clotricina; Diprosone G; Garamicina-V†; Garasone; Miclobet; Prubagen; Quadriderm NF; Qudermin; Triderm; ***Neth.***: Dexagenta-POS; Dexamytrex; Septopal; ***Norw.***: Septopal; ***NZ***: CMW Gentamicin; Palacos with Garamycin; Smartmix; Smartset; Vacu-Mix Plus with CMW gentamicin; ***Philipp.***: Combiderm; Dexamytrex; Diprogenta; Garasone; Infectoflam; Ophtasone; Quadriderm; Quadrotopic; Septopal; Triderm; Xetam-Opta; ***Pol.***: Bedicort G; Belogent; Dexamytrex; Diprogenta; Triderm; ***Port.***: Dexamytrex; Diprogenta; Epione; Gentadexa; Indobiotic; Quadriderme; ***Rus.***: Akriderm Genta (Акридерм Гента); Akriderm GK (Акридерм ГК); Belogent (Белогент); Betaderm (Бетадерм); Betagenot (Бетагенот); Candiderm (Кандидерм); Canison Plus (Канизон Плюс); Celestoderm-V with Garamycin (Целестодерм-В с Гарамицином); Dexa-Gentamicin (Декса-Гентамицин); Fugentin (Фугентин); Garasone (Гаразон); Triderm (Тридерм); ***S.Afr.***: Diprogenta; Palacos R with Garamycin; Quadriderm; Septopal; ***Singapore***: Antasone; B-Tasone-G; Beprogent; Combiderm; Conazole; Dexa-Gentamicin; Dexamytrex†; Diprogenta; Garasone†; Gentriderm; Gentrisone; Infectoflam; Modaderm; Neoderm; Refobacin Bone Cement R†; Saerogenta-A; Septopal; Tri-Micon; Triderm; ***Spain***: Celestoderm Gentamicina; Cuatroderm; Diprogenta; Epitelizante; Flugent†; Flutenal Gentamicina†; Gentadexa; Interderm; Novoter Gentamicina; ***Swed.***: Celeston valerat med gentamicin†; ***Switz.***: Dexagenta-POS; Diprogenta; Infectoflam†; Ophtasone; Septopal; Triderm; Voltamicin; ***Thai.***: Beprogent; Beprogenta; Betagen; Betagram; Dermaheu; Dertec; Dexamytrex†; Genquin; Gental-F; Infectoflam†; Pred Oph; Quadriderm; Refobacin Bone Cement R; Septopal; Skinfect-B; Spectroderm; ***Turk.***: Belogent; Indobiotic; ***UK***: Collatamp EG; Gentisone HC; Palacos LV with Gentamicin; Palacos R with Gentamicin; Septopal; Vipsogal; ***Ukr.***: Betaderm (Бетадерм); Candiderm (Кандидерм); Clotrex (Клотрекс); Cremgen (Кремген); Gentaxan (Гентаксан); Triacutan (Триакутан); Triderm (Тридерм); ***USA***: Pred G; ***Venez.***: Betaderm con Gentamicina; Celestoderm con Gentalyn; Diprogenta; Garabet Garasone; Gentidexa; Gentidexa; Quadriderm; Triderm; Tridetarmon.

Pharmacopoeial Preparations

BP 2014: Gentamicin and Hydrocortisone Acetate Ear Drops; *Gentamicin Cream*; Gentamicin Ear Drops; Gentamicin Eye Drops; Gentamicin Injection; Gentamicin Ointment;

USP 36: Gentamicin and Prednisolone Acetate Ophthalmic Ointment; Gentamicin Injection; Gentamicin Sulfate Cream; Gentamicin Sulfate Ointment; Gentamicin Sulfate Ophthalmic Ointment; Gentamicin Sulfate Ophthalmic Solution.

Gramicidin *(BAN, rINN)*

Gramicidin D; Gramicidin (Dubos); Gramicidina; Gramicidinas; Gramicidine; Gramicidinum; Gramisidiini; Gramisidin; Грамицидин.

CAS — 1405-97-6.
ATC — R02AB30.
ATC Vet — QR02AB30.
UNII — 5IE62321P4.

NOTE. The name gramicidin was formerly applied to tyrothricin.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Gramicidin). It consists of a family of antimicrobial linear polypeptides usually obtained by extraction from tyrothricin, the complex isolated from the fermentation broth of *Bacillus brevis*. The main component is gramicidin A1, together with gramicidins A2, B1, C1, and C2 in particular. The potency is not less than 900 units/mg calculated with reference to the dried substance. A white or almost white, slightly hygroscopic, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; soluble in methyl alcohol. Store in airtight containers. Protect from light.

USP 36: (Gramicidin). An antibacterial substance produced by the growth of *Bacillus brevis* (Bacillaceae); it may be obtained from tyrothricin. It has a potency of not less than 900 micrograms of gramicidin per mg, calculated on the dried basis. A white or practically white, odourless, crystalline, powder. Insoluble in water; soluble in alcohol. Store in airtight containers.

Profile

Gramicidin has properties similar to those of tyrothricin (p. 386.1) and is too toxic to be given systemically. It is used topically for the local treatment of susceptible infections usually with other antibacterials such as neomycin and polymyxin B, and often with a corticosteroid as well.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies gramicidin as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Neo-Argicilline.

Multi-ingredient Preparations. ***Arg.***: Antibiocort; Aseptobron N; Aseptobron N; Biotaer Nasal†; Bucoangin N; Caext; Carnot Colutorio; Collubiazol N; Expectosan Caramelos; Gargaletas;

Graneodin N; Graneodin; Gripaben Caramelos; Kenacomb; Nasomicina; Neo Coltirot; Pantometil†; Proetztotal; Tosedrin NF; ***Austral.***: Kenacomb; Neosporin†; Otocomb Otic; Otodex; Sofradex; Soframycin†; ***Austria***: Volon A antibiotikahaltig†; ***Belg.***: Mycolog; Polyspectran Gramicidine†; ***Braz.***: Fonergin; Londerm-N†; Mud; Neolon D; Omcilon-A M; Oncibel; Oncileg; Onciplus†; ***Canad.***: Ak Spor; Antibiotic Cream; Antibiotic Plus; Complete Antibiotic Ointment; Diosporin†; Neosporin; Opticort; Optimyxin Plus; Optimyxin; Polysporin Complete; Polysporin For Kids; Polysporin Plus Pain Relief; Polysporin Triple Antibiotic; Polysporin; Polytopic; ratio-Triacomb; Sofracort; Soframycin; Soframycin; Triple Antibiotic Ointment; Viaderm-KC; ***Chile***: Oftabiotico; ***China***: Kenacomb (复方康纳乐霜); ***Denm.***: Kenalog Comp med Mycostatin†; Sofradex; ***Fin.***: Bafucin; Polysporin†; ***Ger.***: Polyspectran; ***Gr.***: Neo-Priphen; Neosporin; Sofradex; Thilodexine-N; ***Hong Kong***: Centacomb; Dermawell†; In-quadeicren; Kenacomb†; Neosporin; Polyneospin†; Polyoph; Polyspectran†; Sofradex; Triacomb†; ***Hung.***: Polysport†; ***India***: Kenacomb; Kenalog-S; Neosporin; Sofracort; ***Indon.***: Blecidex; Isotic Enpigi; Neosyd; Sofradex; ***Irl.***: Graneodin†; Kenacomb†; Sofradex; ***Israel***: Dermacombin; ***Ital.***: Eta Biocortilen VC; ***Malaysia***: Kenacomb; Pocin G†; Sofradex; ***Mex.***: Biotarson N†; Biotarson O†; Graneodin D; Kenacomb; Neosporin; Polixin; Poly-Micron; Septilisin; Soperil; Sulned; ***Neth.***: Mycolog†; Sofradex; ***Norw.***: Sofradex; ***NZ***: Kenacomb; Sofradex; Soframycin†; Viaderm-KC; ***Philipp.***: Iporam; Kenacomb†; Lidex NGN; Neosporin; Novasorin; Oticom; Trispec; ***Pol.***: Dicortineff; Triacomb; ***Port.***: Dropdina; ***Rus.***: Sofradex (Софрадекс); ***S.Afr.***: Kenacomb†; Sofradex; ***Singapore***: Sofradex; ***Spain***: Flodermol; Fludronef†; Midacina; Oftalmowell; Tivitis†; ***Swed.***: Bafucin; ***Switz.***: Angidine†; Mycolog N; Neosporin; Sofradex†; Topsym polyvalent; Tyrothricine + Gramicidine†; ***Thai.***: Dermacombin; Kenacomb†; Polyoph; Sofradex; Topifram; Xanalin; ***Turk.***: Neosporin; ***UAE***: Panderm; ***UK***: Neosporin†; Sofradex; ***Ukr.***: Grammidin with Anaesthetic Neo (Грамицидин С Анестетиком Нео); ***USA***: Neosporin; Ocu-Spor-G; Ocutricin; Polymycin; ***Venez.***: Kenacomb.

Pharmacopoeial Preparations

USP 36: Neomycin and Polymyxin B Sulfates and Gramicidin Cream; Neomycin and Polymyxin B Sulfates and Gramicidin Ophthalmic Solution; Neomycin and Polymyxin B Sulfates, Gramicidin, and Hydrocortisone Acetate Cream; Neomycin Sulfate and Gramicidin Ointment; Nystatin, Neomycin Sulfate, Gramicidin, and Triamcinolone Acetonide Cream; Nystatin, Neomycin Sulfate, Gramicidin, and Triamcinolone Acetonide Ointment.

Gramicidin S *(rINN)*

Gramicidin C; Gramicidina S; Gramicidine S; Gramicidinum S; Soviet Gramicidin; Грамицидин С.

$C_{60}H_{92}N_{12}O_{10}$=1141.5

CAS — 113-73-5.

UNII — WHM29QA23F.

Profile

Gramicidin S is an antibacterial polypeptide, produced by *Bacillus brevis*, and has similar properties to tyrothricin (p. 386.1). It is unsuitable for systemic use and is used topically for the local treatment of susceptible infections and as lozenges for infections of the mouth and throat. The hydrochloride is used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Rus.***: Grammidin (Грамицидин).

Multi-ingredient Preparations. ***Indon.***: FG Ointment†; FG Troches; ***Rus.***: Grammidin Neo (Грамицидин Нео); Grammidin with Anesthetic Neo (Грамицидин с АнестетикОм Нео); ***Ukr.***: Grammidin (Граммицидин); Grammidin Neo (Грамицидин Нео); Sofradex (Софрадекс)†.

Halquinol *(BAN)*

Chlorhydroxyquinoline; Chlorquinol; Halquinols (USAN); SQ-16401.

A mixture of the chlorinated products of quinolin-8-ol containing 57 to 74% of 5,7-dichloroquinolin-8-ol (chloroxine, p. 260.1), 23 to 40% of 5-chloroquinolin-8-ol (cloxiquine, p. 577.1), and not more than 4% of 7-chloroquinolin-8-ol.

CAS — 8067-69-4.

UNII — Z7Z4BX535U.

Profile

Halquinol is a halogenated hydroxyquinoline with properties similar to those of clioquinol (p. 273.1). It is used topically in infected skin conditions.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***UK***: Valpeda.

Ibafloxacin *(BAN, USAN, rINN)*

Ibafloksasiini; Ibafloxacine; Ibafloxacino; Ibafloxacinum; R-835; S-25930; Ибафлоксацин.

9-Fluoro-6,7-dihydro-5,8-dimethyl-1-oxo-1*H*,5*H*-benzo[*ij*]quinolizine-2-carboxylic acid.

$C_{15}H_{14}FNO_3$=275.3

CAS — 91618-36-9.

ATC Vet — QJ01MA96.

UNII — 53VPK9R0T5.

Profile

Ibafloxacin is a fluoroquinolone antibacterial that is used in veterinary medicine for the treatment of susceptible infections in cats and dogs.

Iclaprim *(USAN, rINN)*

AR-100; Iclaprime; Iclaprimum; Ro-48-2622; Иклаприм.

5-[(2*RS*)-2-Cyclopropyl-7,8-dimethoxy-2*H*-chromen-5-ylmethyl]pyrimidine-2,4-diamine.

$C_{19}H_{22}N_4O_3$=354.4

CAS — 192314-93-5.

ATC — J01EA03.

ATC Vet — QJ01EA03.

UNII — 42445HUU0O.

Iclaprim Mesilate *(rINNM)*

AR-100.001; Iclaprim Mesylate (USAN); Iclaprime, Mésilate d'; Iclaprimi Mesilas; Mesilato de iclaprim; Иклаприма Мезилат.

5-[[(2*RS*)-2-Cyclopropyl-7,8-dimethoxy-2*H*-1-benzopyran-5-yl]methyl]pyrimidine-2,4-diamine methanesulfonate.

$C_{19}H_{22}N_4O_3.CH_4O_3S$=450.5

CAS — 474793-41-4.

ATC — J01EA03.

ATC Vet — QJ01EA03.

UNII — 7U972CJ5AT.

NOTE. The name Mersarex has been used as a trade mark for iclaprim mesylate.

Profile

Iclaprim is a diaminopyrimidine antibacterial similar to trimethoprim (p. 383.2) that has been investigated for the treatment of complicated infections of the skin and skin structure caused by Gram-positive bacteria, including MRSA.

References.

1. Sincak CA, Schmidt JM. Iclaprim, a novel diaminopyrimidine for the treatment of resistant gram-positive infections. *Ann Pharmacother* 2009; **43**: 1107–14.
2. Sader HS, *et al.* Potency and bactericidal activity of iclaprim against recent clinical Gram-positive isolates. *Antimicrob Agents Chemother* 2009; **53**: 2171–5.
3. Krievins D, *et al.* Multicenter, randomized study of the efficacy and safety of intravenous iclaprim in complicated skin and skin structure infections. *Antimicrob Agents Chemother* 2009; **53**: 2834–40.

Imipenem *(BAN, USAN, rINN)*

N-Formimidoyl Thienamycin; Imipemide; Imipenemi; Imipénem; Imipenem monohydrát; Imipenemas; Imipenemum; Imipenemum Monohydricum; MK-0787; MK-787; Имипенем.

(5*R*,6*S*)-6-[(*R*)-1-Hydroxyethyl]-3-(2-iminomethylaminoethylthio)-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monohydrate.

$C_{12}H_{17}N_3O_4S.H_2O$=317.4

CAS — 64221-86-9 (anhydrous imipenem); 74431-23-5 (imipenem monohydrate).

UNII — 71OTZ9ZE0A (imipenem monohydrate); Q20IM7HE75 (anhydrous imipenem).

Description. Imipenem is the *N*-formimidoyl derivative of thienamycin, an antibiotic produced by *Streptomyces cattleya*.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Imipenem Monohydrate). A white, almost white, or pale yellow slightly hygroscopic powder. Slightly soluble in water and in methyl alcohol. A 0.5% solution in water has a pH of 4.5 to 7.5. Store in airtight containers at a temperature of 2 degrees to 8 degrees.

USP 36: (Imipenem). A white to tan-coloured crystalline powder. Slightly soluble in water and in methyl alcohol. Store at a temperature not exceeding 8 degrees.

Incompatibility and stability. Imipenem is unstable at alkaline or acidic pH and the commercially available injection of imipenem with cilastatin sodium for intravenous use is buffered to provide, when reconstituted, a solution with pH 6.5 to 7.5. Licensed product information advises against mixing with other antibacterials.

References.

1. Bigley FP, *et al.* Compatibility of imipenem-cilastatin sodium with commonly used intravenous solutions. *Am J Hosp Pharm* 1986; **43**: 2803–9.
2. Smith GB, *et al.* Stability and kinetics of degradation of imipenem in aqueous solution. *J Pharm Sci* 1990; **79**: 732–40.
3. Pourroy B, *et al.* Incompatibility of imipenem-cilastatin and amoxicillin. *Am J Health-Syst Pharm* 2009; **66**: 1253–4.

Uses and Administration

Imipenem is a carbapenem beta-lactam antibacterial, differing from the penicillins in that the 5-membered ring is unsaturated and contains a carbon rather than a sulfur atom. Since imipenem is metabolised in the kidney by the enzyme dehydropeptidase I it is always given with cilastatin (p. 260.3), an inhibitor of the enzyme; this enhances urinary concentrations of active drug and was found to protect against the nephrotoxicity of high doses of imipenem seen in *animal* studies.

Imipenem is used for the treatment of infections caused by susceptible Gram-positive and Gram-negative organisms; because of its broad spectrum of activity, it may also be given in the treatment of polymicrobial infections or as empirical therapy before the identification of causative organisms. Such infections include infections in immunocompromised patients (with neutropenia), intra-abdominal infections, bone and joint infections, lower-respiratory-tract infections, skin and skin-structure infections, urinary-tract infections and biliary-tract infections; it is not indicated for CNS infections. It may also be used for surgical infection prophylaxis. Imipenem may be used as part of a multidrug regimen for the treatment of inhalation and gastrointestinal anthrax. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Commercial preparations contain imipenem and cilastatin, as the sodium salt, in a ratio of 1 to 1. Doses of the combination are expressed in terms of the amount of anhydrous imipenem. Imipenem is given by intravenous infusion; doses of 250 or 500 mg are infused over 20 to 30 minutes, and doses of 750 mg or 1 g over 40 to 60 minutes. Products for intramuscular use are available in some countries.

The usual intravenous dose is 1 to 2 g daily in divided doses every 6 or 8 hours, depending on the severity of the infection. Usual doses are based on a body-weight of at least 70 kg; proportionate reduction of the dose is recommended for patients weighing less than this. Up to a maximum daily dose of 50 mg/kg (not exceeding 4 g) has been given in life-threatening infections or infections due to less sensitive organisms.

Imipenem may be given intramuscularly in adults with mild to moderate infections in doses of 500 or 750 mg every 12 hours.

The dose of imipenem should be reduced in renal impairment and in those weighing less than 70 kg, see p. 312.1. See also p. 311.3 for details of doses in children.

General reviews.

1. Balfour JA, *et al.* Imipenem/cilastatin: an update of its antibacterial activity, pharmacokinetics and therapeutic efficacy in the treatment of serious infections. *Drugs* 1996; **51**: 99–136.
2. Hellinger WC, Brewer NS. Carbapenems and monobactams: imipenem, meropenem, and aztreonam. *Mayo Clin Proc* 1999; **74**: 420–34.
3. Norrby SR. Carbapenems in serious infections: a risk-benefit assessment. *Drug Safety* 2000; **22**: 191–4.
4. Rodloff AC, *et al.* Two decades of imipenem therapy. *J Antimicrob Chemother* 2006; **58**: 916–29.
5. Zhanel GG, *et al.* Comparative review of the carbapenems. *Drugs* 2007; **67**: 1027–52.
6. Lo TS, *et al.* A review of the carbapenems in clinical use and clinical trials. *Recent Pat Antiinfect Drug Discov* 2008; **3**: 123–31.
7. Kattan JN, *et al.* New developments in carbapenems. *Clin Microbiol Infect* 2008; **14**: 1102–11.
8. Masterton RG. The new treatment paradigm and the role of carbapenems. *Int J Antimicrob Agents* 2009; **33**: 105–110.

Administration. For the suggestion that extended infusion of imipenem with cilastatin might increase its efficacy see under Meropenem, p. 323.3.

Administration in children. Imipenem (with cilastatin, see Uses and Administration, above) may be given to children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria. It is given by intravenous infusion; doses less than or equal to 500 mg are infused over 15 to 30 minutes, and doses more than 500 mg over 40 to 60 minutes.

Although not licensed for use in children less than 1 year of age in the UK, the *BNFC* recommends the following doses of imipenem:

- neonates under 7 days: 20 mg/kg every 12 hours
- neonates 7 to 21 days: 20 mg/kg every 8 hours
- neonates 21 to 28 days: 20 mg/kg every 6 hours
- children 1 to 3 months: 20 mg/kg every 6 hours

- children 3 months of age and over: 15 mg/kg (to a maximum dose of 500 mg) every 6 hours; for infection caused by Pseudomonas or other less sensitive organisms, life-threatening infection, or for empirical treatment of infection in febrile patients with neutropenia, 25 mg/kg (to a maximum dose of 1 g) is given every 6 hours

For the treatment of *cystic fibrosis* the *BNFC* recommends that children from 1 month of age may be given 25 mg/kg (to a maximum dose of 1 g) every 6 hours.

It should be noted that these recommendations potentially result in higher doses being given to larger children than would be given to an adult of comparable body-weight if the dose in the latter were reduced for being below 70 kg.

US licensed product information recommends the following doses for neonates and children weighing 1.5 kg or more:

- neonates less than 1 week of age: 25 mg/kg every 12 hours
- neonates 1 to 4 weeks of age: 25 mg/kg every 8 hours
- children 1 to 3 months of age: 25 mg/kg every 6 hours
- children 3 months of age and older: 15 to 25 mg/kg every 6 hours to a maximum daily dose of 2 g for fully susceptible organisms or 4 g for moderately susceptible organisms (mainly for strains of *Pseudomonas aeruginosa*). Up to 90 mg/kg daily has been given to older children with cystic fibrosis.

Administration in renal impairment. Intravenous doses of imipenem are generally reduced in patients with renal impairment (creatinine clearance less than 70 mL/minute per 1.73 m^2) regardless of body-weight. A further proportionate reduction in dose is recommended for patients weighing less than 70 kg. Tables to calculate appropriate reductions depending on body-weight, creatinine clearance, and infection characteristics are available in the licensed product information.

Patients with a creatinine clearance of 5 mL/minute or less should only be given imipenem if haemodialysis is started within 48 hours. Imipenem and cilastatin are cleared from the body by haemodialysis and doses should be given after a dialysis session and then every 12 hours.

For critically ill patients undergoing continuous renal replacement therapy, a loading dose of 1 g, and the following maintenance doses have been recommended:[1]

- continuous venovenous haemofiltration (CVVH): 500 mg every 8 hours
- continuous venovenous haemodialysis (CVVHD): 500 mg every 6 to 8 hours
- continuous venovenous haemodiafiltration (CVVHDF): 500 mg every 6 hours

Information is lacking on the safety or efficacy of the *intramuscular* route in patients with renal impairment.

1. Heintz BH, *et al.* Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy* 2009; **29**: 562–77.

Adverse Effects

Imipenem is always given with the enzyme inhibitor cilastatin and thus clinical experience relates to the combination.

Adverse effects with imipenem-cilastatin are similar in general to those with other beta lactams (see Benzylpenicillin, p. 229.2, and Cefalotin, p. 235.2). Hypersensitivity reactions such as rashes, urticaria, eosinophilia, fever, and, rarely, anaphylaxis may occur. Gastrointestinal effects include nausea, vomiting, diarrhoea, tooth or tongue discoloration, and altered taste. Superinfection with non-susceptible organisms such as *Enterococcus faecium*, strains of *Pseudomonas aeruginosa* with acquired resistance, and *Candida* may also occur. Pseudomembranous colitis may develop. Erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported rarely. Increases in liver enzymes and abnormalities in haematological parameters, including a positive Coombs' test, have been noted.

Local reactions such as pain or thrombophlebitis may occur after injection.

Seizures or convulsions have been reported with imipenem-cilastatin, particularly in patients with a history of CNS lesions and/or poor renal function, but sometimes in those without predisposing factors for seizures given recommended doses; it is generally considered to be more epileptogenic than other carbapenems. Mental disturbances and confusion have also been reported.

Cilastatin has protected against the nephrotoxicity seen with high doses of imipenem given experimentally to *animals*. A harmless reddish coloration of urine has been seen in children.

Effects on the nervous system. References.

1. Eng RH, *et al.* Seizure propensity with imipenem. *Arch Intern Med* 1989; **149**: 1881–3.
2. Brown RB, *et al.* Seizure propensity with imipenem. *Arch Intern Med* 1990; **150**: 1551.
3. Job ML, Dretler RH. Seizure activity with imipenem therapy: incidence and risk factors. *DICP Ann Pharmacother* 1990; **24**: 467–9.
4. Leo RJ, Ballow CH. Seizure activity associated with imipenem use: clinical case reports and review of the literature. *DICP Ann Pharmacother* 1991; **25**: 351–4.
5. Duque A, *et al.* Vertigo caused by intravenous imipenem/cilastatin. *DICP Ann Pharmacother* 1991; **25**: 1009.
6. Lucena M, *et al.* Imipenem/cilastatin-associated hiccups. *Ann Pharmacother* 1992; **26**: 1459.
7. Norrby SR. Neurotoxicity of carbapenem antibacterials. *Drug Safety* 1996; **15**: 87–90.

Hypersensitivity. A retrospective analysis[1] involving a total of 211 patients appeared to show that those with a history of reported or documented penicillin allergy had an 11% incidence of hypersensitivity reactions when treated with a carbapenem antibacterial compared with 2.7% for those without such a history of penicillin allergy. There was no difference in the occurrence of allergic-type reactions between imipenem-cilastatin and meropenem. A study[2] in patients with cell-mediated allergy to beta lactams reported a 5.5% rate of cross-sensitivity with imipenem. Others, however, have reported very low rates of cross-sensitivity to imipenem-cilastatin (less than 1%) in adults[3] and children[4] with documented hypersensitivity to penicillins. Similarly low rates of cross-sensitivity to meropenem have been reported[5,6] in patients with IgE-mediated hypersensitivity to penicillins. Based on available data, the authors of a review[7] recommended that penicillin-allergic patients who require a carbapenem first be skin-tested to the carbapenem; if the results are negative, a carbapenem may be safely given in a graded dose challenge.

1. Prescott WA, *et al.* Incidence of carbapenem-associated allergic-type reactions among patients with versus patients without a reported penicillin allergy. *Clin Infect Dis* 2004; **38**: 1102–7.
2. Schiavino D, *et al.* Cross-reactivity and tolerability of imipenem in patients with delayed-type, cell-mediated hypersensitivity to beta-lactams. *Allergy* 2009; **64**: 1644–8.
3. Romano A, *et al.* Imipenem in patients with immediate hypersensitivity to penicillins. *N Engl J Med* 2006; **354**: 2835–7.
4. Atanaskovic-Markovic M, *et al.* Tolerability of imipenem in children with IgE-mediated hypersensitivity to penicillins. *J Allergy Clin Immunol* 2009; **124**: 167–9.
5. Romano A, *et al.* Brief communication: tolerability of meropenem in patients with IgE-mediated hypersensitivity to penicillins. *Ann Intern Med* 2007; **146**: 266–9.
6. Atanaskovic-Markovic M, *et al.* Tolerability of meropenem in children with IgE-mediated hypersensitivity to penicillins. *Allergy* 2008; **63**: 237–40.
7. Frumin J, Gallagher JC. Allergic cross-sensitivity between penicillin, carbapenem, and monobactam antibiotics: what are the chances? *Ann Pharmacother* 2009; **43**: 304–15.

Precautions

Imipenem-cilastatin should not be given to patients known to be hypersensitive to it, and should be given with caution to patients known to be hypersensitive to penicillins, cephalosporins, or other beta lactams because of the possibility of cross-sensitivity (see Hypersensitivity, above).

It should be given with caution to patients with renal impairment, and the dose reduced appropriately. Particular care is necessary in patients with CNS disorders such as epilepsy.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies imipenem-cilastatin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/09/11)

Interactions

Seizures have been reported in patients given ganciclovir with imipenem-cilastatin.

Antiepileptics. For reports of decreased plasma-*valproate* concentrations (sometimes with loss of seizure control) attributed to imipenem, and the view that carbapenems should not be used with valproates, see p. 557.2.

Antimicrobial Action

Imipenem is bactericidal and acts similarly to the penicillins by inhibiting synthesis of the bacterial cell wall. It has a very broad spectrum of activity *in vitro*, including activity against Gram-positive and Gram-negative aerobic and anaerobic organisms, and is stable to hydrolysis by beta-lactamases produced by most bacterial species. Cilastatin, the enzyme inhibitor given with imipenem, appears to have no antibacterial activity.

- Most Gram-positive cocci are sensitive to imipenem including most streptococci, and both penicillinase- and non-penicillinase-producing staphylococci, although MRSA is typically resistant.

  Imipenem generally has good inhibitory (but not bactericidal) activity against *Enterococcus faecalis*, but most *E. faecium* are resistant. *Nocardia*, *Rhodococcus*, *Listeria*, *Bacillus*, and *Corynebacterium* spp. (with the exception of *C. jeikeium* and *C. urealyticum*) are also sensitive.
- Among Gram-negative bacteria, imipenem is active against many of the Enterobacteriaceae including strains that produce extended-spectrum beta-lactamases (ESBLs). Sensitive organisms may include *Citrobacter* and *Enterobacter* spp., *Escherichia coli*, *Klebsiella*, *Proteus*, *Providencia*, *Salmonella*, *Serratia*, *Shigella*, and *Yersinia* spp. Imipenem is also active against *Burkholderia pseudomallei* and *B. mallei*, *Campylobacter jejuni*, *Haemophilus influenzae*, and *Neisseria* spp., including beta-lactamase-producing strains. *Burkholderia cepacia* and *Stenotrophomonas maltophilia* are resistant to imipenem.
- Many anaerobic bacteria, including *Bacteroides* spp., are sensitive to imipenem, but *Clostridium difficile* is only moderately susceptible.
- Rapidly-growing mycobacteria including *Mycobacterium fortuitum*, *M. chelonae*, *M. abscessus*, and *M. marinum* are variably susceptible to imipenem.
- Imipenem is not active against *Chlamydia trachomatis*, *Mycoplasma* spp., fungi, or viruses.

There have been reports of antagonism between imipenem and other beta lactams *in vitro*. Imipenem and aminoglycosides often act synergistically against some isolates of *P. aeruginosa*.

Imipenem is a potent inducer of beta-lactamases of some Gram-negative bacteria, but generally remains stable to them.

Resistance. Imipenem resistance, which generally results from a combination of porin loss with expression of either AmpC-type enzymes or ESBLs, or from the production of carbapenemases (such as the class B metallo-β-lactamases) is increasing among the Enterobacteriaceae. Genes for the expression of carbapenemases tend to be found on plasmids that already contain mutations conferring resistance to other antibacterials such as fluoroquinolones and aminoglycosides; as a result, carbapenemase-producing Enterobacteriaceae are typically extremely drug-resistant and their spread is a cause for significant concern. Carbapenemase production has also contributed to widespread resistance among *Ps. aeruginosa* and *Acinetobacter baumannii*, both of which have historically been susceptible to imipenem.

Resistance. References.

1. Rasmussen BA, Bush K. Carbapenem-hydrolyzing β-lactamases. *Antimicrob Agents Chemother* 1997; **41**: 223–32.
2. Livermore DM. Acquired carbapenemases. *J Antimicrob Chemother* 1997; **39**: 673–6.
3. Modakkas EM, Sanyal SC. Imipenem resistance in aerobic gram-negative bacteria. *J Chemother* 1998; **10**: 97–101.
4. Schwaber MJ, Carmeli Y. Carbapenem-resistant Enterobacteriaceae: a potential threat. *JAMA* 2008; **300**: 2911–3.
5. Zilberberg MD, *et al.* Imipenem resistance of *Pseudomonas* in pneumonia: a systematic literature review. *BMC Pulm Med* 2010; **10**: 45.
6. Cornaglia G, *et al.* Metallo-β-lactamases: a last frontier for β-lactams? *Lancet Infect Dis* 2011; **11**: 381–93.

Pharmacokinetics

Imipenem is not appreciably absorbed from the gastrointestinal tract and is given parenterally.

Imipenem is excreted mainly in the urine by glomerular filtration and, to a lesser extent, by tubular secretion. It undergoes partial metabolism in the kidneys by dehydropeptidase I, an enzyme in the brush border of the renal tubules, to inactive, nephrotoxic metabolites, with only about 5 to 40 or 45% of a dose excreted in the urine as unchanged active drug. Consequently, imipenem is given with cilastatin sodium (p. 260.3), a dehydropeptidase inhibitor, to ensure adequate urinary-imipenem concentrations. While cilastatin may slightly increase serum concentrations of imipenem, half-life is not appreciably affected.

The pharmacokinetics of imipenem and cilastatin are similar and both have plasma half-lives of about 1 hour; half-lives, especially those of cilastatin, may be prolonged in neonates and in patients with renal impairment. Intravenous infusion over 20 to 30 minutes of 500 mg or 1 g of imipenem with cilastatin results in peak plasma-imipenem concentrations of 21 to 58 micrograms/mL and 41 to 83 micrograms/mL respectively. Imipenem is incompletely absorbed after intramuscular injection with a bioavailability of about 60 to 75%, and peak-plasma concentrations occur later and are more prolonged than those after intravenous administration. When imipenem with cilastatin is given in doses of 500 or 750 mg intramuscularly, peak plasma-imipenem concentrations of 10 and 12 micrograms/mL respectively occur at about 2 hours and prolonged absorption results in plasma-imipenem concentrations of above 2 micrograms/mL for 6 to 8 hours. Up to 20% of imipenem and 40% of cilastatin is bound to plasma proteins. Imipenem is widely distributed in body tissues and fluids and crosses the placenta, but concentrations in CSF are only about 1 to 10% of concurrent serum concentrations.

When given with cilastatin about 70% of an intravenous dose of imipenem is recovered unchanged in the urine within 10 hours. A total of 50% of an intramuscular dose is recovered in the urine and urinary concentrations above 10 micrograms/mL are maintained for 12 hours after a dose of 500 or 750 mg. Cilastatin is also excreted mainly in the urine, the majority as unchanged drug and about 12% as *N*-acetyl cilastatin. Both imipenem and cilastatin are removed by haemodialysis.

Less than 1% of imipenem is excreted via the bile in the faeces.

Reviews.
1. Drusano GL. An overview of the pharmacology of imipenem/cilastatin. *J Antimicrob Chemother* 1986; **18** (suppl E): 79–92.
2. Watson ID, *et al.* Clinical pharmacokinetics of enzyme inhibitors in antimicrobial chemotherapy. *Clin Pharmacokinet* 1988; **15**: 133–64.
3. Mouton JW, *et al.* Comparative pharmacokinetics of the carbapenems: clinical implications. *Clin Pharmacokinet* 2000; **39**: 185–201.

The elderly. References.
1. Finch RG, *et al.* Pharmacokinetic studies of imipenem/cilastatin in elderly patients. *J Antimicrob Chemother* 1986; **18** (suppl E): 103–7.

Hepatic impairment. References.
1. Rolando N, *et al.* The penetration of imipenem/cilastatin into ascitic fluid in patients with chronic liver disease. *J Antimicrob Chemother* 1994; **33**: 163–7.

Pregnancy and the neonate. References.
1. Reed MD, *et al.* Clinical pharmacology of imipenem and cilastatin in premature infants during the first week of life. *Antimicrob Agents Chemother* 1990; **34**: 1172–7.
2. Heikkilä A, *et al.* Pharmacokinetics and transplacental passage of imipenem during pregnancy. *Antimicrob Agents Chemother* 1992; **36**: 2652–5.

Renal impairment. References.
1. Verbist L, *et al.* Pharmacokinetics and tolerance after repeated doses of imipenem/cilastatin in patients with severe renal failure. *J Antimicrob Chemother* 1986; **18** (suppl E): 115–20.
2. Alarabi AA, *et al.* Pharmacokinetics of intravenous imipenem/cilastatin during intermittent haemofiltration. *J Antimicrob Chemother* 1990; **26**: 91–8.
3. Pietroski NA, *et al.* Steady-state pharmacokinetics of intramuscular imipenem-cilastatin in elderly patients with various degrees of renal function. *Antimicrob Agents Chemother* 1991; **35**: 972–5.
4. Konishi K, *et al.* Removal of imipenem and cilastatin by hemodialysis in patients with end-stage renal failure. *Antimicrob Agents Chemother* 1991; **35**: 1616–20.
5. Chan CY, *et al.* Pharmacokinetics of parenteral imipenem/cilastatin in patients on continuous ambulatory peritoneal dialysis. *J Antimicrob Chemother* 1991; **27**: 225–32.
6. Tegeder I, *et al.* Pharmacokinetics of imipenem-cilastatin in critically ill patients undergoing continuous venovenous hemofiltration. *Antimicrob Agents Chemother* 1997; **41**: 2640–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Dixabiox; Imipecil; Imistatin; Klonam; Zienam; ***Austral.***: Primaxin; ***Austria***: Zienam; ***Belg.***: Tienam; ***Braz.***: Tienam; Tiepem; ***Canad.***: Primaxin; ***Chile***: Inem; Tienam; ***China***: Bacqure (齐佩能); Prepenem (潜能); Tienam (泰能); *Cz.*: Cilanem; Imecitin; Tienam; ***Fin.***: Tienam; ***Fr.***: Tienam; ***Ger.***: Zienam; ***Gr.***: Imicil; Nimedine; Primagal; Primalix; Primaxin; ***Hong Kong***: Prepenem; Tienam; ***Hung.***: Cilanem; Tienam; ***India***: Cilanem; Cilaspene; Cimispect; Flaminim; I-Nem; Ime-Cila; Imelastin; Imi-Cila; Iminem; Imitop; Lastinem; ***Indon.***: Elastyn; Pelastin; Tienam; Timipen; ***Israel***: Tienam; ***Ital.***: Imipem; Tenacid; Tienam; ***Malaysia***: Bacqure; Tienam; ***Mex.***: Arzomeba; Iminen†; Lemibet†; Opostibac; Tienam; ***Neth.***: Tienam; ***Norw.***: Tienam; ***NZ***: Primaxin; ***Philipp.***: Anipen; Penam; Plastin; Tienam; ***Pol.***: Ranseron; Tienam; ***Port.***: Tienam; ***Rus.***: Cilaspen (ЦИЛАСПЕН); Grimipenem (Тримипенем); Tienam (Тиенам); ***S.Afr.***: Tienam; ***Singapore***: Tienam; ***Spain***: Tienam; ***Swed.***: Tienam; ***Switz.***: Tienam; ***Thai.***: Bacqure; Cilapenem; Prepenem; Tienam; ***Turk.***: Silanem; Tienam; ***UAE***: Maxinem; ***UK***: Primaxin; ***Ukr.***: Lastinem (Ластинем)†; Sinerpen (Синерпен); Tienam (Тиенам); ***USA***: Primaxin; ***Venez.***: Zienam.

Pharmacopoeial Preparations
USP 36: Imipenem and Cilastatin for Injectable Suspension; Imipenem and Cilastatin for Injection.

Isepamicin *(BAN, USAN, rINN)*

HAPA-B; Isepamicina; Isépamicine; Isepamicinum; Sch-21420; Изепамицин.

4-*O*-(6-Amino-6-deoxy-α-D-glucopyranosyl)-1-*N*-(3-amino-L-lactoyl)-2-deoxy-6-*O*-(3-deoxy-4-*C*-methyl-3-methylamino-β-L-arabinopyranosyl)streptamine; 1*N*-(*S*-3-Amino-2-hydroxypropionyl)-gentamicin B.

$C_{22}H_{43}N_5O_{12}$=569.6.

CAS — 58152-03-7; 67479-40-7.
ATC — J01GB11.
ATC Vet — QJ01GB11.
UNII — G7K224460P.

Isepamicin Sulfate *(BANM, rINNM)*

Isepamicin Sulphate; Isepamicina, sulfato de; Isépamicine, Sulfate d'; Isepamicini Sulfas; Isepamisin Sülfat; Sulfato de isepamicina; Изепамицина Сульфат.

$C_{22}H_{43}N_5O_{12}2H_2SO_4$=765.8

CAS — 68000-78-2.
ATC — J01GB11.
ATC Vet — QJ01GB11.
UNII — U606Y00EWE.

Pharmacopoeias. In *Jpn*, which specifies a variable amount of H_2SO_4.

Profile

Isepamicin is a semisynthetic aminoglycoside antibacterial with actions and uses similar to those of gentamicin (p. 304.2). It is reported not to be degraded by many of the enzymes responsible for aminoglycoside resistance. Isepamicin sulfate has been given by intramuscular injection or intravenous infusion in a dose of up to 15 mg/kg daily in 2 divided doses. Once-daily dosage may be possible in selected patients. Dosage should be adjusted based on serum-isepamicin concentration monitoring. In adults, the total daily dose should not exceed 1.5 g.

References.
1. Tod M, *et al.* Clinical pharmacokinetics and pharmacodynamics of isepamicin. *Clin Pharmacokinet* 2000; **38**: 205–23.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Exacin (依克沙); ***Hong Kong***: Isepacin†; ***Jpn***: Exacin; ***Turk.***: Isepacine.

Isoniazid *(BAN, pINN)*

INAH; INH; Isoniatsidi; Isoniazida; Isoniazide; Isoniazidum; Isonicotinic Acid Hydrazide; Isonicotinylhydrazide; Isonicotinylhydrazine; Izoniazid; Izoniazidas; Izoniazyd; Tubazid; Изониазид.

Isonicotinohydrazide.

$C_6H_7N_3O$=137.1

CAS — 54-85-3.
ATC — J04AC01.
ATC Vet — QJ04AC01.
UNII — V83O1VOZ8L.

NOTE. The name Isopyrin, which has been applied to isoniazid, has also been applied to ramifenazone.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Isoniazid). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; sparingly soluble in alcohol. A 5% solution in water has a pH of 6.0 to 8.0.

USP 36: (Isoniazid). Colourless, or white, odourless crystals, or white crystalline powder. Soluble 1 in 8 of water and 1 in 50 of alcohol; slightly soluble in chloroform; very slightly soluble in ether. pH of a 10% solution in water is between 6.0 and 7.5. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Incompatibility. It has been recommended that sugars such as glucose, fructose, and sucrose should not be used in isoniazid syrup preparations because the absorption of the drug was impaired by the formation of a condensation product.[1] Sorbitol may be a suitable substitute if necessary.
1. Rao KVN, *et al.* Inactivation of isoniazid by condensation in a syrup preparation. *Bull WHO* 1971; **45**: 625–32.

Sterilisation. Solutions of isoniazid should be sterilised by autoclaving.

Uses and Administration

Isoniazid is a hydrazide derivative that is the mainstay of the primary treatment of pulmonary and extrapulmonary tuberculosis (p. 210.2). It is used with other antituberculous drugs usually in regimens including rifampicin, ethambutol, and pyrazinamide. Isoniazid is also used in high-risk subjects for the prophylaxis of tuberculosis.

Isoniazid is given in the initial and continuation phases of short-course tuberculosis regimens. The usual oral adult dose is 5 mg/kg, to a maximum of 300 mg, daily on an empty stomach. For intermittent therapy, WHO recommends 10 mg/kg three times a week, to a maximum of 900 mg per dose, while the recommended dose in the UK is 15 mg/kg three times a week and in the USA 15 mg/kg once weekly or two or three times a week is recommended. Caution is required in patients with hepatic impairment and doses may need to be reduced in those with severe renal impairment.

Similar doses to those used orally may be given by intramuscular injection when isoniazid cannot be taken orally; it may also be given by intravenous injection. Isoniazid has also been given intrathecally and intrapleurally.

In the treatment of latent tuberculosis, daily doses of 300 mg for 6 months are recommended by WHO and in the UK, while in the USA the preferred treatment regimen is oral isoniazid 5 mg/kg (to a maximum of 300 mg) daily or 15 mg/kg (to a maximum of 900 mg) twice weekly for 9 months. As an alternative to such regimens, isoniazid may be given with rifampicin for 3 months.

For details of doses in children, see p. 313.3.

Isoniazid aminosalicylate (pasiniazid) and isoniazid sodium glucuronate have also been used in the treatment of tuberculosis.

Fixed-dose combination products containing 2, 3, or 4 drugs have been developed in order to improve patient compliance and avoid monotherapy, thereby decreasing the risk of acquired drug resistance. Products containing isoniazid in various combinations with rifampicin, ethambutol, and pyrazinamide are available in some countries.

References.
1. Anonymous. Isoniazid. *Tuberculosis (Edinb)* 2008; **88**: 112–6.

Administration in children. A study[1] in 56 hospitalised children (median age of 3.22 years and interquartile range of 1.58 to 5.38 years) given isoniazid daily as part of their antituberculosis treatment found that peak concentrations of isoniazid were less than 3 mg/L in 70% of children prescribed a dose of 4 to 6 mg/kg, while those given a dose of 8 to 12 mg/kg had peak concentrations similar to those in adults taking 300 mg of isoniazid daily. The authors concluded that younger children need higher doses of isoniazid per kilogram of body weight to achieve isoniazid concentrations similar to those in adults and recommended a daily dose of 8 to 12 mg/kg.

WHO now therefore recommends[2,3] isoniazid 10 mg/kg daily (replacing an earlier recommendation[4] for 5 mg/kg daily). Specific guidance[3] has also been issued for the use of fixed-dose combinations of isoniazid 30, 60 or 150 mg plus rifampicin (with or without pyrazinamide and ethambutol) to achieve this in children weighing between 5 and 30 kg. Similarly, for the treatment of tuberculosis in infants, children, and adolescents the American Academy of Pediatrics (AAP)[5] suggests an oral dose of isoniazid 10 to 15 mg/kg daily or 20 to 30 mg/kg twice weekly, for both the initial and continuation phases. For children 1 month and older the *BNFC* suggests oral doses of 10 mg/kg once daily or 15 mg/kg three times a week.

For the treatment of *latent* tuberculosis the American Thoracic Society[6] suggests oral doses of 10 to 20 mg/kg (maximum 300 mg) daily or 20 to 40 mg/kg (maximum 900 mg) twice weekly for 9 months. Similar doses have been suggested by the AAP. For children 1 month and older the *BNFC* suggests a dose of 10 mg/kg once daily for 6 months when used alone or for 3 months when given with rifampicin; WHO recommends 5 mg/kg once daily for 6 months.

For daily dosing regimens the maximum oral dose of isoniazid is 300 mg and for intermittent regimens the maximum dose is 900 mg per dose.

1. McIlleron H, *et al.* Isoniazid plasma concentrations in a cohort of South African children with tuberculosis: implications for international pediatric dosing guidelines. *Clin Infect Dis* 2009; **48**: 1547–53.
2. WHO. *WHO model formulary for children: based on the second model list of essential medicines for children 2009*. Geneva: WHO, 2010. Available at: http://www.who.int/selection_medicines/list/WMFc_2010.pdf (accessed 21/01/11)
3. WHO. Dosing instructions for the use of currently available fixed-dose combination TB medicines for children. Available at: http://www.who.int/entity/tb/challenges/interim_paediatric_fdc_dosing_instructions_sept09.pdf (accessed 19/01/11)
4. WHO. *Guidance for national tuberculosis programmes on the management of tuberculosis in children*. Geneva: WHO, 2006. Available at: http://whqlibdoc.who.int/hq/2006/WHO_HTM_TB_2006.371_eng.pdf (accessed 07/06/10)
5. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.
6. American Thoracic Society. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000; **49**: 1–51. Also published in *Am J Respir Crit Care Med* 2000; **111**: S221–S247. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4906a1.htm (accessed 07/06/10)

Adverse Effects

Isoniazid is generally well tolerated at currently recommended doses. However, patients who are slow acetylators of isoniazid and those with advanced HIV disease appear to have a higher incidence of some adverse effects. Also patients whose nutrition is poor are at risk of peripheral neuritis which is one of the commonest adverse effects of isoniazid. Other neurological adverse effects include psychotic reactions and convulsions. Pyridoxine may be given to prevent or treat these adverse effects. Optic neuritis has also been reported.

Transient increases in liver enzymes occur in 10 to 20% of patients during the first few months of treatment and usually return to normal despite continued treatment. Symptomatic hepatitis occurs in about 0.1 to 0.15% of patients given isoniazid as monotherapy, but this can increase with age, regular alcohol consumption, and in those with chronic liver disease. The influence of acetylator status is uncertain. Elevated liver enzymes associated with clinical signs of hepatitis such as nausea and vomiting, or fatigue may indicate hepatic damage; in these circumstances, isoniazid should be stopped pending evaluation and should only be reintroduced cautiously once hepatic function has recovered. Fatalities have occurred due to liver necrosis.

Haematological effects reported on use of isoniazid include various anaemias, agranulocytosis, thrombocytopenia, and eosinophilia.

Hypersensitivity reactions occur infrequently and include skin eruptions (including erythema multiforme), fever, and vasculitis.

Other adverse effects include nausea, vomiting, dry mouth, constipation, pellagra, purpura, hyperglycaemia, lupus-like syndrome, vertigo, hyperreflexia, urinary retention, and gynaecomastia.

Symptoms of overdosage include slurred speech, metabolic acidosis, hallucinations, hyperglycaemia, respiratory distress or tachypnoea, convulsions, and coma; fatalities can occur.

Carcinogenicity. Concern about the carcinogenicity of isoniazid arose in the 1970s when an increased risk of bladder cancer in patients treated with isoniazid was reported.[1-3] However, no evidence to support a carcinogenic effect of isoniazid was found in more than 25 000 patients followed up for 9 to 14 years in studies organised by the USA Public Health Service[4] and in 3842 patients followed up for 16 to 24 years in the UK.[5]

1. Miller CT. Isoniazid and cancer risks. *JAMA* 1974; 230: 1254.
2. Kerr WK, Chipman ML. The incidence of cancer of bladder and other sites after INH therapy. *Am J Epidemiol* 1976; 104: 335–6.
3. Miller CT, *et al.* Relative importance of risk factors in bladder carcinogenesis. *J Chron Dis* 1978; 31: 51–6.
4. Glasroth JL, *et al.* An assessment of the possible association of isoniazid with human cancer deaths. *Am Rev Respir Dis* 1977; 116: 1065–74.
5. Stott H, *et al.* An assessment of the carcinogenicity of isoniazid in patients with pulmonary tuberculosis. *Tubercle* 1976; 57: 1–15.

Effects on the blood. In addition to the effects mentioned on p. 311.3, rare reports of adverse effects of isoniazid on the blood include bleeding associated with acquired inhibition of fibrin stabilisation[1] or of factor XIII,[2] and red cell aplasia.[3-5]

For a reference to neutropenia, see Effects on the Blood, under Ethambutol Hydrochloride, p. 296.2.

1. Otis PT, *et al.* An acquired inhibitor of fibrin stabilization associated with isoniazid therapy: clinical and biochemical observations. *Blood* 1974; 44: 771–81.
2. Krumdieck R, *et al.* Hemorrhagic disorder due to an isoniazid-associated acquired factor XIII inhibitor in a patient with Waldenström's macroglobulinemia. *Am J Med* 1991; 90: 639–45.
3. Claiborne RA, Dutt AK. Isoniazid-induced pure red cell aplasia. *Am Rev Respir Dis* 1985; 131: 947–9.
4. Lewis CR, Manoharan A. Pure red cell hypoplasia secondary to isoniazid. *Postgrad Med J* 1987; 63: 309–10.
5. Veale KS, *et al.* Pure red cell aplasia and hepatitis in a child receiving isoniazid therapy. *J Pediatr* 1992; 120: 146–8.

Effects on the CNS. In addition to the peripheral neuropathy that is a well-established adverse effect of isoniazid, effects on the CNS have also been reported, including ataxia and cerebellar toxicity,[1,2] psychotic reactions[3-5] (generally characterised by delusions, hallucinations, and confusion), and seizures, particularly after overdosage.[6] Encephalopathy has been reported in dialysis patients.[7,8] Encephalopathy may also be a symptom of pellagra, which may be associated with isoniazid treatment.[9]

1. Blumberg EA, Gil RA. Cerebellar syndrome caused by isoniazid. *DICP Ann Pharmacother* 1990; 24: 829–31.
2. Lewin PK, McGreal D. Isoniazid toxicity with cerebellar ataxia in a child. *CMAJ* 1993; 148: 49–50.
3. Pallone KA, *et al.* Isoniazid-associated psychosis: case report and review of the literature. *Ann Pharmacother* 1993; 27: 167–70.
4. Alao AO, Yolles JC. Isoniazid-induced psychosis. *Ann Pharmacother* 1998; 32: 889–91.
5. Witkowski AE, *et al.* Isoniazid-associated psychosis. *Gen Hosp Psychiatry* 2007; 29: 85–6.
6. Shah BR, *et al.* Acute isoniazid neurotoxicity in an urban hospital. *Pediatrics* 1995; 95: 700–4.
7. Cheung WC, *et al.* Isoniazid induced encephalopathy in dialysis patients. *Tubercle Lung Dis* 1993; 74: 136–9.
8. Wang HY, *et al.* Encephalopathy caused by isoniazid in a patient with end stage renal disease with extrapulmonary tuberculosis. *Ren Fail* 2003; 25: 135–8.
9. Ishii N, Nishihara Y. Pellagra encephalopathy among tuberculous patients: its relation to isoniazid therapy. *J Neurol Neurosurg Psychiatry* 1985; 48: 628–34.

Effects on the liver. Transient abnormalities in liver function are common during the early stages of antituberculous therapy with isoniazid and other first-line antituberculous drugs, but sometimes **hepatotoxicity** may be more serious and require a change of treatment. Drug-induced hepatitis usually occurs within the first few weeks of treatment and it may not be possible to identify which drug or drugs are responsible. Isoniazid and pyrazinamide are thought to have a greater potential for hepatotoxicity than rifampicin.[1]

Risk factors for hepatotoxicity include alcoholism, old age, female gender, malnutrition, HIV infection, and chronic hepatitis B and C infections.[1] Speculation that fast acetylators of isoniazid could be at increased risk of hepatotoxicity due to production of a hepatotoxic hydrazine metabolite has not been supported;[2] in fact, slow acetylators have generally been found to have a higher risk than fast acetylators.[3,4] This could reflect a reduced rate of subsequent metabolism to non-toxic compounds. In addition, concentrations of hydrazine in the blood have not been found to correlate with acetylator status.[5,6]

A multicentre study[7] considered the **incidence** of hepatotoxicity from a short-term regimen of daily isoniazid, rifampicin, and pyrazinamide for 8 weeks in the initial phase followed by daily isoniazid and rifampicin for 16 weeks in the continuing phase. Analysis from 617 patients showed an incidence of hepatotoxic reactions of 1.6%; the incidence of elevated aspartate aminotransferase was 23.2%. In the same study, 445 patients on a 9-month regimen of daily isoniazid and rifampicin had a 1.2% incidence of hepatotoxicity and 27.1% incidence of elevated liver enzymes. A similar incidence of hepatitis of 1.4% among 350 patients on a 9-month regimen of rifampicin and isoniazid has also been reported.[8] A retrospective analysis[9] of 430 children on isoniazid and rifampicin revealed hepatotoxic reactions in 3.3%, the highest incidence being in children with severe disease.

The incidence of hepatotoxicity is lower in patients receiving isoniazid for *prophylaxis* than in those receiving treatment for active disease. During a 7-year period[10] an incidence of 0.15% was recorded in 11 141 patients who started prophylactic therapy, whereas it was 1.25% amongst 1427 patients receiving treatment. A similar study[11] in a slightly older patient population reported an incidence of 0.56%. Between 2004 and 2008, the CDC received 17 reports of severe liver injury (leading to hospitalisation or death) in patients receiving isoniazid for treatment of latent tuberculosis infection;[12] injury occurred mainly between the second and ninth month of therapy. Of these 17 patients, 5 subsequently required liver transplantation, and 5 died (including 1 transplant recipient). No cases of hepatotoxicity were reported in 556 HIV-infected patients taking a 3-month prophylactic regimen of isoniazid and rifampicin for latent tuberculosis.[13] A meta-analysis[14] concluded that daily isoniazid and rifampicin for 3 months appeared to be as safe as treatment with isoniazid alone for 6 to 12 months.

The Joint Tuberculosis Committee of the British Thoracic Society has published recommendations[15] for initial measurement of liver function in all patients and regular **monitoring** in patients with known chronic liver disease. Details are given concerning the response to deteriorating liver function depending on the clinical situation, and guidelines included for prompt re-introduction of appropriate antituberculosis therapy once normal liver function is restored. Similar guidelines have been produced in the USA.[16,17]

For further information on hepatotoxicity caused by antituberculous drugs see Effects on the Liver, under Rifampicin, p. 354.1 and Pyrazinamide, p. 347.3.

1. Yew WW, Leung CC. Antituberculosis drugs and hepatotoxicity. *Respirology* 2006; 11: 699–707.
2. Gurumurthy P, *et al.* Lack of relationship between hepatic toxicity and acetylator phenotype in three thousand South Indian patients during treatment with isoniazid for tuberculosis. *Am Rev Respir Dis* 1984; 129: 58–61.
3. Dickinson DS, *et al.* Risk factors for isoniazid (INH)-induced liver dysfunction. *J Clin Gastroenterol* 1981; 3: 271–9.
4. Pande JN, *et al.* Risk factors for hepatotoxicity from antituberculosis drugs: a case-control study. *Thorax* 1996; 51: 132–6.
5. Gent WL, *et al.* Factors in hydrazine formation from isoniazid by paediatric and adult tuberculosis patients. *Eur J Clin Pharmacol* 1992; 43: 131–6.
6. Donald PR, *et al.* Hydrazine production in children receiving isoniazid for the treatment of tuberculous meningitis. *Ann Pharmacother* 1994; 28: 1340–3.
7. Combs DL, *et al.* USPHS tuberculosis short-course chemotherapy trial 21: effectiveness, toxicity, and acceptability: the report of final results. *Ann Intern Med* 1990; 112: 397–406.
8. Dutt AK, *et al.* Short-course chemotherapy for extrapulmonary tuberculosis: nine years' experience. *Ann Intern Med* 1986; 104: 7–12.
9. O'Brien RJ, *et al.* Hepatotoxicity from isoniazid and rifampin among children treated for tuberculosis. *Pediatrics* 1983; 72: 491–9.
10. Nolan CM, *et al.* Hepatotoxicity associated with isoniazid preventive therapy: a 7-year survey from a public health tuberculosis clinic. *JAMA* 1999; 281: 1014–18.
11. Fountain FF, *et al.* Isoniazid hepatotoxicity associated with treatment of latent tuberculosis infection: a 7-year evaluation from a public health tuberculosis clinic. *Chest* 2005; 128: 116–23.
12. CDC. Severe isoniazid-associated liver injuries among persons being treated for latent tuberculosis infection - United States, 2004-2008. *MMWR* 2010; 59: 224–9. Also available at: http://www.cdc.gov/mmwr/pdf/wk/mm5908.pdf (accessed 07/06/10)
13. Whalen CC, *et al.* A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. *N Engl J Med* 1997; 337: 801–8.
14. Ena J, Valls V. Short-course therapy with rifampin plus isoniazid, compared with standard therapy with isoniazid, for latent tuberculosis infection: a meta-analysis. *Clin Infect Dis* 2005; 40: 670–6.
15. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; 53: 536–48.[Although these guidelines were replaced by ones issued by NICE in 2006 the latter do not "*explain tuberculosis or its treatment in detail*" and therefore reference to the earlier guidelines has been retained] Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Tuberculosis/Guidelines/Chemotherapy.pdf (accessed 29/07/08)
16. American Thoracic Society, CDC, and the Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; 52 (RR-11): 1–77. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf (accessed 03/10/07) Correction. *ibid.* 2005; 53: 1203. [dose]
17. Saukkonen JJ, *et al.* American Thoracic Society. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med* 2006; 174: 935–52. Also available at: http://www.thoracic.org/statements/resources/mtpi/hepatotoxicity-of-antituberculosis-therapy.pdf (accessed 16/07/10)

Effects on the pancreas. Cases of isoniazid-induced pancreatitis have been rarely reported;[1-4] pancreatitis resolved in these patients once treatment with isoniazid was stopped, and recurred on rechallenge. It is recommended if isoniazid-induced pancreatitis is proven that the drug should be permanently avoided.[4] Chronic pancreatic insufficiency, after an acute episode, was reported in a patient given isoniazid, rifampicin, ethambutol, and pyrazinamide and was considered to be a drug hypersensitivity reaction.[5]

1. Chan KL, *et al.* Recurrent acute pancreatitis induced by isoniazid. *Tubercle Lung Dis* 1994; 75: 383–5.
2. Rabassa AA, *et al.* Isoniazid-induced acute pancreatitis. *Ann Intern Med* 1994; 121: 433–4.
3. Stephenson I, *et al.* Acute pancreatitis induced by isoniazid in the treatment of tuberculosis. *Am J Gastroenterol* 2001; 96: 2271–2.
4. Chow KM, *et al.* Recurrent acute pancreatitis after isoniazid. *Neth J Med* 2004; 62: 172–4.
5. Liu BA, *et al.* Pancreatic insufficiency due to antituberculous therapy. *Ann Pharmacother* 1997; 31: 724–6.

Effects on the skin and hair. Isoniazid causes cutaneous drug reactions in less than 1% of patients.[1,2] These reactions include urticaria, purpura, acneform syndrome,[3] a lupus erythematosus-like syndrome[4] (see p. 314.3), and exfoliative dermatitis.[5] Pellagra is also associated with isoniazid.[6] Isoniazid was considered the most likely cause of alopecia in 5 patients receiving antituberculosis regimens which also included rifampicin, ethambutol, and pyrazinamide.[7]

1. Arndt KA, Jick H. Rates of cutaneous reactions to drugs: a report from the Boston Collaborative Drug Surveillance Program. *JAMA* 1976; 235: 918–23.
2. Bigby M, *et al.* Drug-induced cutaneous reactions: a report from the Boston Collaborative Drug Surveillance Program on 15 438 consecutive inpatients, 1975 to 1982. *JAMA* 1986; 256: 3358–63.
3. Thorne N. Skin reactions to systemic drug therapy. *Practitioner* 1973; 211: 606–13.
4. Smith AG. Drug-induced photosensitivity. *Adverse Drug React Bull* 1989; 136: 508–11.
5. Rosin MA, King LE. Isoniazid-induced exfoliative dermatitis. *South Med J* 1982; 75: 81.
6. Ishii N, Nishihara Y. Pellagra encephalopathy among tuberculous patients: its relation to isoniazid therapy. *J Neurol Neurosurg Psychiatry* 1985; 48: 628–34.
7. FitzGerald JM, *et al.* Alopecia side-effect of antituberculosis drugs. *Lancet* 1996; 347: 472–3.

Lupus. Antinuclear antibodies have been reported to occur in up to 22% of patients receiving isoniazid; however, patients are usually asymptomatic and overt lupoid syndrome is rare.[1,2] The incidence of antibody induction has been reported to be higher in slow acetylators than in fast acetylators,[3] but the difference was not statistically significant and acetylator phenotype is not considered an important determinant of the risk of isoniazid-induced lupus.[1,4,5] The syndrome appeared to be due to isoniazid itself rather than its metabolite acetylisoniazid.[6]

1. Hughes GRV. Recent developments in drug-associated systemic lupus erythematosus. *Adverse Drug React Bull* 1987; 123: 460–3.
2. Siddiqui MA, Khan IA. Isoniazid-induced lupus erythematosus presenting with cardiac tamponade. *Am J Ther* 2002; 9: 163–5.
3. Alarcon-Segovia D, *et al.* Isoniazid acetylation rate and development of antinuclear antibodies upon isoniazid treatment. *Arthritis Rheum* 1971; 14: 748–52.
4. Clark DWJ. Genetically determined variability in acetylation and oxidation: therapeutic implications. *Drugs* 1985; 29: 342–75.
5. Rychlik-Sych M, *et al.* Acetylation genotype and phenotype in patients with systemic lupus erythematosus. *Pharmacol Rep* 2006; 58: 22–9.
6. Sim E, *et al.* Drugs that induce systemic lupus erythematosus inhibit complement component C4. *Lancet* 1984; ii: 422–4.

Treatment of Adverse Effects

Pyridoxine hydrochloride 10 mg daily is usually recommended for prophylaxis of peripheral neuritis associated with isoniazid although up to 50 mg daily may be used. A dose of 50 mg three times daily may be given for treatment of peripheral neuritis if it develops. In children the *BNFC* recommends the following oral doses according to age:

- 1 month to 12 years: 5 to 10 mg daily (prophylaxis), or 10 to 20 mg 2 or 3 times daily (treatment)
- 12 to 18 years: 10 mg daily (prophylaxis) or 30 to 50 mg 2 or 3 times daily (treatment)

Nicotinamide has been given, usually with pyridoxine, to patients who develop pellagra.

Isoniazid doses of 1.5 g or more are potentially toxic and doses of 10 to 15 g may be fatal without appropriate treatment. Treatment of overdosage is symptomatic and supportive and consists of activated charcoal, correction of metabolic acidosis, and control of convulsions. In addition to a benzodiazepine, large doses of pyridoxine may be needed intravenously for control of convulsions (see Overdose, p. 315.1). Isoniazid is removed by haemodialysis or peritoneal dialysis.

Overdosage. In adults with isoniazid-induced convulsions the UK National Poisons Information Service recommends management with an initial intravenous dose of diazepam or lorazepam; in resistant cases, patients should also be given an intravenous dose of pyridoxine hydrochloride equivalent to the estimated amount of isoniazid ingested (to a maximum of 5 g); this maximum dose should also be used when the amount of isoniazid ingested is unknown. For children the recommended dose of pyridoxine hydrochloride is 70 mg/kg (to a maximum of 5 g). If convulsions continue or recur, this dose may be repeated. Oral activated charcoal (50 g for adults and 1 g/kg for children) may be considered if this is given within 1 hour of an ingestion of isoniazid of more than 20 mg/kg.

Pyridoxine deficiency. Pyridoxine deficiency associated with isoniazid in doses of 5 mg/kg daily is uncommon. Patients at risk of developing pyridoxine deficiency include those with diabetes, uraemia, alcoholism, HIV infection, and malnutrition.[1,2] Supplementation with pyridoxine should be considered for these at-risk groups as well as for pregnant women and patients with seizure disorders.[1] For the prophylaxis of peripheral neuritis it is common practice to give pyridoxine 10 mg daily, although 6 mg daily might be sufficient.[3] However, in one patient a dose of pyridoxine 10 mg daily failed to prevent psychosis, the symptoms of which only resolved after stopping isoniazid and increasing the pyridoxine dosage to 100 mg daily.[4]

1. American Thoracic Society, CDC, and the Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; **52** (RR-11): 1–77. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf (accessed 03/10/07) Correction. *ibid.* 2005; **53**: 1203. [dose]
2. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; **53**: 536–48.[Although these guidelines were replaced by ones issued by NICE in 2006 the latter do not *"explain tuberculosis or its treatment in detail"* and therefore reference to the earlier guidelines has been retained] Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Tuberculosis/Guidelines/Chemotherapy.pdf (accessed 29/07/08)
3. Snider DE. Pyridoxine supplementation during isoniazid therapy. *Tubercle* 1980; **61**: 191–6.
4. Chan TYK. Pyridoxine ineffective in isoniazid-induced psychosis. *Ann Pharmacother* 1999; **33**: 1123–4.

Precautions

Isoniazid should be used with caution in patients with convulsive disorders, a history of psychosis, or hepatic or renal impairment. Patients who are at risk of neuropathy or pyridoxine deficiency, including those who are diabetic, alcoholic, malnourished, uraemic, pregnant, or infected with HIV, should be given pyridoxine, usually in a dose of 10 mg daily, although up to 50 mg daily may be used. If symptoms of hepatitis develop, such as malaise, fatigue, anorexia, and nausea, isoniazid should be stopped pending evaluation.

Liver function should be checked before treatment with isoniazid and special care should be taken in alcoholic patients or those with pre-existing liver disease. Regular monitoring of liver function is recommended in patients with pre-existing liver disease, and the British Thoracic Society has recommended that isoniazid treatment be suspended if serum aminotransferase concentrations are elevated to more than 5 times the normal upper limit or the bilirubin concentration rises. They allow cautious sequential re-introduction of antimycobacterial drugs once liver function has returned to normal: first isoniazid, then rifampicin, and then pyrazinamide. Careful monitoring should be considered for black and Hispanic women, in whom there may be an increased risk of fatal hepatitis.

When visual symptoms occur during isoniazid treatment periodic eye examinations have been suggested.

Breast feeding. Peak concentrations of isoniazid in breast milk were 6 micrograms/mL after a dose of 5 mg/kg and were 16.6 micrograms/mL after a 300-mg dose.[1] However, drug concentrations in the breast milk are too low to prevent or treat tuberculosis in infants. Adverse effects on breast-fed infants have not been reported and the last available guidance from the American Academy of Pediatrics thus considered isoniazid to be usually compatible with breast feeding,[2] although such infants should be monitored for toxic reactions.

1. Snider D, Powell KE. Should women taking antituberculosis drugs breast-feed? *Arch Intern Med* 1984; **144**: 589–90.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 03/10/07)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies isoniazid as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 08/07/11)

Pregnancy and the neonate. In a review[1] of antituberculous treatment in pregnant patients it was reported that over 95% of 1480 pregnancies in which isoniazid had been given resulted in a normal term infant. Slightly more than 1% of the infants/fetuses were abnormal and many of these abnormalities were CNS related. Isoniazid is therefore recognised as being suitable for use in regimens for the **treatment** of tuberculosis in pregnant patients.[2,3] Pyridoxine supplementation is recommended[2] (see Pyridoxine Deficiency under Treatment of Adverse Effects, above). **Preventive therapy** with isoniazid is generally delayed until after delivery unless other risk factors are present.

1. Snider DE, *et al.* Treatment of tuberculosis during pregnancy. *Am Rev Respir Dis* 1980; **122**: 65–79.
2. American Thoracic Society, CDC, and the Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; **52** (RR-11): 1–77. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf (accessed 03/10/07) Correction. *ibid.* 2005; **53**: 1203. [dose]
3. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; **53**: 536–48.[Although these guidelines were replaced by ones issued by NICE in 2006 the latter do not *"explain tuberculosis or its treatment in detail"* and therefore reference to the earlier guidelines has been retained] Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Tuberculosis/Guidelines/Chemotherapy.pdf (accessed 29/07/08)

Interactions

The risk of hepatotoxicity may be increased in patients receiving isoniazid with a rifamycin or other potentially hepatotoxic drugs, including alcohol.

Isoniazid can inhibit the hepatic metabolism of some drugs, in some cases leading to increased toxicity. These include the antiepileptics carbamazepine (p. 516.2), ethosuximide (p. 521.2), primidone, and phenytoin (p. 542.3), the benzodiazepines diazepam and triazolam (p. 1068.2), chlorzoxazone (p. 2023.1), theophylline (p. 1234.1), and disulfiram. The metabolism of enflurane (see Effects on the Kidneys, p. 1903.1) may be increased in patients receiving isoniazid, resulting in potentially nephrotoxic levels of fluoride. Isoniazid has been associated with increased concentrations and enhanced effects or toxicity of clofazimine (p. 274.2), cycloserine (p. 281.1), and warfarin (p. 1531.1).

For interactions affecting isoniazid, see below.

Alcohol. The metabolism of isoniazid may be increased in chronic alcoholics: this may lead to reduced isoniazid efficacy.[1] These patients may also be at increased risk of developing isoniazid-induced peripheral neuropathies and hepatic damage (see Precautions, above).

1. Anonymous. Interaction of drugs with alcohol. *Med Lett Drugs Ther* 1981; **23**: 33–4.

Antacids. Oral absorption of isoniazid is reduced by aluminium-containing antacids; isoniazid should be given at least 1 hour before the antacid.[1]

1. Hurwitz A, Schluzman DL. Effects of antacids on gastrointestinal absorption of isoniazid in rat and man. *Am Rev Respir Dis* 1974; **109**: 41–7.

Antifungals. Serum concentrations of isoniazid were below the limits of detection in a patient also receiving rifampicin and *ketoconazole*.[1] For the effect of isoniazid on ketoconazole, see p. 587.1.

1. Abadie-Kemmerly S, *et al.* Failure of ketoconazole treatment of Blastomyces dermatitidis due to interaction of isoniazid and rifampin. *Ann Intern Med* 1988; **109**: 844–5. Correction. *ibid.* 1989; **111**: 96.

Antivirals. The clearance of isoniazid was approximately doubled when *zalcitabine* was given to 12 HIV-positive patients.[1] In addition, care is needed since *stavudine* and zalcitabine may also cause peripheral neuropathy; use of isoniazid with stavudine has been reported to increase its incidence.[2]

1. Lee BL, *et al.* The effect of zalcitabine on the pharmacokinetics of isoniazid in HIV-infected patients. *Intersci Conf Antimicrob Agents Chemother* 1994; **34**: 3(A4).
2. Breen RAM, *et al.* Increased incidence of peripheral neuropathy with co-administration of stavudine and isoniazid in HIV-infected individuals. *AIDS* 2000; **14**: 615.

Corticosteroids. Giving *prednisolone* 20 mg to 13 slow acetylators and 13 fast acetylators receiving isoniazid 10 mg/kg reduced plasma concentrations of isoniazid by 25 and 40% respectively.[1] Renal clearance of isoniazid was also enhanced in both acetylator phenotypes and the rate of acetylation increased in slow acetylators only.[1]

The clinical significance of this effect is not established.

1. Sarma GR, *et al.* Effect of prednisolone and rifampin on isoniazid metabolism in slow and rapid inactivators of isoniazid. *Antimicrob Agents Chemother* 1980; **18**: 661–6.

Food. Palpitations, headache, conjunctival irritation, severe flushing, tachycardia, tachypnoea, and sweating have been reported in patients taking isoniazid after ingestion of *cheese*,[1,2] *red wine*,[1] and some *fish*.[3,4] Accumulation of tyramine[1] or histamine[3] has been proposed as the cause of these food-related reactions, and they could be mistaken for anaphylaxis.[4]

1. Toutoungi M, *et al.* Cheese, wine, and isoniazid. *Lancet* 1985; **ii**: 671.
2. Carvalho ACC, *et al.* Reaction to cheese during TB treatment. *Thorax* 2004; **59**: 635.
3. Kottegoda SR. Cheese, wine and isoniazid. *Lancet* 1985; **ii**: 1074.
4. O'Sullivan TL. Drug-food interaction with isoniazid resembling anaphylaxis. *Ann Pharmacother* 1997; **31**: 928.

Opioid analgesics. For a report of an interaction between isoniazid and *pethidine*, attributed to isoniazid's inhibitory actions on monoamine oxidase, see p. 123.2.

Antimicrobial Action

Isoniazid is highly active against *Mycobacterium tuberculosis* and may have activity against some strains of other mycobacteria including *M. kansasii*.

Although it is rapidly bactericidal against actively dividing *M. tuberculosis*, it is considered to be only bacteriostatic against semi-dormant organisms and has less sterilising activity than rifampicin or pyrazinamide.

Resistance of *M. tuberculosis* to isoniazid develops rapidly if it is used alone in the *treatment* of clinical infection, and may be due in some strains to loss of the gene for catalase production. Resistance is delayed or prevented by the combination of isoniazid with other antimycobacterials which appears to be highly effective in preventing emergence of resistance to other antituberculous drugs. Resistance does not appear to be a problem when isoniazid is used alone in *prophylaxis*, probably because the bacillary load is low.

Mycobacterium avium complex. Synergistic activity of isoniazid plus streptomycin and, to a lesser degree, isoniazid plus clofazimine, against *Mycobacterium avium* complex (MAC) has been shown *in vitro* and *in vivo*.[1]

1. Reddy MV, *et al.* In vitro and in vivo synergistic effect of isoniazid with streptomycin and clofazimine against Mycobacterium avium complex (MAC). *Tubercle Lung Dis* 1994; **75**: 208–12.

Pharmacokinetics

Isoniazid is readily absorbed from the gastrointestinal tract and after intramuscular injection. Peak concentrations of about 3 to 7 micrograms/mL appear in blood 1 to 2 hours after an oral fasting dose of 300 mg. The rate and extent of absorption of isoniazid is reduced by food. Isoniazid is not considered to be bound appreciably to plasma proteins and distributes into all body tissues and fluids, including the CSF. It appears in fetal blood if given during pregnancy (see p. 316.1), and is distributed into breast milk (see under Precautions, above).

The plasma half-life for isoniazid ranges from about 1 to 6 hours, with shorter half-lives in fast acetylators. The primary metabolic route is the acetylation of isoniazid to acetylisoniazid by *N*-acetyltransferase found in the liver and small intestine. Acetylisoniazid is then hydrolysed to isonicotinic acid and monoacetylhydrazine; isonicotinic acid is conjugated with glycine to isonicotinyl glycine (isonicotinuric acid) and monoacetylhydrazine is further acetylated to diacetylhydrazine. Some unmetabolised isoniazid is conjugated to hydrazones. The metabolites of isoniazid have no tuberculostatic activity and, apart from possibly monoacetylhydrazine, they are also less toxic. The rate of acetylation of isoniazid and monoacetylhydrazine is genetically determined and there is a bimodal distribution of persons who acetylate them either slowly or rapidly. Ethnic groups differ in their proportions of these genetic phenotypes. When isoniazid is given daily or 2 or 3 times weekly, clinical efficacy is not influenced by acetylator status.

In patients with normal renal function, over 75% of a dose appears in the urine in 24 hours, mainly as metabolites. Small amounts of drug are also excreted in the faeces. Isoniazid is removed by haemodialysis.

Distribution. Therapeutic concentrations of isoniazid have been detected in CSF[1,2] and synovial fluid[3] several hours after an oral dose. Diffusion into saliva is good and it has been suggested that salivary concentrations could be used in place of serum concentrations in pharmacokinetic studies.[4]

1. Forgan-Smith R, *et al.* Pyrazinamide and other drugs in tuberculous meningitis. *Lancet* 1973; **ii**: 374.

2. Micell JN, *et al.* Isoniazid (INH) kinetics in children. *Fedn Proc* 1983; **42:** 1140.
3. Mouries D, *et al.* Passage articulaire de l'isoniazide et de l'éthambutol: deux observations de synovite tuberculeuse du genou. *Nouv Presse Med* 1975; **4:** 2734.
4. Gurumurthy P, *et al.* Salivary levels of isoniazid and rifampicin in tuberculous patients. *Tubercle* 1990; **71:** 29–33.

HIV-infected patients. Malabsorption of isoniazid and other antituberculous drugs may occur in patients with HIV infection and tuberculosis, and may contribute to acquired drug resistance and reduced efficacy of tuberculosis treatment. For further information on the absorption of antituberculous drugs in HIV-infected patients see Pharmacokinetics, under Rifampicin, p. 356.1.

Pregnancy. Isoniazid crosses the placenta and average fetal concentrations of 61.5 and 72.8% of maternal serum or plasma concentration have been reported.[1] The half-life of isoniazid may be prolonged in neonates.[1]

1. Holdiness MR. Transplacental pharmacokinetics of the antituberculosis drugs. *Clin Pharmacokinet* 1987; **13:** 125–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Isoniac; Nicotibina; ***Belg.***: Nicotibine; ***Canad.***: Isotamine B; Isotamine; ***China***: Jieheqing (结核清); Pi Jin (匹金); Sheng Jun (胜君); Cz.: Nidrazid; ***Fin.***: Tubilysin; ***Fr.***: Rimifon; ***Ger.***: Isozid comp N; Isozid; tebesium-s; tebesium; ***Gr.***: Cemidon; Dianicotyl; Nicozid†; ***Hong Kong***: Trisofort†; ***Hung.***: Isonicid; ***India***: Iso-Rifa; Isokin; Isonex; Rifacom-EZ; ***Indon.***: INH-Ciba; INHA; Inoxin; Kapedoxin; Medinh-OD†; Niacifort-6; Nufadoxin; Pehadoxin; Pulmolin†; Pyravit; Pyrifort†; Suprazid; TB Vit 6; ***Ital.***: Nicozid; ***Jpn***: Hydra; Hydrazide†; ***Mex.***: Hidrasix; Isodo Tbal; Valifol; ***Philipp.***: Comprilex; Curazid (Reformulated); Eurocoxin; Isodexid; Isonid; Isoprim; Isoxin; Nicetal†; Odinah; Pulmodrin; Techxafort; Terozid; Trisofort†; Vamsoxid†; Zidrid; ***Pol.***: Nidrazid; ***Port.***: Hidrazida; ***Rus.***: Isozid (Изозид); Isozid Comp (Изозид Комп); ***Singapore***: Rimifon; ***Spain***: Cemidon B6; Cemidon; ***Swed.***: Tibinide; ***Switz.***: Rimifon; ***Thai.***: Antimic; Myrin-P†; ***Turk.***: INH; Isovit; ***USA***: Laniazid; Nydrazid.

Multi-ingredient Preparations. ***Arg.***: Bacifim†; Rifinah; ***Austria***: Isoprodiant†; Rifater; Rifoldin mit INH; ***Braz.***: Isoniaton†; ***Canad.***: Rifater; ***China***: An Si Nuo Kang (安斯诺康); Chang Wei Rui Da Xin (长威瑞达欣); Dai Fei Lin (戴菲林); Fei An (费安); Fei Lu De (菲路得); Fei Ning (费宁); Fei Su (菲苏); Fei Ting (菲亭); Hu Fei Te (护菲特); Ke Lao Er Kang (克劳尔康); Pi Lv (匹律); Rui Pu An Kang (瑞福安康); Rui Qing (瑞清); Ti Bi (缇碧); Wei Bao (维葆); Wei Fei (维菲); Yi Bi Fu (依比福); Yi Nuo Ni Kang (怡诺尼康); Yi Ti Bi (伊缇碧); ***Denm.***: Rimactazid; Rimcure; Rimstar; ***Fin.***: Rimactazid; Rimstar; ***Fr.***: Rifater; Rifinah; ***Ger.***: Iso-Eremfat; Rifater†; Rifinah†; tebesium Duo; tebesium Trio; ***Gr.***: Myambutol-INH; Oboliz; Rifater; Rifinah; Rimactazid; ***Hong Kong***: Rifater; Rifinah; ***Hung.***: Rifazid; ***India***: AFB3; AFB4; Akt-2; Akt-3; Akt-4; Akt-FD; Akurit-3; Akurit-4; Akurit-Z; Akurit; Antibin; Arzade; Arzide†; Becox Forte Kit; Becox RH; Bicox Kid; Bicox-E; Bicox; Binex-DT; Binex E; Binex Kid; Binex Z; Binex ZE; Binex; Cavidin INH; Cavirip; Cavitar RHE; Caviter FD; Caviter; Combunex; Confez-3; Coxina-3; Coxina-4; Coxinex; Coxkit-3; Coxpic; Coxrid; Coxter-2; Coxter-3; Coxter-4; Cx-3; Cx-4; Cx-5; Emrif Kit; Emrif; Eufacin Inh; Eufacin Plus; Eufazid; Famcin H; Faminex Forte; Faminex; Forecox; Gocox Compound; Gocox-3; Inabutol Forte†; Inapas; Infez-4; Ipcacin Kid†; Ipcacin; Ipcazide; Iso-Ripharmed; Isokin-300; Isokin-T Forte; Isokoxi; Isorifam; Lifebutol-H; Macox Plus; Macox-ZH; Monto-2; Monto-3; Monto-4; Montonex Forte; Montorip; Mycocox-4; Mycocox-E; Mycocox-Z; Mycocox; Mycodot Kit; Mycodot-4; Mycodot-E; Mycodot-Z; Myconex; Mycospas; Mycurit-3; Mycurit-4; Mycurit-Z; Optirifa Plus; R-Cinex Z; R-Cinex; RHZ Plus; RHZ; Rifa E; Rifa; Rimactazid + Z; Rimpazid; Siticox-INH†; Tibirim INH; Tricox; Wokex-2; Wokex-3; Wokex-4; Xeed 2; Xeed 3E; Xeed 4; ***Indon.***: bacbutINH; Erabutol Plus; Meditam-6†; Metham; Mycothambin-INH†; Niazitol; Pulna; Ramicin-ISO†; Rimactazid; Rimcure; Rimstar; Santibi Plus; ***Irl.***: Rifater; Rifinah; Rimactazid; Rimcure†; Rimstar; ***Ital.***: Etanicoxid B6; Rifater; Rifinah; Rimactazid; Rimcure; Rimstar; ***Malaysia***: Rimactazid; Rimcure; ***Mex.***: Arpisen†; Dotbal-S; Dotbal; Pinater†; Pinateramida†; Rifater; Rifinah; ***Mon.***: Dexambutol-INH†; ***Neth.***: Rifinah; Rimactazid†; Rimcure†; Rimstar†; ***Norw.***: Rimactazid; Rimcure; Rimstar; ***NZ***: Rifinah; ***Philipp.***: 4D; AKurIT-4; AKuriT; Biflx; CombiKids†; CombiPack; Continukit Plus†; Continukit; Continupack†; Duomax; Ebutol; Econoflx; Econokit-MDR; Econokit; Econopack; Ethamizid; Ethl 400; Fixcom 3; Fixcom 4; HR Pedia Kit; HRZ Pedia Kit; Kidz Kit 2; Kidz Kit 3; Myrin-P; Myrin; Quadmax; Quadtab; Refam Duo†; Refam Pedia Kit†; Rifater; Rifinah; Rifzin; Rimactazid; Rimcure; Rimstar; Sthamizide; SVM-Polypac-A†; Tres; Triofix; Tritab; Viper†; ***Pol.***: Rifamazid; ***Port.***: Rifater; Rifinah; ***Rus.***: Combitub (Комбитуб); Forecox (Форкокс); Iso-Eremfat (Изо-Эремфат); Isocomb (Изокомб); Isopask (Изопаск); Laslonvita (Ласлонвита); Lomecomb (Ломекомб); Mac-Pas Plus (Мак-Пас Плюс); Phthizoetham (Фтизоэтам); Phthizopiram (Фтизопирам); Protub-2 (Протуб-2); Protub-3 (Протуб-3); Protub-4 (Протуб-4); Protub-Lome (Протуб-Ломе); Protubetham (Протубэтам); Protubpira (Протубпира); Protubvita (Протубвита); Repin B_6 (Репин B_6); Rifacomb (Рифакомб); Rifacomb Plus (Рифакомб Плюс)†; Rimactazid (Римактазид)†; Rimecure 3-FDC (Римкур 3-ФДС)†; Rimstar 4-FDC (Римстар 4-ФДС)†; Tubavit (Тубавит); ***S.Afr.***: Rifafour; Rifater†; Rifinah; Rimactazid; Rimcure; Rimstar; ***Singapore***: Merip; Rimactazid; ***Spain***: Amiopia†; Duplicalcio B12†; Rifater; Rifinah; Rimactazid†; Rimcure†; Rimstar; Tisobrif†; ***Swed.***: Rimactazid; Rimcure; Rimstar; ***Switz.***: Rifater; Rifinah; Rimactazid; Rimstar; ***Thai.***: Rifafour; Rifampyzid; Rifater; Rifinah; Rimactazid†; Rimcure 3-FDC; Rimstar†; ***UK***: Rifater; Rifinah; Rimstar; Voractiv; ***USA***: IsonaRif; Rifamate; Rifater; ***Venez.***: Rimactazid; Rimcure.

Pharmacopoeial Preparations

BP 2014: Isoniazid Injection; Isoniazid Oral Solution; Isoniazid Tablets;
USP 36: Isoniazid Injection; Isoniazid Syrup; Isoniazid Tablets; Rifampin and Isoniazid Capsules; Rifampin, Isoniazid, and Pyrazinamide Tablets; Rifampin, Isoniazid, Pyrazinamide, and Ethambutol Hydrochloride Tablets.

Josamycin *(BAN, USAN, rINN)*

EN-141; Josamicina; Josamicinas; Josamycine; Josamycinum; Josamysiini; Jozamicin; Leucomycin A_3; Джозамицин.

A stereoisomer of 7-(formylmethyl)-4,10-dihydroxy-5-methoxy-9,16-dimethyl-2-oxo-oxacyclohexadeca-11,13-dien-6-yl 3,6-dideoxy-4-*O*-(2,6-dideoxy-3-*C*-methyl-α-L-*ribo*-hexopyranosyl)-3-(dimethylamino)-β-D-glucopyranoside 4′-acetate 4″-isovalerate.

$C_{42}H_{69}NO_{15}$=828.0

CAS — 16846-24-5; 56689-45-3.
ATC — J01FA07.
ATC Vet — QJ01FA07.
UNII — HV13HFS217.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.*

Ph. Eur. 8: (Josamycin). A macrolide antibiotic produced by certain strains of *Streptomyces narbonensis* var. *josamyceticus* var. *nova*, or obtained by any other means. A white or slightly yellowish, slightly hygroscopic powder. It contains a minimum of 900 units/mg calculated with reference to the dried substance. Very slightly soluble in water; soluble in acetone; freely soluble in dichloromethane and in methyl alcohol. Store in airtight containers.

Josamycin Propionate *(BANM, rINNM)*

Josamicina, propionato de; Josamicino propionatas; Josamycine, Propionate de; Josamycini Propionas; Josamycinpropionat; Josamycin-propionát; Josamysiinipropionaatti; Jozamicin-propionát; Propionato de josamicina; YS-20P; Джозамицина Пропионат.

Josamycin 10-propionate.

$C_{45}H_{73}NO_{16}$=884.1

CAS — 56111-35-4; 40922-77-8.
ATC — J01FA07.
ATC Vet — QJ01FA07.
UNII — 053VA4B06Y.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.*

Ph. Eur. 8: (Josamycin Propionate). It is derived from a macrolide antibiotic produced by certain strains of *Streptomyces narbonensis* var. *josamyceticus* var. *nova*, or obtained by any other means. A white or slightly yellowish, slightly hygroscopic, crystalline powder. It contains a minimum of 843 units/mg, calculated with reference to the dried substance. Practically insoluble in water; soluble in acetone; freely soluble in dichloromethane and in methyl alcohol. Store in airtight containers.

Uses and Administration

Josamycin is a macrolide antibacterial with actions and uses similar to those of erythromycin (p. 292.1). It is given orally as the base or the propionate but doses are expressed in terms of the base; 1.07 g of josamycin propionate is equivalent to about 1 g of josamycin. Usual doses in the treatment of susceptible infections are the equivalent of 1 to 2 g of josamycin daily in 2 or more divided doses.

Adverse Effects and Precautions

As for Erythromycin, p. 293.1. Josamycin is reported to produce less gastrointestinal disturbance than erythromycin.

Oedema. A report of josamycin-induced oedema of the foot.[1]

1. Bosch X, *et al.* Josamycin-induced pedal oedema. *BMJ* 1993; **307:** 26.

Interactions

For a discussion of drug interactions of macrolide antibacterials, see Erythromycin, p. 294.2.

Cytochrome P450 isoenzymes. Josamycin is reported to have little or no effect on hepatic cytochrome P450 isoenzymes and may therefore interact less than erythromycin with other drugs metabolised by this enzyme system (see Mechanism, under Interactions of Erythromycin, p. 294.2). The general absence of an interaction between josamycin and theophylline would appear to support this

Antimicrobial Action

As for Erythromycin, p. 295.1. Some reports suggest that josamycin may be more active against some strains of anaerobic species such as *Bacteroides fragilis.*

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Josalid; ***China***: Bebeisha (贝贝莎); Josamy (娇莎); ***Fr.***: Josacine; ***Ital.***: Iosalid; ***Jpn***: Josamy; ***Rus.***: Wilprafen (Вильпрафен); ***Spain***: Josamin; ***Ukr.***: Wilprafen (Вильпрафен).

Multi-ingredient Preparations. ***Ital.***: Corti-Fluoral.

Kanamycin Acid Sulfate *(BANM)*

Kanamicina, sulfato ácido de; Kanamicino rūgštusis sulfatas Kanamycin Acid Sulphate; Kanamycin sulfát kyselý Kanamycine, sulfate acide de; Kanamycini sulfas acidus Kanamycinsulfat, Saures; Kanamycinsyrasulfat; Kanamysiini happosulfaatti; Savanyú kanamicin-szulfát; Канамицина Кислого Сульфат.

ATC — A07AA08; J01GB04; S01AA24.
ATC Vet — QA07AA08; QJ01GB04; QS01AA24.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Ph. Eur. 8: (Kanamycin Acid Sulfate). A form of kanamycin sulfate prepared by adding sulfuric acid to a solution of kanamycin sulfate and drying by a suitable method. A white or almost white, hygroscopic powder containing not less than 670 units/mg and 23 to 26% of sulfate, calculated with reference to the dried material. Soluble 1 in about 1 of water; practically insoluble in alcohol and in acetone. A 1% solution in water has a pH of 5.5 to 7.5.

Kanamycin Sulfate *(BANM, rINNM)*

Kanamicina, sulfato de; Kanamicin-monoszulfát; Kanamicino monosulfatas; Kanamycin A Sulphate; Kanamycin monosulfát monohydrát; Kananycin Monosulphate; Kanamycin Sulphate; Kanamycine, monosulfate de; Kanamycine, Sulfate de; Kanamycini monosulfas; Kanamycini Monosulfas Monohydricus; Kanamycini Sulfas; Kanamycinmonosulfat Kanamycyny siarczan; Kanamysiinimonosulfaatti; Sulfato de kanamicina; Канамицина Сульфат.

6-*O*-(3-Amino-3-deoxy-α-D-glucopyranosyl)-4-*O*-(6-amino-6-deoxy-α-D-glucopyranosyl)-2-deoxystreptamine sulphate monohydrate.

$C_{18}H_{36}N_4O_{11}.H_2SO_4.H_2O$=600.6

CAS — 59-01-8 (kanamycin); 25389-94-0 (anhydrous kanamycin sulfate).
ATC — A07AA08; J01GB04; S01AA24.
ATC Vet — QA07AA08; QJ01GB04; QS01AA24.
UNII — OW1N4G4R9W (kanamycin sulfate); J80EX28SMC (kanamycin A sulfate).

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Jpn includes the anhydrous substance.

Ph. Eur. 8: (Kanamycin Monosulfate; Kanamycin Sulfate BP 2014). The sulfate of an antimicrobial substance produced by the growth of certain strains of *Streptomyces kanamyceticus.* A white or almost white, crystalline powder containing not less than 750 units/mg and 15.0 to 17.0% of sulfate, calculated with reference to the dried material. Soluble 1 in about 8 of water; practically insoluble in alcohol and in acetone. A 1% solution in water has a pH of 6.5 to 8.5.

USP 36: (Kanamycin Sulfate). A white, odourless crystalline powder. It has a potency equivalent to not less than 750 micrograms of kanamycin per mg, calculated on the dried basis. Freely soluble in water; insoluble in acetone, in ethyl acetate, and in benzene. pH of a 1% solution in water is between 6.5 and 8.5. Store in airtight containers.

Incompatibility. For discussion of the incompatibility of aminoglycosides such as kanamycin with beta lactams, see under Gentamicin Sulfate, p. 304.3. Kanamycin is also reported to be incompatible with various other drugs including some other antimicrobials as well as with some electrolytes.

Uses and Administration

Kanamycin is an aminoglycoside antibacterial with actions similar to those of gentamicin (p. 304.3). It has been used in the treatment of susceptible Gram-negative and staphylococcal infections, including gonorrhoea (p. 204.2) and neonatal gonococcal eye infections (p. 193.2), although its use has declined in many centres because of the

development of resistance. As with gentamicin it may be used with penicillins and with cephalosporins; the injections should be given at separate sites. Kanamycin has also been used as a second-line drug in tuberculosis (p. 210.2), but other, safer drugs are usually preferred.

The sulfate or acid sulfate salts are often used: in the USA, preparations containing the bisulfate ($C_{18}H_{36}N_4O_{11}.2H_2SO_4$), but referred to as the sulfate, are available. Doses are expressed in terms of kanamycin base; 1.2 g of kanamycin sulfate, and 1.34 g of kanamycin acid sulfate, are each equivalent to about 1 g of kanamycin. It is usually given by intramuscular injection, and in acute infections adults may be given 15 mg/kg daily, to a maximum of 1.5 g daily, in 2 to 4 divided doses. The same doses may be given by intravenous infusion of a 0.25 to 0.5% solution over 30 to 60 minutes; in the UK, up to 30 mg/kg daily has been given in 2 or 3 divided doses by this route. Treatment of acute infections should preferably not continue for longer than 7 to 10 days or exceed a cumulative dose of 10 g kanamycin. A dose of 3 to 4 g weekly, given as 1 g on alternate days or as 1 g twice daily on 2 days each week, was formerly suggested in the UK for chronic bacterial infections, up to a maximum cumulative dose of 50 g, but prolonged use increases the risk of nephrotoxicity and is not generally recommended.

A single intramuscular dose of 2 g of kanamycin has been used when other, first-line drugs are not available in the treatment of gonococcal eye infections.

For details of doses in children, see p. 317.1.

Peak plasma concentrations greater than 30 micrograms/mL and trough concentrations greater than 10 micrograms/mL should be avoided. It is recommended that dosage should be adjusted in all patients according to plasma-kanamycin concentrations, and this is particularly important where factors such as age, renal impairment, or prolonged therapy may predispose to toxicity, or where there is a risk of subtherapeutic concentrations. For discussion of the methods of calculating aminoglycoside dosage requirements, see Administration and Dosage, under Gentamicin, p. 305.2.

Kanamycin has been used orally similarly to neomycin (p. 332.1), for the suppression of intestinal flora. For preoperative use, 1 g may be given every hour for 4 hours, then 1 g every 6 hours for 36 to 72 hours. In the management of hepatic encephalopathy, 8 to 12 g daily in divided doses may be given.

Kanamycin has also been given in doses of 250 mg as a nebulised inhalation, 2 to 4 times daily. Solutions of kanamycin 0.25% have been used for the irrigation of body cavities.

Kanamycin tannate has also been used.

Administration in children. For severe infections caused by susceptible bacteria in children beyond the newborn period the American Academy of Pediatrics[1] suggests an intravenous or intramuscular dose equivalent to kanamycin 15 to 30 mg/kg daily, in 3 divided doses.

For prophylaxis in neonates born to mothers with gonococcal infections *or* for the treatment of gonococcal neonatal conjunctivitis, WHO recommends kanamycin 25 mg/kg, up to a maximum of 75 mg, as a single intramuscular dose, if first-line drugs are not available.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Adverse Effects, Treatment, and Precautions

As for Gentamicin Sulfate, p. 306.2.

For patients given standard regimens, peak plasma concentrations of kanamycin >30 micrograms/mL, and trough concentrations >10 micrograms/mL, should be avoided. Auditory (cochlear) toxicity is more frequent than vestibular toxicity.

Local pain and inflammation, as well as bruising and haematoma, have been reported at the site of intramuscular injections.

Gastrointestinal disturbances and a malabsorption syndrome, similar to that seen with oral neomycin (p. 332.2), have occurred after oral kanamycin. Oral kanamycin should be avoided in patients with gastrointestinal ulceration.

Breast feeding. Although kanamycin is distributed into breast milk[1] the American Academy of Pediatrics states that no adverse effects have been seen in breast-fed infants whose mothers were receiving kanamycin, and therefore considers[2] that its use is usually compatible with breast feeding.

1. Chyo N, *et al.* Clinical studies of kanamycin applied in the field of obstetrics and gynecology. *Asian Med J* 1962; **5**: 265–75.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/05/04)

Interactions

As for Gentamicin Sulfate, p. 307.2.

Antimicrobial Action

As for Gentamicin Sulfate, p. 307.2. It is active against a similar range of organisms although it is not active against *Pseudomonas* spp. Some strains of *Mycobacterium tuberculosis* are sensitive.

Resistance has been reported in strains of many of the organisms normally sensitive to kanamycin, and at one time was widespread, but a decline in the use of kanamycin has meant that resistance has become somewhat less prevalent. Cross-resistance occurs between kanamycin and neomycin, framycetin, and paromomycin, and partial cross-resistance has been reported between kanamycin and streptomycin.

References.

1. Ho YH, *et al.* In-vitro activities of aminoglycoside-aminocyclitols against mycobacteria. *J Antimicrob Chemother* 1997; **40**: 27–32.

Pharmacokinetics

As for Gentamicin Sulfate, p. 307.3.

Less than 1% of an oral dose is absorbed, although this may be significantly increased if the gastrointestinal mucosa is inflamed or ulcerated.

After intramuscular injection peak plasma concentrations of kanamycin of about 20 and 30 micrograms/mL occur about 1 hour after doses of 0.5 and 1 g respectively. A plasma half-life of about 3 hours has been reported. Absorption after intraperitoneal instillation is similar to that from intramuscular doses.

Kanamycin is rapidly excreted by glomerular filtration and most of a parenteral dose appears unchanged in the urine within 24 hours. It has been detected in cord blood and in breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Cristalomicina; *Ger.*: Kan-Ophtal†; Kana-Stulln; Kanamytrex; *Gr.*: Eye-Cure Ph-C†; *India*: Efficin; Kanamac; Kancin; Kaycin; Neokanyn; *Indon.*: Kanabiotic†; Kanarco; Kanoxin†; *Ital.*: Keimicina; *Malaysia*: Kancin; *Mex.*: Cancina†; Kanapat; Kantrex; Solkan; Sulmyn†; *Singapore*: Kancin-L; *Thal.*: Anbikan†; Kancin†; Kangen; KMH; *USA*: Kantrex†; *Venez.*: Kantrex.

Multi-ingredient Preparations. *Arg.*: Cristalomicina; *Ital.*: Dermaflogil; *Rus.*: Gelplastan (Гелпластан); *S.Afr.*: Kantrexil; *Spain*: Kanafosal Predni†; Kanafosal†; Kanapomada†; Naso Pekamin†; *Thai.*: KA-Cilone†; *Venez.*: Monosulpa; Rinomax.

Pharmacopoeial Preparations
USP 36: Kanamycin Injection; Kanamycin Sulfate Capsules.

Kitasamycin *(BAN, USAN, rINN)*

Kitasamicina; Kitasamycine; Kitasamycinum; Leucomycin; Китазамицин.

CAS — 1392-21-8 (kitasamycin); 37280-56-1 (kitasamycin tartrate); 178234-32-7 (kitasamycin acetate).
ATC Vet — QJ01FA93.

Pharmacopoeias. In *Chin.* and *Jpn.*

Jpn also includes Kitasamycin Acetate (Acetylkitasamycin) and Kitasamycin Tartrate.

Profile

Kitasamycin is a macrolide antibacterial produced by *Streptomyces kitasatoensis*, consisting mainly of kitasamycins A_4 and A_5. It has actions and uses similar to those of erythromycin (p. 291.2) and has been given orally as the base or intravenously as the tartrate in the treatment of susceptible infections. Kitasamycin acetate has also been given orally.

Kitasamycin has been added to animal feed stuffs in some countries as a growth promotor for pigs.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: An Ji Er Le (安吉儿乐); Le Pu Mei Xin (乐普美欣); Shuang Ning (爽宁); Tian Cao (田草); Xiaojun (小军).

Latamoxef Disodium *(BANM, rINNM)*

Latamoksefidinatrium; Latamoxef disódico; Latamoxef Disodique; Latamoxef Sodium; Latamoxefdinatrium; Latamoxefum Dinatricum; LY-127935; Moxalactam Disodium (USAN); 6059-S; Динатрий Латамоксеф.

(7*R*)-7-[2-Carboxy-2-(4-hydroxyphenyl)acetamido]-7-methoxy-3-(1-methyl-1*H*-tetrazol-5-ylthiomethyl)-1-oxa-3-cephem-4-carboxylic acid, disodium salt.
$C_{20}H_{18}N_6Na_2O_9S$=564.4
CAS — 64952-97-2 (latamoxef); 64953-12-4 (latamoxef disodium).
ATC — J01DD06.
ATC Vet — QJ01DD06.
UNII — 5APW73W3QZ.

Pharmacopoeias. In *Jpn.*

Profile

Latamoxef is an oxacephalosporin antibacterial that has been given intramuscularly or intravenously as the disodium salt in the treatment of susceptible infections. It differs from the cephalosporins in that the sulfur atom of the 7-aminocephalosporanic acid nucleus is replaced by oxygen. Like cefamandole (p. 236.2) it has an *N*-methylthiotetrazole side-chain and may cause hypoprothrombinaemia. Serious bleeding episodes have been reported with latamoxef and prophylaxis with vitamin K and monitoring of bleeding time have been recommended during treatment. In addition to hypoprothrombinaemia, inhibition of platelet function and more rarely immune-mediated thrombocytopenia may be responsible for interference with haemostasis. As with the methylthiotetrazole-containing cephalosporins, a disulfiram-like reaction with alcohol may occur.

Latamoxef has antimicrobial activity similar to that of the third-generation cephalosporin cefotaxime (p. 244.3), although it is generally less active against Gram-positive bacteria and more active against *Bacteroides fragilis*.

Breast feeding. The authors of a pharmacokinetic study[1] in 8 women given latamoxef cautioned that there was a possibility of colonisation of the infant's bowel with Gram-positive bacteria and in consequence a risk of enterocolitis. They therefore advised against breast feeding during maternal use of the drug. However, no adverse effects have been seen in breast-fed infants whose mothers were receiving latamoxef, and the last available guidance from the American Academy of Pediatrics considered[2] that it was therefore usually compatible with breast feeding.

1. Miller RD, *et al.* Human breast milk concentration of moxalactam. *Am J Obstet Gynecol* 1984; **148**: 348–9.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/05/04)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Shiomarin (喋吗灵); *Jpn*: Shiomarin.

Lenampicillin Hydrochloride *(rINNM)*

Hidroclorur de lenampicilina; KBT-1585; Lénampicilline, Chlorhydrate de; Lenampicillini Hydrochloridum; Ленампициллина гидрохлорид.

2,3-Dihydroxy-2-butenyl(2*S*,5*R*,6*R*)-6-[(*R*)-2-amino-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate, cyclic carbonate, hydrochloride.
$C_{21}H_{23}N_3O_7S.HCl$=497.9
CAS — 86273-18-9 (lenampicillin); 80734-02-7 (lenampicillin hydrochloride).

Pharmacopoeias. In *Jpn.*

Profile

Lenampicillin is an ester of the beta-lactam antibacterial ampicillin to which it is hydrolysed *in vivo*. It is used, as the hydrochloride, in the treatment of susceptible infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: ZhenXin (珍欣).

Levofloxacin *(BAN, USAN, rINN)*

DR-3355; HR-355; Levofloksasiini; Levofloksasin; Lévofloxacine; Levofloxacino; Levofloxacinum; S-(-)-Ofloxacin; RWJ-25213; Левофлоксацин.

(-)-(*S*)-9-Fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid.
$C_{18}H_{20}FN_3O_4$=361.4

CAS — 100986-85-4 (levofloxacin); 138199-71-0 (levofloxacin hemihydrate).
ATC — J01MA12; S01AE05.
ATC Vet — QJ01MA12; QS01AE05.
UNII — 6GNT3Y5LMF.

Pharmacopoeias. In *US.*

USP 36: (Levofloxacin). A light yellowish-white to yellow-white crystals or crystalline powder. Sparingly soluble in water, in acetone, and in methyl alcohol; soluble in acetic acid and in dimethyl sulfoxide; practically insoluble in glycerol and in *n*-octanol. Store in airtight containers. Protect from light.

Uses and Administration

Levofloxacin is the *S*-(-)-isomer of the fluoroquinolone antibacterial ofloxacin (p. 336.3). It is given orally, or by intravenous infusion as a 5 mg/mL solution over 30 to 90 minutes, to treat susceptible infections including tuberculosis (but see under Uses and Administration of Ciprofloxacin, p. 262.2). Levofloxacin is given as the hemihydrate but doses are expressed in terms of the base; levofloxacin hemihydrate 256 mg is equivalent to about 250 mg of levofloxacin. Usual doses range from 250 to 500 mg once or twice daily for 7 to 14 days depending on the severity and nature of the infection. A dose of 250 mg once daily for 3 days may be given for uncomplicated urinary-tract infections. A 28-day course of treatment with a dose of 500 mg once daily should be given for chronic bacterial prostatitis. In the USA, doses of 750 mg once daily for 7 to 14 days may be used for complicated skin infections and for hospital-acquired pneumonia; a shorter course of 750 mg once daily for 5 days may be given for community-acquired pneumonia, acute bacterial sinusitis, complicated urinary-tract infections, and acute pyelonephritis. A 60-day course of treatment with a dose of 500 mg once daily is also licensed in the USA for treatment and postexposure prophylaxis of inhalation anthrax.

Doses should be reduced in patients with renal impairment (see p. 318.1).

Levofloxacin is also used topically as the hemihydrate in eye drops. A solution containing the equivalent of 0.5% of levofloxacin is used for the treatment of bacterial conjunctivitis and 1.5% for corneal ulcers caused by susceptible strains of bacteria. The hemihydrate is also being studied for use by inhalation in the treatment of lung infections in patients with cystic fibrosis.

Reviews.
1. Davis R, Bryson HM. Levofloxacin: a review of its antibacterial activity, pharmacokinetics and therapeutic efficacy. *Drugs* 1994; **4**: 677–700.
2. Martin SJ, *et al.* Levofloxacin and sparfloxacin: new quinolone antibiotics. *Ann Pharmacother* 1998; **32**: 320–36.
3. Martin SJ, *et al.* A risk-benefit assessment of levofloxacin in respiratory, skin and skin structure, and urinary tract infections. *Drugs* 2001; **24**: 199–222.
4. Croom KF, Goa KL. Levofloxacin: a review of its use in the treatment of bacterial infections in the United States. *Drugs* 2003; **63**: 2769–2802.
5. Anderson VR, Perry CM. Levofloxacin: a review of its use as a high-dose, short-course treatment for bacterial infection. *Drugs* 2008; **68**: 535–65.
6. Anonymous. Levofloxacin. *Tuberculosis (Edinb)* 2008; **88**: 119–21.
7. Keating GM. Levofloxacin 0.5% ophthalmic solution: a review of its use in the treatment of external ocular infections and in intraocular surgery. *Drugs* 2009; **69**: 1267–86.

Administration in children. Since fluoroquinolones can cause degenerative changes in weight-bearing joints of young *animals* they should only be used in children and adolescents where their use may be justified if the benefits outweigh the risks. In the USA levofloxacin is licensed for use in children 6 months of age and older only for treatment and postexposure prophylaxis of inhalation anthrax. The following doses, based on body-weight, may be given orally or intravenously[1] for 60 days:
- less than 50 kg: 8 mg/kg (maximum 250 mg) every 12 hours
- 50 kg or more: 500 mg once every 24 hours

1. Li F, *et al.* Pharmacometrics-based dose selection of levofloxacin as a treatment for postexposure inhalational anthrax in children. *Antimicrob Agents Chemother* 2010; **54**: 375–9.

Administration in renal impairment. Although initial intravenous and oral doses (see Uses and Administration, above) remain unchanged in patients with renal impairment, subsequent doses of levofloxacin should be adjusted according to creatinine clearance (CC).

In the UK, the following doses are recommended:
- CC 20 to 50 mL/minute: subsequent doses are halved
- CC 10 to 19 mL/minute: subsequent doses are reduced to one-quarter of the usual dose; a regimen of 250 mg daily should be reduced to 125 mg every 48 hours
- CC less than 10 mL/minute (including haemodialysis and continuous peritoneal dialysis patients): usual doses of 250 mg or 500 mg daily are reduced to 125 mg every 48 or 24 hours respectively; a regimen of 500 mg twice daily is reduced to 125 mg every 24 hours

In the USA, the following dose modifications are recommended:

After an initial dose of 750 mg daily,
- CC 20 to 49 mL/minute: subsequent doses are 750 mg every 48 hours
- CC up to 19 mL/minute (including haemodialysis and continuous peritoneal dialysis patients): subsequent doses are 500 mg every 48 hours

After an initial dose of 500 mg daily,
- CC 20 to 49 mL/minute: subsequent doses are 250 mg every 24 hours
- CC up to 19 mL/minute (including haemodialysis and continuous peritoneal dialysis patients): subsequent doses are 250 mg every 48 hours

After an initial dose of 250 mg daily,
- CC 10 to 19 mL/minute: subsequent doses are 250 mg every 48 hours (although no dose adjustment is required for the short-course, low-dose regimen used in uncomplicated urinary-tract infection)

In critically ill patients undergoing continuous renal replacement therapy (CRRT), a loading dose of 500 to 750 mg has been recommended, followed by maintenance doses dependent on the type of CRRT:[1]
- continuous venovenous haemofiltration (CVVH): 250 mg every 24 hours
- continuous venovenous haemodialysis (CVVHD): 250 to 500 mg every 24 hours
- continuous venovenous haemodiafiltration (CVVHDF): 250 to 750 mg every 24 hours

For critically ill patients undergoing intermittent haemodialysis, a dose of 250 to 500 mg every 48 hours (given after the dialysis run) has been recommended.[1]

1. Heintz BH, *et al.* Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy* 2009; **29**: 562–77.

Peptic ulcer disease. For mention of the potential use of levofloxacin in eradication regimens for *Helicobacter pylori*, see p. 1816.2.

References.
1. Gisbert JP, Morena F. Systematic review and meta-analysis: levofloxacin-based rescue regimens after Helicobacter pylori treatment failure. *Aliment Pharmacol Ther* 2006; **23**: 35–44.
2. Gisbert JP, *et al.* First-line triple therapy with levofloxacin for Helicobacter pylori eradication. *Aliment Pharmacol Ther* 2007; **26**: 495–500.
3. Rispo A, *et al.* Levofloxacin in first-line treatment of Helicobacter pylori infection. *Helicobacter* 2007; **12**: 364–5.
4. Perna F, *et al.* Levofloxacin-based triple therapy for Helicobacter pylori re-treatment: role of bacterial resistance. *Dig Liver Dis* 2007; **39**: 1001–5.
5. Zullo A, *et al.* Helicobacter pylori eradication with either quadruple regimen with lactoferrin or levofloxacin-based triple therapy: a multicentre study. *Dig Liver Dis* 2007; **39**: 806–10.
6. Yee YK, *et al.* Clinical trial: levofloxacin-based quadruple therapy was inferior to traditional quadruple therapy in the treatment of resistant Helicobacter pylori infection. *Aliment Pharmacol Ther* 2007; **26**: 1063–7.
7. Gisbert JP, *et al.* H. pylori Study Group of the Asociación Española de Gastroenterología. Second-line rescue therapy with levofloxacin after H. pylori treatment failure: a Spanish multicenter study of 300 patients. *Am J Gastroenterol* 2008; **103**: 71–6.
8. Castro-Fernández M, *et al.* Efficacy of triple therapy with a proton pump inhibitor, levofloxacin, and amoxicillin as first-line treatment to eradicate Helicobacter pylori. *Rev Esp Enferm Dig* 2009; **101**: 395–8, 399–402.
9. Schrauwen RW, *et al.* Seven-day PPI-triple therapy with levofloxacin is very effective for Helicobacter pylori eradication. *Neth J Med* 2009; **67**: 96–101.
10. Di Caro S, *et al.* Second-line levofloxacin-based triple schemes for Helicobacter pylori eradication. *Dig Liver Dis* 2009; **41**: 480–5.

Tuberculosis. For mention of the use of levofloxacin in the treatment of tuberculosis, see under Ciprofloxacin, p. 262.2.

Adverse Effects and Precautions

As for Ciprofloxacin, p. 262.2.

Symptomatic hyperglycaemia and/or hypoglycaemia have been reported, usually in diabetics who are also taking hypoglycaemics or insulin. Such patients should have their blood-glucose concentrations closely monitored and if signs or symptoms of glucose disturbances develop, levofloxacin should be stopped.

Effects on glucose metabolism. See also under Gatifloxacin, p. 303.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies levofloxacin as probably not porphyrinogenic: it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

As for Ciprofloxacin, p. 264.3.

Use of levofloxacin with drugs that alter blood-glucose concentrations increases the risk of blood-glucose disturbances.

Levofloxacin does not appear to interact significantly with theophylline or ciclosporin.

Antimicrobial Action

As for Ciprofloxacin, p. 265.2.

Levofloxacin is generally considered to be about twice as active as ofloxacin (p. 337.1), the racemic substance. Levofloxacin has a broad spectrum of activity which includes Gram-positive bacteria.

References.
1. Brown DFJ, *et al.*, eds. Levofloxacin: an extended spectrum 4-quinolone agent. *J Antimicrob Chemother* 1999; **43** (suppl C): 1–90.

Pharmacokinetics

Levofloxacin is rapidly and almost completely absorbed after oral doses and peak plasma concentrations occur within 1 to 2 hours. It is widely distributed into body tissues including the bronchial mucosa and lungs, but penetration into CSF is relatively poor. Levofloxacin is about 30 to 40% bound to plasma proteins. Only small amounts are metabolised, to inactive metabolites. The elimination half-life of levofloxacin is 6 to 8 hours, although this may be prolonged in patients with renal impairment. Levofloxacin is excreted largely unchanged, mainly in the urine with less than 5% as metabolites. It is not removed by haemodialysis or peritoneal dialysis.

References.
1. Fish DN, Chow AT. The clinical pharmacokinetics of levofloxacin. *Clin Pharmacokinet* 1997; **32**: 101–19.
2. Piscitelli SC, *et al.* Pharmacokinetics and safety of high-dose an extended-interval regimens of levofloxacin in human immunodefi ciency virus-infected patients. *Antimicrob Agents Chemother* 1999; **43** 2323–7.
3. Chien S, *et al.* Levofloxacin pharmacokinetics in children. *J Clin Pharmacol* 2005; **45**: 153–60.
4. Lee CKK, *et al.* Levofloxacin pharmacokinetics in adult cystic fibrosis *Chest* 2007; **131**: 796–802.
5. Zhang J, *et al.* Permeability and concentration of levofloxacin i epithelial lining fluid in patients with lower respiratory tract infections. *Clin Pharmacol* 2010; **50**: 922–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Anuar; Bacfuron; Bactifren; Bactociliina; Benur; Ceplene Plus; Fentaxina; Floxlevo; Grepiflox; Leflumax; Levaquin; Lexobron; Misile; Quinomed L; Septibiotic; Tavanic; Teraquin; Ultraquin; Uniflox; Valiflox; Voflox; Xaflo; Zenic; ***Austria***: Oftaquix; Tavanic; ***Belg.***: Tavanic; ***Braz.***: Levaquin; Levcin; Levotac; Levoxin; Tamiram; Tavagran; Tavanic; Vonax; ***Canad.***: Levaquin; ***Chile***: Auxxil; Medibiox; Novaciliina; Quinobiot; Recamicina; Tavanic; ***China***: An Li Lai (安理莱); Cravit (可乐必妥); Laiwoxing (莱沃幸); Qi Si Ding (齐斯丁); ***Cz.***: Aflobax; Oftaquix; Tavanic; ***Denm.***: Felvosin†; Oftaquix; Voflan†; ***Fin.***: Oftaquix; Tavanic; ***Fr.***: Tavanic; ***Ger.***: Oftaquix; Tavanic; ***Gr.***: Floxator; Levolacin; Levoprolin; Lexacin; Talerin; Tavanic; Zirotan; Zoclix; ***Hong Kong***: Cravit; Levicin†; Levoxin; ***Hung.***: Leflokin; Levoxa; Oftaquix; Savulin; Tavanic; ***India***: Acquire; Adlox; Aflevo; Albactin; Aleflox; Alevo; Alvox; Apoflox; Balleo; Bat; Brilevo; C-Livo; Cuflox; Cutiflox; Day-5; Defox; E-Livo; Eklevo; Elof; Elone; Elvo; Elvox; Enatome; Evabit; Evopic; Flavo; Floquin; Floroxin; Flostar; Fydoliv; Fyflox; Fynal; Gevoflox; Glevo; Gyraze; Hawk; Hileflox; Idalev; Klever; Kylevo; L-Asiflox; L-Cin; L-Flo; L-Flox; L-Oxo; L-Sig; Laffter; Lamiwin; Lavaza; Lavoflox; LCR; Lebact; Lecourse; Ledor; Ledric; Lee; Leefbid; Leeflox; Lefosym; Lek; Lemed; Leocip; Leof; Leoflox; Leon; Leroy; Levace; Levact; Levator; Levend; Levloc; Levoact; Levobact; Levobenz; Levobos; Levobus; Levocad; Levocas; Levocide; Levocos; Levodak; Levoday; Levoden; Levoff; Levoflow; Levoflox; Levofox; Levogram; Levogrm; Levohill; Levokab; Levokem; Levola; Levolab; Levolak; Levolife; Levolon; Levom; Levomag; Levoman; Levomed; Levon; Levonez; Levopet; Levophar; Levopil; Levoquin; Levorax; Levosh; Levosidh; Levosip; Levospan; Levospi; Levosym; Levotab; Levotas; Levotec; Levotech; Levotoz; Levotran; Levotum; Levowa; Levowok; Levox; Levoxin; Levrea; Lewel; Lexacin; Lexiflox; Lexoquin; LF; LFC Med; Liflo; Lift; Lin; Lina; Lipep; Livbest; Livbid; Livestar; Livocin; Livoric; Livota; Livoven; Livox; LMC; Lofel; Lofo; Lotor; Loxof; LQueen; Lufi; LV Flox; LVM; LVX; LXN; Lypestar; Lzen; Mevof; *Milivo*; *Mintoflox*; *Monoflox*; Morelevo; Multivox; NBLox; Novaflox; Novocin; Nutlevo; Olevo; Osibact; Tavanic; ***Indon.***: Armolev; Corvox; Cravit; Cravox; Difloxin; Elvacin; Farlev; Floxacap; Floxacom; Lecrax; Lefos; Lekuicin; Levocin; Levonic; Levores; Levovid; Levoxa; Lexa; Lovequin; LQ-500; Mosardal; Nislev; Nufalev; Prolecin; Prolevox; Reskuin; Rinvox; Tevox; Volequin; VoLox; Voxir; Zenilev; Zidalev; ***Irl.***: Refaz; Tavager; Tavanic; ***Israel***: Levo; Tavanic; ***Ital.***: Agilev; Alvand; Batiflox; Lemaxil; Levoxacin; Levoxigram; Oftaquix; Prixar; Refrain; Sineflox; Summaflox; Tavanic; Trissil; ***Jpn***: Cravit; ***Malaysia***: Cravit; Glevo; Loxo; ***Mex.***: Bredelin; Cina†; Elequine; Evocs-III; Flevox; Levoxin; Prosxaflo; Ran-Levo; Tavanic; Tevotev; Voflaxin; ***Neth.***: Oftaquix†; Prixar†; Tavanic; ***Philipp.***: Day Five; Flevoxcin; Floxe; Glevo; Lefloxin; Levan; Levex; Levobact; Levobet; Levocin; Levoflox; Levomax; Levonox; Levoprime; Levoquin; Levostrar; Levox; Levoxin; Levoxl; Levozef; Lexi; Lexyl; Lexzin; Lezasir; Lotor; Loxeva; Oftaquix; Omnivox; Pneumocal; Pravox; Quinolev; Qumic; Santis; Teravox; Terlev; Voflox; Voleca; Wilovex; ***Pol.***: Aflobax; Levoxa; Oftaquix; Oroflocina; Tavanic; ***Port***: Foxitina†; Oftaquix; Tavanic; ***Rus.***: Ecolevid (Эколевид); Eleflo (Элефлокс); Flexid (Флексид); Floracid (Флорацид); Glev (Глево); Leflobact (Лефлобакт); Lefoxin (Лефоксин); Levole (Леволет); Maclevo (Маклево); Oftaquix (Офтаквикс); Remedi

(Ремедия); Signicef (Сигницеф); Tanflomed (Танфломед); Tavanic (Таваник); *S.Afr.*: Lintrip; Tavaloxx; Tavanic; *Singapore*: Cravit; *Spain*: Asey; Tavanic; *Swed.*: Oftaquix; Tavanic; *Switz.*: Levex; Tavanic; *Thai.*: Cravit; Lefloxin; Levocin; Levoflox; Levox; Loxof; Olfovel; *Turk.*: Cravit; Floxilevo; Lebel; Lefosin; Levokuin; Levolon; Levonat; Levonidin; Levoteva; Lexacin; Nevotek; Potant; Ravivo; Tavanic; Voleflok; *UAE*: Jenoquine†; *UK*: Evoxil; Oftaquix; Tavanic; *Ukr.*: Floxium (Флоксиум); Lefloc (Лефлок); Leflocin (Лефлоцин); Levo-FQ (Лево-ФК); Levobact (Левобакт); Levolet (Леволет); Loxof (Локсоф); Tavanik (Таваник); Taxacin (Таксацин); Zolev (Золев); *USA*: Iquix; Levaquin; Quixin; *Venez.*: Levaquin; Proxime; Tavanic.

Multi-ingredient Preparations. *Braz.*: Pyloripac Retrat; *India*: Aleflox-OZ; Evopic-OZ; Fynal-OZ; Kylevo-OZ; L-Cin-A; L-Cin-OZ; Lebact-AM; Lebact-O; Lefosym-OZ; Lek-OZ; Levact-OZ; Levocide-OZ; Levocos-OZ; Levoflox Oz; Levogyl; Levospan-OZ; Levosym-OZ; Livbest-AM; Novaflox-OZ.

Pharmacopoeial Preparations
USP 36: Levofloxacin Oral Solution.

Lincomycin *(BAN, USAN, rINN)*

Lincomicina; Lincomycine; Lincomycinum; Linkomycin; Linkomysiini; U-10149; Линкомицин.

Methyl 6-amino-6,8-dideoxy-*N*-[(2*S*,4*R*)-1-methyl-4-propylprolyl]-1-thio-α-D-*erythro*-D-*galacto*-octopyranoside.

$C_{18}H_{34}N_2O_6S$=406.5

CAS — 154-21-2.
ATC — J01FF02.
ATC Vet — QJ01FF02.
UNII — 80D072YW0F.

Lincomycin Hydrochloride *(BANM, rINNM)*

Hidrocloruro de lincomicina; Lincomicina, hidrocloruro de; Lincomycine, Chlorhydrate de; Lincomycinhydrochlorid-Monohydrat; Lincomycini hydrochloridum; Lincomycini Hydrochloridum Monohydricum; Linkomicin-hidroklorid; Linkomicino hidrochloridas; Linkomisin Hidroklorür; Linkomycin hydrochlorid monohydrát; Linkomycinhydroklorid; Linkomycyny chlorowodorek; Linkomysiinihydrokloridi; Lyncomycini Hydrochloridum; NSC-70731; Линкомицина Гидрохлорид.

Lincomycin hydrochloride monohydrate.

$C_{18}H_{34}N_2O_6S,HCl,H_2O$=461.0

CAS — 859-18-7 (anhydrous lincomycin hydrochloride); 7179-49-9 (lincomycin hydrochloride, monohydrate).
ATC — J01FF02.
ATC Vet — QJ01FF02.
UNII — M6T05Z2B68 (lincomycin hydrochloride monohydrate); GCW8Y9936L (anhydrous lincomycin hydrochloride).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Lincomycin Hydrochloride). A mixture of antibiotics produced by *Streptomyces lincolnensis* var. *lincolnensis* or obtained by any other means, the main component being lincomycin hydrochloride monohydrate. A white or almost white crystalline powder. It contains not more than 5% of lincomycin B. Very soluble in water; slightly soluble in alcohol; very slightly soluble in acetone. A 10% solution in water has a pH of 3.5 to 5.5. Store at a temperature not exceeding 30 degrees. If the substance is sterile, store in airtight containers.

USP 36: (Lincomycin Hydrochloride). A white or practically white crystalline powder, odourless or with a faint odour. Freely soluble in water; very slightly soluble in acetone; soluble in dimethylformamide. pH of a 10% solution in water is between 3.0 and 5.5. Store in airtight containers.

Incompatibility. Solutions of lincomycin hydrochloride have an acid pH and incompatibility may be expected with alkaline preparations, or with drugs unstable at low pH. Licensed product information for the injectable solution states that physical incompatibility has been reported with novobiocin, kanamycin, and phenytoin.

Uses and Administration

Lincomycin is a lincosamide antibacterial with actions and uses similar to those of its chlorinated derivative, clindamycin (p. 270.1). Clindamycin is usually preferred to lincomycin because of its greater activity and better absorption, although the usefulness of both drugs is limited by the risk of pseudomembranous colitis.

Lincomycin is given orally or parenterally as the hydrochloride but doses are expressed in terms of the base; 1.13 g of lincomycin hydrochloride is equivalent to about 1 g of lincomycin. The usual adult oral dose is 500 mg 3 or 4 times daily, taken at least 1 or 2 hours before or after food. It is given parenterally by intramuscular injection in a dose of 600 mg once or twice daily, or by slow intravenous infusion in a dose of 0.6 to 1 g two or three times daily. Higher intravenous doses have been given in very severe infections, up to a total daily dose of about 8 g. For intravenous use, lincomycin 1 g should be diluted in not less than 100 mL of diluent and infused over at least 1 hour.

For details of reduced doses in renal impairment, see p. 319.2.

For details of doses in infants and children, see p. 319.2.

Lincomycin hydrochloride may be given by subconjunctival injection in a dose equivalent to 75 mg of lincomycin.

Administration in children. The usual oral dose of lincomycin for infants and children aged 1 month and over is 30 to 60 mg/kg daily in divided doses. It is given parenterally to those over 1 month old in a dose of 10 to 20 mg/kg daily in divided doses by intramuscular injection or intravenous infusion.

For suggested doses in children with renal impairment see p. 319.2.

Administration in renal impairment. Oral and parenteral doses of lincomycin may need to be reduced in patients with severe renal impairment; a reduction down to 25 to 30% of the usual dose (see Uses and Administration, above) may be appropriate.

Adverse Effects, Treatment, and Precautions

As for Clindamycin, p. 271.2.

Hypersensitivity reactions such as rashes, urticaria, and angioedema may be less frequent with lincomycin than with clindamycin. Other adverse effects reported rarely with lincomycin include aplastic anaemia, pancytopenia, tinnitus, and vertigo.

Lincomycin should be used with caution in patients with hepatic or renal impairment; consideration should be given to decreasing the dosage frequency and serum concentrations should be monitored during high-dose therapy. Reduced doses may be necessary in those with severe renal impairment (see above).

Interactions

As for Clindamycin, p. 272.1.

Absorption of lincomycin is reduced by adsorbent antidiarrhoeals and cyclamate sweeteners.

Antimicrobial Action

As for Clindamycin, p. 272.1, but it is less potent. There is complete cross-resistance between clindamycin and lincomycin. Some cross-resistance with erythromycin, including the phenomenon known as dissociated cross-resistance or inducible MLS_B phenotype, has been reported.

Pharmacokinetics

About 20 to 35% of an oral dose of lincomycin is rapidly absorbed from the gastrointestinal tract; after a 500-mg dose, peak plasma concentrations of about 2 to 3 micrograms/mL are reached within 2 to 4 hours. Food markedly reduces the rate and extent of absorption. An intramuscular injection of 600 mg produces average peak plasma concentrations of between 11 and 12 micrograms/mL at 60 minutes and a 2-hour intravenous infusion of 600 mg produces an average of about 16 micrograms/mL.

The biological half-life of lincomycin is about 5 hours and may be prolonged in hepatic or renal impairment. Serum half-life may be doubled in patients with hepatic impairment and up to 3 times longer in those with severe renal impairment. Lincomycin is widely distributed in the tissues including bone and body fluids but diffusion into the CSF is poor, although it may be slightly better when the meninges are inflamed. It diffuses across the placenta and is distributed into breast milk.

Lincomycin is partially inactivated in the liver; unchanged drug and metabolites are excreted in the urine, bile, and faeces. Lincomycin is not effectively removed from the blood by haemodialysis or peritoneal dialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Frademicina; *Austral.*: Lincocin; *Belg.*: Lincocin; *Braz.*: Farmicina; Frademicina; Linatron; Lincoflan; Lincomiral; Lincovax; Lindemicina; Neo Linco; *Canad.*: Lincocin; *Chile*: Lincocin; *China*: Hu Gu (护谷); LiKe (力克); Lincocin (丽可胜); *Cz.*: Neloren; *Fr.*: Lincocine; *Gr.*: Lincocin; Pecasolin; *Hong Kong*: Lincocin; *India*: Admycin-L; Amlinc; Lincocin; Lincosa; Lincozin; Lincy; Lines; Link; Linka; Linkam; Lintop; Liod; Lycin; Lynx; *Indon.*: Biolincom; Ethilin; Linco†; Lincocin; Lincophar; Lincyn; Lintropsin; Nichomycin; Nolipo; Percocyn; Pritalinc; Tamcocin; Tismamisin; Zencocin; Zumalin; *Ital.*: Lincocin; *Malaysia*: Linco; Lincosa; *Mex.*: Bactokina; Libiocid; Limidrax; Linbac; Lincocin; Lincopat; Lincover; Lisonin; Lortz; Princol†; Rimsalin; Yectolin; *NZ*: Lincocin; *Philipp.*: Adlynx; Lincocin; *Pol.*: Lincocin; Neloren; *Port.*: Lincocina; *Rus.*: Neloren (Нелорен)†; *S.Afr.*: Lincocin; *Singapore*: Lincocin; *Spain*: Cillimicina†; Lincocin; *Thai.*: Linco-P; Linco; Lincocilin; Lincocin; Lincolan; Lincomax†; Lincono; Lincosa; Lingo; Linmycin; Unolin; Uto Lincomycin; *Turk.*: Lincocin; Linkoles; Linkomed; Linkosol; Linosin; *Ukr.*: Lincocin (Линкоцин)†; *USA*: Lincocin; *Venez.*: Formicina; Lincocin.

Multi-ingredient Preparations. *Arg.*: Nicozinc.

Pharmacopoeial Preparations
BP 2014: Lincomycin Capsules; Lincomycin Injection;
USP 36: Lincomycin Hydrochloride Capsules; Lincomycin Hydrochloride Syrup; Lincomycin Injection.

Linezolid *(BAN, USAN, rINN)*

Linetsolidi; Linézolide; Linezolidum; PNU-100766; U-100766; Линезолид.

N-[[(*S*)-3-(3-Fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide.

$C_{16}H_{20}FN_3O_4$=337.4

CAS — 165800-03-3.
ATC — J01XX08.
ATC Vet — QJ01XX08.
UNII — ISQ9I6J12J.

Incompatibility and stability. References.
1. Zhang Y, *et al.* Compatibility and stability of linezolid injection admixed with three quinolone antibiotics. *Ann Pharmacother* 2000; 34: 996–1001.

Uses and Administration

Linezolid is an oxazolidinone antibacterial used for the treatment of Gram-positive infections of the skin and respiratory tract, including those due to vancomycin-resistant enterococci and meticillin-resistant *Staphylococcus aureus*.

It is given, orally or by intravenous infusion (over 30 to 120 minutes), in a usual adult dose of 600 mg every 12 hours for 10 to 14 days; treatment for up to 28 days may be necessary if there is vancomycin resistance. In uncomplicated skin and skin structure infections an oral dose of 400 mg every 12 hours for 10 to 14 days is usually sufficient.

For doses in children, see p. 319.3.

Reviews.
1. Plouffe JF. Emerging therapies for serious gram-positive bacterial infections: a focus on linezolid. *Clin Infect Dis* 2000; 31 (suppl 4): S144–S149.
2. Perry CM, Jarvis B. Linezolid: a review of its use in the management of serious gram-positive infections. *Drugs* 2001; 61: 525–51.
3. Bain KT, Wittbrodt ET. Linezolid for the treatment of resistant gram-positive cocci. *Ann Pharmacother* 2001; 35: 566–75.
4. Paladino JA. Linezolid: an oxazolidinone antimicrobial agent. *Am J Health-Syst Pharm* 2002; 59: 2413–25.
5. Birmingham MC, *et al.* Linezolid for the treatment of multidrug-resistant, Gram-positive infections: experience from a compassionate-use program. *Clin Infect Dis* 2003; 36: 159–68.
6. Wilcox MH. Efficacy of linezolid versus comparator therapies in Gram-positive infections. *J Antimicrob Chemother* 2003; 51 (suppl S2): ii27–ii35.
7. Falagas ME, *et al.* Linezolid for the treatment of patients with endocarditis: a systematic review of the published evidence. *J Antimicrob Chemother* 2006; 58: 273–80.
8. Ntziora F, Falagas ME. Linezolid for the treatment of patients with central nervous system infection. *Ann Pharmacother* 2007; 41: 296–308.
9. Falagas ME, *et al.* Linezolid for the treatment of adults with bone and joint infections. *Int J Antimicrob Agents* 2007; 29: 233–9.
10. Manfredi R. Le prospettive terapeutiche di linezolid nelle infezioni da patogeni Gram-positivi multiresistenti. *Recenti Prog Med* 2007; 98: 143–54.
11. Falagas ME, *et al.* Linezolid versus glycopeptide or beta-lactam for treatment of Gram-positive bacterial infections: meta-analysis of randomised controlled trials. *Lancet Infect Dis* 2008; 8: 53–66.
12. Falagas ME, Vardakas KZ. Benefit-risk assessment of linezolid for serious gram-positive bacterial infections. *Drug Safety* 2008; 31: 753–68.
13. Di Paolo A, *et al.* Pharmacological issues of linezolid: an updated critical review. *Clin Pharmacokinet* 2010; 49: 439–47.

Administration in children. UK licensed product information does not recommend the use of linezolid in children and adolescents below 18 years of age. However, the *BNFC* suggests the following doses of linezolid in the treatment of pneumonia or *complicated* skin and soft-tissue infections, given orally or by intravenous infusion over 30 to 120 minutes:

- neonates up to 7 days old: 10 mg/kg every 12 hours, increasing to every 8 hours if response is poor
- 7 days to 12 years of age: 10 mg/kg (to a maximum of 600 mg) every 8 hours
- 12 to 18 years: usual adult doses (see Uses and Administration, above).

Similar doses are licensed in the USA. US licensed product information also suggests that in the treatment of *uncomplicated skin* and *skin structure* infections, oral doses given every 12 hours are sufficient in those aged 5 to 11 years.

Further references.
1. Cuzzolin L, Panos V. Linezolid: a new antibiotic for newborns and children? *J Chemother* 2006; 18: 573–81.
2. Velissariou IM. Use of linezolid in children: an overview of recent advances. *Expert Rev Anti Infect Ther* 2006; 4: 947–52.
3. Chiappini E, *et al.* Clinical efficacy and tolerability of linezolid in pediatric patients: a systematic review. *Clin Ther* 2010; 32: 66–88.

Administration in renal impairment. Linezolid should be used with caution in patients with renal impairment (creatinine clearance less than 30 mL/minute). Although no dosage adjustment is required, licensed product information states that peak plasma concentrations of linezolid's two major metabolites were about tenfold higher in such patients after several days of treatment. As about 30% of a dose is removed during 3 hours of haemodialysis it is recommended that linezolid should be given after dialysis.

Mycobacterial infections. A systematic review[1] noted that linezolid has been used with some success as an adjunct in the treatment of multidrug-resistant tuberculosis (p. 210.2); it has also been tried in nontuberculous mycobacterial infections (p. 194.1). Usual initial doses were 600 mg twice daily. However, serious adverse effects such as peripheral or optic neuropathy (in 11 of 24 patients), and anaemia (10 of 24) occurred. The review concluded that although there was limited evidence suggesting linezolid may be effective as second-line adjunct therapy for patients with mycobacterial infections, its usefulness is limited by the frequent potentially severe complications of prolonged linezolid use.

A subsequent case series[2] reported that treatment with a linezolid-containing regimen (600 mg twice daily) resulted in sputum conversion as well as clinical and radiographical improvement in 7 patients with extensively drug-resistant tuberculosis; the average time to sputum conversion was 53 days. However, 3 patients developed reversible neutropenia, and 2 developed peripheral neuropathy. Lower dose linezolid-containing regimens (600 mg daily) were better tolerated in a retrospective study of 30 patients with multidrug-resistant tuberculosis;[3] adverse effects (such as peripheral and optic neuropathy, anaemia/thrombocytopenia, rash and diarrhoea) occurred in 9 patients but linezolid needed to be stopped in only 3.

1. Nziora F, Falagas ME. Linezolid for the treatment of patients with mycobacterial infections: a systematic review. *Int J Tuberc Lung Dis* 2007; 11: 606–11. Correction. *ibid.*: 936. (title change)
2. Condos R, *et al.* Case series report of a linezolid-containing regimen for extensively drug-resistant tuberculosis. *Chest* 2008; 134: 187–92.
3. Schecter GF, *et al.* Linezolid in the treatment of multidrug-resistant tuberculosis. *Clin Infect Dis* 2010; 50: 49–55.

Adverse Effects and Precautions

The adverse effects most frequently reported in patients given linezolid include diarrhoea, nausea and vomiting, metallic taste, headache, insomnia, constipation, rashes, dizziness, fever, oral and vaginal candidiasis, and abnormal liver function tests. Superficial discoloration of the teeth has occurred in some patients. Lactic acidosis has been reported. Convulsions have also been reported in patients treated with linezolid. In some of these cases, a history of seizures or risk factors for seizures was reported. There have been rare reports of bullous skin eruptions including Stevens-Johnson syndrome. Peripheral and optic neuropathy, sometimes progressing to loss of vision, have occurred rarely, mainly in patients given linezolid for more than 28 days. Visual blurring has been reported in some patients given less than 28 days of treatment.

Reversible myelosuppression including anaemia, leucopenia, pancytopenia and, in particular, thrombocytopenia has been reported and blood counts should be monitored weekly in patients receiving linezolid. Patients particularly at risk are those who have received linezolid for more than 10 to 14 days, who are receiving other bone marrow suppressant drugs, or who have pre-existing myelosuppression or severe renal impairment.

Patients with mixed (Gram-negative and Gram-positive) infections are at a higher risk of mortality when linezolid is given as monotherapy (see Increased Mortality, p. 320.3); linezolid must therefore be used with appropriate antibacterial cover for Gram-negative organisms in such patients.

References.

1. Rubinstein E, *et al.* Worldwide assessment of linezolid's clinical safety and tolerability: comparator-controlled phase III studies. *Antimicrob Agents Chemother* 2003; 47: 1824–31.
2. Bishop E, *et al.* Good clinical outcomes but high rates of adverse reactions during linezolid therapy for serious infections: a proposed protocol for monitoring therapy in complex patients. *Antimicrob Agents Chemother* 2006; 50: 1599–1602.
3. Falagas ME, Vardakas KZ. Benefit-risk assessment of linezolid for serious gram-positive bacterial infections. *Drug Safety* 2008; 31: 753–68.
4. Metaxas EI, Falagas ME. Update on the safety of linezolid. *Expert Opin Drug Safety* 2009; 8: 485–91.
5. Vinh DC, Rubinstein E. Linezolid: a review of safety and tolerability. *J Infect* 2009; 59 (suppl 1): S59–S74.

Effects on the blood. Reversible myelosuppression with red cell hypoplasia occurred in 3 patients treated with linezolid.[1] Features of the myelosuppression were considered by some[1,2] to be similar to those associated with chloramphenicol, although this was disputed by the manufacturers.[3]

There have been reports of thrombocytopenia occurring at a higher incidence than that reported by the manufacturers; in one study,[4] 6 of 19 patients who had been treated with linezolid developed thrombocytopenia, while another[5] found that it occurred in 23 of 48 patients given the drug for more than 5 days.

During the initial 8 months of licensed use in the UK 12 reports of haematopoietic disorders (including thrombocytopenia, anaemia, leucopenia, and pancytopenia) were received by the UK CSM.[6]

Studies have shown that the risk of thrombocytopenia and anaemia is increased in patients on prolonged linezolid therapy with pre-existing myelosuppression[7,8] or severe renal impairment.[9]

1. Green SL, *et al.* Linezolid and reversible myelosuppression. *JAMA* 2001; 285: 1291.
2. Lawyer MC, Lawyer EZ. Linezolid and reversible myelosuppression. *JAMA* 2001; 286: 1974.
3. Arellano FM. Linezolid and reversible myelosuppression. *JAMA* 2001; 286: 1973–4.
4. Attassi K, *et al.* Thrombocytopenia associated with linezolid therapy. *Clin Infect Dis* 2002; 34: 695–8.
5. Orrick JJ, *et al.* Thrombocytopenia secondary to linezolid administration: what is the risk? *Clin Infect Dis* 2002; 35: 348–9.
6. CSM/MCA. Reminder: linezolid (Zyvox) and myelosuppression. *Current Problems* 2001; 27: 14. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON0074566&RevisionSelectionMethod=LatestReleased (accessed 11/01/08)
7. Senneville E, *et al.* Risk factors for anaemia in patients on prolonged linezolid therapy for chronic osteomyelitis: a case-control study. *J Antimicrob Chemother* 2004; 54: 798–802.
8. Grau S, *et al.* Linezolid: low pre-treatment platelet values could increase the risk of thrombocytopenia. *J Antimicrob Chemother* 2005; 56: 440–1.
9. Wu V-C, *et al.* High frequency of linezolid-associated thrombocytopenia and anemia among patients with end-stage renal disease. *Clin Infect Dis* 2006; 42: 66–72.

Effects on the eyes. See under Effects on the Nervous System, p. 320.2.

Effects on mitochondria. Linezolid appears to inhibit mitochondrial protein synthesis when given for prolonged courses. This decreases cellular energy production in tissues that are highly dependent on oxidative phosphorylation, such as the optic nerve, skeletal muscles, liver, and kidneys, leading to adverse effects such as lactic acidosis[1] or hyperlactataemia,[1,2] rhabdomyolysis,[3] and optic[4] and/or peripheral neuropathy[1] (see also p. 320.2). Encephalopathy, lactic acidosis, optic neuropathy, skeletal myopathy, and renal failure were reported[1] in a 63-year-old woman after a 4-month course of linezolid. The symptoms resolved when linezolid was stopped; however, the patient remained blind and disorientated. In contrast, bilateral mitochondrial optic neuropathy seen[4] in a 6-year-old boy after a 1-year course of oral linezolid resolved 3 months after linezolid treatment was stopped. In another study[2] reversible hyperlactataemia was reported in 5 patients given linezolid for 1 to 3 months. Mitochondrial activity and lactic acid levels returned to normal when linezolid therapy was stopped.

1. De Vriese AS, *et al.* Linezolid-induced inhibition of mitochondrial protein synthesis. *Clin Infect Dis* 2006; 42: 1111–1117.
2. Garrabou G, *et al.* Reversible inhibition of mitochondrial protein synthesis during linezolid-related hyperlactatemia. *Antimicrob Agents Chemother* 2007; 51: 962–7.
3. Carroll MW, *et al.* Rhabdomyolysis in a patient treated with linezolid for extensively drug-resistant tuberculosis. *Clin Infect Dis* 2012; 54: 1624–7.
4. Javaheri M, *et al.* Linezolid-induced optic neuropathy: a mitochondrial disorder? *Br J Ophthalmol* 2007; 91: 111–15. Correction. *ibid.*; 403.

Effects on the nervous system. The Australian Adverse Drug Reactions Advisory Committee[1] stated in February 2003 that it had received 4 reports of *peripheral neuropathy* in patients who had taken linezolid for 6 to 9 months; none of these cases had resolved at the time of the report. They suggested that the risk of peripheral neuropathy should be considered when treatment was extended beyond 28 days. There have been several published reports of peripheral and *optic neuropathy* associated with linezolid,[2-9] with some attributing these effects to the inhibition of mitochondrial protein synthesis by linezolid. For further discussion see Effects on Mitochondria, above. The regulatory authority in the UK has warned that patients should be advised to report any symptoms of visual impairment immediately, including changes in visual acuity or colour vision, blurred vision, or visual field defects.[10] Any linezolid-treated patient with new visual symptoms should be evaluated promptly and referred to an ophthalmologist if necessary; regular monitoring is advised in all patients who may require treatment for more than 28 days.

In one case report, deterioration of *seizure* control occurred in an epileptic woman treated with linezolid, leading to complex partial status epilepticus. A subsequent rechallenge also led to more prolonged and frequent seizures. The authors suggest that linezolid should be used with caution in patients with a history of epilepsy.[11]

1. Adverse Drug Reactions Advisory Committee (ADRAC). Linezolid and peripheral neuropathy. *Aust Adverse Drug React Bull* 2003; 22: 3. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0302.htm (accessed 11/01/08)
2. Corallo CE, Paull AE. Linezolid-induced neuropathy. *Med J Aust* 2002; 177: 332.
3. Rho JP, *et al.* Linezolid-associated peripheral neuropathy. *Mayo Clin Proc* 2004; 79: 927–30.
4. Lee E, *et al.* Linezolid-associated toxic optic neuropathy: a report of 2 cases. *Clin Infect Dis* 2003; 37: 1389–91.
5. Bressler AM, *et al.* Peripheral neuropathy associated with prolonged use of linezolid. *Lancet Infect Dis* 2004; 4: 528–31.
6. Health Canada. Linezolid (Zyvoxam) and neuropathy. *Can Adverse React News* 2005; 15 (1): 2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v15neng.pdf (accessed 24/07/09)
7. Zivkovic SA, Lacomis D. Severe sensory neuropathy associated with long-term linezolid use. *Neurology* 2005; 64: 926–7.
8. Legout L, *et al.* Linezolid-induced neuropathy. *Clin Infect Dis* 2004; 38: 767–8.
9. Rucker JC, *et al.* Linezolid-associated toxic optic neuropathy. *Neurology* 2006; 66: 595–8.
10. CHM/MHRA. Linezolid (Zyvox): severe optic neuropathy. *Current Problems* 2006; 31: 2–3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023860&RevisionSelectionMethod=LatestReleased (accessed 11/01/08)
11. Shneker BF, *et al.* Linezolid inducing complex partial status epilepticus in a patient with epilepsy. *Neurology* 2009; 72: 378–9.

Increased mortality. In March 2007, the FDA[1] issued an alert advising that an open-label, randomised study comparing linezolid to vancomycin, oxacillin, or dicloxacillin in the treatment of seriously ill patients with intravascular catheter-related bloodstream infections, including catheter-site infections, had found that death rates were significantly higher in patients treated with linezolid (78 of 363) than in the comparator arm (58 of 363), particularly in those with Gram-negative or mixed infections. Mortality did not differ for patients with purely Gram-positive infections.

The FDA[1] and the UK manufacturer[2] therefore advised that linezolid should not be used in infections caused by Gram-negative bacteria and should only be used in mixed Gram-positive and Gram-negative infections when appropriate cover for Gram-negative organisms is given at the same time. Licensed product information now reflects these warnings.

1. FDA. Information for healthcare professionals: linezolid (marketed as Zyvox) (issued 16th March 2007). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/linezolidHCP.pdf (accessed 11/01/08)
2. Pfizer, UK. Important safety information (issued 28th February, 2007). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=con2030646&RevisionSelectionMethod=Latest (accessed 11/01/08)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies linezolid as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

Linezolid is a reversible, nonselective MAOI and therefore has the potential to interact with adrenergic and serotonergic drugs. Enhanced pressor activity has been reported in patients receiving linezolid with phenylpropanolamine or pseudoephedrine and initial doses of dopamine or adrenaline should be reduced. There have also been cases of serotonin syndrome when linezolid was taken with serotonin reuptake inhibitors, and similar symptoms when it was taken with dextromethorphan. The interactions of conventional MAOIs, both with other drugs and with foods, are described under Phenelzine, p. 446.3 and p. 447.1.

The peak plasma concentration and AUC of linezolid were decreased by about 20 and 30% respectively in healthy subjects given concomitant rifampicin, possibly due to the induction of hepatic enzymes; other strong inducers of hepatic enzymes may therefore also cause decreases in linezolid exposure.

Antidepressants. Serotonin syndrome has been reported in patients taking linezolid with serotonergic antidepressants such as *venlafaxine* (see p. 458.3) and *SSRIs* (though concomitant use may be possible, see p. 426.1).

Opioid analgesics. For a report of an interaction between linezolid and *pethidine*, attributed to linezolid's inhibitory actions on monoamine oxidase, see p. 123.2.

Antimicrobial Action

Linezolid is an oxazolidinone antibacterial with activity against a range of aerobic Gram-positive bacteria including vancomycin-resistant enterococci and meticillin-resistant *Staphylococcus aureus*. It is less active against Gram-negative bacteria, but has some *in-vitro* activity against *Haemophilus influenzae*, *Legionella* spp., *Moraxella catarrhalis* (*Branhamella catarrhalis*), *Neisseria gonorrhoeae*, and *Pasteurella* spp. It is not active against *Acinetobacter* spp., Enterobacteriaceae, or *Pseudomonas* spp.

Oxazolidinone antibacterials are bacteriostatic and act by inhibition of ribosomal protein synthesis. Cross-resistance between oxazolidinones and other classes of antibacterial is considered unlikely.

Resistant strains of enterococci and meticillin-resistant *Staph. aureus* have been reported.

References.
1. Noskin GA, *et al.* In vitro activities of linezolid against important Gram-positive bacterial pathogens including vancomycin-resistant enterococci. *Antimicrob Agents Chemother* 1999; **43**: 2059–62.
2. Cercenado E, *et al.* In vitro activity of linezolid against multiply resistant Gram-positive clinical isolates. *J Antimicrob Chemother* 2001; **47**: 77–81.
3. Gemmell CG. Susceptibility of a variety of clinical isolates to linezolid: a European inter-country comparison. *J Antimicrob Chemother* 2001; **48**: 47–52.
4. Livermore DM. Linezolid in vitro: mechanism and antibacterial spectrum. *J Antimicrob Chemother* 2003; **51** (suppl S2): ii9–ii16.
5. Jones RN, *et al.* Activity of linezolid against 3,251 strains of uncommonly isolated Gram-positive organisms: report from the SENTRY Antimicrobial Surveillance Program. *Antimicrob Agents Chemother* 2007; **51**: 1491–3.

Resistance. There have been reports of linezolid resistance in enterococci, involving both *Enterococcus faecium*[1–4] and *E. faecalis*.[2] There is also concern over the emergence of linezolid resistance in staphylococci, such as meticillin-resistant *Staphylococcus aureus*,[5–7] *Staph. auricularis*,[8] and *Staph. epidermidis*.[8,9] A survey[10] of reported resistance to linezolid in the USA found that it was still rare but was no longer limited to enterococci having also occurred in *Staph. epidermidis* and *Streptococcus oralis*.

1. Gonzales RD, *et al.* Infections due to vancomycin-resistant Enterococcus faecium resistant to linezolid. *Lancet* 2001; **357**: 1179.
2. Auckland C, *et al.* Linezolid-resistant enterococci: report of the first isolates in the United Kingdom. *J Antimicrob Chemother* 2002; **50**: 743–6.
3. Herrero IA, *et al.* Nosocomial spread of linezolid-resistant, vancomycin-resistant Enterococcus faecium. *N Engl J Med* 2002; **346**: 867–9.
4. Seedat J, *et al.* Rapid emergence of resistance to linezolid during linezolid therapy of an Enterococcus faecium infection. *Antimicrob Agents Chemother* 2006; **50**: 4217–19.
5. Tsiodras S, *et al.* Linezolid resistance in a clinical isolate of Staphylococcus aureus. *Lancet* 2001; **358**: 207–8.
6. Wilson P, *et al.* Linezolid resistance in clinical isolates of Staphylococcus aureus. *J Antimicrob Chemother* 2003; **51**: 186–8.
7. Morales G, *et al.* Resistance to linezolid is mediated by the cfr gene in the first report of an outbreak of linezolid-resistant *Staphylococcus aureus*. *Clin Infect Dis* 2010; **50**: 821–5.
8. Cieloszyk K, *et al.* Linezolid resistance in three isolates of coagulase-negative staphylococci. *Ann Pharmacother* 2007; **41**: 526–7.
9. Kelly S, *et al.* Linezolid resistance in coagulase-negative staphylococci. *J Antimicrob Chemother* 2006; **58**: 898–9.
10. Mutnick AH, *et al.* Linezolid resistance since 2001: SENTRY Antimicrobial Surveillance Program. *Ann Pharmacother* 2003; **37**: 769–74.

Pharmacokinetics

Linezolid is rapidly and extensively absorbed after oral doses and peak plasma concentrations occur after 1 to 2 hours. It is about 31% bound to plasma proteins. Linezolid is reported to be distributed into bone, fat, lungs, muscle, skin blister fluids, and into the CSF. It is metabolised mainly by oxidation to 2 main inactive metabolites, the hydroxyethyl glycine metabolite (PNU-142586) and the aminoethoxyacetic acid metabolite (PNU-142300); other minor inactive metabolites have also been identified. About 40% of a dose is excreted in the urine as PNU-142586, 30% as linezolid, and 10% as PNU-142300. Small amounts of metabolites are excreted in the faeces. The elimination half-life of linezolid is about 5 to 7 hours.

Children exhibit more rapid clearance of linezolid than adults; half-life is reported to range from about 2 to 4 hours, increasing with age.

References.
1. MacGowan AP. Pharmacokinetic and pharmacodynamic profile of linezolid in healthy volunteers and patients with Gram-positive infections. *J Antimicrob Chemother* 2003; **51** (suppl S2): ii17–ii25.
2. Stalker DJ, Jungbluth GL. Clinical pharmacokinetics of linezolid, a novel oxazolidinone antibacterial. *Clin Pharmacokinet* 2003; **42**: 1129–40.
3. Whitehouse T, *et al.* Pharmacokinetic studies of linezolid and teicoplanin in the critically ill. *J Antimicrob Chemother* 2003; **53**: 333–40.
4. Vardakas KZ, *et al.* Association of pharmacokinetic and pharmacodynamic aspects of linezolid with infection outcome. *Curr Drug Metab* 2009; **10**: 2–12.
5. Santos RP, *et al.* Pharmacokinetics and pharmacodynamics of linezolid in children with cystic fibrosis. *Pediatr Pulmonol* 2009; **44**: 148–54.
6. Abe S, *et al.* Population pharmacokinetic analysis of linezolid in patients with infectious disease: application to lower body weight and elderly patients. *J Clin Pharmacol* 2009; **49**: 1071–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Litrecan; Zyvox; *Austral.*: Zyvox; *Austria*: Zyvoxid; *Belg.*: Zyvoxid; *Braz.*: Zyvox; *Canad.*: Zyvoxam; *Chile*: Zyvox; *China*: Zyvox; *Cz.*: Zyvoxid; *Denm.*: Zyvoxid; *Fin.*: Zyvoxid; *Fr.*: Zyvoxid; *Ger.*: Zyvoxid; *Gr.*: Anti-zolid; Zyvoxid; *Hong Kong*: Zyvox; *India*: Alzolid; Anzolid; Infulid; Limet; Linid; Linoplus; Linosept; Linospan; Linox; Lintran; Linzid; Lizbid; Lizemox; Lizoforce; Lizolid; Lizomed; *Indon.*: Zyvox; *Irl.*: Zyvox; *Israel*: Zyvoxid; *Ital.*: Zyvoxid; *Malaysia*: Zyvox; *Mex.*: Zyvoxam; *Neth.*: Zyvoxid; *Norw.*: Zyvoxid; *NZ*: Zyvox; *Philipp.*: Zyvox; *Pol.*: Zyvoxid; *Port.*: Zyvoxid; *Rus.*: Zyvox (Зивокс); *S.Afr.*: Zyvoxid; *Singapore*: Zyvox; *Spain*: Zyvoxid; *Swed.*: Zyvoxid; *Switz.*: Zyvoxid; *Thai.*: Zyvox; *Turk.*: Linoxid; Zizolid; Zyvoxid; *UK*: Zyvox; *Ukr.*: Zyvox (Зивокс); *USA*: Zyvox; *Venez.*: Zyvox.

Lomefloxacin Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de lomefloxacino; Lomefloksasiinihydrokloridi; Lomefloksasin Hidroklorür; Lométloxacine, Chlorhydrate de; Lomefloxacinhydroklorid; Lomefloxacini Hydrochloridum; Lomefloxacino, hidrocloruro de; NY-198; SC-47111; SC-47111A (lomefloxacin); Ломефлоксацина Гидрохлорид.

(*RS*)-1-Ethyl-6,8-difluoro-1,4-dihydro-7-(3-methylpiperazin-1-yl)-4-oxoquinoline-3-carboxylic acid hydrochloride.

$C_{17}H_{19}F_2N_3O_3$,HCl=387.8

CAS — 98079-51-7 (lomefloxacin); 98079-52-8 (lomefloxacin hydrochloride).

ATC — J01MA07; S01AE04.

ATC Vet — QJ01MA07; QS01AE04.

UNII — 9VC7S3ZXX8.

Uses and Administration

Lomefloxacin is a fluoroquinolone antibacterial with actions and uses similar to those of ciprofloxacin (p. 261.2).

It is given orally for the treatment of susceptible infections, including bronchitis due to *Haemophilus influenzae* or *Moraxella catarrhalis* (*Branhamella catarrhalis*), and urinary-tract infections. It is also used for surgical infection prophylaxis. Lomefloxacin is given as the hydrochloride but doses are expressed in terms of the base; lomefloxacin hydrochloride 441.5 mg is equivalent to about 400 mg of lomefloxacin. Dosage in the evening may minimise the risk of phototoxic reactions.

The usual dose is 400 mg once daily for 10 to 14 days. A dose of 400 mg once daily for 3 days is suitable in women with acute uncomplicated cystitis. For details of reduced doses in renal impairment, see p. 321.2.

For surgical infection prophylaxis a single 400-mg dose is given 1 to 6 hours before the procedure.

Lomefloxacin is also used topically as the hydrochloride in eye drops and ear drops containing the equivalent of 0.3% of lomefloxacin for the treatment of bacterial conjunctivitis and for the treatment of otitis externa and otitis media, respectively.

General references.
1. Wadworth AN, Goa KL. Lomefloxacin: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1991; **42**: 1018–60.
2. Neu HC, ed. Lomefloxacin: development of a once-a-day quinolone. *Am J Med* 1992; **92** (suppl 4A): 1S–137S.

Administration in renal impairment. Oral doses of lomefloxacin should be reduced in patients with renal impairment; the initial dose of 400 mg should be followed by maintenance doses of 200 mg daily in those with a creatinine clearance of 10 to 40 mL/minute per 1.73 m^2 and in those on haemodialysis.

Adverse Effects and Precautions

As for Ciprofloxacin, p. 262.2.

A relatively high incidence of phototoxic reactions has been seen in patients taking lomefloxacin. Patients should be advised to avoid exposure to sunlight during, and for a few days after, lomefloxacin therapy, and to stop the drug immediately if phototoxicity occurs. Risk of phototoxicity may be reduced by taking lomefloxacin in the evening.

Effects on the skin. Lomefloxacin has been associated with a higher incidence of phototoxic reactions, particularly in patients over 60 years of age and/or with a history of fluoroquinolone treatment; the incidence was also high when used for 30 days or longer.[1] *In-vitro* results[2] suggest that use of sunscreens to protect against lomefloxacin-induced phototoxicity may be feasible.

1. Arata J, *et al.* Photosensitivity reactions caused by lomefloxacin hydrochloride: a multicenter survey. *Antimicrob Agents Chemother* 1998; **42**: 3141–5.
2. Reinhardt P, *et al.* Broad-spectrum sunscreens prevent the secretion of proinflammatory cytokines in human keratinocytes exposed to ultraviolet A and phototoxic lomefloxacin. *Can J Physiol Pharmacol* 2006; **84**: 221–6.

Interactions

As for Ciprofloxacin, p. 264.3.

Lomefloxacin does not appear to interact significantly with theophylline or caffeine.

Antimicrobial Action

As for Ciprofloxacin, p. 265.2.

Most streptococci, including *Streptococcus pneumoniae*, are relatively resistant to lomefloxacin.

Pharmacokinetics

Lomefloxacin is rapidly and almost completely absorbed after oral doses and peak plasma concentrations of about 3 micrograms/mL occur about 1.5 hours after a 400-mg dose. Lomefloxacin is about 10% bound to plasma proteins. It is widely distributed into body tissues including the lungs and prostate.

The elimination half-life of lomefloxacin is about 7 to 8 hours, and is prolonged in patients with renal impairment. Lomefloxacin is excreted in the urine, about 65% as unchanged drug, 9% as the glucuronide, and less than 0.5% as other metabolites. Small amounts (about 10%) are also eliminated unchanged in the faeces. Negligible amounts of lomefloxacin are removed by haemodialysis or peritoneal dialysis.

References.
1. Freeman CD, *et al.* Lomefloxacin clinical pharmacokinetics. *Clin Pharmacokinet* 1993; **25**: 6–19.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Okacin; *Austria*: Okacin; Uniquin†; *Belg.*: Okacin†; *Braz.*: Maxaquin; *China*: Ai Bang (爱邦); Ao Mei Xin (奥每欣); Bai De (百德); Bai Ye Xing (百夜星); Bei Luo Te (贝洛特); Duo Long (多龙); Fu Yue (孚悦); Ge Tai (哥台); Ji Ping (吉平); Keqi (科奇); KuiTai (喹泰); Le Bei Xin (乐贝新); Lefen (乐芬); Long Hua Su (龙化素); Luo Wei (洛威); Nuo Ling Dun (诺灵盾); Qi Mi Gao (奇米高); Qian Di (迁迪); Qiluoxian (奇洛先); Qing Xing (庆兴); Shajunda (沙君达); Wanfuluo (万夫洛); Wei Pu (维普); Xin Li Wei (欣立威); Xingfuxin (兴福欣); Yi Lin (逸林); Yi Lu (益禄); Zhong Bao Luo Tai (中宝洛泰); Zhuo Yue (卓悦); *Cz.*: Okacin†; *Fr.*: Decalogiflox; Logiflox; *Ger.*: Okacin†; *Gr.*: Okacin; *Hong Kong*: Lomeflox; Maxaquin; Okacin; *Hung.*: Okacin†; *India*: Floxaday; Foxil; Gynalom; Lomaday; Lomedon; Lomef; Lomewon; Lomexel; Lomflox; Lomibact; Lomitas; Loxipen; Mahaquin; Okacin; Ontop†; *Israel*: Okacin†; *Ital.*: Chimono; Lomebact; Maxaquin; Okacin; Uniquin; *Jpn*: Bareon; Lomeflon; *Mex.*: Lomacin; Maxaquin; *Philipp.*: Okacin; *Pol.*: Okacin†; *Port.*: Loransil; Maxaquin; Okacin; Uniquin†; *Rus.*: Ksenakvin (Ксенаквин); Lofox (Лофокс); Lomacin (Ломацин); Lomflox (Ломфлокс); Okacin (Окацин)†; *S.Afr.*: Maxaquin†; Okacyn†; Uniquin†; *Singapore*: Lomflox; Okacin; *Spain*: Ocacin†; *Switz.*: Maxaquin†; Okacin†; *Thai.*: Okacin†; *Turk.*: Qkacin; *UAE*: Lomax; *Ukr.*: Ksenakvin (Ксенаквин)†; Lomaday (Ломадей)†; Okacin (Окацин)†; *USA*: Maxaquin†; *Venez.*: Loflox; Lomex; Maxaquin; Okacin.

Multi-ingredient Preparations. *Rus.*: Combitub-Neo (Комбитуб-Нео); Lomecomb (Ломекомб); Protiocomb (Протиокомб); Protub-5 (Протуб-5); Protub-Lome (Протуб-Ломе).

Loracarbef *(BAN, USAN, rINN)*

KT-3777; Loracarbefum; Lorakarbef; Lorakarbefi; LY-163892; Лоракарбеф.

(6*R*,7*S*)-3-Chloro-8-oxo-7-(2-phenylglycylamino)-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid monohydrate.

$C_{16}H_{16}ClN_3O_4.H_2O$=367.8

CAS — 76470-66-1 (anhydrous loracarbef); 121961-22-6 (loracarbef monohydrate).

ATC — J01DC08.

ATC Vet — QJ01DC08.

UNII — 3X11EVM5SU (loracarbef); W72I5ZT78Z (anhydrous loracarbef).

Pharmacopoeias. In *US*.

USP 36: (Loracarbef). pH of a 10% suspension in water is between 3.0 and 5.5. Store in airtight containers.

Uses and Administration

Loracarbef is an oral carbacephem antibacterial. The carbacephems are closely related to the cephalosporins, but replacement of the sulfur atom in the 7-aminocephalosporanic acid nucleus by a methylene group is said to enhance stability. It is used similarly to cefaclor in the treatment of infections due to susceptible Gram-positive and Gram-negative bacteria including infections of the respiratory and urinary tracts and of skin and skin-structures. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Loracarbef should be given 1 hour before food or on an empty stomach. Loracarbef is given as the monohydrate. Doses are expressed in terms of the equivalent amount of anhydrous loracarbef. The usual adult dose is 200 to 400 mg every 12 hours. In uncomplicated urinary-tract infections, a dose of 200 mg daily may be adequate.

The dose of loracarbef may need to be reduced in renal impairment, see p. 322.1. For details of doses in children, see also p. 322.1.

General references.
1. Moellering RC, Jacobs NF. Advances in outpatient antimicrobial therapy: loracarbef. *Am J Med* 1992; **92** (suppl 6A): 1S–103S.
2. Brogden RN, McTavish D. Loracarbef: a review of its antimicrobial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1993; **45**: 716–36.
3. Roos K, Larsson P. Loracarbef versus phenoxymethylpenicillin in the treatment of recurrent streptococcal pharyngotonsillitis. *Scand J Infect Dis* 1997; **29**: 141–5.
4. Gooch WM, *et al.* Loracarbef versus clarithromycin in children with acute otitis media with effusion. *Clin Ther* 1999; **21**: 711–22.

Administration in children. Loracarbef may be given orally to children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria. A usual dose for children weighing 7 kg or more is 7.5 mg/kg every 12 hours for uncomplicated infections or 15 mg/kg every 12 hours for acute otitis media or acute maxillary sinusitis.

Administration in renal impairment. Oral doses of loracarbef should be reduced in patients with renal impairment; patients with a creatinine clearance of 10 to 49 mL/minute may be given half the usual dose at the usual dosage interval or the full usual dose at twice the usual interval; patients with a creatinine clearance of less than 10 mL/minute may be treated with the usual dose given every 3 to 5 days. Patients on haemodialysis should receive another dose following dialysis.

Adverse Effects and Precautions

Adverse effects of loracarbef are generally similar to those of other beta lactams (see Benzylpenicillin, p. 229.2, and Cefalotin, p. 235.2). They include gastrointestinal disturbances, particularly diarrhoea, and hypersensitivity reactions such as skin rashes. Increases in liver enzymes and abnormalities in haematological parameters have been reported.

Loracarbef should not be given to patients known to be hypersensitive to it or to other beta lactams because of the possibility of cross-sensitivity. It should be given with caution, with appropriate dosage reduction, in patients with renal impairment.

Effects on the kidneys. References.

1. Thieme RE, *et al.* Acute interstitial nephritis associated with loracarbef therapy. *J Pediatr* 1995; **127**: 997–1000.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies loracarbef as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/09/11)

Interactions

Probenecid decreases the renal excretion of loracarbef thereby increasing its plasma concentrations.

Antimicrobial Action

Loracarbef is bactericidal with antibacterial activity similar to that of cefaclor (p. 233.1).

Pharmacokinetics

Loracarbef is well absorbed from the gastrointestinal tract with a bioavailability of 90%. Peak plasma concentrations after 200- and 400-mg doses as capsules are about 8 and 14 micrograms/mL respectively at 1.2 hours. Peak concentrations occur more rapidly after an oral suspension and a paediatric dose of 15 mg/kg produces a concentration of about 19 micrograms/mL within 40 to 60 minutes. Absorption is delayed by the presence of food. A plasma half-life of about 1 hour has been reported which is prolonged in renal impairment. About 25% is bound to plasma proteins.

Loracarbef is excreted largely unchanged in the urine, and therapeutic concentrations are maintained in the urine for up to 12 hours. Probenecid delays excretion. Loracarbef is removed by haemodialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Lorafem†; *Gr.*: Lorbet; *S. Afr.*: Lorabid; *Swed.*: Lorabid†; *Turk.*: Lorabid.

Pharmacopoeial Preparations
USP 36: Loracarbef Capsules; Loracarbef for Oral Suspension.

Lymecycline *(BAN, rINN)*

Limeciclina; Limeciklin; Limesiklin; Lymecyclin; Lymécycline; Lymecyclinum; Lymecyklin; Lymecyklina; Lymesyklilni; Tetracyclinemethylene lysine; Лимециклин.

(+)-*N*-(5-Amino-5-carboxypentylaminomethyl)-4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxonapthacene-2-carboxamide; N^2-[[(+)-5-Amino-5-carboxypentylamino]methyl]tetracycline.

$C_{29}H_{38}N_4O_{10}$=602.6

CAS — 992-21-2.

ATC — J01AA04.

ATC Vet — QJ01AA04.

UNII — 7D6EM3S13P.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Lymecycline). A reaction product of formaldehyde, lysine, and tetracycline. A yellow, hygroscopic powder. Very soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane. A 1% solution in water has a pH of 7.8 to 8.2. Store in airtight containers. Protect from light.

Profile

Lymecycline is a tetracycline derivative with general properties similar to those of tetracycline (p. 375.1). Although its absorption is not significantly affected by moderate amounts of milk, it is still affected by divalent and trivalent cations such as aluminium, bismuth, calcium, iron, magnesium, and zinc.

Lymecycline is given orally and doses are expressed in terms of the equivalent amount of tetracycline base. Lymecycline 407 mg is equivalent to about 300 mg of tetracycline and to about 325 mg of tetracycline hydrochloride. The usual adult dose is the equivalent of 300 mg of tetracycline base twice daily. In severe infections total daily doses of up to the equivalent of 1.2 g may be given. In the treatment of acne, the equivalent of 300 mg is given daily for at least 8 weeks.

For details of use in children and adolescents, see p. 322.2.

Administration in children. In children, the effects on teeth should be considered and tetracyclines only used when absolutely essential. In the UK, lymecycline is licensed for use in children aged 12 years and over; the usual oral adult dose (see above) may be given. However, in some countries, it is licensed for use in those over 8 years old.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies lymecycline as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 15/08/11)

Skin disorders. For reference to the use of lymecycline in the treatment of acne, see under Tetracycline, p. 376.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Eficiclina; Tetralysal; *Belg.*: Tetralysal; *Braz.*: Tetralysal; *Chile*: Tetralysal; *Denm.*: Tetralysal; *Fin.*: Tetralysal; *Fr.*: Tetralysal; *Hong Kong*: Tetralysal; *Hung.*: Tetralysal; *Irl.*: Tetralysal; *Ital.*: Tetralysal; *Mex.*: Tetralisal; *Norw.*: Tetralysal; *NZ*: Tetralysal; *Philipp.*: Tetralysal; *S.Afr.*: Tetralysal; *Swed.*: Tetralysal; *Switz.*: Tetralysal; *UK*: Tetralysal; *Venez.*: Tetralysal.

Pharmacopoeial Preparations
BP 2014: Lymecycline Capsules.

Mafenide *(BAN, USAN, rINN)*

Mafenid; Mafenida; Maféníde; Mafenidi; Mafenidum; NSC-34632; Мафенид.

α-Aminotoluene-*p*-sulphonamide.

CAS — 138-39-6.

ATC — D06BA03.

ATC Vet — QD06BA03.

UNII — 58447S8P4L.

Mafenide Acetate *(BANM, rINNM)*

Acetato de mafenida; Mafenida, acetato de; Maféníde, Acétate de; Mafenidi Acetas; Мафенида Ацетат.

$C_7H_{10}N_2O_2S,C_2H_4O_2$=246.3

CAS — 13009-99-9.

ATC — D06BA03.

ATC Vet — QD06BA03.

UNII — RQ6LP6Z0WY.

Pharmacopoeias. In *Chin.* and *US.*

USP 36: (Mafenide Acetate). A white to pale yellow crystalline powder. Freely soluble in water. pH of a 10% solution in water is between 6.4 and 6.8. Store in airtight containers. Protect from light.

Uses and Administration

Mafenide is a short-acting sulfonamide that is not inactivated by *p*-aminobenzoic acid or by pus and serum. The acetate is used as a cream, containing the equivalent of mafenide 8.5%, for the prevention and treatment of infection, including *Pseudomonas aeruginosa*, in second- and third-degree burns (p. 1683.1). A solution containing mafenide acetate 5% is also available for use under moist dressings in burns. Mafenide hydrochloride and mafenide propionate have also been used.

Adverse Effects, Treatment, and Precautions

Mafenide is absorbed to some extent after topical application and may produce systemic effects similar to those of other sulfonamides (see Sulfamethoxazole, p. 367.3). Fatal haemolytic anaemia with disseminated intravascular coagulation, related to G6PD deficiency, has been reported.

Mafenide cream may cause pain or a burning sensation on application to the burnt area, with occasional bleeding or excoriation. The separation of the eschar may be delayed and fungal invasion of the wound has been reported. By its action in inhibiting carbonic anhydrase, mafenide may cause metabolic acidosis and hyperventilation; acid–base balance should therefore be monitored, particularly in patients with extensive burns, or with pulmonary or renal impairment. If persistent acidosis occurs, mafenide treatment should be temporarily suspended and fluid therapy continued.

Hypersensitivity. References.

1. Firoz EF, *et al.* Allergic contact dermatitis to mafenide acetate: a case series and review of the literature. *J Drugs Dermatol* 2007; **6**: 825–8.

Pharmacokinetics

Mafenide is absorbed from wounds into the circulation and is metabolised to *p*-carboxybenzenesulfonamide, which is excreted in the urine. The metabolite has no antibacterial action but retains the ability to inhibit carbonic anhydrase.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Sulfamylon.

Multi-ingredient Preparations. *Indon.*: FG Ointment†.

Pharmacopoeial Preparations
USP 36: Mafenide Acetate Cream; Mafenide Acetate for Topical Solution.

Magainins

Magaininas; Магаинины.

Profile

The magainins are a group of antibacterial peptides derived from amphibians. Several semisynthetic derivatives including pexiganan acetate (MSI-78), MSI-93, and MSI-94 have been investigated as topical anti-infectives.

References.

1. Lamb HM, Wiseman LR. Pexiganan acetate. *Drugs* 1998; **56**: 1047–52.
2. Rao N, Lipsky BA. Optimising antimicrobial therapy in diabetic foot infections. *Drugs* 2007; **67**: 195–214.
3. Andrès E, Dimarcq JL. Peptides antimicrobiens cationiques: de l'étude de l'immunité innée à la production de médicaments. Mise à jour. *Med Mal Infect* 2007; **37**: 194–9.
4. Lipsky BA, *et al.* Topical versus systemic antimicrobial therapy for treating mildly infected diabetic foot ulcers: a randomized, controlled, double-blinded, multicenter trial of pexiganan cream. *Clin Infect Dis* 2008; **47**: 1537–45.

Mandelic Acid

Ácido fenilglicólico; Ácido mandélico racémico; Amygdalic Acid; Mandélico, ácido; Phenylglycolic Acid; Racemic Mandelic Acid; Миндальная Кислота.

2-Hydroxy-2-phenylacetic acid.

$C_8H_8O_3$=152.1

CAS — 90-64-2; 17199-29-0 ((+)-mandelic acid); 611-71-2 ((-)-mandelic acid); 611-72-3 ((±)-mandelic acid).

ATC — B05CA06; J01XX06.

ATC Vet — QB05CA06; QJ01XX06.

UNII — NH496X0UJX.

Profile

Mandelic acid has bacteriostatic properties and is used as a 1% flushing solution for the maintenance of indwelling urinary catheters. Mandelic acid and acetyl mandelic acid are used topically in preparations for the treatment of acne. It was formerly given orally in the treatment of urinary-tract infections, usually as the ammonium or calcium salt.

Mandelic acid is a component of methenamine mandelate (p. 325.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Rolip.

Multi-ingredient Preparations. *Chile*: NeoStrata; *Fr.*: Zeniac LP Fort; Zeniac LP; Zeniac; Zeniac; *Ital.*: Neoceuticals Clear Skin†; Neoceuticals Spot Treatment†.

Marbofloxacin *(BAN, rINN)*

Marbofloksasiini; Marbofloxacine; Marbofloxacino; Marbofloxacinum; Марбофлоксацин.

9-Fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7*H*-pyrido[3,2,1-*ij*][4,1,2]benzoxadiazine-6-carboxylic acid.

$C_{17}H_{19}FN_4O_4$=362.4

CAS — 115550-35-1.

ATC Vet — QJ01MA93.

UNII — 8X09WU898T.

Pharmacopoeias. In *Eur.* (see p. vii) for veterinary use only.

Ph. Eur. 8: (Marbofloxacin for Veterinary Use). A light yellow, crystalline powder. Slightly soluble in water; very slightly soluble in alcohol; sparingly soluble or slightly soluble in dichloromethane. Protect from light.

Profile

Marbofloxacin is a fluoroquinolone antibacterial used in veterinary medicine.

Mecillinam *(BAN, rINN)*

Amdinocillin (USAN); FL-1060; Mecilinam; Mécillinam; Mecillinamum; Mesillinaami; Ro-10-9070; Мециллинам.

(6*R*)-6-(Perhydroazepin-1-ylmethyleneamino)penicillanic acid.

$C_{15}H_{23}N_3O_3S$=325.4

CAS — 32887-01-7.

ATC — J01CA11.

ATC Vet — QJ01CA11.

UNII — V10579P3QZ.

Uses and Administration

Mecillinam is a semisynthetic penicillin with a substituted amidino group at the 6-position of the penicillanic acid nucleus. It is given by slow intravenous injection, by intravenous infusion, or intramuscularly, in the treatment of susceptible Gram-negative infections (see under Antimicrobial Action, p. 323.1).

For urinary-tract infections a dose of 800 mg is given every 6 to 8 hours. A total dose of up to 60 mg/kg daily may be used in very severe infections.

Mecillinam has been used with other beta lactams to extend the spectrum of antimicrobial activity to Gram-positive organisms and because of reported synergism against Gram-negative bacteria *in vitro*.

The pivaloyloxymethyl ester of mecillinam, pivmecillinam, is used orally (see p. 344.2).

Adverse Effects and Precautions

As for Benzylpenicillin, p. 229.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mecillinam as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Interactions

As for Benzylpenicillin, p. 230.1.

Antimicrobial Action

Mecillinam is a derivative of amidinopenicillanic acid. Unlike benzylpenicillin and related antibacterials, it is active against many Gram-negative bacteria.

- Sensitive organisms include Enterobacteriaceae such as *Escherichia coli, Enterobacter, Klebsiella, Salmonella,* and *Shigella* spp. The susceptibility of *Proteus* spp. varies; *Serratia marcescens* is generally resistant.
- It is less active against *Neisseria* spp. and *Haemophilus influenzae*. *Pseudomonas aeruginosa* and *Bacteroides* spp. are considered to be resistant.
- It is much less active against Gram-positive bacteria; enterococci including *Enterococcus faecalis* are resistant.

Mecillinam interferes with the synthesis of the bacterial cell wall by binding with a different penicillin-binding protein from benzylpenicillin. This difference in mode of action may explain the synergism against many Gram-negative organisms that has been reported *in vitro* between mecillinam and various penicillins or cephalosporins.

Mecillinam is inactivated by beta-lactamases, but is more stable than ampicillin.

Pharmacokinetics

Mecillinam is poorly absorbed from the gastrointestinal tract. Peak plasma concentrations of about 6 and 12 micrograms/mL have been achieved half an hour after intramuscular doses of 200 and 400 mg, respectively. The usual plasma half-life of about 1 hour has been reported to be prolonged to 3 to 5 hours or more in severe renal impairment. Between 5 and 10% of mecillinam is bound to plasma proteins. Mecillinam is widely distributed into body tissues and fluids; little passes into the CSF unless the meninges are inflamed. It crosses the placenta into the fetal circulation; little appears to be distributed into breast milk.

Mecillinam is metabolised to only a limited extent. From 50 to 70% of a parenteral dose may be excreted in the urine within 6 hours by glomerular filtration and tubular secretion. Renal tubular secretion can be reduced by probenecid. Some mecillinam is excreted in bile where high concentrations occur.

Mecillinam is removed by haemodialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Denm.*: Selexid; *Gr.*: Selexid.

Meclocycline *(BAN, USAN, rINN)*

GS-2989; Meclociclina; Meclocyclin; Méclocycline; Meclocyclinum; Meklocyklin; Meklosykliini; NSC-78502; Меклоциклин.

(4*S*,4a*R*,5*S*,5a*R*,6*S*,12a*S*)-7-Chloro-4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methylene-1,11-dioxonaphthacene-2-carboxamide; 7-Chloro-6-demethyl-6-deoxy-5β-hydroxy-6-methylenetetracycline.

$C_{22}H_{21}ClN_2O_8$=476.9

CAS — 2013-58-3.

ATC — D10AF04.

ATC Vet — QD10AF04.

UNII — 23Q8M2HE6S.

Meclocycline Sulfosalicylate *(USAN)*

Meclociclina, sulfosalicilato de; Meclocycline Sulphosalicylate; Меклоциклина Сульфосалицилат.

Meclocycline 5-sulphosalicylate.

$C_{22}H_{21}ClN_2O_8C_7H_6O_6S$=695.0

CAS — 73816-42-9.

ATC — D10AF04.

ATC Vet — QD10AF04.

UNII — 46VZA7RX28.

Pharmacopoeias. In *US.*

USP 36: (Meclocycline Sulfosalicylate). pH of a 1% solution in water is between 2.5 and 3.5. Store in airtight containers. Protect from light.

Profile

Meclocycline is a tetracycline antibacterial (p. 375.1) that is applied topically as the sulfosalicylate for the treatment of acne vulgaris (p. 1682.2) and superficial skin infections (p. 207.1). Potency is expressed in terms of meclocycline. Preparations containing the equivalent of 1 or 2% are available. Meclocycline sulfosalicylate has also been given as a pessary in the treatment of vulvovaginal infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Meclosorb; *Ital.*: Mecloderm Ovuli; Mecloderm.

Multi-ingredient Preparations. *Ital.*: Anti-Acne; Mecloderm F.

Pharmacopoeial Preparations

USP 36: Meclocycline Sulfosalicylate Cream.

Meleumycin

Pharmacopoeias. In *Chin.*

Profile

Meleumycin, a macrolide antibacterial produced by the growth of *Streptomyces mycarofaciens*, consists of a mixture of midecamycin A_1 and kitasamycin A_6. It has actions and uses similar to those of erythromycin (p. 291.2) and is given orally in the treatment of susceptible infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Si Qi Le (司奇乐).

Meropenem *(BAN, USAN, rINN)*

ICI-194660; Meropeneemi; Meropeném; Méropénem; Meropenemum; SM-7338; Меропенем.

(4*R*,5*S*,6*S*)-3-[(3*S*,5*S*)-5-Dimethylcarbamoylpyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid trihydrate.

$C_{17}H_{25}N_3O_5S,3H_2O$=437.5

CAS — 96036-03-2 (meropenem); 119478-56-7 (meropenem trihydrate).

ATC — J01DH02.

ATC Vet — QJ01DH02.

UNII — FV9J3JU88T (meropenem); YOP6PX0BAO (anhydrous meropenem).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Meropenem Trihydrate). A white or light yellow, crystalline powder. Sparingly soluble in water; practically insoluble in alcohol and in dichloromethane. A 1% solution in water has a pH of 4.0 to 6.0.

USP 36: (Meropenem). Colourless to white crystals. Sparingly soluble in water; very slightly soluble in alcohol; practically insoluble in acetone and in ether; soluble in dimethylformamide and in 5% monobasic potassium phosphate solution. pH of a 1% solution in water is between 4.0 and 6.0. Store in airtight containers.

Uses and Administration

Meropenem is a carbapenem beta-lactam antibacterial with actions and uses similar to those of imipenem (p. 309.3). It is more stable to renal dehydropeptidase I than imipenem and need not be given with an enzyme inhibitor such as cilastatin. It is used in the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria including intra-abdominal infections, gynaecological infections, meningitis, respiratory-tract infections, skin and skin-structure infections, urinary-tract infections, and infections in immunocompromised patients. It may also be of use for initial empirical treatment of such conditions because of its broad spectrum of action. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Meropenem is given intravenously as the trihydrate, but doses are expressed in terms of the amount of anhydrous meropenem; 1.14 g of meropenem trihydrate is equivalent to about 1 g of anhydrous meropenem. It is given as an infusion over 15 to 30 minutes in a usual adult dose of 0.5 to 1 g every 8 hours; 2 g every 8 hours is recommended for meningitis and for bronchopulmonary infections in cystic fibrosis. Doses of up to 1 g may alternatively be given by slow intravenous injection over 3 to 5 minutes.

The dose of meropenem may need to be reduced in renal impairment, see p. 324.1. See also p. 323.3 for details of doses in infants and children.

Reviews.

1. Wiseman LR, *et al.* Meropenem: a review of its antibacterial activity, pharmacokinetic properties and clinical efficacy. *Drugs* 1995; **50**: 73–101.
2. Finch RG, *et al.* eds. Meropenem: focus on clinical performance. *J Antimicrob Chemother* 1995; **36** (suppl A): 1–223.
3. Hellinger WC, Brewer NS. Carbapenems and monobactams: imipenem, meropenem, and aztreonam. *Mayo Clin Proc* 1999; **74**: 420–34.
4. Hurst M, Lamb HM. Meropenem: a review of its use in patients in intensive care. *Drugs* 2000; **59**: 653–80.
5. Lowe MN, Lamb HM. Meropenem: an updated review of its use in the management of intra-abdominal infections. *Drugs* 2000; **60**: 619–46.
6. Edwards SJ, *et al.* Systematic review comparing meropenem with imipenem plus cilastatin in the treatment of severe infections. *Curr Med Res Opin* 2005; **21**: 785–94.
7. Linden P. Safety profile of meropenem: an updated review of over 6000 patients treated with meropenem. *Drug Safety* 2007; **30**: 657–68.
8. Baldwin CM, *et al.* Meropenem: a review of its use in the treatment of serious bacterial infections. *Drugs* 2008; **68**: 803–38.
9. Perrott J, *et al.* Comparing outcomes of meropenem administration strategies based on pharmacokinetic and pharmacodynamic principles: a qualitative systematic review. *Ann Pharmacother* 2010; **44**: 557–64.

Administration. Similarly to doripenem (see p. 287.2) extended infusion of meropenem or imipenem with cilastatin over 3 hours rather than 30 minutes has been suggested[1] as a way of increasing the efficacy of these drugs, particularly against severe or resistant infections.

1. Lee LS, *et al.* Comparison of 30-min and 3-h infusion regimens for imipenem/cilastatin and for meropenem evaluated by Monte Carlo simulation. *Diagn Microbiol Infect Dis* 2010; **68**: 251–8.

Administration in children. Meropenem may be given to children for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria. It is usually given by intravenous infusion over 15 to 30 minutes but

doses of up to 20 mg/kg may alternatively be given by slow intravenous injection over 3 to 5 minutes. Meropenem is licensed in both the UK and the USA for infants and children aged 3 months and over. The usual dose is 10 to 20 mg/kg every 8 hours. A dose of 40 mg/kg is given every 8 hours for meningitis and for bronchopulmonary infections in cystic fibrosis. Children weighing over 50 kg should be dosed as for adults (see Uses and Administration, p. 321.3).

In addition, the *BNFC* suggests the following doses for those under 3 months of age:

- neonates under 7 days of age: 20 mg/kg every 12 hours (or 40 mg/kg every 12 hours in severe infections and in meningitis)
- neonates 7 to 28 days of age: 20 mg/kg every 8 hours (or 40 mg/kg every 8 hours in severe infections and in meningitis)
- infants 1 to 3 months of age: 10 to 20 mg/kg every 8 hours (or 40 mg/kg every 8 hours in meningitis and for bronchopulmonary infections in cystic fibrosis)

Administration in renal impairment. Intravenous doses of meropenem should be reduced in patients with renal impairment. The following doses may be given to adults based on creatinine clearance (CC):

- CC 26 to 50 mL/minute: the usual dose given every 12 hours
- CC 10 to 25 mL/minute: one-half the usual dose every 12 hours
- CC less than 10 mL/minute: one-half the usual dose every 24 hours
- haemodialysis patients: the usual dose after the dialysis session

Alternatively, a review[1] of antimicrobial dosing in critically ill patients receiving renal replacement therapy has recommended that those undergoing intermittent haemodialysis receive a dose of 500 mg every 24 hours (given after the dialysis run). For those undergoing continuous renal replacement therapy, the authors suggest a loading dose of 1 g, with the following maintenance doses:

- continuous venovenous haemofiltration (CVVH): 500 mg to 1 g every 12 hours (although 500 mg every 8 hours can also be considered). Other authors[2] have suggested that patients on high-volume CVVH will require doses of 1 g every 8 hours to treat infections caused by less susceptible bacteria
- continuous venovenous haemodialysis (CVVHD) and haemodiafiltration (CVVHDF): 500 mg to 1 g every 8 to 12 hours (500 mg every 6 to 8 hours can also be considered for CVVHDF)

1. Heintz BH, *et al.* Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy* 2009; **29:** 562–77.
2. Bilgrami I, *et al.* Meropenem dosing in critically ill patients with sepsis receiving high-volume continuous venovenous hemofiltration. *Antimicrob Agents Chemother* 2010; **54:** 2974–8.

Adverse Effects and Precautions

As for Imipenem, p. 310.1.

Meropenem is more stable to renal dehydropeptidase I than imipenem and use with cilastatin, which inhibits this enzyme, is not required. Meropenem may have less potential to induce seizures than imipenem (see p. 324.1).

Effects on the liver. Vanishing bile-duct syndrome, a potentially life-threatening cause of cholestatic liver injury, has been associated with the use of meropenem.[1]

1. Schumaker AL, Okulicz JF. Meropenem-induced vanishing bile duct syndrome. *Pharmacotherapy* 2010; **30:** 933.

Effects on the nervous system. *Animal* studies have indicated that meropenem induces fewer seizures than imipenem-cilastatin and clinical data from the manufacturer have confirmed this.[1] Comparison of data[2] from 4872 patients with a variety of infections (including meningitis) treated with meropenem with that from 4752 patients given other antibacterials, mainly cephalosporin-based regimens or imipenem-cilastatin, showed that meropenem was not associated with any greater risk of seizures than the other antibacterials and was likely to have less neurotoxic potential than imipenem-cilastatin, making it suitable to use in the treatment of meningitis.

1. Norrby SR, *et al.* Safety profile of meropenem: international clinical experience based on the first 3125 patients treated with meropenem. *J Antimicrob Chemother* 1995; **36** (suppl A): 207–23.
2. Norrby SR, Gildon KM. Safety profile of meropenem: a review of nearly 5,000 patients treated with meropenem. *Scand J Infect Dis* 1999; **31:** 3–10.

Hypersensitivity. For suggestions that the rate of cross-sensitivity to carbapenems, including meropenem, in patients with penicillin hypersensitivity may be lower than previously thought, see p. 310.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies meropenem as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/09/11)

Interactions

Probenecid inhibits the renal excretion of meropenem thereby increasing its plasma concentrations and prolonging its elimination half-life.

Antiepileptics. For reports of decreased plasma-*valproate* concentrations (sometimes with loss of seizure control) attributed to meropenem, and the view that carbapenems should not be used with valproates, see p. 557.2.

Antimicrobial Action

As for Imipenem, p. 310.2.

Meropenem is slightly more active than imipenem against Enterobacteriaceae and slightly less active against Gram-positive organisms.

Pharmacokinetics

After intravenous injection of meropenem 0.5 and 1 g over 5 minutes, peak plasma concentrations of about 50 and 112 micrograms/mL respectively are attained. The same doses infused over 30 minutes produce peak plasma concentrations of 23 and 49 micrograms/mL, respectively.

Meropenem has a mean plasma elimination half-life of about 1 hour; this may be prolonged in patients with renal impairment and is also slightly prolonged in children. Meropenem is widely distributed into body tissues and fluids including the CSF and bile. It is about 2% bound to plasma proteins. It is more stable to renal dehydropeptidase I than imipenem and is mainly excreted in the urine by tubular secretion and glomerular filtration. About 70% of a dose is recovered unchanged in the urine over a 12-hour period and urinary concentrations above 10 micrograms/mL are maintained for up to 5 hours after a 500-mg dose. Meropenem is reported to have one metabolite (ICI-213689), which is inactive and is excreted in the urine.

Meropenem is removed by haemodialysis.

References.
1. Mouton JW, Van den Anker JN. Meropenem clinical pharmacokinetics. *Clin Pharmacokinet* 1995; **28:** 275–86.
2. Thalhammer F, Horl WH. Pharmacokinetics of meropenem in patients with renal failure and patients receiving renal replacement therapy. *Clin Pharmacokinet* 2000; **39:** 271–9.
3. Ververs TF, *et al.* Pharmacokinetics and dosing regimen of meropenem in critically ill patients receiving continuous venovenous hemofiltration. *Crit Care Med* 2000; **28:** 3412–16.
4. van Enk JG, *et al.* Pharmacokinetics of meropenem in preterm neonates. *Ther Drug Monit* 2001; **23:** 198–201.
5. Goldstein SL, *et al.* Meropenem pharmacokinetics in children and adolescents receiving hemodialysis. *Pediatr Nephrol* 2001; **16:** 1015–18.
6. Ariano RE, *et al.* Pharmacokinetics and pharmacodynamics of meropenem in febrile neutropenic patients with bacteremia. *Ann Pharmacother* 2005; **39:** 32–8.
7. Novelli A, *et al.* Pharmacokinetic evaluation of meropenem and imipenem in critically ill patients with sepsis. *Clin Pharmacokinet* 2005; **44:** 539–49.
8. Du X, *et al.* Population pharmacokinetics and pharmacodynamics of meropenem in pediatric patients. *J Clin Pharmacol* 2006; **46:** 69–75.
9. Nicolau DP. Pharmacokinetic and pharmacodynamic properties of meropenem. *Clin Infect Dis* 2008; **47** (suppl 1): S32–S40.
10. van den Anker JN, *et al.* Meropenem pharmacokinetics in the newborn. *Antimicrob Agents Chemother* 2009; **53:** 3871–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Meroefectil; Merotenk; Merozen; Merpem; ***Austral.***: Merrem; ***Austria***: Merinfec; Optinem; ***Belg.***: Meronem; ***Braz.***: Mepenox; Meronem; Zylpen; ***Canad.***: Merrem; ***Chile***: Acus; Meronem; ***China***: Meite (美特); Mepem (美平); Painon (倍能); ***Cz.***: Menoinfex; Meronem; ***Denm.***: Meronem; Merospira; ***Fin.***: Meronem; ***Fr.***: Meronem; ***Ger.***: Meronem; ***Gr.***: Carbenem; Merobact; Meronem; Merovia; Merozan; Nemerop; Ronepem; Rulmenem; Santamer; ***Hong Kong***: Meronem; ***Hung.***: Meronem; ***India***: Ameropem; Amropenem; Aripnem; Cosmor; Curepin; Erope; Etopen; Exmer; Feropenem; Geriopen; Gonem; Inlife; Inpenam; Insomer; Kanam; Map; Marnif; Marzipan; Maxinem; Maxopem; Maxopen; Medinumm; Medipenam; Menem; Merenz; Merobact; Merobest; Merobus; Merocad; Merocrit; Merod; Merofact; Merofit; Merokem; Meromate; Meromer; Meronem; Meronis; Meropam; Meroplan; Merosan; Merospect; Merotec; Merotop; Merotrol; Merover; Merowor; Meroza; Mery; Micon; Moira; Morep; MPenem; Myopan; Neumer; Onmero; Open; Pacetaker; ***Indon.***: Caprenem; Eradix; Lanmer; Merem; Merobat; Merocef; Merofen; Meronem; Meropex; Merosan; Merotik; Propenem; Rindonem; Ronem; Sefanem; Tripenem; ***Irl.***: Merapem; Meronem; ***Israel***: Meronem; ***Ital.***: Mepereost; Merrem; Reopemest; ***Jpn***: Meropen; ***Malaysia***: Meronem; ***Mex.***: Lusantem; Merrem; Pisapem; Strinem; ***Neth.***: Mepereost; Meronem; Reopemest†; ***Norw.***: Meronem; ***NZ***: Merrem; ***Philipp.***: Mepenem; Merix; Meromax; Meronem; Merop; Meropen; Ropen; Ropenem; ***Pol.***: Mepereost; Meronem; Reopemest; ***Port.***: Meronem; ***Rus.***: Merexid (Мерексид); Meronem (Меронем); Meropenabol (Меропенабол); Syronem (Сайронем); ***S.Afr.***: Mercide; Meronem; ***Singapore***: Meronem; ***Spain***: Meronem; ***Swed.***: Meronem; ***Switz.***: Meronem; ***Thal.***: Bestinem; Enem; Mapenem; Mero; Meronem; Monem; Penem; Romenem; Zaxter; ***Turk.***: Meronem; Merosid; Merozan; Mopem; ***UAE***: Miran; ***UK***: Meronem; ***Ukr.***: Mepenam (Мепенам); Meronem (Меронем); Mezonex (Мезонекс)†; Panlactam (Панлактам); Ronem (Ронем); ***USA***: Merrem; ***Venez.***: Meronem.

Pharmacopoeial Preparations
USP 36: Meropenem for Injection.

Methacycline *(BAN, USAN)*

GS-2876; Metaciclina; Metacycline (pINN); Métacycline; Metacyclinum; Metacyklin; Metasykliini; Метациклин.

(4*S*,4a*R*,5*S*,5a*R*,6*S*,12a*S*)-4-Dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methylene-1,11-dioxonaphthacene-2-carboxamide; 6-Demethyl-6-deoxy-5β-hydroxy-6-methylenetetracycline.

$C_{22}H_{22}N_2O_8$=442.4

CAS — 914-00-1.

ATC — J01AA05.

ATC Vet — QJ01AA05.

UNII — IR23517CSP.

Methacycline Hydrochloride *(BANM)*

Hidrocloruro de metaciclina; Metaciclina, hidrocloruro de; Métacycline, Chlorhydrate de; Metacycline Hydrochloride (pINNM); Metacyclini Chloridum; Metacyclini Hydrochloridum; Metacykliny chlorowodorek; Méthylènecycline Chlorhydrate; 6-Methyleneoxytetracycline Hydrochloride; Метациклина Гидрохлорид.

$C_{22}H_{22}N_2O_8$.HCl=478.9

CAS — 3963-95-9.

ATC — J01AA05.

ATC Vet — QJ01AA05.

UNII — 9GJ0N7ZAP0.

Pharmacopoeias. In *Chin.*, *Pol.*, and *US.*

USP 36: (Methacycline Hydrochloride). A yellow to dark yellow crystalline powder. Soluble 1 in 100 of water, 1 in 300 of alcohol, and 1 in 25 of 0.1N sodium hydroxide; very slightly soluble in chloroform and in ether. pH of a solution in water containing the equivalent of methacycline 1% is between 2.0 and 3.0. Store in airtight containers. Protect from light.

Profile

Methacycline is a tetracycline derivative with uses similar to those of tetracycline (p. 375.1). Like demeclocycline, it is excreted more slowly than tetracycline and effective blood concentrations are maintained for longer periods; the plasma elimination half-life is about 14 hours.

Methacycline hydrochloride is given orally in a usual adult dose of 600 mg daily in 2 divided doses, preferably 1 hour before or 2 hours after meals.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Zuobenneng (佐本能); ***Fr.***: Lysocline; Physiomycine; ***Ital.***: Esarondil; Rotilen.

Pharmacopoeial Preparations
USP 36: Methacycline Hydrochloride Capsules; Methacycline Hydrochloride Oral Suspension.

Methenamine *(rINN)*

Aminoform; E239; Esametilentetrammina; Esammina; Formine; Heksamin; Hexamethylenamine; Hexamine; Metenamiini; Metenamin; Meténamin; Metenamina; Metenaminas; Metenammina; Methenamin; Méthénamine; Methenaminum; Urotropine; Метенамин.

Hexamethylenetetramine; 1,3,5,7-Tetraazatricyclo[3.3.1.1^{3,7}]decane.

$C_6H_{12}N_4$=140.2

CAS — 100-97-0.

ATC — J01XX05.

ATC Vet — QJ01XX05.

UNII — J50OJX95QV.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Methenamine). A white, or almost white, crystalline powder or colourless crystals. Freely soluble in water; soluble in alcohol and in dichloromethane. Protect from light.

USP 36: (Methenamine). Colourless, practically odourless, lustrous crystals or white crystalline powder. Soluble 1 in 1.5 of water, 1 in 12.5 of alcohol, 1 in 10 of chloroform, and 1 in 320 of ether. Its solutions are alkaline to litmus.

Methenamine Hippurate (BAN, USAN, rINNM)

Heksamin Hippurat; Hexamine Hippurate; Hipurato de metenamina; Metenamin Hippurat; Metenamina, hipurato de; Méthénamine, Hippurate de; Methenamini Hippuras; Метенамина Гиппурат.

Hexamethylenetetramine hippurate.

$C_6H_{12}N_4.C_9H_9NO_3$=319.4

CAS — 5714-73-8.

ATC — J01XX05.

ATC Vet — QJ01XX05.

UNII — M329791L57.

Pharmacopoeias. In *US*.

Methenamine Mandelate (rINNM)

Heksamin Mandelat; Hexamine Amygdalate; Hexamine Mandelate; Mandelato de metenamina; Metenamin Mandelat; Metenamina, mandelato de; Méthénamine, Mandelate de; Methenamini Mandelas; Метенамина Манделат.

Hexamethylenetetramine mandelate.

$C_6H_{12}N_4.C_8H_8O_3$=292.3

CAS — 587-23-5.

ATC — J01XX05.

ATC Vet — QJ01XX05.

UNII — 695N30CINR.

Pharmacopoeias. In *US*.

USP 36: (Methenamine Mandelate). A white, practically odourless crystalline powder. Very soluble in water; soluble 1 in 10 of alcohol, 1 in 20 of chloroform, and 1 in 350 of ether. Its solutions have a pH of about 4.

Uses and Administration

Methenamine is used, usually as the hippurate or mandelate, in the prophylaxis and long-term suppression of chronic or recurrent, uncomplicated, lower urinary-tract infections and asymptomatic bacteriuria. It has been considered suitable for long-term use because acquired resistance does not appear to develop.

Methenamine and its salts should not be used in upper urinary-tract infections because it is eliminated too rapidly to exert an effect, nor in acute urinary infections. It is only active in acidic urine, when formaldehyde is released, and although hippuric or mandelic acid helps to acidify the urine, ammonium chloride or ascorbic acid may be tried. If urea-splitting bacteria such as *Proteus* or some *Pseudomonas* spp. are present they may produce so much ammonia that the urine cannot be acidified (see also Antimicrobial Action, p. 325.2).

The usual oral adult dose of methenamine or methenamine mandelate is 1 g given four times daily. Methenamine hippurate is given orally in a usual dose of 1 g twice daily; the dose may be increased to three times daily in catheterised patients.

For details of doses in children, see p. 325.1.

Methenamine has been used topically in deodorant preparations, since in the presence of acid sweat it liberates formaldehyde. Methenamine calcium thiocyanate has been used in combination preparations for upper respiratory-tract disorders.

Reviews.

1. Schiotz HA, Guttu K. Value of urinary prophylaxis with methenamine in gynecologic surgery. *Acta Obstet Gynecol Scand* 2002; 81: 743–6.
2. Lee BB, *et al.* Methenamine hippurate for preventing urinary tract infections. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 11/01/08).

Administration in children. In children, methenamine and its salts may be given orally for prophylaxis and long-term suppression of chronic or recurrent, uncomplicated lower urinary-tract infections and asymptomatic bacteriuria.

In the USA, the usual recommended dose of methenamine mandelate in children up to 6 years old is about 18 mg/kg given four times daily; those aged 6 to 12 years may be given methenamine or methenamine mandelate 500 mg four times daily.

In the UK, methenamine hippurate may be given in a usual oral dose of 500 mg twice daily in children aged 6 to 12 years. Doses of up to 1 g twice daily have been given in the USA.

Adverse Effects and Precautions

Methenamine and its salts are generally well tolerated but may cause gastrointestinal disturbances such as nausea, vomiting, and diarrhoea. Skin rashes, pruritus, and occasionally other hypersensitivity reactions, may occur.

Comparatively large amounts of formaldehyde may be formed during prolonged use or when large doses are given. This may produce irritation and inflammation of the urinary tract, especially the bladder, as well as painful and frequent micturition, haematuria, and proteinuria. The effect of the formaldehyde may be reduced by alkalinising drugs, such as sodium bicarbonate, or large quantities of water, but it is then less effective.

Methenamine and its salts are contra-indicated in patients with hepatic impairment because of the liberation of ammonia in the gastrointestinal tract. Although methenamine itself is not contra-indicated in renal impairment, its salts should be avoided in severe impairment because of the risk of mandelate or hippurate crystalluria. They should also be avoided in patients with severe dehydration, metabolic acidosis, or gout.

Interference with laboratory estimations for catecholamines, 17-hydroxycorticosteroids, and oestrogens in the urine has been reported.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies methenamine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

The use of drugs that alkalinise the urine, including some antacids, potassium citrate, and diuretics such as acetazolamide or the thiazides, should be avoided because the activation of methenamine to formaldehyde may be inhibited (but see above).

Use of methenamine with sulfonamides may increase the risk of crystalluria since methenamine requires low urinary pH for its effect, at which sulfonamides and their metabolites are poorly soluble; methenamine may also form poorly soluble compounds with some sulfonamides.

Antimicrobial Action

Methenamine owes its antibacterial properties to formaldehyde, a non-specific bactericide, which is slowly liberated by hydrolysis at acid pH. Most Gram-positive and Gram-negative organisms and fungi are susceptible. Hippuric and mandelic acids have some antibacterial activity *in vitro*, but their contribution to the antibacterial action of the salts *in vivo*, beyond assisting the maintenance of low urinary pH, is uncertain. Urea-splitting organisms such as *Proteus* and some *Pseudomonas* spp. tend to increase urinary pH and inhibit the release of formaldehyde, thereby decreasing the efficacy of methenamine. Use with acetohydroxamic acid, a potent inhibitor of bacterial urease, has been suggested for urinary infections due to these organisms. True resistance to formaldehyde does not appear to be a problem in clinical use.

Pharmacokinetics

Methenamine is readily absorbed from the gastrointestinal tract and widely distributed in the body. Under acid conditions methenamine is slowly hydrolysed to formaldehyde and ammonia: about 10 to 30% of an oral dose may be converted in the stomach unless it is given as an enteric-coated preparation. Almost no hydrolysis of methenamine takes place at physiological pH, and it is therefore virtually inactive in the body. The half-life is reported to be about 4 hours. Methenamine is rapidly and almost completely eliminated in the urine, and provided this is acidic (preferably below pH 5.5) bactericidal concentrations of formaldehyde occur. Because of the time taken for hydrolysis, however, these do not occur until the urine reaches the bladder, with peak concentrations occurring up to 2 hours after an oral dose. Absorption, and hence excretion, may be somewhat delayed in patients given enteric-coated formulations.

Methenamine crosses the placenta and small amounts may be distributed into breast milk.

The mandelate and hippurate moieties are also rapidly absorbed and are excreted in urine by tubular secretion as well as glomerular filtration.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Hiprex; *Canad.*: Dehydral; Mandelamine; Urasal†; *Denm.*: Haiprex; *Fin.*: Hipeksal; Hiprex; *Ger.*: Antihydral; *Gr.*: Amigdalin; *Hong Kong*: Antihydral; *India*: Mandelamin; *Israel*: Hiprex; *Malaysia*: Hiprex; *Mex.*: Bioran; *Neth.*: Reflux; *Norw.*: Hiprex; *NZ*: Hiprex; *Philipp.*: Hiprex†; *Pol.*: Stoppot; *Swed.*: Hiprex; *Turk.*: Helpa; Hippurin; Manuprin; Neturone; Purinol; Uron; *UK*: Hiprex; *USA*: Hiprex; Mandelamine; Urex; *Venez.*: Mandelamine.

Multi-ingredient Preparations. *Belg.*: Carbobel; Mictasol; *Braz.*: Acridin; Cystex; Sepurin; *Chile*: Uroknop; *Hung.*: Aknesol; *Pol.*: Dezorol; Pedipur; Urosal; *Rus.*: Teimurov (Теймурова); *Turk.*: Helmo-Blue; Helmobleu; *USA*: Atrosept; Cystex; Darpaz†; Hyophen; MHP-A; MSP-Blu; Phosphasal; Prosed/DS; UAA; Urelle; Uretron; Urimar-T; Urimax; Uriseptic; Uritact; Uro Blue; Urogesic Blue; Uryl; Ustell; Utac; Uticap; Utira; Utrona-C; *Venez.*: Azo-Mandelamine.

Homoeopathic Preparations. *Fr.*: L 8.

Pharmacopoeial Preparations

USP 36: Methenamine Elixir; Methenamine Hippurate Tablets; Methenamine Mandelate Delayed-release Tablets; Methenamine Mandelate for Oral Solution; Methenamine Mandelate Oral Suspension; Methenamine Mandelate Tablets; Methenamine Tablets.

Meticillin Sodium (rINNM)

BRL-1241; Dimethoxyphenecillin Sodium; Dimethoxyphenyl Penicillin Sodium; Methicillin Sodium (USAN); Methicillin Sodium (BANM); Meticilina sódica; Méticilline Sodique; Meticillinum Natricum; Natrii Meticillinum; SQ-16123; X-1497; Натрий Метициллин.

Sodium (6*R*)-6-(2,6-dimethoxybenzamido)penicillanate monohydrate.

$C_{17}H_{19}N_2NaO_6S.H_2O$=420.4

CAS — 61-32-5 (meticillin); 132-92-3 (anhydrous meticillin sodium); 7246-14-2 (meticillin sodium monohydrate).

ATC — J01CF03.

ATC Vet — QJ01CF03.

UNII — AO9YF4MN30.

Incompatibility. Meticillin sodium has been reported to be incompatible with aminoglycosides and some other antimicrobials. It has also been reported to be incompatible with acidic and alkaline drugs.

Uses and Administration

Meticillin is a penicillinase-resistant penicillin and has been used similarly to flucloxacillin (p. 299.2) in the treatment of staphylococcal infections resistant to benzylpenicillin. It is not active orally and has been given by injection as the sodium salt.

Adverse Effects and Precautions

As for Benzylpenicillin, p. 229.2.

Meticillin is the penicillin most commonly associated with acute interstitial nephritis.

Effects on the kidneys. References.

1. Sanjad SA, *et al.* Nephropathy, an underestimated complication of methicillin therapy. *J Pediatr* 1974; 84: 873–7.
2. Galpin JE, *et al.* Acute interstitial nephritis due to methicillin. *Am J Med* 1978; 65: 756–65.

Sodium content. Each g of meticillin sodium contains about 2.4 mmol of sodium.

Interactions

As for Benzylpenicillin, p. 230.1.

Antimicrobial Action

Meticillin has a mode of action similar to that of benzylpenicillin (p. 230.1) but it is resistant to staphylococcal penicillinase. There is evidence that meticillin is more stable to staphylococcal penicillinase than the other penicillinase-resistant penicillins.

Meticillin is active against both penicillinase-producing and non-penicillinase-producing staphylococci, and also against *Streptococcus pyogenes* (group A beta-haemolytic streptococci), *Str. pneumoniae*, and some viridans streptococci. Its activity against penicillin-sensitive staphylococci and streptococci is less than that of benzylpenicillin. It is virtually ineffective against *Enterococcus faecalis*.

Resistance of staphylococci to meticillin is due to the expression of an altered penicillin-binding protein and is not dependent on penicillinase production. There is cross-resistance with other penicillins, including the penicillinase-resistant penicillins cloxacillin, dicloxacillin, flucloxacillin, nafcillin, and oxacillin, and with the cephalosporins. Meticillin-resistant staphylococci are also frequently resistant to other antibacterials, including aminoglycosides, chloramphenicol, ciprofloxacin, clindamycin, erythromycin, and tetracycline. The incidence of such resistance has varied considerably. However, both endemic (restricted to one hospital) and epidemic (affecting more than one hospital) strains of meticillin-resistant *Staphylococcus aureus* (MRSA) are now recognised and infections are a problem in many hospitals. Community-acquired strains of MRSA have also been recognised, but are generally susceptible to a wider range of antibacterials than strains acquired in hospital.

There have been fewer studies on coagulase-negative staphylococci, but patterns of meticillin resistance in *Staph. epidermidis* are similar to those for MRSA and the frequency of resistance may be higher.

For further details on meticillin-resistant staphylococci and the management of infections, see under Staphylococcal Infections, p. 208.2.

Resistance. References to meticillin-resistant staphylococci.

1. Rybak MJ, Akins RL. Emergence of methicillin-resistant Staphylococcus aureus with intermediate glycopeptide resistance: clinical significance and treatment options. *Drugs* 2001; 61: 1–7.
2. Stapleton PD, Taylor PW. Methicillin resistance in Staphylococcus aureus: mechanisms and modulation. *Sci Prog* 2002; 85: 57–72.
3. Berger-Bächi B, Rohrer S. Factors influencing methicillin resistance in staphylococci. *Arch Microbiol* 2002; 178: 165–71.
4. Eady EA, Cove JH. Staphylococcal resistance revisited: community-acquired methicillin resistant Staphylococcus aureus—an emerging problem for the management of skin and soft tissue infections. *Curr Opin Infect Dis* 2003; 16: 103–24.
5. Boyce JM, *et al.* Meticillin-resistant Staphylococcus aureus. *Lancet Infect Dis* 2005; 5: 653–63.
6. Martins A, Cunha M de LRS. Methicillin resistance in Staphylococcus aureus and coagulase-negative staphylococci: epidemiological and molecular aspects. *Microbiol Immunol* 2007; 51: 787–95.
7. Millar BC, *et al.* Proposed definitions of community-associated meticillin-resistant Staphylococcus aureus (CA-MRSA). *J Hosp Infect* 2007; 67: 109–13.
8. Boucher HW, Corey GR. Epidemiology of methicillin-resistant Staphylococcus aureus. *Clin Infect Dis* 2008; 46 (suppl 5): S344–S349.
9. Deurenberg RH, Stobberingh EE. The molecular evolution of hospital- and community-associated methicillin-resistant Staphylococcus aureus. *Curr Mol Med* 2009; 9: 100–15.

Pharmacokinetics

Meticillin is inactivated by gastric acid and must be given by injection. Peak plasma concentrations occur within 0.5 to 1 hour of an intramuscular injection; concentrations of up to 18 micrograms/mL occur after a dose of 1 g. A half-life of 0.5 to 1 hour has been reported, although this may be increased to 3 to 6 hours in renal impairment. About 40% of the meticillin in the circulation is bound to plasma proteins. It is widely distributed in body fluids and in tissues, but there is little diffusion into the CSF unless the meninges are inflamed. Meticillin also crosses the placenta and appears in breast milk. Relatively high concentrations occur in bile compared with plasma, although only small amounts are excreted in bile. The majority is rapidly excreted by tubular secretion and glomerular filtration; up to 80% of an injected dose has been detected unchanged in the urine.

Plasma concentrations are enhanced by probenecid. They may be reduced in patients with cystic fibrosis.

Mezlocillin *(BAN, USAN, rINN)*

Metslosilliini; Mezlocilina; Mezlocilline; Mezlocillinum; Мезлоциллин.

6-[*N*-(3-Methylsulfonyl-2-oxoimidazolidin-1-ylcarbonyl)-D-phenylglycylamino]penicillanic acid.

$C_{21}H_{25}N_5O_8S_2$=539.6

CAS — 51481-65-3.

ATC — J01CA10.

ATC Vet — QJ01CA10.

UNII — OH2O403D1G.

Mezlocillin Sodium *(BANM, rINNM)*

Bay-f-1353; Mezlocilina sódica; Mezlocilline Sodique; Natrii Mezlocillinum; Натрий Мезлоциллин.

Sodium (6*R*)-6-[D-2-(3-mesyl-2-oxoimidazolidine-1-carboxamido)-2-phenylacetamido]penicillanate monohydrate.

$C_{21}H_{24}N_5NaO_8S_2.H_2O$=579.6

CAS — 42057-22-7 (anhydrous mezlocillin sodium); 80495-46-1 (mezlocillin sodium monohydrate).

ATC — J01CA10.

ATC Vet — QJ01CA10.

UNII — 3CWW8B5904 (mezlocillin sodium monohydrate); RX227TP94U (mezlocillin sodium).

Pharmacopoeias. In *US*.

USP 36: (Mezlocillin Sodium). A white to pale yellow crystalline powder. Freely soluble in water. pH of a 10% solution in water is between 4.5 and 8.0. Store in airtight containers.

Incompatibility. Mezlocillin sodium has been reported to be incompatible with aminoglycosides, ciprofloxacin, metronidazole, and tetracyclines.

Uses and Administration

Mezlocillin is a ureidopenicillin with uses similar to those of piperacillin (p. 342.1). It is commonly used with an aminoglycoside; however they should be given separately as they have been shown to be incompatible.

Mezlocillin is given by injection as the sodium salt. Doses are expressed in terms of the equivalent amount of mezlocillin; 1.07 g of mezlocillin sodium is equivalent to about 1 g of mezlocillin. Dosage may need to be reduced in renal impairment. It may be given by slow intravenous injection over 3 to 5 minutes, by intravenous infusion over 30 minutes, or by deep intramuscular injection. Single intramuscular doses should not exceed 2 g.

For the treatment of serious infections, 200 to 300 mg/kg daily in divided doses may be given intravenously. For life-threatening infections, up to 350 mg/kg daily may be used, but the total daily dose should not normally exceed 24 g. For uncomplicated urinary-tract infections, a dose of 1.5 to 2 g may be given intramuscularly or intravenously every 6 hours.

Uncomplicated gonorrhoea may be treated by a single intramuscular or intravenous dose of mezlocillin 1 to 2 g. Probenecid 1 g orally may be given at the same time or up to 30 minutes before the injection.

For the prophylaxis of infection during surgery, an intravenous pre-operative dose of mezlocillin 4 g, repeated at 6-hourly intervals for 2 further doses, may be given.

Adverse Effects and Precautions

As for Carbenicillin Sodium, p. 232.1.

Prolongation of bleeding time has been less frequent and less severe with mezlocillin than with carbenicillin.

Sodium content. Each g of mezlocillin sodium contains about 1.7 mmol of sodium. As mezlocillin sodium has a lower sodium content than carbenicillin sodium, hypernatraemia and hypokalaemia are less likely to occur.

Interactions

As for Benzylpenicillin, p. 230.1.

Antibacterial. For the effect of mezlocillin on the clearance of *cefotaxime*, see p. 244.3.

Neuromuscular blockers. Mezlocillin and other ureidopenicillins are reported to prolong the action of competitive muscle relaxants such as *vecuronium* (see Atracurium, p. 2032.1).

Antimicrobial Action

Mezlocillin has a similar antimicrobial action to piperacillin (p. 343.1). Its activity against *Pseudomonas aeruginosa* is less than that of azlocillin or piperacillin.

Pharmacokinetics

Mezlocillin is not absorbed from the gastrointestinal tract to any significant extent. It is well absorbed after intramuscular injection, with peak plasma concentrations of 15 to 25 micrograms/mL 45 to 90 minutes after a single dose of 1 g. It is reported to have nonlinear dose-dependent pharmacokinetics. Between 16 and 42% of mezlocillin in the circulation is bound to plasma proteins. Mezlocillin is reported to have a plasma half-life of about 1 hour; this is slightly prolonged in neonates, and in patients with renal impairment half-lives of up to about 6 hours have been reported.

Mezlocillin is widely distributed in body tissues and fluids. It crosses the placenta into the fetal circulation and small amounts are distributed into breast milk. There is little diffusion into CSF except when the meninges are inflamed.

Mezlocillin is reported to be metabolised to a limited extent. About 55% of a dose is excreted unchanged in the urine by glomerular filtration and tubular secretion within 6 hours of a dose, hence achieving high urinary concentrations. High concentrations are also found in the bile; up to 30% of a dose has been reported to be excreted by this route.

Plasma concentrations are enhanced by probenecid.

Mezlocillin is removed by haemodialysis, and to some extent by peritoneal dialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Baypen; ***China***: Baypen (拜朋); Li Yang (力扬); Meige (美各); Nuomei (诺美); Yi Mei (亿美); ***Fr.***: Baypen†; ***Ger.***: Baypen†; ***Ital.***: Baypen.

Multi-ingredient Preparations. ***China***: Han Guang (汉光); Jia Luo Tan (佳洛坦); Kai Wei Ke (凯韦可); KaiLin (开林).

Pharmacopoeial Preparations

USP 36: Mezlocillin for Injection.

Micronomicin Sulfate *(pINNM)*

Gentamicin C_{2B} Sulphate; KW-1062 (micronomicin); Micronomicin Sulphate; Micronomicina, sulfato de; Micronomicine, Sulfate de; Micronomicini Sulfas; Sagamicin Sulphate; Sulfato de micronomicina; Микрономицина Сульфат; 6′*N*-Methylgentamicin C_{1A} Sulphate.

O-2-Amino-2,3,4,6-tetradeoxy-6-(methylamino)-α-D-*erythro*-hexopyranosyl-(1→4)-*O*-[3-deoxy-4-*C*-methyl-3-(methylamino)-β-L-arabinopyranosyl-(1→6)]-2-deoxy-D-streptamine hemipentasulphate.

$(C_{20}H_{41}N_5O_7)_2.5H_2SO_4$=1417.5

CAS — 52093-21-7 (micronomicin).

ATC — S01AA22.

ATC Vet — QS01AA22.

Pharmacopoeias. In *Chin.* and *Jpn.*

Profile

Micronomicin is an aminoglycoside antibacterial with general properties similar to those of gentamicin (p. 304.2). It is given as the sulfate and doses are expressed in terms of micronomicin; 183 mg of micronomicin sulfate is equivalent to about 120 mg of micronomicin. It is given by intramuscular injection or by intravenous infusion over 30 minutes to 1 hour in doses of 120 to 240 mg daily in 2 or 3 divided doses. Dosage should be adjusted based on serum micronomicin concentration monitoring. It is also used topically as eye drops or ointment in a concentration of 0.3% for infections of the eye.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Jun Jia (君佳); Jun Wei (君为); LuoYi (洛意); Mei Luo Ke (美罗克); Rui Nuo Mei Xin (瑞诺美新); ***Ital.***: Luxomicina; ***Jpn***: Sagamicin†; ***Singapore***: Sagamicin.

Midecamycin *(rINN)*

Midecamicina; Midecamycin A_1; Midécamycine; Midecamycinum; Mydecamycin; Мидекамицин.

7-(Formylmethyl)-4,10-dihydroxy-5-methoxy-9,16,-dimethyl-2-oxo-oxacyclohexadeca-11,13-dien-6-yl 3,6-dideoxy-4-*C*-(2,6-dideoxy-3-*C*-methyl-α-L-*ribo*-hexopyranosyl)-3-(dimethylamino)-β-D-glucopyranoside 4′,4″-dipropionate.

$C_{41}H_{67}NO_{15}$=814.0

CAS — 35457-80-8.

ATC — J01FA03.

ATC Vet — QJ01FA03.

UNII — N34Z0Y5UH7.

Pharmacopoeias. In *Jpn*.

Midecamycin Acetate *(rINNM)*

Acecamycin; Acetato de midecamicina; Midecamicina, acetato de; Midecamycin Diacetate; Midécamycine, Acétate de; Midecamycini Acetas; Miocamycin; Miokamycin; MOM; Ponsinomycin; 1532-RB; Мидекамицина Ацетат.

9,3″-Diacetylmidecamycin; Leucomycin V 3^B, 9-diacetate $3,4^B$-dipropanoate.

$C_{45}H_{71}NO_{17}$=898.1

CAS — 55881-07-7.

ATC — J01FA11.

ATC Vet — QJ01FA11.

Pharmacopoeias. In *Jpn*.

Profile

Midecamycin is a macrolide antibacterial produced by the growth of *Streptomyces mycarofaciens* with actions and uses similar to those of erythromycin (p. 291.2) but it is somewhat less active. It is given orally for the treatment of susceptible infections as the acetate in usual doses of 0.9 to 1.8 g daily in 2 or 3 divided doses. It has also been given as the base.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Merced; ***China***: Mei Jia Xin (美加欣); Mei Ou Ka (美欧卡); Meilitai (美力泰); ***Fr.***: Mosil; ***Gr.***: Miocacin; Miocamen; ***Hong Kong***: Medemycin; ***Ital.***: Macroral; Midecin†; Miocamen; Miokacin; ***Jpn***: Medemycin; Miocamycin; ***Port.***: Miocacin; ***Rus.***: Macropen (Макропен); ***Spain***: Momicine; Myoxam; ***Thai.***: Miotin; ***Ukr.***: Macropen (Макропен).

Minocycline *(BAN, USAN, rINN)*

Minociclina; Minocyclin; Minocyclinum; Minocyklin; Minocyklina; Minosiklin; Minosykliini; Миноциклин.

(4*S*,4a*S*,5a*R*,12a*S*)4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxonaphthacene-2-carboxamide; 6-Demethyl-6-deoxy-7-dimethylamino-tetracycline.

$C_{23}H_{27}N_3O_7$=457.5

CAS — 10118-90-8.

ATC — A01AB23; J01AA08.

ATC Vet — QA01AB23; QJ01AA08.
UNII — FYY3R43WGO.

Minocycline Hydrochloride *(BANM, rINNM)*

Hidrocloruro de minociclina; Minociclina, hidrocloruro de; Minociklin-hidroklorid; Minociklino hidrochloridas; Minocycline, Chlorhydrate de; Minocyclini hydrochloridum; Minocyklin-hydrochlorid; Minocyklinhydroklorid; Minocykliny chlorowodorek; Minosykliinihydrokloridi; Миноциклина Гидрохлорид.

$C_{23}H_{27}N_3O_7$,HCl=493.9
CAS — 13614-98-7.
ATC — A01AB23; J01AA08.
ATC Vet — QA01AB23; QJ01AA08.
UNII — 0020414E5U.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Minocycline Hydrochloride Dihydrate). A yellow, hygroscopic, crystalline powder. Sparingly soluble in water; slightly soluble in alcohol. It dissolves in solutions of alkali hydroxides and carbonates. A 1% solution in water has a pH of 3.5 to 4.5. Store in airtight containers. Protect from light.

USP 36: (Minocycline Hydrochloride). A yellow crystalline powder. Sparingly soluble in water; slightly soluble in alcohol; practically insoluble in chloroform and in ether; soluble in solutions of alkali hydroxides and carbonates. pH of a solution in water containing the equivalent of minocycline 1% is between 3.5 and 4.5. Store in airtight containers. Protect from light.

Incompatibility. Preparations of minocycline hydrochloride have an acid pH and incompatibility may reasonably be expected with alkaline preparations or with drugs unstable at low pH.

Uses and Administration

Minocycline is a tetracycline derivative with uses similar to those of tetracycline (p. 375.3). It is also a component of multidrug regimens for the treatment of leprosy (p. 188.3) and has been used in the prophylaxis of meningococcal infection to eliminate the carrier state, but the high incidence of vestibular disturbances means that it is not the drug of choice for the latter.

Minocycline is usually given orally as the hydrochloride; doses are expressed in terms of the base. Minocycline hydrochloride 108 mg is equivalent to about 100 mg of minocycline. Minocycline capsules and tablets should be taken with plenty of fluid, with the patient in an upright position, and well before going to bed.

In patients in whom oral therapy is not feasible, minocycline hydrochloride has been given by slow intravenous infusion in doses equivalent to those given orally. In some countries it has also been given by intramuscular injection.

The usual adult oral dose is 200 mg daily in divided doses, usually every 12 hours; an initial loading dose of 200 mg may be given.

An oral dose of 50 mg twice daily or 100 mg once daily is used for the treatment of acne; alternatively, a dose of about 1 mg/kg once daily is also given as a modified-release preparation to patients weighing 45 kg and over. In asymptomatic meningococcal carriers, 100 mg has been given orally twice daily for 5 days, usually followed by a course of rifampicin.

For multibacillary leprosy an oral dose of minocycline 100 mg daily with clofazimine and ofloxacin *or* 100 mg monthly with rifampicin and ofloxacin have been recommended by WHO as alternative multidrug therapy regimens. As an alternative regimen for patients with single-lesion paucibacillary leprosy WHO suggests a single dose of minocycline 100 mg with rifampicin and ofloxacin.

For details of doses in children and adolescents, see p. 327.1.

For dosage recommendations in patients with renal impairment, see p. 327.2.

In adults with periodontitis (p. 192.3), a modified-release subgingival gel containing minocycline hydrochloride has been inserted into the periodontal pocket as an adjunct to scaling and root planing; each cartridge contains the equivalent of 1 mg of minocycline and the total used depends on the size, shape, and number of pockets being treated. Minocycline has also been applied as a 2% gel for periodontal infections.

Administration in children. In children, the effects on teeth should be considered and tetracyclines only used when absolutely essential. In the UK, minocycline is licensed for use in children aged 12 years and over; the usual adult dose (see above) may be given orally. However, in the USA, it may be given to those over 8 years old in usual oral doses of 4 mg/kg initially followed by 2 mg/kg every 12 hours.

Administration in renal impairment. US licensed product information states that pharmacokinetics in patients with renal impairment have not been fully characterised and therefore recommends that no more than 200 mg in any 24-hour period should be given to these patients.

Asthma. For reference to the use of minocycline in the treatment of asthma, see under Tetracycline, p. 376.1.

Musculoskeletal and joint disorders. For reference to the use of minocycline in the treatment of rheumatoid arthritis, see under Tetracycline, p. 376.2.

Neuroprotective effect. Minocycline has been shown to have a neuroprotective effect[1] in *animal* models of stroke (p. 1269.2), brain and spinal cord injury, and neurodegenerative disorders such as Huntington's chorea (p. 1029.3), multiple sclerosis (p. 998.3), Parkinson's disease (p. 890.1), and amyotrophic lateral sclerosis (ALS, a form of motor neurone disease, p. 2605.2); however it is unclear whether it can produce clinical benefits. Clinical studies in a few patients with **Huntington's chorea** indicated that minocycline was well tolerated[2] and had a neuroprotective effect.[3] Similarly, an open-label study[4] in 152 patients with acute ischaemic **stroke** suggested that giving minocycline at the acute stage improved the outcome. However, a randomised placebo-controlled study[5] in 412 patients with **ALS**, given minocycline in escalating doses (up to 400 mg daily) for 9 months reported a harmful effect. Minocycline has also been proposed[6,7] as an adjunct in the management of schizophrenia (p. 1031.3).

1. Plane JM, *et al.* Prospects for minocycline neuroprotection. *Arch Neurol* 2010; 67: 1442–8.
2. Huntington Study Group. Minocycline safety and tolerability in Huntington disease. *Neurology* 2004; 63: 547–9.
3. Bonelli RM, *et al.* Neuroprotection in Huntington's disease: a 2-year study on minocycline. *Int Clin Psychopharmacol* 2004; 19: 337–42.
4. Lampl Y, *et al.* Minocycline treatment in acute stroke: an open-label, evaluator-blinded study. *Neurology* 2007; 69: 1404–10.
5. Gordon PH, *et al.* Efficacy of minocycline in patients with amyotrophic lateral sclerosis: a phase III randomised trial. *Lancet Neurol* 2007; 6: 1045–53.
6. Miyaoka T. Clinical potential of minocycline for schizophrenia. *CNS Neurol Disord Drug Targets* 2008; 7: 376–81.
7. Levkovitz Y, *et al.* A double-blind, randomized study of minocycline for the treatment of negative and cognitive symptoms in early-phase schizophrenia. *J Clin Psychiatry* 2010; 71: 138–49.

Skin disorders. For reference to the use of minocycline in the treatment of various skin disorders, see under Tetracycline, p. 376.3.

Adverse Effects and Precautions

As for Tetracycline, p. 377.1.

Gastrointestinal disturbances with minocycline are reported to be less frequent than with the less well absorbed tetracyclines.

Oesophageal ulceration has occurred and may be a particular problem if capsules or tablets are taken with insufficient fluid or in a recumbent posture: minocycline should be taken with at least half a glass of water, in an upright position, and well before going to bed.

Vestibular adverse effects including dizziness or vertigo may occur with minocycline, particularly in women. Patients should be advised not to drive or operate machinery if affected. Tinnitus and decreased hearing have been reported rarely.

There have also been reports, some fatal, of a hypersensitivity syndrome (comprising eosinophilia, fever, rash, and varying additional symptoms), a lupus-like syndrome, and a serum-sickness-like syndrome (both comprising arthralgia, fever, and joint stiffness or swelling, amongst other symptoms).

Minocycline may also cause hyperpigmentation of the skin (see p. 328.1).

Although minocycline, unlike many tetracyclines, does not appear to accumulate in patients with renal impairment, usual doses can lead to higher serum concentrations resulting in possible liver toxicity; reduced doses and monitoring of renal function may be necessary, particularly in those with severe impairment.

The *BNF* recommends that if treatment continues for longer than 6 months patients should be monitored every 3 months for hepatotoxicity, pigmentation, and SLE.

Incidence of adverse effects. Severe complications have been reported in patients given minocycline for acne, including serum-sickness-like disease,[1,2] lupus erythematosus,[3] and hepatitis.[3,4] The number of cases reported probably reflects the widespread use of this drug and the true incidence of such adverse effects is difficult to assess.[5] A study of 700 patients receiving minocycline for acne revealed adverse effects in 13.6%, mostly benign.[6] Gastrointestinal disturbances and vestibular disturbances were the most common, each occurring in about 2% of patients, and pigmentation in up to 4% of patients.

Another problem is that of assessing the efficacy of minocycline and the incidence of severe adverse effects relative to other antibacterials commonly used in acne such as tetracycline and erythromycin. A systematic review[7] suggested that the incidence of adverse effects might be greater with minocycline than with doxycycline. A retrospective analysis[8] of a UK population database found that minocycline was associated with an increased risk for drug-induced lupus erythematosus; no increased risk was reported for the other tetracyclines. Other systematic reviews[9,10] concluded that minocycline should not be used as a first-line oral tetracycline in patients with acne since there is no compelling evidence that it is more effective than some other tetracyclines or commonly used treatments; the risk of rare but serious adverse effects also makes it less suitable.[10]

1. Knowles SR, *et al.* Serious adverse reactions induced by minocycline: report of 13 patients and review of the literature. *Arch Dermatol* 1996; 132: 934–9.
2. Harel L, *et al.* Serum-sickness-like reaction associated with minocycline therapy in adolescents. *Ann Pharmacother* 1996; 30: 481–3.
3. Gough A, *et al.* Minocycline induced autoimmune hepatitis and systemic lupus erythematosus-like syndrome. *BMJ* 1996; 312: 169–72.
4. Australian Adverse Drug Reactions Advisory Committee (ADRAC). Minocycline and the liver, the CNS, the skin. *Aust Adverse Drug React Bull* 1996; 15: 14. Also available at: http://www.tga.gov.au/adr/aadrb/aadr9611.htm (accessed 11/08/08)
5. Seukeran DC, *et al.* Benefit-risk assessment of acne therapies. *Lancet* 1997; 349: 1251–2.
6. Goulden V, *et al.* Safety of long-term high-dose minocycline in the treatment of acne. *Br J Dermatol* 1996; 134: 693–5.
7. Smith K, Leyden JJ. Safety of doxycycline and minocycline: a systematic review. *Clin Ther* 2005; 27: 1329–42.
8. Margolis DJ, *et al.* Association or lack of association between tetracycline class antibiotics used for acne vulgaris and lupus erythematosus. *Br J Dermatol* 2007; 157: 540–6.
9. Garner SE, *et al.* Minocycline for acne vulgaris: efficacy and safety. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 16/05/05).
10. McManus P, Theanacho I. Don't use minocycline as first line oral antibiotic in acne. *BMJ* 2007; 334: 154.

Effects on intracranial pressure. Minocycline has been associated with benign intracranial hypertension; for further details, see under Tetracycline, p. 377.2.

Effects on the liver. A systematic review[1] considered 65 published case reports of hepatitis or liver damage associated with the use of minocycline for acne, including 4 fatalities, and also data held by WHO concerning 493 reactions involving the liver in 393 patients in whom the indication for the use of minocycline was largely unspecified.

Of the 65 published cases, 38 occurred in females and 61 in patients under 40 years of age. These cases appeared to be of the following types:

- 16 cases appeared to be attributable to a hypersensitivity reaction, with a rapid onset usually within 1 month of starting treatment and sometimes associated with eosinophilia and exfoliative dermatitis
- 29 cases of hepatitis (of which 20 were in females) appeared to be of an auto-immune nature, occurring after 1 year or more of therapy and sometimes associated with lupus-like symptoms
- 20 cases could not be definitively classified into either group

The 393 patients described by the WHO data had 22 different types of hepatic reaction that could be broadly grouped into 4 categories:

- hepatic dysfunction (32% of patients)
- hepatitis (26%)
- abnormal liver function tests (24%)
- hyperbilirubinaemia or jaundice (14%)

There were, in addition, several other reactions, including hepatic damage or necrosis in 11 patients and fatty liver in 7. Gender distribution was almost even. Of the 393 patients, 14 also had lupus-like symptoms. The outcome of the hepatic reactions was reported in less than half of the patients, although it was apparent that there had been at least 3 fatalities.

Despite these findings, the reviewers concluded[1] that there was no clear information regarding the absolute or relative risks of hepatitis in patients given minocycline, and that it was inappropriate to comment as to whether monitoring would be worthwhile. A study of the comparative rates of hepatitis in people exposed to minocycline compared with those who were not was required.

1. Lawrenson RA, *et al.* Liver damage associated with minocycline use in acne: a systematic review of the published literature and pharmacovigilance data. *Drug Safety* 2000; 23: 333–49.

Effects on the lungs. Hypersensitivity pneumonitis, characterised by pulmonary infiltrates and eosinophilia, has been reported[1-6] with minocycline. In most cases, the pneumonitis resolved after stopping minocycline but some required corticosteroid therapy; however, residual lung

damage can occur. In one case[6] relapsing acute respiratory failure that required mechanical ventilation was reported.

1. Guillon J-M, *et al.* Minocycline-induced cell-mediated hypersensitivity pneumonitis. *Ann Intern Med* 1992; 117: 476–81.
2. Bridges AJ. Minocycline-induced pneumonia. *Ann Intern Med* 1993; 118: 749–50.
3. Sigmann P. Minocycline-induced pneumonia. *Ann Intern Med* 1993; 118: 750.
4. Sitbon O, *et al.* Minocycline pneumonitis and eosinophilia: a report on 8 patients. *Arch Intern Med* 1994; 154: 1633–40.
5. Dykhuizen RS, *et al.* Minocycline and pulmonary eosinophilia. *BMJ* 1995; 310: 1520–1.
6. Oddo M, *et al.* Relapsing acute respiratory failure induced by minocycline. *Chest* 2003; 123: 2146–8.

Hyperpigmentation. Minocycline has been associated with pigmentation of the skin and other tissues.[1-5] Three patterns of skin pigmentation have been described:[1] blue-black macules occurring in areas of inflammation and scarring, possibly due to an iron chelate of minocycline within macrophages; blue-grey macules or hyperpigmentation affecting normal skin, which may be due to a breakdown product of minocycline; or a greyish-brown discoloration occurring particularly in sun-exposed areas of skin ('muddy skin syndrome'), apparently due to melanin deposition. In general, pigmentation results from long-term use of minocycline at cumulative doses greater than 100 g; however, skin or oral mucosal pigmentation may occur regardless of dose or duration of therapy.[2] Indeed, there have been reports[3] of skin pigmentation developing after short-term use ranging from 3 to 28 days. Pigmentation of the skin and oral mucosa usually appears to resolve slowly on stopping the drug although recovery may be incomplete; pigmentation is often permanent when other sites are involved.[2]

1. Basler RSW. Minocycline-related hyperpigmentation. *Arch Dermatol* 1985; 121: 606–8.
2. Elsen D, Hakim MD. Minocycline-induced pigmentation: incidence, prevention and management. *Drug Safety* 1998; 18: 431–40.
3. Nakamura S, *et al.* Acute pigmentation due to minocycline therapy in atopic dermatitis. *Br J Dermatol* 2003; 148: 1073–4.
4. Geria AN, *et al.* Minocycline-induced skin pigmentation: an update. *Acta Dermatovenerol Croat* 2009; 17: 123–6.
5. Youssef S, *et al.* Minocycline-induced pigmentation mimicking persistent ecchymosis. *Cutis* 2009; 84: 22–6.

Minocycline-induced autoimmunity. It has been suggested that some rare adverse effects of minocycline, such as drug-induced lupus, auto-immune hepatitis, serum sickness, and vasculitis, with or without the development of antinuclear antibodies or other autoantibodies, might all represent aspects of a single process, referred to as minocycline-induced autoimmunity (MIA). Patients usually show constitutional symptoms such as fever, malaise, loss of appetite, rash, arthralgia, myalgia, and auto-immune hepatitis; most cases occur in young women being treated for acne.[1,2]

In a retrospective cohort study[2] (from September 1996 to September 2006) that identified 27 children (19 female) with MIA, symptoms on stopping minocycline resolved rapidly in 14 of the children and within 12 months in another 6 but 7 had chronic auto-immune disease 13 to 48 months later. All patients with chronic disease had evidence of arthritis at presentation and required long-term treatment with immunosuppressives. No association was found between the duration of use, cumulative dose, and clinical outcomes. Long-term immune system alteration, after a drug hypersensitivity reaction, has also been reported in a 15-year-old girl given minocycline for the treatment of acne vulgaris. She developed auto-immune hyperthyroidism 7 weeks after stopping the minocycline and auto-immune type 1 diabetes mellitus 7 months after stopping the minocycline. In addition, she developed elevated titres of several markers of systemic auto-immune disease, including antinuclear, anti-Sjögren syndrome A, and anti-Smith antibodies.[3]

A retrospective literature review from 1966 to April 1998 identified more than 60 cases of minocycline-induced SLE and 24 cases of minocycline-induced auto-immune hepatitis after long-term use of minocycline (4 to 120 months).[4] Thirteen patients (10 female) with both auto-immune disorders were reviewed. Symptoms in all these patients included symmetrical polyarthralgias and polyarthritis, raised liver enzyme values, and positive antinuclear antibodies; 10 patients reported constitutional symptoms. Four patients received treatment with corticosteroids, alone or with hydroxychloroquine and/or azathioprine, but symptoms resolved, and laboratory results normalised or significantly improved in all patients after minocycline was stopped.[4]

1. Moore TL. Autoimmunity and minocycline. *J Pediatr* 2008; 153: 303–4.
2. El-Hallak M, *et al.* Chronic minocycline-induced autoimmunity in children. *J Pediatr* 2008; 153: 314–9.
3. Brown RJ, *et al.* Minocycline-induced drug hypersensitivity syndrome followed by multiple autoimmune sequelae. *Arch Dermatol* 2009; 145: 63–6.
4. Angulo JM, *et al.* Coexistent minocycline-induced systemic lupus erythematosus and autoimmune hepatitis. *Semin Arthritis Rheum* 1998; 28: 187–92.

Interactions

As for Tetracycline, p. 377.3.

Minocycline has a lower affinity for binding with calcium than tetracycline. Consequently its absorption is less likely to be affected by milk or food, although it is still affected by calcium-containing antacids and other divalent and trivalent cations such as aluminium, bismuth, iron, magnesium, and zinc.

Antimicrobial Action

Minocycline has a spectrum of activity and mode of action similar to that of tetracycline (p. 377.3) but it is more active against many species including *Staphylococcus aureus*, streptococci, *Neisseria meningitidis*, various enterobacteria, *Acinetobacter*, *Bacteroides*, *Haemophilus*, *Nocardia*, and some mycobacteria, including *M. leprae*.

Partial cross-resistance exists between minocycline and other tetracyclines but some strains resistant to other drugs of the group remain sensitive to minocycline, perhaps because of better cell-wall penetration.

Pharmacokinetics

For the general pharmacokinetics of the tetracyclines, see Tetracycline, p. 378.2.

Minocycline is readily and almost completely absorbed from the gastrointestinal tract and absorption is not significantly affected by the presence of food or moderate amounts of milk. After an oral loading dose of 200 mg peak plasma concentrations ranging from 2 to 4 micrograms/mL occur after 2 to 4 hours and fall to about 1 microgram/mL after 24 hours; a maintenance dose of 100 mg every 12 hours keeps the plasma concentration at about 2.3 to 3.5 micrograms/mL. On intravenous infusion of a dose of 100 mg a mean peak plasma concentration of 8.75 micrograms/mL is produced, and falls to 1.32 micrograms/mL after 24 hours; after daily infusions of a dose of 200 mg plasma concentrations of 1 to 4 micrograms/mL are maintained.

Minocycline is more lipid-soluble than doxycycline and the other tetracyclines and is widely distributed in body tissues and fluids with high concentrations being achieved in the hepatobiliary tract, lungs, sinuses and tonsils, as well as in tears, saliva, and sputum. Penetration into the CSF is relatively poor, although a higher ratio of CSF to blood concentrations has been reported with minocycline than with doxycycline and other tetracyclines. It crosses the placenta and is distributed into breast milk. About 75% of minocycline in the circulation is bound to plasma proteins. The plasma half-life is about 16 hours after the first dose and 21 hours after repeated doses.

It has a low renal clearance: only about 8 to 13% of a dose is excreted unchanged in the urine and up to about 20 to 30% is excreted unchanged in the faeces. However, in contrast to most tetracyclines it appears to undergo some metabolism in the liver, mainly to 9-hydroxyminocycline. Sources differ as to whether the normal plasma half-life is prolonged in patients with renal impairment, with a consequent risk of accumulation; hepatic impairment does not appear to lead to accumulation. Little minocycline is removed by haemodialysis and peritoneal dialysis.

Reviews.

1. Saivin S, Houin G. Clinical pharmacokinetics of doxycycline and minocycline. *Clin Pharmacokinet* 1988; 15: 355–66.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Acneclin; Clinax; Melbi; Minocin†; Pimple†; Sebodear; *Austral.*: Akamin; Minomycin; *Austria*: Auramin†; Minostad; Udima; *Belg.*: Klinotab; Mino-50; Minocin; Minotab; *Braz.*: Minoderm; *Canad.*: Arestin; Enca†; Minocin; *Chile*: Bagomicina; Pracne; *China*: Kang Ni (康尼); Mei Nong (美依); Mei Nuo Xing (美诺星); Meikewei (美克威); Minocin (玫瑞); Periocline (派丽奥); *Fr.*: Mestacine; Minolis†; Mynocine; Parocline; Zacnan†; *Ger.*: Aknefug Mino†; Aknosan; Klinomycin†; Minakne; Minoclir; Minoplus†; Skid; Skinocyclin†; Udima; *Gr.*: Cycline; Minocin; Periocline; *Hong Kong*: Minaxen†; Minocin†; *India*: CNN; Cynomycin; Divaine; Minolox; Minoz; *Indon.*: Minocin†; *Irl.*: Aknemin; Dentomycin; Minocin; Minodene; Minosil; Minox; *Israel*: Arestin; Minoclin; *Ital.*: Minocin; Minotek; *Jpn*: Periocline; *Malaysia*: Borymycin; Minoclin; *Mex.*: Banimed; Micromycin; Minocin; Ranmino†; *Neth.*: Aknemin; Minocin†; Minotab†; Minotek; Peritrol†; *NZ*: Minomycin; Minotabs; *Philipp.*: Miriocin; *Port.*: Arestin; Cipancin; Minocin; Minotrex; *S.Afr.*: Cyclimycin; Minotabs; Triomin†; *Singapore*: Borymycin; Minocin; *Spain*: Minocin; *Swed.*: Arestin†; *Switz.*: Aknin-N†; Aknoral†; Minac 50; Minocin; *Thai.*: Minocin; *UK*: Aknemin; Dentomycin; Minocin; Sebomin; Sebren; *USA*: Arestin; Cleeravue-M; Dynacin; Minocin; Myrac†; Solodyn; Ximino.

Pharmacopoeial Preparations

BP 2014: Minocycline Tablets; Prolonged-release Minocycline Capsules;

USP 36: Minocycline for Injection; Minocycline Hydrochloride Capsules; Minocycline Hydrochloride Oral Suspension; Minocycline Hydrochloride Tablets; Minocycline Periodontal System.

Morinamide *(pINN)*

Morfazinamide; Morinamida; Morinamidum; Morphazinamide; Моринамид.

N-Morpholinomethylpyrazine-2-carboxamide.

$C_{10}H_{14}N_4O_2$=222.2

CAS — 952-54-5.

ATC — J04AK04.

ATC Vet — QJ04AK04.

UNII — 8CFL28PA3W.

Profile

Morinamide is an antimycobacterial that has been given orally as the hydrochloride in the treatment of tuberculosis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Turk.*: Morfozid.

Moxifloxacin Hydrochloride

(BANM, USAN, rINNM)

Bay-12-8039; Hidrocloruro de moxifloxacino; Moxifloxacine, chlorhydrate de; Moxifloxacinhydrochlorid; Moxifloxacini Hydrochloridum; Moxifloxacino, hidrocloruro de; Моксифлоксацина Гидрохлорид.

1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[(4aS,7aS)-octahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl]-4-oxo-3-quinolinecarboxylic acid hydrochloride.

$C_{21}H_{24}FN_3O_4HCl$=437.9

CAS — 151096-09-2 (moxifloxacin); 186826-86-8 (moxifloxacin hydrochloride).

ATC — J01MA14; S01AE07.

ATC Vet — QJ01MA14; QS01AE07.

UNII — C5359859ST.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Moxifloxacin Hydrochloride). Produced using a method validated to show the satisfactory enantiomeric purity of the final product. A light yellow or yellow powder or crystals, slightly hygroscopic. Sparingly soluble in water; slightly soluble in alcohol; practically insoluble in acetone. A 0.2% solution in water has a pH of 3.9 to 4.6. Store in airtight containers. Protect from light.

USP 36: (Moxifloxacin Hydrochloride). Slightly yellow to yellow powder or crystals. Sparingly soluble in water and in methyl alcohol; slightly soluble in alcohol, in dimethylformamide, and in 0.1N hydrochloric acid; practically insoluble in acetone, in dichloromethane, in ethyl acetate, and in toluene; soluble in 0.1N sodium hydroxide; insoluble in *n*-heptane and in methyl *tert*-butyl ether. Store in airtight containers. Protect from light.

Uses and Administration

Moxifloxacin is a fluoroquinolone antibacterial with actions and uses similar to those of ciprofloxacin (p. 261.2).

It may be given orally, or by intravenous infusion over 60 minutes, for the treatment of susceptible infections including respiratory, skin and skin structure, and intra-abdominal infections. However, due to safety concerns, its use has now been restricted in the EU to the treatment of acute bacterial sinusitis, acute exacerbation of chronic bronchitis, or community-acquired pneumonia only when other medicines cannot be prescribed or have failed. Moxifloxacin is given as the hydrochloride but doses are expressed in terms of the base; moxifloxacin hydrochloride 436.3 mg is equivalent to about 400 mg of moxifloxacin. The usual dose is 400 mg once daily.

Moxifloxacin is also used topically as the hydrochloride in eye drops containing the equivalent of 0.5% of moxifloxacin for the treatment of bacterial conjunctivitis.

Reviews.

1. Keating GM, Scott LJ. Moxifloxacin: a review of its use in the management of bacterial infections. *Drugs* 2004; 64: 2347–77.
2. O'Brien TP. Evidence-based review of moxifloxacin. *Int Ophthalmol Clin* 2006; 46: 61–72.
3. Miravitlles M, *et al.* Eficacia clínica del moxifloxacino en el tratamiento de las agudizaciones de la bronquitis crónica: revisión sistemática y metaanálisis. *Arch Bronconeumol* 2007; 43: 22–8.
4. Miravitlles M. Moxifloxacin in the management of exacerbations of chronic bronchitis and COPD. *Int J Chron Obstruct Pulmon Dis* 2007; 2: 191–204.
5. O'Brien TP, *et al.* Perspectives on antibiotics for postoperative endophthalmitis prophylaxis: potential role of moxifloxacin. *J Cataract Refract Surg* 2007; 33: 1790–800.
6. Anonymous. Moxifloxacin. *Tuberculosis (Edinb)* 2008; 88: 127–31.
7. Ludlam HA, Enoch DA. Doxycycline or moxifloxacin for the management of community-acquired pneumonia in the UK? *Int J Antimicrob Agents* 2008; 32: 101–5.

Eye infections. In order to attain therapeutic concentrations most antibacterials used in the treatment of bacterial endophthalmitis need to be given by the intravitreal route but moxifloxacin given systemically may produce adequate concentrations. An oral dose of moxifloxacin 400 mg daily may be given for 10 days.[1]

1. Moorfields Eye Hospital NHS Foundation Trust. *Pharmacists Handbook 2006*. London: Moorfields Pharmaceuticals, 2006.

Tuberculosis. For mention of the use of moxifloxacin in the treatment of tuberculosis, see under Ciprofloxacin, p. 262.2.

Adverse Effects and Precautions

As for Ciprofloxacin, p. 262.2.

References.

1. Faich GA, *et al.* Clinical experience with moxifloxacin in patients with respiratory tract infections. *Ann Pharmacother* 2004; 38: 749–54.
2. Ball P, *et al.* Safety profile of oral and intravenous moxifloxacin: cumulative data from clinical trials and postmarketing studies. *Clin Ther* 2004; 26: 940–50.
3. Andriole VT, *et al.* Retrospective analysis of the safety profile of oral moxifloxacin in elderly patients enrolled in clinical trials. *Drug Safety* 2005; 28: 443–52.
4. Van Bambeke F, Tulkens PM. Safety profile of the respiratory fluoroquinolone moxifloxacin: comparison with other fluoroquinolones and other antibacterial classes. *Drug Safety* 2009; 32: 359–78.

Effects on the liver. Like other fluoroquinolones (p. 263.1) moxifloxacin has been associated with rare cases of severe and even fatal liver toxicity.[1-3] Although a review of the relative toxicities of moxifloxacin and other fluoroquinolones and antibacterials considered that the incidence of such reactions with moxifloxacin was not significantly different than with other fluoroquinolones, and less than that reported with amoxicillin plus clavulanic acid,[3] an analysis by regulatory authorities in the EU[4] considered that they were of sufficient concern that use of moxifloxacin should be restricted (see Uses and Administration, p. 326.3).

1. Soto S, *et al.* Moxifloxacin-induced acute liver injury. *Am J Gastroenterol* 2002; 97: 1853–4.
2. Nori S, *et al.* Moxifloxacin-associated drug hypersensitivity syndrome with toxic epidermal necrolysis and fulminant hepatic failure. *Arch Dermatol* 2004; 140: 1537–8.
3. Van Bambeke F, Tulkens PM. Safety profile of the respiratory fluoroquinolone moxifloxacin: comparison with other fluoroquinolones and other antibacterial classes. *Drug Safety* 2009; 32: 359–78.
4. EMEA/CHMP. European Medicines Agency recommends restricting the use of oral moxifloxacin-containing medicines (issued 24/07/08). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/38292708en.pdf (accessed 18/09/09)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies moxifloxacin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

As for Ciprofloxacin, p. 264.3.

Moxifloxacin does not appear to interact significantly with theophylline or probenecid.

Antimicrobial Action

As for Ciprofloxacin, p. 265.2.

Moxifloxacin is reported to have greater activity against Gram-positive bacteria, including pneumococci, than ciprofloxacin.

References.

1. Stein GE, *et al.* Bactericidal activities of methoxyfluoroquinolones gatifloxacin and moxifloxacin against aerobic and anaerobic respiratory pathogens in serum. *Antimicrob Agents Chemother* 2003; 47: 1308–12.
2. Pletz MWR, *et al.* Early bactericidal activity of moxifloxacin in treatment of pulmonary tuberculosis: a prospective, randomized study. *Antimicrob Agents Chemother* 2004; 48: 780–2.

Pharmacokinetics

Moxifloxacin is readily absorbed from the gastrointestinal tract after oral doses with an absolute bioavailability of about 90%. It is widely distributed throughout the body tissues and is about 30 to 50% bound to plasma proteins. Moxifloxacin has an elimination half-life of about 12 hours, allowing once-daily dosing. It is metabolised mainly via sulfate and glucuronide conjugation, and is excreted in the urine and the faeces as unchanged drug and as metabolites, the sulfate conjugate mainly in the faeces and the glucuronide exclusively in the urine. Distribution into milk has been found in *animals*.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Avelox; Moflag; Vigamox; *Austral.*: Avelox; *Austria*: Actira; Avelox; Octegra; *Belg.*: Avelox; Kanavig; Proflox; *Braz.*: Avalox; Vigamox; *Canad.*: Avelox; Vigamox; *Chile*: Avelox; Flovacil; Imix; Moxaval; Moxicino; Moxof; Vigamox; *China*: Avelox (拜复乐); *Cz.*: Avelox; Vigamox; *Denm.*: Avelox; Infekt; Vigamox; *Fin.*: Avelox; Vigamox; *Fr.*: Izilox; *Ger.*: Avalox; Vigamox; *Gr.*: Avelox; Mikrobiel; Octegra; Proflox; Rucela; Vigamox; *Hong Kong*: Avelox; Vigamox; *Hung.*: Avelox; Octegra†; *India*: Apdrops; Emef; Eye-Quin; Floxsafe; Hinemox; Inmox; L-Floxin; M-Moflo; Mediflox; Mo-Floren; Mofil; Mosi; Moxiblu; Moxicip; Moxif; Moxigram; Moximycin; Moxl; Otymox-MF; *Indon.*: Avelox; Vigamox; *Irl.*: Avelox; Moxivig; Vigamox†; *Israel*: Megaxin; Vigamox; *Ital.*: Actira; Avalox; Octegra; *Jpn*: Avelox; *Malaysia*: Avelox; Vigamox; *Mex.*: Avelox; Vigamoxi; *Neth.*: Avelox; Octegra†; Vigamox; *NZ*: Avelox; Vigamox; *Philipp.*: Avelox; Moxiflox; Vigamox; *Pol.*: Avelox; Vigamox; *Port.*: Avelox; Proflox; *Rus.*: Avelox (Авелокс); Moximac (Моксимак); Plevilox (Плевилокс); Vigamox (Вигамокс); *S.Afr.*: Avebact; Avelon; Litares; Moxibay; Numoxx; Vigamox; *Singapore*: Avelox; Vigamox; *Spain*: Actira; Havelox†; Octegra†; Proflox; Vigamox; *Swed.*: Avelox; Vigamox; *Switz.*: Avalox; Vigamox; *Thai.*: Avelox; Vigamox; *Turk.*: Atafloks; Avelox; Mofelox; Moxal; Moxifor; Moxitec; Pitoxil; Vigamox; *UK*: Avelox; Moxivig; *Ukr.*: Avelox (Авелокс); Maxicin (Максицин); *USA*: Avelox; Moxeza; Vigamox; *Venez.*: Avelox; Vigamox.

Multi-ingredient Preparations. *Arg.*: Moflag D; Vigadexa; *India*: Milflox Plus; Mosi-D; Moxi-Mep-D; Moxiblu-D; Moxigram-DX; *Thai.*: Vigadexa.

Pharmacopoeial Preparations

USP 36: Moxifloxacin Ophthalmic Solution.

Mupirocin *(BAN, USAN, rINN)*

BRL-4910A; Mupirocina; Mupirocinas; Mupirocine; Mupirocinum; Mupirosiini; Pseudomonic Acid; Мупироцин.

9-[(2*E*)-4-[(2*S*,3*R*,4*R*,5*S*)-5-[(2*S*,3*S*,4*S*,5*S*)-2,3-Epoxy-5-hydroxy-4-methylhexyl]tetrahydro-3,4-dihydroxypyran-2-yl]-3-methylbut-2-enoyloxy]nonanoic acid; (2*S*-[2α(*E*),3β,4β,5α[2*R**,3*R**(1*R**,2*R**)]])-9-[[3-Methyl-1-oxo-4-(tetrahydro-3,4-dihydroxy-5-[[3-(2-hydroxy-1-methyl-propyl)oxiranyl]methyl]-2*H*-pyran-2-yl)-2-butenyl]oxy]nonanoic acid.

$C_{26}H_{44}O_9$=500.6

CAS — 12650-69-0.

ATC — D06AX09; R01AX06.

ATC Vet — QD06AX09; QR01AX06.

UNII — D0GX863OA5.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Mupirocin). A white or almost white powder. It shows polymorphism. Slightly soluble in water; freely soluble in dehydrated alcohol, in acetone, and in dichloromethane. The pH of a freshly prepared saturated solution in water is 3.5 to 4.0. Protect from light.

USP 36: (Mupirocin). A white to off-white crystalline solid. Very slightly soluble in water; freely soluble in dehydrated alcohol, in acetone, in chloroform, and in methyl alcohol; slightly soluble in ether. pH of a saturated solution in water is between 3.5 and 4.5. Store in airtight containers.

Mupirocin Calcium *(BANM, USAN, rINNM)*

BRL-4910F; Calcii Mupirocinum; Mupirocin-Calcium; Mupirocin vápenatá sůl dihydrát; Mupirocina cálcica; Mupirocine Calcique; Mupirocinkalcium; Mupirocin-kalcium; Mupirocino kalcio druska; Mupirocinum calcicum; Mupirocinum Calcium Dihydricum; Mupirosiinikalsium; Кальций Мупироцин.

$C_{52}H_{86}O_{18}Ca,2H_2O$=1075.4

CAS — 104486-81-9 (anhydrous mupirocin calcium); 115074-43-6 (mupirocin calcium dihydrate).

ATC — D06AX09; R01AX06.

ATC Vet — QD06AX09; QR01AX06.

UNII — RG38I2P540.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Mupirocin Calcium). A white or almost white powder. Very slightly soluble in water; sparingly soluble in dehydrated alcohol and in dichloromethane.

USP 36: (Mupirocin Calcium). Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Mupirocin is an antibacterial produced by *Pseudomonas fluorescens*. It is applied topically as a 2% ointment in a macrogol base, or as a cream containing mupirocin calcium equivalent to 2% mupirocin, in the treatment of various bacterial skin infections. These preparations should be applied up to 3 times daily for up to 10 days; treatment should be re-evaluated if there is no response after 3 to 5 days. They are not suitable for application to mucous membranes, and therefore a nasal ointment containing mupirocin calcium equivalent to 2% mupirocin in a paraffin basis is used for eradication of the nasal carriage of *Staphylococcus aureus*, particularly epidemic meticillin-resistant strains. The nasal ointment should be applied into each nostril 2 or 3 times daily for a maximum of 7 days.

For further details of skin infections and staphylococcal infections and their treatment, see under Choice of Antibacterial, p. 207.1 and p. 208.2 respectively.

References.

1. Roth VR, *et al.* Should we routinely use mupirocin to prevent staphylococcal infections? *Infect Control Hosp Epidemiol* 2000; 21: 745–9.
2. Perl TM, *et al.* Mupirocin and the Risk of Staphylococcus Aureus Study Team. Intranasal mupirocin to prevent postoperative Staphylococcus aureus infections. *N Engl J Med* 2002; 346: 1871–7.
3. Takahashi S, *et al.* The preventive effects of mupirocin against nasotracheal intubation-related bacterial carriage. *Anesth Analg* 2003; 97: 222–5.
4. Laupland KB, Conly JM. Treatment of Staphylococcus aureus colonization and prophylaxis for infection with topical intranasal mupirocin: an evidence-based review. *Clin Infect Dis* 2003; 37: 933–8.
5. Tacconelli E, *et al.* Mupirocin prophylaxis to prevent Staphylococcus aureus infection in patients undergoing dialysis: a meta-analysis. *Clin Infect Dis* 2003; 37: 1629–38.
6. Wertheim HF, *et al.* Mupirocin prophylaxis against nosocomial Staphylococcus aureus infections in nonsurgical patients: a randomized study. *Ann Intern Med* 2004; 140: 419–25.
7. Kallen AJ, *et al.* Perioperative intranasal mupirocin for the prevention of surgical-site infections: systematic review of the literature and meta-analysis. *Infect Control Hosp Epidemiol* 2005; 26: 916–22.
8. Unemura Y, *et al.* Impact of prophylactic mupirocin for radical esophagectomy. *J Infect Chemother* 2006; 12: 257–63.
9. Sit D, *et al.* Prophylactic intranasal mupirocin ointment in the treatment of peritonitis in continuous ambulatory peritoneal dialysis patients. *Adv Therapy* 2007; 24: 387–93.
10. van Rijen M, *et al.* Mupirocin ointment for preventing Staphylococcus aureus infections in nasal carriers. Available in The Cochrane Database of Systematic Reviews: Issue 4. Chichester: John Wiley; 2008 (accessed 02/09/09).
11. Coates T, *et al.* Nasal decolonization of Staphylococcus aureus with mupirocin: strengths, weaknesses and future prospects. *J Antimicrob Chemother* 2009; 64: 9–15.
12. Xu G, *et al.* Mupirocin for preventing exit-site infection and peritonitis in patients undergoing peritoneal dialysis. *Nephrol Dial Transplant* 2010; 25: 587–92.

Adverse Effects and Precautions

Mupirocin is usually well tolerated but local reactions such as burning, stinging, and itching may occur after the application of mupirocin to the skin.

Some mupirocin products are formulated in a macrogol base: such formulations are not suitable for application to mucous membranes and should be used with caution in patients with extensive burns or wounds because of the possibility of macrogol toxicity. Care is also required in patients with renal impairment.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mupirocin as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Antimicrobial Action

Mupirocin is an antibacterial that inhibits bacterial protein synthesis by binding to isoleucyl transfer RNA synthetase. It is mainly bacteriostatic at low concentrations, although it is usually bactericidal in the high concentrations achieved by topical application to the skin. At these concentrations it may have some activity against organisms reported to be relatively resistant to mupirocin *in vitro*.

- It is mainly active against Gram-positive aerobes. Most strains of staphylococci (including meticillin-resistant and multiply-resistant *Staph. aureus*) and streptococci are susceptible *in vitro*, although the enterococci are relatively resistant.
  Mupirocin is also active against *Listeria monocytogenes* and *Erysipelothrix rhusiopathiae*.
- The Gram-negative organisms are generally insensitive, but *Haemophilus influenzae*, *Neisseria* spp. and a few others are sensitive.
- Anaerobic organisms, both Gram-positive and Gram-negative, are generally resistant, and activity against fungi is low.

Mupirocin is more active *in vitro* at acid pH than in alkaline conditions.

Naturally resistant strains of *Staph. aureus* occur rarely but resistance, including high-level plasmid-mediated transferable resistance, has emerged, particularly during long-term use. There has been some concern that inappropriate prescribing of mupirocin has led to this steadily increasing resistance.

Activity against fungi. Activity of mupirocin 2% *in vitro* against *Candida albicans* was comparable to that of other commonly used topical antifungals. Although MICs were considerably in excess of those reported for susceptible bacteria, clinical responses in 10 patients suggested that

adequate concentrations of mupirocin were achieved after topical application.[1]

1. Rode H, *et al.* Efficacy of mupirocin in cutaneous candidiasis. *Lancet* 1991; 338: 578.

Resistance. References.

1. Cookson BD. The emergence of mupirocin resistance: a challenge to infection control and antibiotic prescribing practice. *J Antimicrob Chemother* 1998; 41: 11–18.
2. Schmitz F-J, *et al.* The prevalence of low- and high-level mupirocin resistance in staphylococci from 19 European hospitals. *J Antimicrob Chemother* 1998; 42: 489–95.
3. Upton A, *et al.* Mupirocin and Staphylococcus aureus: a recent paradigm of emerging antibiotic resistance. *J Antimicrob Chemother* 2003; 51: 613–17.
4. Kresken M, *et al.* Prevalence of mupirocin resistance in clinical isolates of Staphylococcus aureus and Staphylococcus epidermidis: results of the Antimicrobial Resistance Surveillance Study of the Paul-Ehrlich-Society for Chemotherapy, 2001. *Int J Antimicrob Agents* 2004; 23: 577–81.
5. Walker ES, *et al.* A decline in mupirocin resistance in methicillin-resistant Staphylococcus aureus accompanied administrative control of prescriptions. *J Clin Microbiol* 2004; 42: 2792–5.
6. Patel JB, *et al.* Mupirocin resistance. *Clin Infect Dis* 2009; 49: 935–41.

Pharmacokinetics

Only very small amounts of topically applied mupirocin are absorbed into the systemic circulation where it is rapidly metabolised to monic acid, which is excreted in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Bactroban; Dimsa; Mupax; Mupirox; Paldar; Quemicetina Nasal NF; Vidox; *Austral.*: Bactroban; *Austria*: Bactroban; *Belg.*: Bactroban; *Braz.*: Bactrocin; Bactocin; Bactroban; Bactroneo; Dermoban; Supirocin; *Canad.*: Bactroban; *Chile*: Bactroban; Bantix; Paldar; Ultrabiotic; Underan; *China*: Bactroban (百多邦); *Cz.*: Bactroban; *Denm.*: Bactroban; *Fin.*: Bactroban; *Fr.*: Bactroban; Mupiderm; *Ger.*: InfectoPyoderm; Turixin; *Gr.*: Bactroban; Bactrocine; Hevronaz; Micoban; Mupider; Mupiran; Veltion; *Hong Kong*: Bactroban; Muprin; *Hung.*: Bactroban; *India*: Bactroban; Brodisym; I-Bact; MPower; Mu-Oint; Mufect; Mupiban; Mupinova; Mupirax; Murocl; Supirocin; *Indon.*: Bactoderm; Bactroban; Pibaksin; *Irl.*: Bactroban; *Israel*: Bactroban; *Ital.*: Bactroban; Mupiskin; *Jpn*: Bactroban; *Malaysia*: Bactroban; Muprin; Supirocin; *Mex.*: Bacskin; Bactroban; Sinpebac; *Neth.*: Bactroban; *NZ*: Bactroban; *Philipp.*: Bactifree; Bactroban; Bactrocin; Foskina; Mupicin; Mupiderm; Muprin; *Pol.*: Bactroban; Mupirox; *Port.*: Bactroban; *Rus.*: Bactroban (Бактробан); Supirocin (Супроцин); *S.Afr.*: Bactroban; Supiroban; *Singapore*: Bactroban; Mupider; Mupirax; Supirocin; *Spain*: Bactroban; Plasimine; *Swed.*: Bactroban; *Switz.*: Bactroban; *Thai.*: Bacidal; Bactex; Bactokil; Bactroban; Banbact; Muporin; *Turk.*: Bactroban; *UK*: Bactroban; *Ukr.*: Bactroban (Бактробан); *USA*: Bactroban; Centany; *Venez.*: Bactroban.

Multi-ingredient Preparations. *India*: Flutibact; Mupimet; Supirocin-B; *Mex.*: Dermucor-H; *Philipp.*: Foskina-B; *Rus.*: Supirocin-B (Супроцин-Б).

Pharmacopoeial Preparations

BP 2014: Mupirocin Cream; Mupirocin Nasal Ointment; Mupirocin Ointment;

USP 36: Mupirocin Cream; Mupirocin Nasal Ointment; Mupirocin Ointment.

Nadifloxacin *(BAN, rINN)*

Jinofloxacin; Nadifloxacine; Nadifloxacino; Nadifloxacinum; OPC-7251; Надифлоксацин.

(±)-9-Fluoro-6,7-dihydro-8-(4-hydroxypiperidino)-5-methyl-1-oxo-1*H*,5*H*-benzo[*ij*]quinolizine-2-carboxylic acid.

$C_{19}H_{21}FN_2O_4$=360.4

CAS — 124858-35-1.

UNII — 6CL9Y5YZEQ.

Profile

Nadifloxacin is a fluoroquinolone antibacterial used in topical treatment of acne. It is applied twice daily as a 1% cream or ointment.

Reviews.

1. Jacobs MR, Appelbaum PC. Nadifloxacin: a quinolone for topical treatment of skin infections and potential for systemic use of its active isomer, WCK 771. *Expert Opin Pharmacother* 2006; 7: 1957–66.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Pingfu (萍敷); Xin Ke Fei (欣可菲); Yi You Ning (依尤宁); *Ger.*: Nadixa; *Gr.*: Nadixa; *India*: Nadibact; Nadicin; Nadiderm; Nadiflox; Nadim; Nadiskin; Nadoxin; *Indon.*: Acuatim; *Ital.*: Nadixa; *Jpn*: Acuatim; *Mex.*: Nadixa; *Philipp.*: Nadoxin; *Port.*: Nadixa; *Spain*: Nadixa; *Turk.*: Nadixa; *Ukr.*: Nadoxin (Надоксин).

Multi-ingredient Preparations. *India*: Metazole; Motoso; Nadicin-C; Nadoxin-C.

Nafcillin Sodium *(BANM, USAN, rINNM)*

Nafcilina sódica; Nafcilline Sodique; Nafcillinnatrium; Nafcillinum Natricum; Nafsilliininatrium; Natrii Nafcillinum; Wy-3277; Натрий Нафциллин.

Sodium (6*R*)-6-(2-ethoxy-1-naphthamido)penicillanate monohydrate.

$C_{21}H_{21}N_2NaO_5S,H_2O$=454.5

CAS — 147-52-4 (nafcillin); 985-16-0 (anhydrous nafcillin sodium); 7177-50-6 (nafcillin sodium monohydrate).

ATC — J01CF06.

UNII — SY07234TTS (anhydrous nafcillin sodium); 49G3001BCK (nafcillin sodium monohydrate).

Pharmacopoeias. In *US*.

USP 36: (Nafcillin Sodium). A white to yellowish-white powder having not more than a slight characteristic odour. Freely soluble in water and in chloroform; soluble in alcohol. pH of a 3% solution in water is between 5.0 and 7.0. Store in airtight containers.

Incompatibility. Nafcillin sodium has been reported to be incompatible with aminoglycosides and some other antibacterials. It has also been reported to be incompatible with acidic and alkaline drugs.

Uses and Administration

Nafcillin is a penicillinase-resistant penicillin used similarly to flucloxacillin (p. 299.2) in the treatment of infections due to staphylococci resistant to benzylpenicillin.

It is given by injection as the sodium salt. Doses are expressed in terms of the equivalent amount of nafcillin; 1.1 g of nafcillin sodium is equivalent to about 1 g of nafcillin. Nafcillin sodium may be given intravenously by slow injection over 5 to 10 minutes or by slow infusion over at least 30 to 60 minutes; usual adult doses are 0.5 to 1 g of nafcillin every 4 hours, although it is usually recommended that it be used for not more than 24 to 48 hours because of the risk of thrombophlebitis. Up to 12 g daily, in divided doses, has been used in deep-seated infections such as endocarditis and osteomyelitis. It has also been given by intramuscular injection in doses of 0.5 to 1 g of nafcillin every 4 to 6 hours.

For details of doses in children, see p. 330.2.

Nafcillin sodium has also been given orally but other penicillinase-resistant penicillins are preferred.

Administration in children. Nafcillin may be given to neonates and children for the treatment of infections caused by susceptible strains of penicillinase-producing staphylococci by intramuscular injection, slow intravenous injection over 5 to 10 minutes, or by intravenous infusion over 30 to 60 minutes.

In the USA, the American Academy of Pediatrics[1] recommends the following doses:

- all neonates with a birth-weight of less than 1.2 kg, and neonates less than 1 week of age with a birth-weight of 1.2 to 2 kg: 25 mg/kg every 12 hours
- neonates less than 1 week of age with a birth-weight of more than 2 kg: 25 mg/kg every 8 hours
- neonates 1 week of age or older with a birth-weight of 1.2 to 2 kg: 25 mg/kg every 8 hours
- neonates 1 week of age or older with a birth-weight of more than 2 kg: 25 to 35 mg/kg every 6 hours
- children 1 month and older: 50 to 100 mg/kg daily in 4 divided doses; 100 to 150 mg/kg daily may be used for severe infections

1. American Academy of Pediatrics. *2009 Red Book: Report of the Committee on Infectious Diseases*, 28th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2009.

Adverse Effects and Precautions

As for Benzylpenicillin, p. 229.2.

Thrombophlebitis may occur when nafcillin is given by intravenous injection, and tissue damage has been reported on extravasation.

Effects on the kidneys. References.

1. Lestico MR, *et al.* Hepatic and renal dysfunction following nafcillin administration. *Ann Pharmacother* 1992; 26: 985–90.
2. Guharoy SR, *et al.* Suspected nafcillin-induced interstitial nephritis. *Ann Pharmacother* 1993; 27: 170–3.
3. Hoppes T, *et al.* Four cases of nafcillin-associated acute interstitial nephritis in one institution. *Nat Clin Pract Nephrol* 2007; 3: 456–61.

Effects on the liver. References.

1. Lestico MR, *et al.* Hepatic and renal dysfunction following nafcillin administration. *Ann Pharmacother* 1992; 26: 985–90.
2. Presti ME, *et al.* Nafcillin-associated hepatotoxicity: report of a case and review of the literature. *Dig Dis Sci* 1996; 41: 180–4.

Lupus erythematosus. A report[1] of apparent drug-induced lupus erythematosus associated with nafcillin.

1. Blazes DL, Martin GJ. Drug-induced lupus erythematosus secondary to nafcillin: the first reported case. *Rheumatol Int* 2004; 24: 242–3.

Sodium content. Each g of nafcillin sodium contains about 2.2 mmol of sodium.

Interactions

As for Benzylpenicillin, p. 230.1.

Immunosuppressants. For the effect of nafcillin on *ciclosporin*, see p. 1956.2.

Antimicrobial Action

As for Flucloxacillin, p. 300.1.

Pharmacokinetics

Nafcillin is incompletely and irregularly absorbed from the gastrointestinal tract, especially when given after food. After intramuscular injection it is absorbed more reliably, an injection of 0.5 to 1 g producing peak plasma concentrations of 5 to 8 micrograms/mL within about 0.5 to 1 hour. Up to 90% of nafcillin in the circulation is bound to plasma proteins. Nafcillin has been reported to have a plasma half-life of about 0.5 to 1.5 hours. The half-life is prolonged in neonates.

Nafcillin crosses the placenta into the fetal circulation and is distributed into breast milk. There is little diffusion into the CSF except when the meninges are inflamed. Nafcillin is distributed into pleural and synovial fluids and into bone.

Nafcillin differs from most other penicillins in that it is largely inactivated by hepatic metabolism. It is excreted via the bile although some reabsorption takes place in the small intestine. Only about 10% of a dose given orally before food, and about 30% of a dose given intramuscularly, is excreted in the urine.

Plasma concentrations are enhanced by probenecid.

Preparations

Pharmacopoeial Preparations

USP 36: Nafcillin for Injection; Nafcillin Injection; Nafcillin Sodium Capsules; Nafcillin Sodium for Oral Solution; Nafcillin Sodium Tablets.

Nalidixic Acid *(BAN, USAN, rINN)*

Acide Nalidixique; Ácido nalidíxico; Acidum Nalidixicum; Kwas nalidyksowy; Kyselina nalidixová; Nalidiksiinihappo; Nalidiksik Asit; Nalidikso rūgštis; Nalidíxico, ácido; Nalidixinic Acid; Nalidixinsäure; Nalidixinsyra; Nalidixsav; NSC-82174; Win-18320; Налидиксовая Кислота.

1-Ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid.

$C_{12}H_{12}N_2O_3$=232.2

CAS — 389-08-2.

ATC — J01MB02.

ATC Vet — QJ01MB02.

UNII — 3B91HWA56M.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Nalidixic Acid). An almost white or pale yellow, crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in acetone; soluble in dichloromethane. It dissolves in dilute solutions of alkali hydroxides. Store in airtight containers. Protect from light.

USP 36: (Nalidixic Acid). A white to very pale yellow, odourless crystalline powder. Very slightly soluble in water and in ether; soluble 1 in 910 of alcohol and 1 in 29 of chloroform; slightly soluble in acetone, in *methyl alcohol*, and in toluene; soluble in dichloromethane and in solutions of fixed alkali hydroxides and carbonates. Store in airtight containers.

Uses and Administration

Nalidixic acid is a 4-quinolone antibacterial used in the treatment of urinary-tract infections due to Gram-negative bacteria other than *Pseudomonas* spp. (p. 213.1) and in the treatment of selected gastrointestinal infections caused by susceptible organisms. It has also been used to treat shigellosis (bacillary dysentery) (p. 186.1), although widespread resistance has now limited its usefulness.

The usual oral dose is 900 mg 4 times daily for at least 7 days in acute infections, reducing thereafter to 600 mg 4 times daily in chronic infections. Since bacterial resistance may develop rapidly it has been suggested that if treatment with nalidixic acid has not resulted in a negative urine culture within 48 hours another antimicrobial should be used.

For details of reduced doses in renal impairment, see p. 331.1. See also p. 331.1 for details of doses in infants and children.

Although the antibacterial activity of nalidixic acid does not appear to be influenced by urinary pH, the use of

sodium bicarbonate or sodium citrate does increase the concentration of active drug in the urine. Commercial preparations containing nalidixic acid, sodium bicarbonate, and sodium citrate have been used in some countries.

It is also used with the analgesic phenazopyridine.

Administration in children. Although nalidixic acid is not generally recommended for use in patients under 18 years of age (see Precautions, p. 331.1), it may be used for the treatment of urinary-tract or selected gastrointestinal infections caused by susceptible Gram-negative bacteria in infants and children over 3 months of age. The usual oral dose is 55 to 60 mg/kg daily in 4 divided doses for at least 7 days, reducing thereafter to about 30 mg/kg daily in 4 divided doses for prolonged treatment.

In addition, the *BNFC* suggests that a dose of 30 mg/kg daily in 2 divided doses may be given for prophylaxis of urinary-tract infections.

Administration in renal impairment. In the UK, some products of nalidixic acid have been licensed for use at half the usual oral dose in patients with a creatinine clearance below 20 mL/minute. However, other licensed product information does not include this information and suggests that nalidixic acid should not be used in patients with severe renal impairment. The *BNF* suggests avoiding use in those with a estimated glomerular filtration rate less than 20 mL/minute per 1.73 m^2.

Adverse Effects

The most frequent adverse reactions to nalidixic acid involve the gastrointestinal tract, skin, and CNS. Gastrointestinal effects have been reported in about 8% of patients and include nausea, vomiting, diarrhoea, and abdominal pain.

Adverse effects on the skin include photosensitivity reactions with erythema and bullous eruptions, allergic rashes, urticaria, and pruritus. Erythema multiforme and Stevens-Johnson syndrome have been reported rarely. Eosinophilia, fever, angioedema, and, rarely, anaphylactoid reactions have occurred.

Neurological effects include visual disturbances, headache, dizziness or vertigo, drowsiness, and sometimes confusion, depression, excitement, and hallucinations. Toxic psychoses or convulsions have occurred, especially after large doses; convulsions are most likely in patients with predisposing factors such as cerebral arteriosclerosis or epilepsy. There have been reports of intracranial hypertension, especially in infants and young children, and also of metabolic acidosis.

Peripheral neuropathies, muscular weakness, and myalgia are occasional adverse effects. Sixth cranial nerve palsy has been reported rarely.

Arthralgia has been reported (degenerative changes in weight-bearing joints of young *animals* are documented). Tendon damage has occasionally been associated with nalidixic acid and related compounds, the fluoroquinolones (see Effects on the Musculoskeletal System, under Ciprofloxacin, p. 263.2).

Cholestatic jaundice, thrombocytopenia, and leucopenia have occurred rarely, as has haemolytic anaemia in patients who may or may not have G6PD deficiency. There have been isolated reports of fatal auto-immune haemolytic anaemia in elderly patients.

Precautions

Nalidixic acid is contra-indicated in patients with a history of convulsive disorders and in those with severe renal impairment. It should be given with care to patients with hepatic or moderate renal impairment, severe cerebral arteriosclerosis, or G6PD deficiency. Blood counts and renal and hepatic function should be monitored if treatment continues for more than 2 weeks.

It should be avoided in infants less than 3 months old. Since nalidixic acid and related antimicrobials have been shown to cause degenerative changes in weight-bearing joints of young *animals*, it has been suggested that these compounds should not generally be used in patients aged under 18 years, pregnant women, or during breast feeding (but see also p. 331.1) unless the benefits outweigh the risks. Treatment should be stopped if symptoms of neuropathy or arthralgia occur. Tendon damage may occur rarely and treatment should be stopped if patients have tendon pain, inflammation, or rupture.

Exposure to strong sunlight or sunlamps should be avoided during treatment with nalidixic acid.

Nalidixic acid may cause false-positive reactions in urine tests for glucose using copper reduction methods.

Breast feeding. The American Academy of Pediatrics[1] states that nalidixic acid is usually compatible with breast feeding, although haemolytic anaemia has been reported[2] in a breast-fed infant, with no evidence of G6PD deficiency, whose mother had received nalidixic acid.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/05/04)
2. Belton EM, Jones RV. Haemolytic anaemia due to nalidixic acid. *Lancet* 1965; **ii**: 691.

G6PD deficiency. Licensed product information for nalidixic acid advises that it should be used with caution in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency as there may be a risk of haemolysis. However, a review[1] found only 3 reports of haemolysis in G6PD-deficient patients given nalidixic acid; the scarcity of reports despite its wide use, suggested that nalidixic acid could be given in therapeutic doses to patients with G6PD deficiency.

1. Youngster I, *et al.* Medications and glucose-6-phosphate dehydrogenase deficiency: an evidence-based review. *Drug Safety* 2010; **33**: 713–26.

Porphyria. Although nalidixic acid has not been classified in the Drug Database for Acute Porphyria compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden,[1] UK licensed product information contra-indicates its use in patients with a history of porphyria.

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 12/10/11)

Interactions

The absorption of nalidixic acid is reduced by sucralfate, and divalent and trivalent cations such as aluminium, calcium, iron, magnesium, and zinc, and therefore use of nalidixic acid with antacids, iron preparations, or other preparations containing such cations, whether as active ingredients or excipients, may result in subtherapeutic serum concentrations of the antibacterial. It is recommended that such products should not be given within 2 hours before or after nalidixic acid.

The excretion of nalidixic acid is reduced and plasma concentrations increased by probenecid. Other antibacterials such as chloramphenicol, nitrofurantoin, and tetracycline have been shown to antagonise the action of nalidixic acid *in vitro* and should not be used together.

Fatal haemorrhagic enterocolitis has been associated with the use of nalidixic acid and high-dose intravenous melphalan in children; use with other alkylating antineoplastics is also contra-indicated. There is a possible risk of increased nephrotoxicity when nalidixic acid is given with ciclosporin.

Nalidixic acid is reported to enhance the effect of oral anticoagulants such as warfarin (see p. 1531.1); this may be due in part to displacement of anticoagulant from its plasma binding sites. The dose of anticoagulant may need to be reduced.

The effect of some quinolone antibacterials on xanthines is discussed under Caffeine, p. 1206.1, and Theophylline, p. 1234.2.

Convulsions may be precipitated by the use of some quinolones with NSAIDs (see Analgesics, under Interactions of Ciprofloxacin, p. 264.3), although this has not been reported with nalidixic acid.

Antimicrobial Action

Nalidixic acid is considered to act by interfering with the replication of bacterial DNA, probably by inhibiting DNA gyrase (topoisomerase) activity. It is active against Gram-negative bacteria including *Escherichia coli*, *Klebsiella* spp., *Proteus* spp., *Enterobacter* spp., *Salmonella* spp., and *Shigella* spp., and is usually bactericidal. *Pseudomonas aeruginosa*, Gram-positive bacteria, and anaerobes are not generally susceptible.

Bacterial resistance may develop rapidly, sometimes within a few days of starting treatment, but it does not appear to be transferable or R-plasmid mediated (see also p. 331.2). Cross-resistance occurs with oxolinic acid and cinoxacin.

The antibacterial activity of nalidixic acid is not significantly affected by differences in urinary pH. Antagonism between nalidixic acid and other antibacterials such as chloramphenicol, nitrofurantoin, and tetracycline has been shown *in vitro*.

Resistance. Bacterial plasmid-mediated resistance to quinolones had not been seen by the late 1980s.[1] A report[2] of such resistance to nalidixic acid in *Shigella dysenteriae* responsible for an epidemic of shigellosis in Bangladesh in 1987, was questioned at the time.[3] On reinspection of the data, chromosomal mutation rather than plasmid-mediated resistance was confirmed as the mechanism responsible so far for resistance to quinolones.[1] Subsequent data[4] in an isolate of *Klebsiella pneumoniae* have, however, suggested that plasma-mediated resistance to quinolones may be possible.

1. Courvalin P. Plasmid-mediated 4-quinolone resistance: a real or apparent absence? *Antimicrob Agents Chemother* 1990; **34**: 681–4.
2. Munshi MH, *et al.* Plasmid-mediated resistance to nalidixic acid in Shigella dysenteriae type 1. *Lancet* 1987; **ii**: 419–21.
3. Crumplin GC. Plasmid-mediated resistance to nalidixic acid and new 4-quinolones? *Lancet* 1987; **ii**: 854–5.
4. Martínez-Martínez L, *et al.* Quinolone resistance from a transferable plasmid. *Lancet* 1998; **351**: 797–9.

Pharmacokinetics

Nalidixic acid is rapidly and almost completely absorbed from the gastrointestinal tract, and peak plasma concentrations of 20 to 40 micrograms/mL have been reported 1 to 2 hours after a 1-g oral dose. Plasma half-lives of about 1 to 2.5 hours have been reported (but see p. 331.3).

Nalidixic acid is partially metabolised to hydroxynalidixic acid, which has antibacterial activity similar to that of nalidixic acid and accounts for about 30% of active drug in the blood. About 93% of nalidixic acid and 63% of hydroxynalidixic acid are bound to plasma proteins. Both nalidixic acid and hydroxynalidixic acid are rapidly metabolised to inactive glucuronide and dicarboxylic acid derivatives; the major inactive metabolite 7-carboxynalidixic acid is usually only detected in urine.

Nalidixic acid and its metabolites are excreted rapidly in the urine, nearly all of a dose being eliminated within 24 hours. More than 80% of the drug excreted in the urine is as inactive metabolites, but peak urinary concentrations of active drug averaging about 150 to 200 micrograms/mL occur 3 to 4 hours after a single 1-g dose. Hydroxynalidixic acid accounts for about 80 to 85% of activity in the urine. Urinary excretion is reduced by probenecid. About 4% of a dose is excreted in the faeces.

Traces of nalidixic acid are distributed into breast milk and appear to cross the placenta.

Half-life. Although a plasma half-life of 1 to 2.5 hours is generally cited for nalidixic acid, values of 6 to 7 hours have been reported for active drug (nalidixic acid and hydroxynalidixic acid) after using more specific and sensitive assay techniques and longer sampling periods than previously.[1]

The elimination rate of nalidixic acid appears to be not markedly altered by renal impairment, but the elimination of hydroxynalidixic acid is significantly reduced. 7-Carboxynalidixic acid has appeared in the plasma of patients with renal impairment.[2] Plasma concentrations of active drug were higher and the half-life prolonged in elderly subjects.[3]

1. Ferry N, *et al.* Nalidixic acid kinetics after single and repeated oral doses. *Clin Pharmacol Ther* 1981; **29**: 695–8.
2. Cuisinaud G, *et al.* Nalidixic acid kinetics in renal insufficiency. *Br J Clin Pharmacol* 1982; **14**: 489–93.
3. Barbeau G, Belanger P-M. Pharmacokinetics of nalidixic acid in old and young volunteers. *J Clin Pharmacol* 1982; **22**: 490–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Naluril; Wintomylon; ***Gr.***: Nal-acid; Uridril; Wintomylon; ***Hong Kong***: Wintomylon†; ***Hung.***: Nevigramon; ***India***: Diarlop; Dix; Gramoneg; Nadix; Negadix; ***Indon.***: Urineg; ***Irl.***: Negram†; ***Mex.***: A-N-Dix†; Acidix; Kamilon; Nalix; Nalomin; Pronal Dix; Uronalin; Wintomylon†; ***Pol.***: Nevigramon†; ***Rus.***: Negram (Нерам); Nevigarmon (Невиграмон); ***S.Afr.***: Puromylon; Winlomylon†; ***UK***: Uriben; ***USA***: NegGram†.

Multi-ingredient Preparations. ***India***: Abdogyl-N; Aldiagram; Amibex-NA; Bactomet; Darmed; Diarlop Plus; Entrozyme-M; Gramogyl; Gramoneg-M; Matrix-MN; Nalidys; Negadix-M; ***Mex.***: Azo-Uronalin; Azo-Wintomylon; Azogen; Azuron; Nalixone; Naxilan-Plus; Pirifur.

Pharmacopoeial Preparations

BP 2014: Nalidixic Acid Oral Suspension; Nalidixic Acid Tablets; USP 36: Nalidixic Acid Oral Suspension; Nalidixic Acid Tablets.

Neomycin *(BAN, rINN)*

Neomicina; Néomycine; Neomycinum; Neomysiini; Неомицин.

CAS — 1404-04-2 (neomycin); 3947-65-7 (neomycin A); 119-04-0 (neomycin B); 66-86-4 (neomycin C).

ATC — A01AB08; A07AA01; B05CA09; D06AX04; J01GB05; R02AB01; S01AA03; S02AA07; S03AA01.

ATC Vet — QA01AB08; QA07AA01; QB05CA09; QD06AX04; QJ01GB05; QR02AB01; QS01AA03; QS02AA07; QS03AA01.

UNII — I16QD7X297 (neomycin); 5981U00LY0 (neomycin A).

Description. A mixture of 2 isomers, neomycin B ($C_{23}H_{46}N_6O_{13}$ = 614.6) and neomycin C ($C_{23}H_{46}N_6O_{13}$ = 614.6) with neomycin A (neamine, $C_{12}H_{26}N_4O_6$ = 322.4); neomycins B and C are glycoside esters of neamine and neobiosamines B and C. Framycetin (p. 301.2) consists of neomycin B.

Neomycin Sulfate (BANM, rINNM)

Fradiomycin Sulfate; Neomicina, sulfato de; Neomicino sulfatas; Neomicin-szulfát; Neomisin Sülfat; Neomycin Sulphate; Néomycine, sulfate de; Neomycini Sulfas; Neomycinsulfat; Neomycin-sulfát; Neomycyny siarczan; Neomysilnisulfaatti; Sulfato de neomicina; Неомицина Сульфат.

CAS — 1405-10-3.

ATC — A01AB08; A07AA01; B05CA09; D06AX04; J01GB05; R02AB01; S01AA03; S02AA07; S03AA01.

ATC Vet — QA01AB08; QA07AA01; QB05CA09; QD06AX04; QJ01GB05; QR02AB01; QS01AA03; QS02AA07; QS03AA01.

UNII — 057Y626693.

NOTE. NEO is a code approved by the BP 2014 for use on single unit doses of eye drops containing neomycin sulfate where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Neomycin Sulfate). A mixture of the sulfates of substances produced by the growth of certain selected strains of *Streptomyces fradiae*, the main component being the sulfate of neomycin B. The potency is not less than 680 units/mg, calculated with reference to the dried substance. A white or yellowish-white, hygroscopic powder. Very soluble in water; very slightly soluble in alcohol; practically insoluble in acetone. A 1% solution in water has a pH of 5.0 to 7.5. Store in airtight containers. Protect from light.

USP 36: (Neomycin Sulfate). The sulfate salt of a kind of neomycin, an antibacterial substance produced by the growth of *Streptomyces fradiae* (Streptomycetaceae), or a mixture of two or more such salts. It has a potency equivalent to not less than 600 micrograms of neomycin per mg, calculated on the dried basis. A white to slightly yellow powder, or cryodesiccated solid. It is odourless or practically so, and is hygroscopic. Soluble 1 in 1 of water; very slightly soluble in alcohol; insoluble in acetone, in chloroform, and in ether. pH of a solution in water containing the equivalent of neomycin 3.3% is between 5.0 and 7.5. Store in airtight containers. Protect from light.

Neomycin Undecenoate (BANM)

Neomicina, undecilenato de; Neomycin Undecylenate (rINNM); Neomycin Undecylenate (USAN); Néomycine, Undécylénate de; Neomycini Undecylenas; Undecilenato de neomicina; Неомицина Ундециленат.

The 10-undecenoate salt of neomycin.

CAS — 1406-04-8.

ATC — A01AB08; A07AA01; B05CA09; D06AX04; J01GB05; R02AB01; S01AA03; S02AA07; S03AA01.

ATC Vet — QA01AB08; QA07AA01; QB05CA09; QD06AX04; QJ01GB05; QR02AB01; QS01AA03; QS02AA07; QS03AA01.

Uses and Administration

Neomycin is an aminoglycoside antibacterial used topically in the treatment of infections of the skin, ear, and eye due to susceptible staphylococci and other organisms. Most preparations contain the sulfate, but neomycin undecenoate is also used. Neomycin is often used with another antibacterial such as bacitracin, colistin, gramicidin, or polymyxin B. Such combinations have been used topically in the eye before ophthalmic surgery for infection prophylaxis and, with propamidine isetionate, in the treatment of acanthamoeba keratitis (p. 921.2). A cream containing neomycin sulfate and chlorhexidine hydrochloride has been used for application to the nostrils in the treatment of staphylococcal nasal carriers (p. 208.2) but, as with other topical antibacterial preparations, development of resistance may be a problem. Neomycin is often used with topical corticosteroids, but such preparations should be used with caution because of the risk that signs of resistant infection may be suppressed. Care must also be taken where there is skin trauma because of the risk of increased absorption and toxicity (see Adverse Effects, p. 332.2). For details of bacterial skin infections and their treatment, see p. 207.1.

Because neomycin sulfate is poorly absorbed from the gastrointestinal tract, it has been given orally for bowel preparation before abdominal surgery, often with erythromycin (p. 209.1). Neomycin sulfate is also given orally with other antibacterials and antifungals in the selective decontamination of the digestive tract in patients in intensive care (p. 187.3).

Neomycin is rarely used in the treatment of existing gastrointestinal infections. Although it has been used in the treatment of diarrhoea due to infection with enteropathogenic *Escherichia coli* (EPEC) (p. 184.3), the use of neomycin in children with acute diarrhoea is generally not recommended.

Neomycin sulfate may be given orally to patients with incipient hepatic encephalopathy (p. 1811.2) to reduce the flora of the gastrointestinal tract.

Neomycin has also been used for the irrigation of wounds and body cavities but such use is no longer recommended because of the risk of toxicity.

Oral administration. For pre-operative use, 1 g of neomycin sulfate has been given hourly for 4 hours and then every 4 hours for 2 or 3 days before surgery.

As an adjunct in the management of hepatic encephalopathy, 4 to 12 g may be given daily in divided doses, usually for 5 to 7 days; up to 4 g daily may be given over an indefinite period to those with chronic hepatic insufficiency. Prolonged use may cause malabsorption.

For details of doses in children, see p. 332.2.

Topical preparations typically contain the equivalent of 0.35% neomycin base.

Neomycin hydrochloride has also been used.

Administration in children. Neomycin sulfate has been given orally for *bowel preparation* before abdominal surgery, often with erythromycin. UK licensed product information recommends the following doses, taken every 4 hours for 2 or 3 days before the operation:

- in those 6 to 12 years of age: 250 to 500 mg
- in those over 12 years of age: 1 g

As an adjunct in the management of *hepatic encephalopathy* children may be given oral neomycin sulfate 50 to 100 mg/kg daily in divided doses for 5 to 7 days.

For some *enteric infections* caused by susceptible bacteria in children beyond the newborn period the American Academy of Pediatrics[1] suggests oral doses of 100 mg/kg daily in 4 divided doses.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*. 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Adverse Effects and Treatment

As for Gentamicin Sulfate, p. 306.2.

Neomycin has particularly potent nephrotoxic and ototoxic properties and so is generally no longer given parenterally. However, enough may be absorbed after use by other routes (e.g. orally, instillation into cavities or open wounds, or topical application to damaged skin) to produce irreversible partial or total deafness. The effect is dose-related and is enhanced by renal impairment. Nephrotoxic effects may also occur.

Large oral doses of neomycin cause nausea, vomiting, and diarrhoea. Prolonged oral use can lead to a potentially severe malabsorption syndrome with steatorrhoea and diarrhoea. Superinfection may occur, especially with prolonged treatment.

Neomycin has a stronger neuromuscular-blocking action than other aminoglycosides, and respiratory depression and arrest has followed the intraperitoneal instillation of neomycin. Fatalities have occurred.

Hypersensitivity reactions, such as rashes, pruritus, and sometimes drug fever or even anaphylaxis, can develop during local treatment with neomycin and may be masked by the combined use of a corticosteroid. Cross-sensitivity with other aminoglycosides may occur.

Precautions

As for Gentamicin Sulfate, p. 306.3. Parenteral use of neomycin, or its use for irrigation of wounds or serous cavities such as the peritoneum, is no longer recommended.

Neomycin is contra-indicated for intestinal disinfection when an obstruction is present, in patients with a history of allergy to aminoglycosides, and in infants under 1 year. It should be used with great care in patients with renal or hepatic impairment, or with neuromuscular disorders, and in those with impaired hearing. The topical use of neomycin in patients with extensive skin damage or perforated tympanic membranes may result in deafness.

Prolonged local use should be avoided as it may lead to skin sensitisation and possible cross-sensitivity to other aminoglycosides.

Hypersensitivity and vaccination. Neomycin was thought to be responsible for a hypersensitivity reaction[1] in a child given measles, mumps, and rubella vaccine containing neomycin 25 micrograms. However, there is also a report of successful vaccination with measles, mumps, and rubella vaccine in a neomycin-sensitive child.[2] Although the vaccine may contain small amounts of neomycin or kanamycin, and sensitivity to either is considered a contra-indication to its use, it is only rarely necessary to withhold it once appropriate expert advice has been taken. There is little logic to intradermal testing since test solutions contain 4 to 40 times as much neomycin as the vaccine.[2]

1. Kwittken PL, *et al.* MMR vaccine and neomycin allergy. *Am J Dis Child* 1993; 147: 128–9.
2. Biliman D, Dhanraj B. Safe MMR vaccination despite neomycin allergy. *Lancet* 1991; 337: 365.

Interactions

As for Gentamicin Sulfate, p. 307.2. Absorption after oral or local use may be sufficient to produce interactions with other drugs given systemically.

Neomycin orally has been reported to impair the absorption of other drugs including phenoxymethylpenicillin, digoxin, and methotrexate; the efficacy of oral contraceptives might be reduced. The effects of acarbose may be enhanced by oral neomycin.

Antimicrobial Action

Neomycin has a mode of action and spectrum of activity similar to that of gentamicin (p. 307.2) but it lacks activity against *Pseudomonas aeruginosa*. It is reported to be active against *Mycobacterium tuberculosis*.

Because of its extensive topical use, resistance has been reported to be relatively widespread, notably among staphylococci, and some *Salmonella*, *Shigella*, and *Escherichia coli* strains. Cross-resistance with kanamycin, framycetin, and paromomycin occurs.

Pharmacokinetics

Neomycin is poorly absorbed from the gastrointestinal tract, about 97% of an oral dose being excreted unchanged in the faeces. Doses of 3 g orally produce peak plasma concentrations of up to 4 micrograms/mL and absorption is similar after an enema. Absorption may be increased in conditions which damage or inflame the mucosa. Absorption has also been reported to occur from the peritoneum, respiratory tract, bladder, wounds, and inflamed skin.

Once neomycin is absorbed it is rapidly excreted by the kidneys in active form. It has been reported to have a half-life of 2 to 3 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Concatag; Neomas; *Austral.*: Neosulf; *Braz.*: Cinaderm; Nemicina; Neocina†; Neodermicina; Neomed; Neomicon; Pomicina; *China*: Xian Ke Xin (显克欣); *Ger.*: Cysto-Myacyne N; Myacyne; Uro-Nebacetin N†; Vagicillin†; *Gr.*: Nivemycin; *Hong Kong*: Neoate†; Uni-Neoderm†; *India*: Methacin; *Israel*: Neocin; *Jpn*: Francetin; *Mex.*: Neomixen; *Port.*: Enteromicina; Oto-Synalar N; *Thai.*: Myneocin; *UK*: Nivemycin; *USA*: Neo-fradin.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

BP 2014: Dexamethasone and Neomycin Ear Spray; Hydrocortisone Acetate and Neomycin Ear Drops; Hydrocortisone Acetate and Neomycin Eye Drops; Hydrocortisone Acetate and Neomycin Eye Ointment; Hydrocortisone and Neomycin Cream; Neomycin Eye Drops; Neomycin Eye Ointment; Neomycin Tablets;

USP 36: Colistin and Neomycin Sulfates and Hydrocortisone Acetate Otic Suspension; Neomycin and Polymyxin B Sulfates and Bacitracin Ointment; Neomycin and Polymyxin B Sulfates and Bacitracin Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates and Bacitracin Zinc Ointment; Neomycin and Polymyxin B Sulfates and Bacitracin Zinc Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates and Dexamethasone Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates and Dexamethasone Ophthalmic Suspension; Neomycin and Polymyxin B Sulfates and Gramicidin Cream; Neomycin and Polymyxin B Sulfates and Gramicidin Ophthalmic Solution; Neomycin and Polymyxin B Sulfates and Hydrocortisone Acetate Cream; Neomycin and Polymyxin B Sulfates and Hydrocortisone Acetate Ophthalmic Suspension; Neomycin and Polymyxin B Sulfates and Hydrocortisone Ophthalmic Suspension; Neomycin and Polymyxin B Sulfates and Hydrocortisone Otic Solution; Neomycin and Polymyxin B Sulfates and Hydrocortisone Otic Suspension; Neomycin and Polymyxin B Sulfates and Lidocaine Cream; Neomycin and Polymyxin B Sulfates and Pramoxine Hydrochloride Cream; Neomycin and Polymyxin B Sulfates and Prednisolone Acetate Ophthalmic Suspension; Neomycin and Polymyxin B Sulfates Cream; Neomycin and Polymyxin B Sulfates Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates Ophthalmic Solution; Neomycin and Polymyxin B Sulfates Solution for Irrigation; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Acetate Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Lidocaine Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin, and Hydrocortisone Acetate Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin, and Hydrocortisone Acetate Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin, and Lidocaine Ointment; Neomycin and Polymyxin B Sulfates, Gramicidin, and Hydrocortisone Acetate Cream; Neomycin for Injection; Neomycin Sulfate and Bacitracin Ointment; Neomycin Sulfate and Bacitracin Zinc Ointment; Neomycin Sulfate and Dexamethasone Sodium Phosphate Cream; Neomycin Sulfate and

Dexamethasone Sodium Phosphate Ophthalmic Ointment; Neomycin Sulfate and Dexamethasone Sodium Phosphate Ophthalmic Solution; Neomycin Sulfate and Fluocinolone Acetonide Cream; Neomycin Sulfate and Fluorometholone Ointment; Neomycin Sulfate and Flurandrenolide Cream; Neomycin Sulfate and Flurandrenolide Lotion; Neomycin Sulfate and Flurandrenolide Ointment; Neomycin Sulfate and Gramicidin Ointment; Neomycin Sulfate and Hydrocortisone Acetate Cream; Neomycin Sulfate and Hydrocortisone Acetate Lotion; Neomycin Sulfate and Hydrocortisone Acetate Ointment; Neomycin Sulfate and Hydrocortisone Acetate Ophthalmic Ointment; Neomycin Sulfate and Hydrocortisone Acetate Ophthalmic Suspension; Neomycin Sulfate and Hydrocortisone Cream; Neomycin Sulfate and Hydrocortisone Ointment; Neomycin Sulfate and Hydrocortisone Otic Suspension; Neomycin Sulfate and Methylprednisolone Acetate Cream; Neomycin Sulfate and Prednisolone Acetate Ointment; Neomycin Sulfate and Prednisolone Acetate Ophthalmic Ointment; Neomycin Sulfate and Prednisolone Acetate Ophthalmic Suspension; Neomycin Sulfate and Prednisolone Sodium Phosphate Ophthalmic Ointment; Neomycin Sulfate and Triamcinolone Acetonide Cream; Neomycin Sulfate and Triamcinolone Acetonide Ophthalmic Ointment; Neomycin Sulfate Cream; Neomycin Sulfate Ointment; Neomycin Sulfate Ophthalmic Ointment; Neomycin Sulfate Oral Solution; Neomycin Sulfate Tablets; Neomycin Sulfate, Sulfacetamide Sodium, and Prednisolone Acetate Ophthalmic Ointment; Nystatin, Neomycin Sulfate, Gramicidin, and Triamcinolone Acetonide Cream; Nystatin, Neomycin Sulfate, Gramicidin, and Triamcinolone Acetonide Ointment.

Netilmicin Sulfate *(BANM, USAN, rINNM)*

Netilmicin Sulphate; Netilmicina, sulfato de; Nétilmicine, Sulfate de; Netilmicini Sulfas; Netilmicino sulfatas; Netilmicinsulfat; Netilmicin-sulfát; Netilmicin-szulfát; Netilmisiinisulfaatti; Netilmisin sülfat; Netylmycyny siarczan; Sch-20569; Sulfato de netilmicina; N^1-Ethylsissomicin; Нетилмицина Сульфат.

4-*O*-[(2*R*,3*R*)-*cis*-3-Amino-6-aminomethyl-3,4-dihydro-2*H*-pyran-2-yl]-2-deoxy-6-*O*-(3-deoxy-4-*C*-methyl-3-methylamino-β-L-arabinopyranosyl)-1-*N*-ethylstreptamine sulphate.

$(C_{21}H_{41}N_5O_7)_2.5H_2SO_4$=1441.5

CAS — 56391-56-1 (netilmicin); 56391-57-2 (netilmicin sulfate).

ATC — J01GB07; S01AA23.

ATC Vet — QJ01GB07; QS01AA23.

UNII — S741ZJS97U.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Netilmicin Sulfate). A substance obtained by synthesis from sisomicin. The potency is not less than 650 units/mg, calculated with reference to the dried substance. A white or yellowish-white, very hygroscopic, powder. Very soluble in water; practically insoluble in alcohol and in acetone. A 4% solution in water has a pH of 3.5 to 5.5. Store in airtight containers. Protect from light.

USP 36: (Netilmicin Sulfate). The potency is equivalent to not less than 595 micrograms of netilmicin per milligram, calculated on the dried basis. A white to pale yellowish-white powder. Freely soluble in water; practically insoluble in dehydrated alcohol and in ether. pH of a solution in water containing the equivalent of netilmicin 4% is between 3.5 and 5.5. Store in airtight containers. Protect from moisture.

Incompatibility. For discussion of the incompatibility of aminoglycosides, including netilmicin, with beta lactams, see under Gentamicin Sulfate, p. 304.3. Netilmicin is also reported to be incompatible with furosemide, heparin, and vitamin B complex.

Uses and Administration

Netilmicin is a semisynthetic aminoglycoside antibacterial with actions and uses similar to those of gentamicin (p. 304.3). It may be used as an alternative to amikacin (p. 214.2) in the treatment of infections caused by susceptible bacteria that are resistant to gentamicin and tobramycin. As with gentamicin, netilmicin may be used with penicillins and with cephalosporins; the injections should be given separately.

Netilmicin is given as the sulfate but doses are expressed in terms of the equivalent amount of base; 1.5 g of netilmicin sulfate is equivalent to about 1 g of netilmicin. It is usually given intramuscularly in doses of 4 to 6 mg/kg daily as a single dose; alternatively, it may be given in equally divided doses every 8 or 12 hours; for the control of life-threatening infections, up to 7.5 mg/kg may be given daily in divided doses every 8 hours for short periods.

The same doses may be given by slow intravenous injection over 3 to 5 minutes or infused intravenously over 0.5 to 2 hours in 50 to 200 mL of infusion fluid.

Peak plasma concentrations below 12 micrograms/mL and troughs below 2 micrograms/mL have been recommended for divided daily dose regimens.

Dosage should be adjusted in all patients according to plasma-netilmicin concentrations, and this is particularly important where factors such as age, renal impairment, or prolonged therapy may predispose to toxicity, or where there is a risk of subtherapeutic concentrations. For discussion of the methods of calculating aminoglycoside dosage requirements, see Administration and Dosage, under Gentamicin, p. 305.2.

For details of doses in children, see p. 333.2.

Administration in children. Dosage recommendations for netilmicin in infants and children vary somewhat. One regimen is 7.5 to 9 mg/kg daily in infants and neonates older than 1 week, and 6 to 7.5 mg/kg daily in children aged 12 months and over, both given in divided doses every 8 hours. Premature infants and neonates less than 1 week old may be given 3 mg/kg every 12 hours.

Doses may be given by intramuscular or slow intravenous injection or by intravenous infusion.

Adverse Effects, Treatment, and Precautions

As for Gentamicin Sulfate, p. 306.2. Some studies suggest that netilmicin is less nephrotoxic and ototoxic than gentamicin or tobramycin, although others have not found any significant differences in their toxicity.

It has been suggested that peak plasma concentrations of netilmicin should not exceed 12 micrograms/mL for prolonged therapy, and troughs should be below 2 micrograms/mL.

Effects on the cardiovascular system. Severe hypotension was associated with netilmicin in a patient undergoing artificial ventilation.[1] Hypotensive episodes were of short duration and coincided with netilmicin injection. They almost disappeared when sedation was stopped.

1. Rygnestad T. Severe hypotension associated with netilmicin treatment. *BMJ* 1997; **315**: 31.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies netilmicin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

As for Gentamicin Sulfate, p. 307.2.

Antimicrobial Action

As for Gentamicin Sulfate, p. 307.2. It is active against a similar range of organisms although it is also reported to have some activity against *Nocardia*. It may be somewhat less effective against *Pseudomonas aeruginosa*. It is not degraded by all of the enzymes responsible for aminoglycoside resistance, and may be active against some strains resistant to gentamicin or tobramycin, but this is less marked than with amikacin: for example, gentamicin-resistant *Providencia*, *Pseudomonas*, and *Serratia* are usually also netilmicin-resistant. Between about 5 and 20% of Gram-negative isolates are reported to be resistant to netilmicin.

Pharmacokinetics

As for Gentamicin Sulfate, p. 307.3.

After intramuscular injection of netilmicin, peak plasma concentrations occur within 0.5 to 1 hour, and concentrations of about 7 micrograms/mL have been reported after doses of 2 mg/kg; similar concentrations are obtained after intravenous infusion of the same dose over 1 hour. Peak concentrations after rapid intravenous injection may transiently be 2 or 3 times higher than those after infusion. Standard, once-daily doses may produce transient peak concentrations of 20 to 30 micrograms/mL. In multiple dosing studies, netilmicin in usual doses every 12 hours produced steady-state concentrations on the second day which were less than 20% higher than those seen after the first dose.

The half-life of netilmicin is usually 2.0 to 2.5 hours. About 80% of a dose is excreted in the urine within 24 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Certomycin; ***Braz.***: Netromicina; ***China***: Ai Hong (爱宏); Ai Jia Xin (艾佳欣); An Jie Xing (安捷星); Ao Guang Su (奥广素); Ao Tian Yu (奥天禹); Changfu TianXin (长富天欣); De Luo Jia (德洛佳); Fei Te (菲特); Feng Ke Nai (锋可耐); Fu Yin (孚茵); Heng Shi (衡实); Jia Nai (佳萘); Jie Nai (洁萘); JunXin (君欣); Kai Bao Min (凯保敏); Kang Li Xing (康力星); Lang Fan (浪凡); Luoji (洛吉); Nai Di (乃迪); Nai Kang (萘康); Nai Te (奈特); Nai Xing Long (耐兴龙); Nai Yi (奈怡); Naidufuxing (奈狄福星); Netromycin (力确兴); Pu Nai Xin (普奈新); Puqi (普奇); Rui Peng (瑞朋); Rui Shan (瑞杉); Sheng Di (圣迪); Sheng Di Xin (圣迪新); Shensuo (深索); Su Meng (苏盟); Tian Quan Tai Ning (天泉泰宁); Tuo Xing (妥星); Yan Pa Rui (延帕瑞); ***Cz.***: Netromycine; Nettacin†; ***Fin.***: Netilyn†; ***Fr.***: Netromicine; ***Ger.***: Certomycin†; ***Gr.***: Netromycin; Rizaldon; Zaby; ***Hong Kong***: Netromycin; ***Hung.***: Netromycine†; ***India***: Neticin; Netilcin; Netmicin; Netromax; Netromycin; Netspan; ***Indon.***: Hypobhac; Netromycin; ***Ital.***: Nettacin; Nettavisc; Zetamicin; ***Malaysia***: Lotifar; Netromycin; ***Mex.***: Netira; Netromicina; ***Philipp.***: Keunmixin; Netilcin; Netromycin†; Netrozin; ***Pol.***: Netromycine; ***Port.***: Netromicina; Tilcin; ***Rus.***: Netromycin (Нетромицин); ***S.Afr.***: Netromycin; ***Singapore***: Netromycin; ***Swed.***: Netilyn†; ***Switz.***: Netromycine†; ***Thai.***: Bactrocin; Nelin; Netil; Netromycin; ***Turk.***: Netira; Netromycin; ***Venez.***: Netromicina.

Multi-ingredient Preparations. ***China***: Bei Xing (倍兴); ***Ital.***: Netildex; Xantemet; ***Turk.***: Netildex.

Pharmacopoeial Preparations

USP 36: Netilmicin Sulfate Injection.

Nifuroxazide *(BAN, rINN)*

Nifuroksatsidi; Nifuroksazid; Nifuroksazidas; Nifuroxazid; Nifuroxazida; Nifuroxazidum; Нифуроксазид.

2′-(5-Nitrofurfurylidene)-4-hydroxybenzohydrazide.

$C_{12}H_9N_3O_5$=275.2

CAS — 965-52-6.

ATC — A07AX03.

ATC Vet — QA07AX03.

UNII — PM5LI0P38J.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Nifuroxazide). A bright yellow crystalline powder. Practically insoluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane. Protect from light.

Profile

Nifuroxazide is an antibacterial that is poorly absorbed from the gastrointestinal tract. It is given orally in a dose of 800 mg daily in divided doses in the treatment of colitis and diarrhoea.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Passifuril; ***Cz.***: Endiex; Ercefuryl; ***Fr.***: Bacterix; Bifix†; Diafuryl; Diarmonis; Ediston; Ercefuryl; Imoseptyl; Panfurex; Perabacticel; ***Gr.***: Enorep; Ercefuryl; Kaofuryl; ***Hong Kong***: Ercefuryl; Panfurex; ***Indon.***: Fuzide; Nifudiar; Nifural; ***Mex.***: Akabar; Eskapar†; Topron; ***Philipp.***: Ercefuryl; ***Pol.***: Endiex; ***Rus.***: Enterofuryl (Энтерофурил); Ersefuryl (Эрсефурил); ***Singapore***: Ercefuryl; Niraben; ***Thai.***: Debby; Ercefuryl†; Erfuzide; Mifuzide; ***Turk.***: Diafuryl; Durisal; Endosin; Ercefuryl; Erfulyn; Furil†; Nifuryl†; Nufro; ***Ukr.***: Enterofuril (Энтерофурил); Lecor (Лекор).

Multi-ingredient Preparations. ***Chile***: Diaren; Enterol Con Nifuroxacida; Esancol; Imecol; Liracol; Liracol; Nifurat; Testisan; ***Mex.***: Dia-Par Compuesto; Eskapar Compuesto.

Nifurpirinol *(USAN, rINN)*

Furpirinol; Nifurpirinolum; P-7138; Нифурпиринол.

$C_{12}H_{10}N_2O_4$=246.2

CAS — 13411-16-0.

UNII — 705A98XY8U.

Profile

Nifurpirinol is a nitrofuran antimicrobial used in veterinary medicine for the treatment of bacterial and fungal infections in ornamental fish.

Nifurtoinol *(rINN)*

Hydroxymethylnitrofurantoin; Nifurtoinol; Nifurtoinolum; Нифуртоинол.

3-Hydroxymethyl-1-(5-nitrofurylideneamino)hydantoin.

$C_8H_8N_4O_6$=268.2

CAS — 1088-92-2.

ATC — J01XE02.

ATC Vet — QJ01XE02.

UNII — 980688H13O.

Profile

Nifurtoinol is a nitrofuran antibacterial with properties similar to those of nitrofurantoin (p. 334.1) and is used in the treatment of urinary-tract infections. It is given orally in doses of up to 300 mg daily in divided doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Urfadyn PL.

Nifurzide *(rINN)*

Nifurzida; Nifurzidum; Нифурзид.
5-Nitro-2-thiophenecarboxylic acid [3-(5-nitro-2-furyl)allylidene]hydrazide.
$C_{12}H_8N_4O_6S$=336.3
CAS — 39978-42-2.
ATC — A07AX04.
ATC Vet — QA07AX04.
UNII — Z35R6K4C26.

Profile

Nifurzide is an antibacterial that is poorly absorbed from the gastrointestinal tract. It has been given orally in the treatment of diarrhoea.

Nisin

E234; Nisina; Низин.
CAS — 1414-45-5.
UNII — EN8XKG133D.

Profile

Nisin is a polypeptide antibacterial produced by *Lactococcus lactis* (*Streptococcus lactis*). It is used as a food preservative.

It has been investigated for the treatment of various infections, including those caused by *Helicobacter pylori* and *Clostridium difficile*.

Nitrofurantoin *(BAN, rINN)*

Furadoninum; Nitrofurantoiini; Nitrofurantoina; Nitrofurantoína; Nitrofurantoinas; Nitrofurantoine; Nitrofurantoinum; Нитрофурантоин.
1-(5-Nitrofurfurylideneamino)hydantoin; 1-(5-Nitrofurfurylideneamino)imidazolidine-2,4-dione.
$C_8H_6N_4O_5$=238.2
CAS — 67-20-9 (anhydrous nitrofurantoin); 17140-81-7 (nitrofurantoin monohydrate).
ATC — J01XE01.
ATC Vet — QJ01XE01.
UNII — 927AH8112L (nitrofurantoin); E1QI2CQQ1I (nitrofurantoin monohydrate).

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Int. and *US* specify anhydrous or monohydrate.

Ph. Eur. 8: (Nitrofurantoin). A yellow, crystalline powder or crystals. Very slightly soluble in water and in alcohol; soluble in dimethylformamide. Store at a temperature not exceeding 25 degrees. Protect from light.

USP 36: (Nitrofurantoin). It is anhydrous or contains one molecule of water of hydration. Lemon-yellow, odourless crystals or fine powder. Nitrofurantoin and its solutions are discoloured by alkalis and by exposure to light, and are decomposed on contact with metals other than stainless steel or aluminium. Very slightly soluble in water and in alcohol; soluble in dimethylformamide. Store in airtight containers. Protect from light.

Uses and Administration

Nitrofurantoin is a nitrofuran antibacterial that is used in the treatment of uncomplicated lower urinary-tract infections (p. 213.1), including prophylaxis or long-term suppressive therapy in recurrent infection.

It is given orally, in a usual dose of 50 to 100 mg four times daily, with food or milk. Treatment is usually continued for 7 days. A dual-release formulation, consisting of macrocrystalline nitrofurantoin and nitrofurantoin monohydrate, is available in some countries and is given in a dose of 100 mg twice daily. A usual long-term prophylactic dose is 50 to 100 mg at bedtime.

For details of doses in children, see p. 334.1.

Reviews.

1. Guay DR. An update on the role of nitrofurans in the management of urinary tract infections. *Drugs* 2001; **61**: 353–64.

Administration in children. In the UK, nitrofurantoin may be given to children aged 3 months to 12 years for the *treatment* of urinary-tract infection in a usual oral dose of 3 mg/kg daily given in 4 divided doses; 1 mg/kg may be given at night for long-term *prophylactic* therapy. However, a systematic review[1] concluded, on the basis of the rather low-grade evidence available, that the adverse effects of nitrofurantoin may outweigh its benefits and render it unacceptable for long-term therapy.

Higher oral doses of 5 to 7 mg/kg daily in 4 divided doses are recommended for the *treatment* of urinary-tract infection in the USA in children aged 1 month and above; for long-term *prophylactic* therapy 1 mg/kg daily given in one or two divided doses is considered adequate.

Older children may be given usual adult doses (see Uses and Administration, above).

1. Williams GJ, *et al.* Long-term antibiotics for preventing recurrent urinary tract infection in children. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 11/01/08).

Adverse Effects

The estimated incidence of adverse effects with nitrofurantoin has varied enormously, but may be around 10% overall; an incidence of serious reactions of about 0.001% for pulmonary, and 0.0007% for neurological reactions has been suggested. The most common adverse effects of nitrofurantoin involve the gastrointestinal tract. They are dose-related and generally include nausea, vomiting, and anorexia; abdominal pain and diarrhoea occur less frequently. It has been reported that adverse effects on the gastrointestinal tract are less common when nitrofurantoin is given in a macrocrystalline form or with food.

Neurological adverse effects include headache, drowsiness, vertigo, dizziness, nystagmus, and benign intracranial hypertension. Severe and sometimes irreversible peripheral neuropathy has developed, particularly in patients with renal impairment and in those given prolonged therapy.

Hypersensitivity reactions such as skin rashes, urticaria, pruritus, fever, sialadenitis, and angioedema may occur. Anaphylaxis, erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, pancreatitis, a lupus-like syndrome, myalgia, and arthralgia have also been reported. Patients with a history of asthma may have acute asthmatic attacks.

Acute pulmonary sensitivity reactions characterised by sudden onset of fever, chills, eosinophilia, cough, chest pain, dyspnoea, pulmonary infiltration or consolidation, and pleural effusion may occur within hours to a few days of beginning therapy, but they usually resolve on stopping treatment.

Subacute or chronic pulmonary symptoms including interstitial pneumonitis and pulmonary fibrosis may develop more insidiously in patients on long-term therapy and the latter are not always reversible, particularly if therapy is continued after onset of symptoms.

Hepatotoxicity including cholestatic jaundice, hepatitis, and hepatic necrosis may develop rarely, particularly in women, and may represent a hypersensitivity reaction. Other adverse effects include megaloblastic anaemia, leucopenia, granulocytopenia or agranulocytosis, thrombocytopenia, aplastic anaemia, and haemolytic anaemia in persons with a genetic G6PD deficiency. Transient alopecia has been reported.

Nitrofurantoin may cause a brownish discoloration of the urine.

There is limited evidence from *animal* studies that nitrofurantoin may be carcinogenic, although this has not been shown conclusively in humans.

References.

1. Koch-Weser J, *et al.* Adverse reactions to sulfisoxazole, sulfamethoxazole, and nitrofurantoin: manifestations and specific reaction rates during 2118 courses of therapy. *Arch Intern Med* 1971; **128**: 399–404.
2. Holmberg L, *et al.* Adverse reactions to nitrofurantoin: analysis of 921 reports. *Am J Med* 1980; **69**: 733–8.
3. Penn RG, Griffin JP. Adverse reactions to nitrofurantoin in the United Kingdom, Sweden, and Holland. *BMJ* 1982; **284**: 1440–2.
4. D'Arcy PF. Nitrofurantoin. *Drug Intell Clin Pharm* 1985; **19**: 540–7.
5. Karpman E, Kurzrock EA. Adverse reactions of nitrofurantoin, trimethoprim and sulfamethoxazole in children. *J Urol (Baltimore)* 2004; **172**: 648–53.

Effects on the lungs. References[1,2] to pulmonary toxicity associated with long-term nitrofurantoin treatment, and to acute pulmonary reactions.[3] Sporadic cases of chronic lung disease continue to be reported,[4-10] and the importance of monitoring during long-term therapy has been stressed.[8]

1. Adverse Drug Reactions Advisory Committee (ADRAC). Pulmonary toxicity with long-term nitrofurantoin. *Aust Adverse Drug React Bull* 2004; **23**: 15. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0408.htm (accessed 11/01/08)
2. Mendez JL, *et al.* Chronic nitrofurantoin-induced lung disease. *Mayo Clin Proc* 2005; **80**: 1298–1302.
3. Williams EM, Triller DM. Recurrent acute nitrofurantoin-induced pulmonary toxicity. *Pharmacotherapy* 2006; **26**: 713–8.
4. Hargett CW, *et al.* Giant cell interstitial pneumonia associated with nitrofurantoin. *Lung* 2006; **184**: 147–9.
5. Bhullar S, *et al.* Severe nitrofurantoin lung disease resolving without the use of steroids. *J Postgrad Med* 2007; **53**: 111–3.
6. Koulaouzidis A, *et al.* Nitrofurantoin-induced lung- and hepatotoxicity. *Ann Hepatol* 2007; **6**: 119–21.
7. Lin DC, Bhally H. Nitrofurantoin-induced interstitial lung disease. *N Z Med J* 2007; **120**: U2753.
8. Mrozek N, *et al.* Pneumopathie à la nitrofurantoïne: à propos de deux observations. *Rev Med Interne* 2008; **29**: 149–51.
9. Martins RR, *et al.* Chronic eosinophilic pneumonia secondary to long-term use of nitrofurantoin: high-resolution computed tomography findings. *J Bras Pneumol* 2008; **34**: 181–4.
10. Fenton ME, *et al.* Nitrofurantoin-associated bronchiolitis obliterans organizing pneumonia: report of a case. *Can Respir J* 2008; **15**: 311–2.

Precautions

Nitrofurantoin should not be given to patients with renal impairment since antibacterial concentrations in the urine may not be attained and toxic concentrations in the plasma can occur. Nitrofurantoin is also contra-indicated in patients known to be hypersensitive to nitrofurans, in those with G6PD deficiency, and in infants (in the UK it is contra-indicated below 3 months of age, though the USA permits use from 1 month old).

Nitrofurantoin should be used with care in the elderly, who may be at increased risk of toxicity, particularly acute pulmonary reactions. All patients undergoing prolonged therapy should be monitored for changes in pulmonary function, and the drug withdrawn at the first signs of pulmonary damage. Care is required in patients with pre-existing pulmonary, hepatic, neurological, or allergic disorders, and in those with conditions (such as anaemia, diabetes mellitus, electrolyte imbalance, debility, or vitamin B deficiency) which may predispose to peripheral neuropathy. Nitrofurantoin should be withdrawn if signs of peripheral neuropathy develop. Although hepatic reactions such as hepatitis, cholestatic jaundice, and hepatic necrosis rarely occur, fatalities have been reported. Patients should be monitored, and the drug stopped immediately if hepatitis occurs.

Nitrofurantoin may cause false positive reactions in urine tests for glucose using copper reduction methods.

Breast feeding. The American Academy of Pediatrics considers that, although nitrofurantoin appears in breast milk, it is usually compatible with breast feeding, but caution is necessary in breast-fed infants with G6PD deficiency.[1] The *BNFC* suggests that the amount ingested may be enough to produce haemolysis in G6PD-deficient infants; it recommends that nitrofurantoin should be avoided in mothers who are breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 11/01/08)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies nitrofurantoin as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 12/10/11)

Pregnancy. Licensed product information contra-indicates the use of nitrofurantoin in pregnant patients at term (38 to 42 weeks), or during labour and delivery, because of the possibility of producing haemolytic anaemia in the neonate.

Interactions

Nitrofurantoin and the quinolone antibacterials are antagonistic *in vitro* but the clinical significance is unknown. The antibacterial activity of nitrofurantoin may be decreased in the presence of carbonic anhydrase inhibitors and other drugs that alkalinise the urine.

Probenecid or sulfinpyrazone should not be given with nitrofurantoin as they may reduce its excretion. Magnesium trisilicate may reduce the absorption of nitrofurantoin but it is not clear whether this applies to other antacids.

Antiepileptics. For reference to the effect of nitrofurantoin on *phenytoin* concentrations, see p. 542.3.

Antifungals. An elderly patient who had been taking nitrofurantoin daily for 5 years developed combined hepatic and pulmonary toxicity 2 months after also starting *fluconazole* therapy.[1] Although either drug may have caused the hepatic toxicity, possible pharmacokinetic changes induced by an interaction with fluconazole may have precipitated the nitrofurantoin-induced pulmonary toxicity.

1. Linnebur SA, Parnes BL. Pulmonary and hepatic toxicity due to nitrofurantoin and fluconazole treatment. *Ann Pharmacother* 2004; **38**: 612–16.

Hormonal contraceptives. For mention of a possible decrease in contraceptive efficacy when nitrofurantoin was used with oral contraceptives, see under Hormonal Contraceptives, p. 2243.1.

Antimicrobial Action

Nitrofurantoin is bactericidal *in vitro* to most Gram-positive and Gram-negative urinary-tract pathogens. The mode of action is uncertain but appears to depend on the formation of reactive intermediates by reduction; this process occurs more efficiently in bacterial than in mammalian cells.

It is effective against the enterococci *in vitro*, as well as various other Gram-positive species including staphylococci, streptococci, and corynebacteria, although this is of little clinical significance. Most strains of *Escherichia coli* are particularly sensitive to nitrofurantoin but *Enterobacter* and *Klebsiella* spp. are less susceptible and some may be resistant. *Pseudomonas aeruginosa* is resistant as are most strains of *Proteus*spp.

Nitrofurantoin is most active in acid urine, and if the pH exceeds 8 most of the antibacterial activity is lost. Resistance rarely develops during nitrofurantoin treatment but may occur during prolonged treatment. Plasmid-encoded resistance has been reported in *E. coli*. Resistance may be due to the loss of nitrofuran reductases which generate the active intermediates.

Pharmacokinetics

Nitrofurantoin is readily absorbed from the gastrointestinal tract. The absorption rate is dependent on crystal size. The macrocrystalline form has slower dissolution and absorption rates, produces lower serum concentrations than the microcrystalline form, and takes longer to achieve peak concentrations in the urine. The presence of food in the gastrointestinal tract may increase the bioavailability of nitrofurantoin and prolong the duration of therapeutic urinary concentrations. Preparations of nitrofurantoin from different sources may not be bioequivalent, and care may be necessary if changing from one brand to another.

On absorption, concentrations in blood and body tissues are low because of rapid elimination, and antibacterial concentrations are not achieved. Nitrofurantoin crosses the placenta and the blood-brain barrier and traces have been detected in breast milk. There is some disagreement about the degree of protein binding, and although figures of up to about 60% are quoted by some sources, others suggest that the figure should be as much as 90%. The plasma half-life is reported to range from 0.3 to 1 hour.

Nitrofurantoin is metabolised in the liver and most body tissues while about 30 to 40% of a dose is excreted rapidly in the urine as unchanged nitrofurantoin. Some tubular reabsorption may occur in acid urine. Average doses give a concentration of 50 to 200 micrograms/mL in the urine in patients with normal renal function.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Furadantina; Uratina; Urodantina; Urofuran; ***Austral.***: Furadantin†; Macrodantin; ***Austria***: Furadantin; ***Belg.***: Furadantine; ***Braz.***: Hantina; Macrodantina; Nitrofen; Urogem†; ***Canad.***: Macrobid; Macrodantin†; Novo-Furantoin†; ***Chile***: Macrodantina; Macrosan; Matidan; ***China***: Tanding (坦啶); ***Fin.***: Nitrofur-C; ***Fr.***: Furadantine; Furadoine; Microdoine; ***Ger.***: Furadantin; Nifurantin; Nifuretten; Uro-Tablinen; ***Gr.***: Furolin; Londofurol; Nitrotoin; ***India***: Furadantin; Furasoz; Martifur; Niftas; Niftran; ***Irl.***: Furadantin; Macrobid; Macrodantin; ***Israel***: Uvamin; ***Ital.***: Furedan; Furil†; Macrodantin†; Neo-Puradantin; ***Mex.***: Biofurin; Furadantina; Furitex; Futroken; Macrodantina; Macrofurin; Promac†; Suronit; ***Neth.***: Furabid; Furadantine MC; ***Norw.***: Furadantin; ***NZ***: Furadantin†; Nifuran; ***Philipp.***: Macrodantin; ***Pol.***: Siraliden†; ***Port.***: Furadantina; ***Rus.***: Furadonin (Фурадонин); ***S.Afr.***: Furadantin†; Macrodantin; ***Spain***: Furantoina; Furobactina†; ***Swed.***: Furadantin; ***Switz.***: Furadantine; Urodin†; Uvamine retard; ***Turk.***: Piyeloseptyl; ***UK***: Furadantin†; Macrobid; Macrodantin; ***USA***: Furadantin; Macrobid; Macrodantin; ***Venez.***: Macrodantina.

Multi-ingredient Preparations. ***Arg.***: Bagociletas con Anestesia†; ***Braz.***: Uropac; ***Ger.***: Nifurantin B 6; ***Hong Kong***: Urobilin†; ***India***: Nephrogesic; ***Turk.***: Uriseptin.

Pharmacopoeial Preparations

BP 2014: Nitrofurantoin Oral Suspension; Nitrofurantoin Tablets;

USP 36: Nitrofurantoin Capsules; Nitrofurantoin Oral Suspension; Nitrofurantoin Tablets.

Nitrofurazone *(BAN)*

Furacilinum; Nitrofuraali; Nitrofural (pINN); Nitrofural; Nitrofurál; Nitrofuralis; Nitrofuralum; Nitrofuratsoni; Nitrofurazon; Nitrofurazonum; Нитрофурал.

5-Nitro-2-furaldehyde semicarbazone.

$C_6H_6N_4O_4$=198.1

CAS — 59-87-0.

ATC — B05CA03; D08AF01; D09AA03; P01CC02; S01AX04; S02AA02.

ATC Vet — QB05CA03; QD08AF01; QD09AA03; QG01AX90; QP51AC02; QS01AX04; QS02AA02.

UNII — X8XI70B5Z6.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Nitrofural; Nitrofurazone BP 2014). A yellow or brownish-yellow, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol. The filtrate from a 1% suspension in water has a pH of 5.0 to 7.0. Protect from light.

USP 36: (Nitrofurazone). A lemon-yellow, odourless crystalline powder. It darkens slowly on exposure to light. Soluble 1 in 4200 of water, 1 in 590 of alcohol, and 1 in 350 of propylene glycol; practically insoluble in chloroform and in ether; soluble in dimethylformamide; slightly soluble in polyethylene glycol mixtures. The filtrate from a 1% suspension in water has a pH of 5.0 to 7.5. Store in airtight containers at a temperature not exceeding 40 degrees. Protect from light.

Sterilisation. Autoclaving gauze dressings impregnated with nitrofurazone, as recommended by the US manufacturer, resulted in over 10% loss of the drug.[1] Since the spectroscopic assay used may not have distinguished between nitrofurazone and some of its degradation products, the degree of degradation might have been greater than this.

1. **Phillips C, Fisher E. Effect of autoclaving on stability of nitrofurazone soluble dressing.** *Am J Health-Syst Pharm* **1996; 53: 1169–71.**

Uses and Administration

Nitrofurazone is a nitrofuran derivative that is used topically for wounds, burns, ulcers, and skin infections, and for the preparation of surfaces before skin grafting. It is usually applied in a concentration of 0.2% in a water-soluble or water-miscible basis. A solution of nitrofurazone is used for bladder irrigation.

Urinary catheters impregnated with nitrofurazone, to reduce bacterial colonisation and infection, are available in some countries.

Adverse Effects

Sensitisation and generalised allergic skin reactions may be produced by topical nitrofurazone.

Nitrofurazone is a toxic drug when given orally and serious adverse effects include severe peripheral neuropathy; haemolysis may occur in patients with G6PD deficiency. Nitrofurazone in high oral doses is carcinogenic in *rats*.

Precautions

Nitrofurazone is contra-indicated in patients with known hypersensitivity. Preparations containing macrogols should be used with caution in patients with renal impairment since macrogols can be absorbed and their accumulation in such patients may result in symptoms of further impairment.

Oral nitrofurazone should be used with caution in patients with G6PD deficiency because of the risk of haemolysis.

Antimicrobial Action

Nitrofurazone is a nitrofuran derivative with a broad spectrum of antibacterial activity, but with little activity against *Pseudomonas* spp. It also has antitrypanosomal activity.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Furacin; NitroMed; ***Belg.***: Furacine; ***Braz.***: Caziderm; Furacin; Sensiderme; ***Chile***: Furacin; ***Ger.***: Furacin-Sol; ***India***: Emfurazone; Furacin; ***Mex.***: Furacin; Kufrot†; Nifurol; Probizal; Vulnizol; ***Philipp.***: Furacin; ***Port.***: Rayonfur; ***S.Afr.***: Furacin†; Furasept; Furex; Germex†; ***Spain***: Botinit; Furacin; ***Thai.***: Bactacin; Mytrocin; Polycin; ***Turk.***: Dermikolin; Furacin; Furaderm; Furazol; ***Venez.***: Furacin; Furfuril; Fuxal.

Multi-ingredient Preparations. ***Arg.***: Fadanasal; O-Biol; Vagicural; Vagisan Compuesto; Vagisan; Vislus; ***Braz.***: Nitrileno; ***India***: Furacin-S†; ***Ital.***: Furotricina; ***Mex.***: Madecassol C; Madecassol N; ***Spain***: Dertrase; ***Thai.***: Denson†.

Pharmacopoeial Preparations

USP 36: Nitrofurazone Ointment; Nitrofurazone Topical Solution.

Nitroxoline *(BAN, pINN)*

Nitroxolina; Nitroxolinum; Нитроксолин.

5-Nitroquinolin-8-ol.

$C_9H_6N_2O_3$=190.2

CAS — 4008-48-4.

ATC — J01XX07.

ATC Vet — QJ01XX07.

UNII — A8M33244M6.

Profile

Nitroxoline has antibacterial and antifungal properties and is used in the treatment of urinary-tract infections in oral doses of 400 to 600 mg daily given in divided doses after meals. It has also been given with sulfamethizole.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ger.***: Cysto-Saar†; Nilox; ***Rus.***: 5-Nitrox (5-Нитрокс)†; 5-Nok (5-Нок); ***S.Afr.***: Nicene N†; ***Ukr.***: 5-NOK (5-НОК).

Multi-ingredient Preparations. ***Braz.***: Minazol.

Norfloxacin *(BAN, USAN, rINN)*

AM-715; *N*-Desmethylpefloxacin; MK-366; Norfloksacinas; Norfloksacyna; Norfloksasiini; Norfloksasin; Norfloxacine; Norfloxacino; Norfloxacinum; Норфлоксацин.

1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(piperazin-1-yl)quinoline-3-carboxylic acid.

$C_{16}H_{18}FN_3O_3$=319.3

CAS — 70458-96-7.

ATC — J01MA06; S01AE02.

ATC Vet — QJ01MA06; QS01AE02.

UNII — N0F8P22L1P.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Norfloxacin). A white or pale yellow, hygroscopic, photosensitive, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol and in acetone. Store in airtight containers. Protect from light.

USP 36: (Norfloxacin). A white to pale yellow crystalline powder. Slightly soluble in water, in alcohol, and in acetone; freely soluble in acetic acid; sparingly soluble in chloroform; practically insoluble in ether; very slightly soluble in ethyl acetate and in methyl alcohol. Store in airtight containers. Protect from light.

Norfloxacin Pivoxil *(BANM, rINNM)*

Norfloxacine, Pivoxil de; Norfloxacini Pivoxil; Norfloxacino pivoxilo; Норфлоксацина Пивоксил.

Pivaloyloxymethyl 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(piperazin-1-yl)quinoline-3-carboxylic acid.

$C_{22}H_{28}FN_3O_5$=433.5

ATC — J01MA06; S01AE02.

ATC Vet — QJ01MA06; QS01AE02.

Uses and Administration

Norfloxacin is a fluoroquinolone antibacterial with properties similar to those of ciprofloxacin (p. 261.1), but it is generally less potent *in vitro*.

Norfloxacin is used mainly in the treatment of urinary-tract infections (p. 213.1), although based on concerns regarding efficacy, regulatory authorities in the EU have advised against its use for treatment of complicated pyelonephritis specifically. It may also be used for the treatment of gonorrhoea (p. 204.2).

Norfloxacin is given orally at least 1 hour before, or 2 hours after, food or milk.

In urinary-tract infections the usual dose is 400 mg twice daily for 3 to 10 days. Treatment may need to be continued for up to 12 weeks in chronic relapsing urinary-tract infections; it may be possible to reduce the dose to 400 mg once daily if there is an adequate response within the first 4 weeks. A 28-day course of treatment with a dose of 400 mg twice daily should be given for acute or chronic bacterial prostatitis.

Doses may need to be reduced in renal impairment, see p. 335.3.

A single oral dose of 800 mg is given in the treatment of uncomplicated gonorrhoea.

Eye drops containing 0.3% of norfloxacin are used to treat eye infections.

The pivaloyloxymethyl salt of norfloxacin, norfloxacin pivoxil, is also used in some countries.

Administration in renal impairment. Oral doses of norfloxacin may need to be reduced in renal impairment; for urinary-tract infections, 400 mg once daily should be given to patients with a creatinine clearance of 30 mL/minute per 1.73 m^2 or less.

Adverse Effects and Precautions

As for Ciprofloxacin, p. 262.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies norfloxacin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

As for Ciprofloxacin, p. 264.3.

Antimicrobial Action

As for Ciprofloxacin, p. 265.2, although norfloxacin is less potent *in vitro*. Norfloxacin is not active against Chlamydiaceae, mycoplasmas, or mycobacteria.

Pharmacokinetics

About 30 to 40% of an oral dose of norfloxacin is absorbed. Peak plasma concentrations of about 1.5 micrograms/mL occur about 1 to 2 hours after a 400-mg oral dose; the presence of food can delay absorption. Norfloxacin is about 14% bound to plasma proteins. It is probably widely distributed, but information is limited. Norfloxacin penetrates well into tissues of the genito-urinary tract. It crosses the placenta. Relatively high concentrations occur in bile.

The plasma half-life is 3 to 4 hours and may be prolonged in renal impairment; a value of 6.5 hours or more has been reported when creatinine clearance is below 30 mL/minute per 1.73 m^2. About 30% of a dose is excreted unchanged in the urine within 24 hours, producing high urinary concentrations; norfloxacin is least soluble at a urinary pH of 7.5. Urinary excretion is by tubular secretion and glomerular filtration and is reduced by probenecid, although plasma concentrations of norfloxacin are not generally affected. Some metabolism occurs, possibly in the liver, and several metabolites, some with antibacterial activity, have been identified in urine. About 30% of an oral dose appears in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Bio Tarbun; Floxamicin; Floxatral; Prifloxacina; Memento NF; Nefronet; Norflol; Noroxin; Norsol; Parcetin; Ritromine; Uro-Linfol; Urofos; Uronovag; Uroseptal; Urotem; Uroxacin; Wenflox; *Austral.*: Insensye†; Norflohexal†; Noroxin; Nufloxib; Roxin; *Austria*: Floxacin; Zoroxin; *Belg.*: Zoroxin; *Braz.*: Andrefloxin; Flox; Floxacin; Floxanor; Floxinol; Genitoflox†; Neofloxin; Norf; Norflox†; Norfloxasan; Norfloxil; Norfloxmed; Norxin; Quinoform; Respexil; Uni Norflox; Uritrat; Uroseptal; Urotrobel; Uroxazol-N; *Canad.*: Apo-Norflox; *Chile*: Fulgram; *China*: Ai Li Ke (艾立克); Jin Ya Jie (金娅捷); Cz.: Gyrablock; Nolicin; *Fr.*: Chibroxine; Noroxine; *Ger.*: Bactracid†; Barazan; Chibroxin†; Firin†; Norflohexal†; Norflosal†; Norflox†; Norfluxx; *Gr.*: Alenbit; Azoxina; Constilax; Dirunez; Fluseminal; Grenis; Lemorcan; Lorcamin; Norocin; Ovinol; Pistofil; Setanol; Sinobid; Sofasin; Steinaclox; Urisold; Urobacid; Urospes-N; Vetamol; Zolmic; *Hong Kong*: Floxen†; Janacin†; Lexiflox†; Mitatonin; Surflox; Uroctal†; *Hung.*: Nolicin; *India*: Actiflox-400; Alflox; Anquin; Bacigyl; Biofloxin; Denar; Enteroflox; Flox; Floxiren; Gyrax; Harflox; Loxone; Meriflox; N-Flox; Negaflox; Nitdin; Nor-U; Noralox; Norbactin; Norbid; Norflox; Norigyl; Norilet; Norin; Normax; Nornij; Norrit; Norvit; Norzen; Nox; Optoflox; *Indon.*: Pyrflox†; *Israel*: Apirol†; *Ital.*: Diperflox; Flossac Naflox; Norflox; Noroxin; Renoxacin; Sebercim; Theanorf; Uticina; Utinor; *Jpn*: Baccidal; *Malaysia*: Janacin; Norfloxin; Rexacin; Trizolin; Urinox; Urobacid; *Mex.*: Baxamed; Difoxacil; Floxacin; Microxin; Noflorox; Norbactin†; Noroxin; Norquinol; Oranor; *Neth.*: Chibroxol†; Noroxin†; *NZ*: Noroxin†; *Philipp.*: Euroflox†; Fasqilon†; Flamorel; Heiwin; Jaydisyn; Lexiflox; Lexinor†; Norbactin†; Norex; Nortram†; NRX; Septinor; Uritracin; Urobacid†; Utiflox; Utinor; Winafloxt; *Pol.*: Chibroxin; Nolicin; Norsept; *Port.*: Besflox; Chibroxol; Noroxin; Uroflox; *Rus.*: Gyrablock (Гираблок)†; Locsone (Локсон); Negaflox (Негафлокс)†; Nolicin (Нолицин); Norbactin (Норбактин); Norfacin (Норфацин); Norilet (Норилет); Normax (Нормакс); Sofasin (Софазин); Utibid (Утибид); *S.Afr.*: Floxin; Noroxin†; Utifloxa; Utin; *Singapore*: Bexinor; Foxgoria; Gyrablock; Loxone; Norbactin; Sefnor; Trizolin; *Spain*: Amicrobin; Chibroxin; Esdebin†; Espeden†; Nallon†; Norflok†; Noroxin†; Senro†; Uroctal†; Xasmun; *Swed.*: Lexinor†; *Switz.*: Norflocin; Noroxin; Norsol; *Thai.*: Crossa; Floximed; Foxin; Foxinon; Gonorcin; Janacin; Lexfor; Lexinor†; Loxone†; M-Flox; Manoflox; Medic Nor; Myfloxin; Noracin; Norbactin; Norcin; Norfa; Norfan; Norfass†; Norficin; Norflacil; Norflo; Norflocin; Norflox; Norfloxin; Norfloxpac; Norfloxyl; Norfox; Norxacin; Norxia; Noxine; Noxinor; Proxacin; Proxinor; Rexacin; Sanorflox; Sefnor; Snoffocin; Solexin; Urinox; Uritracin†; Vesxacin†; Xacin; Zinor; *Turk.*: Noroxin; *UAE*: Uroxin; *UK*: Utinor; *Ukr.*: Norbactin (Норбактин); Norfloxhexal (Норфлогексал)†; *USA*: Noroxin; *Venez.*: Danilon; Noroxin.

Multi-ingredient Preparations. *Arg.*: Nor 2; Urotem Dol; *India*: Actiflox-T; Actinor-MZ; Actinor-TZ; Amibex-TZ; Bioflox-TZ; C-Dial; C-Nor Plus; Cinzole; Conaz; Dazonor; Diaba-M; Diaba; Digyl; Duonor; Dysnilox; Elnor-TZ; Emflox-TZ; Entamizole TN; Enteroflox-T; Fenigyl; Flontin; Gastogyl-M; Gramogyl; Gramoneg-TN; Harflox-T; Klassak; Lotinor; Loxamet; Loxitin-P; Loxone-T; Mangogyl; Mapgyl; Mapgyl; Matinor; Matrix; Meganeg; Metnox; Metronor-P; N-Flox D; N-Flox TZ; N-Tiz; N-TZ; Nedge; Neflox-TZ; Nex-M; Nitdin-TZ; NM Power; Nogit-M; Nor T; Nor-Metrogyl; Nor-T; Noragyl-OZ; Noragyl; Noragyl; Norazol; Norbactin-Z; Norbit; Nordys; Norfagyl; Norfazole; Norfen TZ; Norflox TZ; Norgrade; Norilet-A; Norin-MZ; Norin-TD; Norlex-TZ; Norlon; Normax TZ; Normide; Normint; Nornij-TZ; Norrit-Ord; Norrit; Nort; Norzee-TZ; Notisym-LB; Notty; Nox-TZ; Noxigyl; NT-Z; NTD; NTD; Nugit-M; Okagyl; Oniflox; Parabact†; Powergyl; Tinvista-NF; *Mex.*: Mictasol; Norflen.

Pharmacopoeial Preparations

BP 2014: Norfloxacin Eye Drops; Norfloxacin Tablets;
USP 36: Norfloxacin Ophthalmic Solution; Norfloxacin Tablets.

Norvancomycin Hydrochloride

56-Demethylvancomycin; *N*-Demethylvancomycin.

(*S*$_a$)-(3*S*,6*R*,7*R*,22*R*,23*S*,26*S*,36*R*,38a*R*)-44-{[2-*O*-(3-Amino-2,3,6-trideoxy-3-*C*-methyl-α-L-*lyxo*-hexopyranosyl)-β-D-glucopyranosyl]oxy}-3-(carbamoylmethyl)-10,19-dichloro-2,3,4,5,6,7,23,24,25,26,36,37,38,38a-tetradecahydro-7,22,28,30,32-pentahydroxy-6-[(2*R*)-4-methyl-2-(amino)valeramido]-2,5,24,38,39-pentaoxo-22*H*-8,11:18,21-dietheno-23,36-(iminomethano)-13,16:31,35-dimetheno-1*H*,16*H*-[1,6,9]oxadiazacyclohexadecino[4,5-*m*][10,2,16]-benzoxadiazacyclotetracosine-26-carboxylic acid, monohydrochloride.

$C_{65}H_{73}Cl_2N_9O_{24}$,HCl=1471.7

CAS — 91700-98-0 (norvancomycin).

Pharmacopoeias. In *Chin.*

Profile

Norvancomycin is a glycopeptide antibacterial with properties similar to those of vancomycin (p. 386.2).

Novobiocin *(BAN, rINN)*

Crystallinic Acid; Novobiocina; Novobiocine; Novobiocinum; Novobiosiini; Novobiosin; PA-93; Streptonivicin; U-6591; Новобиоцин.

4-Hydroxy-3-[4-hydroxy-3-(3-methylbut-2-enyl)benzamido]-8-methylcoumarin-7-yl 3-*O*-carbamoyl-5,5-di-*C*-methyl-α-L-lyxofuranoside.

$C_{31}H_{36}N_2O_{11}$=612.6

CAS — 303-81-1.

UNII — 17EC1995IN.

Description. Novobiocin is an antimicrobial substance produced by the growth of *Streptomyces niveus* and *S. spheroides* or related organisms.

Novobiocin Calcium *(BANM, rINNM)*

Calcii Novobiocinum; Calcium Novobiocin; Novobiocina cálcica; Novobiocine Calcique; Novobiocinum Calcium; Кальций Новобиоцин.

$(C_{31}H_{35}N_2O_{11})_2Ca$=1263.3

CAS — 4309-70-0.

UNII — RHW5BU180N.

Novobiocin Sodium *(BANM, rINNM)*

Natrii Novobiocinum; Novobiocina sódica; Novobiocine Sodique; Novobiocinum Natricum; Sodium Novobiocin; Натрий Новобиоцин.

$C_{31}H_{35}N_2NaO_{11}$=634.6

CAS — 1476-53-5.

UNII — Q9S9NQ5YIY.

Pharmacopoeias. In *Fr.* and *US.*

USP 36: (Novobiocin Sodium). A white or yellowish-white, odourless, hygroscopic crystalline powder. Freely soluble in water, in alcohol, in methyl alcohol, in glycerol, and in propylene glycol; practically insoluble in acetone, in chloroform, and in ether; slightly soluble in butyl acetate. pH of a 2.5% solution in water is between 6.5 and 8.5. Store in airtight containers.

Profile

Novobiocin is an antibacterial which is structurally related to coumarin. It is active against Gram-positive bacteria such as *Staphylococcus aureus* (including meticillin-resistant strains) and other staphylococci; *Enterococcus faecalis* is usually resistant but *E. faecium* may be sensitive. Some Gram-negative organisms including *Haemophilus influenzae* and *Neisseria* spp. are also susceptible, as are some strains of *Proteus*, but most of the Enterobacteriaceae are resistant. Its action is primarily bacteriostatic, although it may be bactericidal against more sensitive species at high concentrations. It is an inhibitor of DNA gyrase and is effective in eliminating plasmids, but resistance to novobiocin develops readily *in vitro* and during therapy.

Although novobiocin has been used alone or with other drugs such as rifampicin or sodium fusidate in the treatment of infections due to staphylococci and other susceptible organisms, it has been largely superseded by other drugs because of the problems of resistance and toxicity.

Novobiocin is a potent sensitiser and hypersensitivity reactions are relatively common; they include rashes, fever, and pruritus, and more serious reactions such as Stevens-Johnson syndrome and pneumonitis. Jaundice and liver damage have occurred, although apparent jaundice may be due to a yellow metabolite of the drug rather than hyperbilirubinaemia. Other adverse effects include eosinophilia, leucopenia, thrombocytopenia, agranulocytosis, and haemolytic anaemia; gastrointestinal disturbances are common.

Ofloxacin *(BAN, USAN, rINN)*

DL-8280; Hoe-280; Ofloksacinas; Ofloksasiini; Ofloksasin; Ofloxacine; Ofloxacino; Ofloxacinum; RU-43280; Офлоксацин.

(±)-9-Fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid.

$C_{18}H_{20}FN_3O_4$=361.4

CAS — 82419-36-1; 83380-47-6.

ATC — J01MA01; S01AE01; S02AA16.

ATC Vet — QJ01MA01; QS01AE01; QS02AA16.

UNII — A4P49JAZ9H.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Ofloxacin). A pale yellow or bright yellow crystalline powder. Slightly soluble in water and in methyl alcohol; slightly soluble to soluble in dichloromethane; soluble in glacial acetic acid. Store in airtight containers. Protect from light.

USP 36: (Ofloxacin). Pale yellowish-white to light yellowish-white crystals or crystalline powder. Slightly soluble in water, in alcohol, and in methyl alcohol; sparingly soluble in chloroform. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Ofloxacin Hydrochloride *(BANM, rINNM)*

Hidrocloruro de ofloxacino; Ofloxacine, Chlorhydrate d'; Ofloxacini Hydrochloridum; Офлоксацина Гидрохлорид.

$C_{18}H_{20}FN_3O_4$,HCl=397.8

ATC — J01MA01; S01AE01; S02AA16.

ATC Vet — QJ01MA01; QS01AE01; QS02AA16.

UNII — I2UWV315WA.

Uses and Administration

Ofloxacin is a fluoroquinolone antibacterial used similarly to ciprofloxacin (p. 261.2). It is also used in *Chlamydia* or *Chlamydophila* infections including nongonococcal urethritis (p. 177.1 and p. 212.3) and in mycobacterial infections such as leprosy (p. 188.3) and tuberculosis (see under Uses and Administration of Ciprofloxacin, p. 262.2).

Ofloxacin is given orally as the base or by intravenous infusion as the hydrochloride. All doses are expressed in terms of the base; ofloxacin hydrochloride 220.2 mg is equivalent to about 200 mg of ofloxacin.

The usual oral or intravenous dose ranges from 200 mg daily to 400 mg twice daily depending on the severity and the nature of the infection. Oral doses of up to 400 mg may be given as a single dose, preferably in the morning. For intravenous use a 0.2% solution is infused over 30 minutes.

An oral dose of 200 mg twice daily for 3 days is suitable in women with acute uncomplicated cystitis. A 6-week course of treatment with an oral dose of 300 mg twice daily should be given for chronic bacterial prostatitis. A single 400-mg dose of ofloxacin may be given orally for uncomplicated gonorrhoea.

Oral doses of 400 mg *daily* given with clofazimine and minocycline or 400 mg *monthly* given with rifampicin and minocycline have been recommended by WHO as alternative multidrug therapy regimens for multibacillary leprosy. As an alternative regimen for single-lesion paucibacillary leprosy WHO suggests a single dose of ofloxacin 400 mg with rifampicin and minocycline.

Ofloxacin is used topically as 0.3% eye drops for the treatment of conjunctivitis and corneal ulcers caused by susceptible strains of bacteria. It is also used as 0.3% ear drops for the treatment of otitis externa and otitis media.

For details of reduced doses in hepatic or renal impairment, see p. 337.1.

Reviews.
1. Todd PA, Faulds D. Ofloxacin: a reappraisal of its antimicrobial activity, pharmacology and therapeutic use. *Drugs* 1991; 42: 825–76.
2. Onrust SV, *et al.* Ofloxacin: a reappraisal of its use in the management of genitourinary tract infections. *Drugs* 1998; 56: 895–928.
3. Simpson KL, Markham A. Ofloxacin otic solution: a review of its use in the management of ear infections. *Drugs* 1999; 58: 509–31.
4. Wai TKH, Tong MCF. A benefit-risk assessment of ofloxacin otic solution in ear infection. *Drug Safety* 2003; 26: 405–20.

Administration in hepatic impairment. The clearance of ofloxacin is reduced in patients with severe hepatic impairment or cirrhosis and lower doses should be used; a maximum oral dose of 400 mg daily has been recommended.

Administration in renal impairment. Lower doses of ofloxacin may be necessary in patients with renal impairment. After the usual initial oral dose (see Uses and Administration, p. 334.3), subsequent doses are adjusted according to creatinine clearance (CC):
- CC 20 to 50 mL/minute: doses halved to 100 to 200 mg daily or the usual dose is given every 24 hours
- CC less than 20 mL/minute: dose reduced to 100 mg every 24 hours
- patients on haemodialysis or peritoneal dialysis: 100 mg every 24 hours

BCG toxicity. For mention of the possible use of ofloxacin to reduce the incidence of toxicity after BCG intravesicular instillation, see p. 2379.3.

Tuberculosis. For mention of the use of ofloxacin in the treatment of tuberculosis, see under Ciprofloxacin, p. 262.2.

Adverse Effects and Precautions

As for Ciprofloxacin, p. 262.2.

Symptomatic hyperglycaemia and/or hypoglycaemia have been reported, usually in diabetics who are also taking hypoglycaemics or insulin. Such patients should have their blood-glucose concentrations closely monitored and if signs or symptoms of glucose disturbances develop, ofloxacin should be stopped.

A reduction in blood pressure may occur rarely after intravenous infusion. Similarly, sudden reductions in blood pressure may occur when intravenous ofloxacin is given with hypotensive drugs. Cardiovascular function should be monitored in such patients and in those also receiving barbiturate anaesthetics.

Ofloxacin eye drops may increase the risk of corneal perforation in those with pre-existing corneal ulcers or epithelial defects.

Breast feeding. The American Academy of Pediatrics has stated that no adverse effects have been seen in breast-fed infants whose mothers were receiving ofloxacin and that it is therefore usually compatible with breast feeding.[1] However, in a study[2] of 10 women given ofloxacin after termination of pregnancy, drug concentrations in breast milk were sufficiently high to recommend that the use of ofloxacin in lactating women should be avoided.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/05/04)
2. Giamarellou H, *et al.* Pharmacokinetics of three newer quinolones in pregnant and lactating women. *Am J Med* 1989; 87 (suppl 5A): 495–515.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ofloxacin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

As for Ciprofloxacin, p. 264.3.

Use of ofloxacin with drugs that alter blood-glucose concentrations increases the risk of blood-glucose disturbances.

Antimicrobial Action

As for Ciprofloxacin, p. 265.2.

Ofloxacin is more active than ciprofloxacin against *Chlamydia trachomatis*. It is also active against *Mycobacterium leprae* as well as *M. tuberculosis* and some other *Mycobacterium* spp. Synergistic activity against *M. leprae* has been reported between ofloxacin and rifabutin.

The optically active *S*-(-)-isomer levofloxacin (p. 315.3) has twice the activity of the racemate ofloxacin.

Resistance has been reported in some strains of *Neisseria gonorrhoeae*.

Pharmacokinetics

Ofloxacin is rapidly and well absorbed from the gastrointestinal tract. Oral bioavailability is almost 100% and a peak plasma concentration of about 3 to 5 micrograms/mL occurs 1 to 2 hours after an oral 400-mg dose. Absorption may be delayed by the presence of food, but the extent of absorption is not substantially affected.

About 25% is bound to plasma proteins. Ofloxacin is widely distributed in body fluids, including the CSF, and tissue penetration is good. It crosses the placenta and is distributed into breast milk. It also appears in the bile.

The elimination of ofloxacin is biphasic; half-lives of about 4 to 5 and 20 to 25 hours have been reported for the 2 phases, respectively. In renal impairment values of 15 to 60 hours have been reported. There is limited metabolism to desmethyl and *N*-oxide metabolites; desmethylofloxacin has moderate antibacterial activity. Ofloxacin is eliminated mainly by the kidneys. Excretion is by tubular secretion and glomerular filtration and 65 to 80% of a dose is excreted unchanged in the urine over 24 to 48 hours, resulting in high urinary concentrations. Less than 5% is excreted in the urine as metabolites. From 4 to 8% of a dose may be excreted in the faeces.

Only small amounts of ofloxacin are removed by haemodialysis or peritoneal dialysis.

References.
1. Lamp KC, *et al.* Ofloxacin clinical pharmacokinetics. *Clin Pharmacokinet* 1992; 22: 32–46.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Floxil; Ingeflox†; Klonalflox; Newflox; Oflox; Otoflox; Quinomed; Rafoclina; *Austral.*: Ocuflox; *Austria*: Floxal; Oflox†; Tarivid; *Belg.*: Docofloxacine†; Tarivid; Trafloxal; *Braz.*: Flogirax; Floxina; Floxstat; Genoxacin; Nostil; Oflox; *Canad.*: Apo-Ofloxt; Ocuflox; *Chile*: Oflox; Poenflox†; *China*: An Fu Le (安福乐); Anli (安利); Ao Di Fu Kang (奥迪扶康); Ao Wei Te (奥卫特); Aofuxing (奥复星); Bei Li De (贝立德); Di Ke Luo (迪可罗); Dong Kang Ming (东康明); Fei Ning Da (菲宁达); Geiluoxian (盖洛仙); Hao Te (浩特); Heng Run (恒润); JieFu (捷孚); Nuo Qing (诺青); Pu Guang (普光); Rui Da (瑞达); Tai Fu Kang (泰福康); Tarivid (泰利必妥); Xin Long (信龙); Xinlituo (信利妥); Yan Hua Xing (延华星); Yang Da Ning (阳达宁); Zanocin (赞诺欣); *Cz.*: Floxal; Ofloxin; Tarivid†; Taroflox; Zanocin; *Denm.*: Exocin; Tarivid†; *Fin.*: Exocin; Tarivid; *Fr.*: Exocine; Monoflocet; Oflocet; *Ger.*: Floxal; Gyroflox†; Oflohexal†; Oflox†; Ofloxbeta†; Tarivid; Uro-Tarivid; *Gr.*: Ermofan; Exocin; Grenis-Oflo; Hetacloxacin; Oflocollyre; Tabrin; Urimax; *Hong Kong*: Flovid; Floxan†; Lessin; Maproxacin†; Marfloxacin†; Ofus; Puiritol; Quotavil; Tarivid; Viotisone; *Hung.*: Floxal; Oflogen; Tarivid; Zanocin; *India*: Abof; Aflox; Agroflox; Alocin; Alof; Alox; Alproxen; Ariflox; Arviflox; Asiflox-OZ; Asiflox; Atoflox; Aviflox; B-Flox; Bacter; Bactof; Bactoff; Bekker; Bestoflox; Bidoflox; Bio Flo; Biofast; Bioff; Bioz; Broflox; Bru-O; C-Flox; Cadof; Canocin; Casflox; CG Flox; Chekmet; Cinflox; Clofcin; Covax; Cozan; Crof; Cucin; Curadex; Cyflox; Denof; Doact; Duflox; E-Flox; Ecoflox; Eflobid; Emucin; Entof DPS; Essasin; Esterflox; Eufox; Exocin; Falcon; Festive; Fixiflox; Flex; Flobacin; Flogard; Florida; Flow; Flox-200; Flox-O; Floxar; Floxicontin; Floxil-O; Floxine; Floxole; Floxur; Floxzen; GBO; Genflox; GFlox; Gilflox; Glofty; Gyroflox; Harpoon; Hineoflox; Hoflo; Indocin; Indof; Inflobact; Inflobid; Inflox; Infoxin; Jflo; Jox; Kaiflox; Kureflox; Laflox; Lexof; Loft; Logflox; Loxin; Magof; Megaflox; Mep-Orva; Meuflox; Mintof; Mofcare; Moflo; Monoflox; NBox; Neobid; Neva; Nida; Niolox; Noff; Novofran; O-Cebran; O-Fact; O-Quin; O-Tab; OA; Obactin; Obid-ER; Obit; Ocin; Ociz; Ocucin; Oculone; Of Plus; Of; Ofac; Ofacin; Ofal; Ofax; Ofbid; Ofcare; Ofcura; Ofel; Ofelder; Ofet; Offy; Ofia; Ofkab; Ofkair; OFL; Ofla; Oflabin; Oflacin; Oflact; Oflagard; Oflage; Oflahill; Oflak; Oflamed; Oflaquin; Oflas; Oflaset; Oflatoon-OZ; Oflatoon; Oflavid; Oflawin; Oflee; Oflem; Ofler; Oflex; Oflict; Oflin; Oflo; Oflocos; Ofloday; Ofloden; Oflog; Ofloine; Oflomac; Oflomil; Oflomits; Oflon; Oflopar; Oflopip; Ofloren; Oflostar; Oflotas; Oflotec; Oflotet; Oflovid; Oflox; Oflozen; Ofixcin; Offy; Ofmed; Ofnet; Ofnij; Ofnis; Ofo; Ofor; Ofoxin; Ofpil; Ofral; Ofran; Ofras; Ofsis; Ofspan; Ofspin; Oftacin; Oftar; Oftarx; Oftec; Oftum; Ofven; Ofwin; Ofzac; Ofzen; Ojen; Okaflox; Okil; Oks; Ol; Olfi; Olfic; Olfo; Olife; Olpit; Oltaur; Olumpil; Omeflox; Opeq; Opex; Ophar; OQN; Oqueen; Orixa; Osani-DS; Osani-M; Osani; Oseflox; Osflox; Oshflox; Osiflox; Otago; Otic; Oxal; Oxalic; Oxdrin; Oxiflox; Oxit; Oxo; Oxoism; Oxop; Oxwal; Oza; Tariflox; Tarivid; Zanocin; *Indon.*: Akilen; Danoflox; Efexin†; Ethiflox; Flotavid; Floxan†; Floxika; Loxinter; Mefoxa; Nilavid; Nufafloqo; Ostrid; Pharflox; Poncoquin; Qipro; Quinovid; Rilox; Tariflox; Tarivid; Tarivid; Zelavel; Zyflox; *Irl.*: Biravid; Exocin; Tarivid; *Israel*: Oflodex; Oflox; Ofloxacina; Tarivid; Uro-Tarivid†; *Ital.*: Exocin; Oflocin; *Jpn*: Tarivid; *Malaysia*: Evaflox; Healoxt; Inoflox†; Medofloxine; Ofcin; Ofloxol; Tarivid; Zanocin; *Mex.*: Bactocin; Flonacin; Flosep; Floxil; Floxstat; Forxanix; Loxtev†; Oculflox; Oxken; Quiflural; Rixivoc; Zanocin†; *Neth.*: Tarivid; Trafloxal; *Norw.*: Tarivid; *Philipp.*: Cinoflox; Delbysen; Dizoflox; Dolocep; Effexin; Exogan; Flodemex; Flovid; Flox; Floxagen; Floxwin; Floxy; Fluraxid; Gonocin; Gyros; Iflox; Imoflox; Inoflex; Inoflox; Iquinol Otic; Iquinol; Itex; Keftil; Lofection; Loxin; Mergexin; Ofbeat; Ofcin; Ofladon; Oflosyn; Onexacin; Otoflox; Oxyflox; Ponebac; Prozut†; Qiflon; Qinolon; Sensoflox; Terioxan; Vioson; Zofex; *Pol.*: Floxal; Tarivid; *Port.*: Bactoflox; Bioquil; Exocin; Floxedol; Oflocet; Tarivid; *Rus.*: Dancil (Данцил); Floxal (Флоксал); Geoflox (Джеофлокс); Oflo (Офло); Oflocide (Офлоцид); Ofloxabol (Офлоксабол); Ofloxin (Офлоксин); Taricin (Тарицин); Tariferid (Тарифферид); Tarivid (Тариивд); Uniflox (Унифлокс); Zanocin (Заноцин); Zoflox (Зофлокс); *S.Afr.*: Exocin; Octin; Tafloc; Tarivid; Zanocin; *Singapore*: Aflacin; Akilen; Flovid; Fugacin; Ofcin; Tarivid; *Spain*: Exocin; Oflovir; Surnox; *Swed.*: Tarivid; *Switz.*: Floxal; Tarivid; *Thai.*: Exocin; Floxy†; Hyflox; Konovid; Mifloxin; O-Flox; Occidal; Ocin; Ofacin; Ofla; Oflo; Oflobac; Oflocee; Oflomet; Oflox; Ofloxa; Ofloxcin; Orivid; Qinolon; Seracin; Tarivid; Travid; Vesoflox; Viotisone; *Turk.*: Drovid; Exocin; Girasid†; Kozoksin; Menefloks; Menofloks; Ofkozin; Oflocide; Oflok; Tarivid; Urosin; *UK*: Exocin; Tarivid; *Ukr.*: Floksan (Флоксан); Floxal (Флоксал); Oflo (Офло); Oflohexal (Офлогексал)†; Ofloxin (Офлоксин); Zanocin (Заноцин); *USA*: Floxin Otic; Floxin; Ocuflox; *Venez.*: Floxstat; Norlamine; Oflox; Poenflox.

Multi-ingredient Preparations. *India*: A-Flox M; A-Flox-OZ; A-Flox; Abof-NZ; Abof-OZ; Adeflox-O; Aflox-OZ; AFlox-TZ; Alocin-OZ; Alocin; Alof-T; Alox-OD; Ariflox-OZ; Arilif-OZ; Armbid OZ; Arviflox-OZ; Atasol; Atoflox-OZ; Aviflox-M; Aviflox-OZ; Aviflox-ST; Aviflox-TZ; Bacter-M; Bacter-NZ; Bacter-OZ; Bacter-TZ; Bactezoa-LB; Bactoff-OZ; Baseflox OZ; Bekker-M; Bekker-OZ; Bestoflox N; Biofast-OZ; Biosin; Bonflox; Brakke; Broflox Plus; Bru-OZ; C-Flox-M; C-Flox-OZ; Canocin-OZ; Casflox-OZ; Casflox-TZ; Chekmet-O; Cinflox-OZ; Clofcin-M; Clofcin-T; Covax-OZ; Cozan-O; Cozan-T; Cucin-O; Cucin-T; Diof; Doact-TZ; Doloket-O; DTO; Ducidal-OZ; Duochek; Ecoflox-OZ; Edilox-OZ; Edilox-S; Emucin-TN; Essasin-OZ; Esterflox-OZ; Eufox-O; Eufox-TZ; Exopred; Falcon-TZ; Fern; Festive B; Festive D; Festive-OZ; Festive-TZ; Fixiflox-D; Fixiflox-H; Fixiflox-OZ; Flagynor; Flex-OZ; Flexril-Ord; Flobacin-OZ; Flobacin-TZ; Flogard-O; Florida-T; Flow-OZ; Floxaquin-O; Floxar-OZ; Floxine-NT; Floxine-OZ; Floxole-MZ; Floxole-NT; Floxole-OZ; Floxur-TZ; Floxzen-M; Floxzen-OZ; Floxzen-ST; Fouz; Ftz; Fydof; Gazal-O; Genflox TZ; Geryl-O; GFlox-OZ; Gic-O; Glofty-D; Glofty-OZ; Harpoon-DD; Harpoon-TZ; Hoflo-O; Hoflox-O; Indocin-D; Indocin-OZ; Indof OZ; Infloback-D; Infloback-OZ; Inflobid TZ; Inflobid-D; Inflobid-NXT; Inflobid-OZ; Inflox-OZ; Infoxin-OZ; Jflo-OZ; Jox-TZ; Kareof-OZ; Ketlur Plus; Ketoflox; Kooz; Kureflox-OZ; Laflox-O; Lamizol-O; Lexof-OZ; Lexof-TZ; Logflox-OZ; Loobid; Lumigard; Magof-OZ; MCFlox-OZ; Megaflox-M; Megaflox-TZ; Meganor; Meuflox-OZ; Mintof-OZ; Mof-OZ; Mofcare-TZ; Moflo-OZ; NBox-OZ; Netazox-OF; Netflox-OZ; Neva-OZ; Niolox-D; Niolox-OZ; Nita-O; Nitazet-O; Nitzix-O; Nizonide-O; Noff-OR; Normet; O & O; O-Cebran-O; O-Cebran-OZ; O-Dex; O-Fact-OZ; O2; O2H; Obactin-OZ; Obactin-TZ; Obid-OZ; Obid; Obit-M; Obit-OZ; Obit-TZ; Ocepred; Ociz-OR; Of-M; Ofac-O; Ofac-T; Ofacin-M; Ofacin-O; Ofacin-TZ; Ofal-M; Ofal-OZ; Ofal-TZ; Ofax-TZ; Ofbid-OZ; Ofcare-NT; Ofcare-OD; Ofcura-OZ; Ofdaz; Ofdex; Ofelder-D; Ofelder-PA; Ofet-D; Ofet-H; Ofet-O; Ofet-T; Ofia-OZ; Ofkab-OZ; Ofkair-OZ; Ofla-OZ; Ofla-TZ; Oflab-OZ; Oflab; Oflabin+LB; Oflabin-TZ; Oflacin-DX; Oflacin-P; Oflact-M; Oflact-OZ; Oflagard-O; Oflagard-OL; Oflage-OZ; Oflamed-MN; Oflamed-OZ; Oflamed-TZ; Oflaquin-M; Oflaquin-OZ; Oflark-O; Oflas-OZ; Oflaset-OZ; Oflatoon-MZ; Oflavid-TZ; Oflavid; Oflawin-OZ; Oflawin-TZ; Oflee-M; Oflee-NT; Oflee-OZ; Oflem-D; Oflem-OZ; Ofler-TZ; Oflict-OZ; Oflin-TZ; Oflina-OZ; Oflo-D; Oflo-DT; Oflo-M; Oflo-OZ; Oflo-TZ; Oflocos-OZ; Oflocos-TZ; Ofloday-OZ; Ofloden-O; Ofloden-T; Ofloine-OZ; Oflomac-TZ; Oflomet; Oflomil-OZ; Oflon-OZ; Oflon-TZ; Oflopar-OR; Oflopip-O; Ofloren-OZ; Ofloren-TZ; Oflostar-D; Oflostar-M; Oflostar-OZ; Oflostar-TZ; Oflotas-OZ; Oflotec-OZ; Oflox D; Oflox TZ; Oflozen-D; Ofixcin-TZ; Offy-OZ; OFM; Ofmed-OZ; Ofnet-OZ; Ofnida-LB; Ofnida; Ofnis-OZ; Ofo-OZ; Ofo-TZ; Ofor-OZ; Ofpil-O; Ofpil-TZ; Ofral-OZ; Ofral-TZ; Ofran-OZ; Ofsis-OZ; Ofspan-OZ; Ofspan-TZ; Ofspin-OZ; Oft; Oftacin-OZ; Oftec-M; Oftech-OZ; Oftini; Oftum-OZ; Oftum-TZ; Oftwo; Ofven-TZ; Ofwin-OZ; Ofzac-OZ; Ofzen-OZ; Ofzo; Ojen-OZ; Ojen-TZ; Okaflox M; Okaflox-TZ; Okil-OZ; Oks-OZ; Oley-OZ; Olfi TZ; Olfi-O; Olfic-OZ; Olfon-OR; Olife-M; Olife-OZ; Olife-TZ; Olife; Olpit-NZ; Olpit-OZ; Oltaur-TZH; Omeflox-KT; On-OZ; Oniz-O; Opeq-OZ; Ophar-OZ; OQN-O; Oqueen-OZ; Orflo; Orflo; Orin-O; Orni-O; Ornidox; Orniflox; Ornilox; Ornof; Oroflox-OZ; Osani-D; Osani-NT; Osani-O; Osani-T; Osflox-OR; Osiflox-OZ; Osiflox-TZ; Ospol-OZ; Ot; Otago-O; Otek-O; Otic-O; Otichek; Otiflox; Otocin-O; Oxacin-OZ; Oxalic-NZ; Oxcin-Ord; Oxdrin-D; Oxdrin-Ord; Oxiflox-OZ; Oxiflox-TZ; Oxit-OZ; Oxo-D; Oxo-M; Oxo-Ord; Oxo-TZ; Oxoism-OZ; Oxop-D; Oxwal-OZ; Oxwal-TZ; Oxyna; Oza-O; Satrogyl-O; Satromax-O; Tariflox Plus; *Mex.*: Orecil NF; *Philipp.*: Exopred; *Rus.*: Oflomelid (Офломелид); *Thai.*: Exopred; *Ukr.*: Oflocain (Офлокаин); Ofor (Офор); Tiflox (Тифлокс)†.

Pharmacopoeial Preparations
USP 36: Ofloxacin Ophthalmic Solution; Ofloxacin Tablets.

Oleandomycin Phosphate *(BANM, rINNM)*

Fosfato de oleandomicina; Oleandomicina, fosfato de; Oléandomycine, Phosphate d'; Oleandomycini Phosphas; PA-105 (oleandomycin); Олеандомицина Фосфат.

(2*R*,3*S*,4*R*,5*S*,6*S*,8*R*,10*R*,11*S*,12*R*,13*R*)-3-(2,6-Dideoxy-3-*O*-methyl-α-*L*-*arabino*-hexopyranosyloxy)-8,8-epoxymethano-11-hydroxy-2,4,6,10,12,13-hexamethyl-9-oxo-5-(3,4,6-tri-

The symbol † denotes a preparation no longer actively marketed

deoxy-3-dimethylamino-β-D-*xylo*-hexopyranosyloxy)tridecan-13-olide phosphate.
$C_{35}H_{61}NO_{12},H_3PO_4$=785.9
CAS — 3922-90-5 (oleandomycin); 7060-74-4 (oleandomycin phosphate).
ATC — J01FA05.
ATC Vet — QJ01FA05.
UNII — 8681H0C27P.

Profile

Oleandomycin is a macrolide antibacterial produced by the growth of certain strains of *Streptomyces antibioticus* with actions and uses similar to those of erythromycin (p. 291.2). It has antimicrobial activity weaker than that of erythromycin. It has been given orally or intravenously as the phosphate in the treatment of susceptible infections.

Troleandomycin (p. 385.2) is the triacetyl ester.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Rus.*: Oletetrin (Олететрин).

Orbifloxacin *(BAN, rINN)*

Orbifloksasiini; Orbifloxacine; Orbifloxacino; Orbifloxacinum; Орбифлоксацин.
1-Cyclopropyl-7-(*cis*-3,5-dimethyl-1-piperazinyl)-5,6,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid.
$C_{19}H_{20}F_3N_3O_3$=395.4
CAS — 113617-63-3.
ATC Vet — QJ01MA95.
UNII — 660932TPY6.

Pharmacopoeias. In *US.* In *Eur.* (see p. vii) for veterinary use only.

Ph. Eur. 8: (Orbifloxacin for Veterinary Use). White or pale yellow, crystals or crystalline powder. It exhibits polymorphism. Very slightly soluble in water; practically insoluble dehydrated alcohol; soluble in glacial acetic acid.

USP 36: (Orbifloxacin). White to pale yellow, odourless crystals or crystalline powder. Very slightly soluble in water, in methyl alcohol, and in chloroform; practically insoluble in alcohol and in diethyl ether; soluble in acetic acid. pH of a 1% solution in water is between 6.5 and 7.8.

Profile

Orbifloxacin is a fluoroquinolone antibacterial used in veterinary medicine for the treatment of susceptible infections in dogs.

Preparations

Pharmacopoeial Preparations
USP 36: Orbifloxacin Tablets.

Oritavancin *(rINN)*

LY-333328; Oritavancina; Oritavancine; Oritavancinum; Оритаванцин.
(4″*R*)-22-*O*-(3-Amino-2,3,6-trideoxy-3-*C*-methyl-α-L-*arabino*-hexopyranosyl)-*N*$^{3''}$-[*p*-(*p*-chlorophenyl)benzyl]vancomycin.
$C_{86}H_{97}Cl_3N_{10}O_{26}$=1793.1
CAS — 171099-57-3.
ATC — J01XA05.
ATC Vet — QJ01XA05.
UNII — PUG62FRZ2E.

Oritavancin Phosphate *(rINNM)*

Fosfato de oritavancina; Oritavancin Diphosphate (USAN); Oritavancine, Phosphate d'; Oritavancini Phosphas; Оритаванцина фосфат.
$C_{86}H_{97}Cl_3N_{10}O_{26},2H_3PO_4$=1989.1
CAS — 192564-14-0.
ATC — J01XA05.
UNII — VL1P93MKZN.

Profile

Oritavancin is a lipoglycopeptide antibacterial under investigation for the treatment of complicated infections of the skin and soft tissues due to Gram-positive bacteria.

References.[1-6] See also under Uses and Administration of Telavancin, p. 373.1.

1. Van Bambeke F, *et al.* Glycopeptide antibiotics: from conventional molecules to new derivatives. *Drugs* 2004; 64: 913–36.
2. Ward KE, *et al.* Oritavancin—an investigational glycopeptide antibiotic. *Expert Opin Invest Drugs* 2006; 15: 417–29.
3. Poulakou G, Giamarellou H. Oritavancin: a new promising agent in the treatment of infections due to Gram-positive pathogens. *Expert Opin Invest Drugs* 2008; 17: 225–43.
4. Crandon J, Nicolau DP. Oritavancin: a potential weapon in the battle against serious Gram-positive pathogens. *Future Microbiol* 2008; 3: 251–63.
5. Rubino CM, *et al.* Oritavancin population pharmacokinetics in healthy subjects and patients with complicated skin and skin structure infections or bacteremia. *Antimicrob Agents Chemother* 2009; 53: 4422–8.
6. Zhanel GG, *et al.* New lipoglycopeptides: a comparative review of dalbavancin, oritavancin and telavancin. *Drugs* 2010; 70: 859–86.

Ormetoprim *(USAN, rINN)*

NSC-95072; Ormetoprima; Ormétoprime; Ormetoprimum; Ro-5-9754; Орметоприм.
5-(4,5-Dimethoxy-2-methylphenyl)methyl-2,4-pyrimidinediamine.
$C_{14}H_{18}N_4O_2$=274.3
CAS — 6981-18-6.
UNII — M3EFS94984.

Profile

Ormetoprim is a diaminopyrimidine antibacterial used similarly to trimethoprim (p. 383.2) as a sulfonamide potentiator, in veterinary medicine. Preparations usually contain 1 part of ormetoprim to 5 parts of sulfonamide.

Oxacillin Sodium *(BANM, USAN, rINNM)*

(5-Methyl-3-phenyl-4-isoxazolyl)penicillin Sodium; Natrii Oxacillinum; Oksacylina sodowa jednowodna; Oksasilliininatriummonohydraatti; Oxacilin sodná sůl monohydrát; Oxacilina sódica; Oxacilline Sodique; Oxacilline sodique monohydratée; Oxacillinnatriummonohydrat; Oxacillinum natricum monohydricum; Oxacillinum Natrium; P-12; SQ-16423; Натрий Оксациллин.
Sodium (6*R*)-6-(5-methyl-3-phenylisoxazole-4-carboxamido) penicillanate monohydrate.
$C_{19}H_{18}N_3NaO_5S,H_2O$=441.4
CAS — 66-79-5 (oxacillin); 1173-88-2 (anhydrous oxacillin sodium); 7240-38-2 (oxacillin sodium monohydrate).
ATC — J01CF04.
ATC Vet — QJ01CF04.
UNII — G0V6C994Q5 (oxacillin monohydrate); 4TWD2995UP (anhydrous oxacillin sodium).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Oxacillin Sodium Monohydrate). A white or almost white powder. Freely soluble in water; practically insoluble in dichloromethane; soluble in methyl alcohol. A 3.0% solution in water has a pH of 4.5 to 7.5.

USP 36: (Oxacillin Sodium). A fine white crystalline powder, odourless or having a slight odour. Freely soluble in water, in dimethyl sulfoxide, and in methyl alcohol; slightly soluble in dehydrated alcohol, in chloroform, in methyl acetate, and in pyridine; insoluble in ether, in ethyl acetate, in ethylene chloride, and in benzene. pH of a 3% solution in water is between 4.5 and 7.5. Store in airtight containers at a mean temperature not exceeding 25 degrees.

Incompatibility. Oxacillin sodium has been reported to be incompatible with aminoglycosides and tetracyclines.

Uses and Administration

Oxacillin is an isoxazolyl penicillin used similarly to flucloxacillin (p. 299.2) in the treatment of infections due to staphylococci resistant to benzylpenicillin.

Oxacillin is given orally or by injection as the sodium salt. Doses are expressed in terms of the equivalent amount of oxacillin; 1.1 g of oxacillin sodium is equivalent to about 1 g of oxacillin. Oral doses should preferably be given at least 1 hour before, or 2 hours after, meals. The usual oral dose is 1 g of oxacillin twice daily. Oxacillin may be given by intramuscular injection, by slow intravenous injection over about 10 minutes, or by intravenous infusion. Usual parenteral doses are 250 to 500 mg every 4 to 6 hours. Doses may be increased to 1 g every 4 to 6 hours for severe infections, although total daily doses of up to 12 g have been used for deep-seated infections such as endocarditis and osteomyelitis.

For details of doses in children, see p. 338.2.

Administration in children. Oxacillin may be given to neonates and children for the treatment of infections caused by susceptible strains of penicillinase-producing staphylococci by intramuscular or intravenous injection, or by intravenous infusion.

In the USA, the American Academy of Pediatrics[1] recommends the following *parenteral* doses:

- all neonates with a birth-weight less than 1.2 kg: 25 mg/kg every 12 hours
- neonates less than 1 week of age with a birth-weight of 1.2 to 2 kg: 25 to 50 mg/kg every 12 hours
- neonates less than 1 week of age with a birth-weight more than 2 kg, or neonates 1 week of age or older with a birth-weight of 1.2 to 2 kg: 25 to 50 mg/kg every 8 hours
- neonates 1 week of age or older with a birth-weight of more than 2 kg: 25 to 50 mg/kg every 6 hours
- children 1 month and older: 100 to 150 mg/kg daily in 4 divided doses; 150 to 200 mg/kg daily in 4 or 6 divided doses may be used for severe infections

In infants and children, the *oral* route has also been used in some countries in the following doses:

- infants: 125 mg for every 5 kg of body-weight, twice daily
- children: 500 mg twice daily

1. American Academy of Pediatrics. *2009 Red Book: Report of the Committee on Infectious Diseases*, 28th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2009.

Adverse Effects and Precautions

As for Flucloxacillin, p. 299.3.

Effects on the liver. References.

1. Onorato IM, Axelrod JL. Hepatitis from intravenous high-dose oxacillin therapy: findings in an adult inpatient population. *Ann Intern Med* 1978; 89: 497–500.
2. Saliba B, Herbert PN. Oxacillin hepatotoxicity in HIV-infected patients. *Ann Intern Med* 1994; 120: 1048.
3. Maraqa NF, *et al.* Higher occurrence of hepatotoxicity and rash in patients treated with oxacillin, compared with those treated with nafcillin and other commonly used antimicrobials. *Clin Infect Dis* 2002; 34: 50–4.
4. Lee CY, *et al.* Reversible oxacillin-associated hepatitis in a 9-month-old boy. *J Paediatr Child Health* 2008; 44: 146–8.

Sodium content. Each g of oxacillin sodium contains about 2.3 mmol of sodium.

Interactions

As for Benzylpenicillin, p. 230.1.

Antimicrobial Action

As for Flucloxacillin, p. 300.1.

Resistance. The isolation of pneumococci resistant to oxacillin but sensitive to benzylpenicillin has been reported.[1,2] The resistance was due to acquisition of a low-affinity penicillin-binding protein and conferred cross-resistance to meticillin and cloxacillin, and, to a lesser degree, to cefotaxime.

1. Johnson AP, *et al.* Oxacillin-resistant pneumococci sensitive to penicillin. *Lancet* 1993; 341: 1222.
2. Dowson CG, *et al.* Genetics of oxacillin resistance in clinical isolates of Streptococcus pneumoniae that are oxacillin resistant and penicillin susceptible. *Antimicrob Agents Chemother* 1994; 38: 49–53.

Pharmacokinetics

Oxacillin is incompletely absorbed from the gastrointestinal tract. Absorption is reduced by the presence of food in the stomach and is less than with cloxacillin. Peak plasma concentrations of 3 to 6 micrograms/mL occurred 1 hour after an oral dose of 500 mg given to fasting subjects. After intramuscular injection of 500 mg, peak plasma concentrations of up to 15 micrograms/mL have been achieved by 30 minutes. Doubling the dose can double the plasma concentration. About 93% of the oxacillin in the circulation is bound to plasma proteins. Oxacillin has been reported to have a plasma half-life of about 0.5 hours. The half-life is prolonged in neonates.

The distribution of oxacillin into body tissues and fluids is similar to that of cloxacillin (p. 275.2).

Oxacillin undergoes some metabolism, and the unchanged drug and metabolites are excreted in the urine by glomerular filtration and renal tubular secretion.

About 20 to 30% of an oral dose, and more than 40% of an intramuscular dose, is rapidly excreted in the urine. Oxacillin is also excreted in the bile.

Plasma concentrations are enhanced by probenecid.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Penstapho; *Braz.*: Oxanon; Oxapen; Prodoxacilina†; Roxacilin; Staficilin N; *Cz.*: Prostaphlin; *Fr.*: Bristopen; *Ger.*: InfectoStaph†; *Ital.*: Penstapho; *Philipp.*: Oxal; Oxapen; Oxatalis; Panadox; Prostaphlin†; Stafcil; Wydox; *Venez.*: Biocilina; OxiPen; Prostafilina.

Multi-ingredient Preparations. *Rus.*: Oxamp (Оксами); Oxampicine (Оксампицин); Oxamsar (Оксамсар).

Pharmacopoeial Preparations
USP 36: Oxacillin for Injection; Oxacillin Injection; Oxacillin Sodium Capsules; Oxacillin Sodium for Oral Solution.

Oxolinic Acid *(BAN, USAN, rINN)*

Acide Oxolinique; Ácido oxolínico; Acidum Oxolinicum; Kyselina oxolinová; NSC-110364; Oksoliinihappo; Oksolinik

Asit; Oksolino rūgštis; Oxolínico, ácido; Oxolinsäure; Oxolinsav; Oxolinsyra; W-4565; Оксолиновая Кислота.
5-Ethyl-5,8-dihydro-8-oxo-1,3-dioxolo[4,5-g]quinoline-7-carboxylic acid.
$C_{13}H_{11}NO_5$=261.2
CAS — 14698-29-4.
ATC — J01MB05.
ATC Vet — QJ01MB05.
UNII — L0A22B22FT.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Oxolinic Acid). An almost white or pale yellow crystalline powder. Practically insoluble in water and in alcohol; very slightly soluble in dichloromethane; dissolves in dilute solutions of alkali hydroxides. Protect from light.

Profile

Oxolinic acid is a 4-quinolone antibacterial with properties similar to those of nalidixic acid (p. 328.3), although adverse effects on the CNS may be more frequent. It has been given orally in the treatment of urinary-tract infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Turk.*: Oksolin.

Oxytetracycline *(BAN, rINN)*

Glomycin; Hydroxytetracycline; Oksitetraciklinas; Oksitetrasiklin; Oksitetrasykliini; Oksytetracyklina; Ossitetraciclina; Oxitetraciclina; Oxitetraciklin; Oxitetracyklin; Oxytetracyclin; Oxytétracycline; Oxytetracyclinum; Oxytetracyklin; Riomitsin; Terrafungine; Окситетрациклин.
4*S*,4a*R*,5*S*,5a*R*,6*S*,12a*S*-4-Dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,5,6,10,12,12a-hexahydroxy-6-methylene-1,11-dioxonaphthacene-2-carboxamide; 5β-Hydroxytetracycline.
$C_{22}H_{24}N_2O_9$=460.4
CAS — 79-57-2 (anhydrous oxytetracycline); 6153-64-6 (oxytetracycline dihydrate).
ATC — D06AA03; G01AA07; J01AA06; S01AA04.
ATC Vet — QD06AA03; QG01AA07; QG51AA01; QJ01AA06; QJ51AA06; QS01AA04.
UNII — SLF0D9077S (anhydrous oxytetracycline); X20I9EN955 (oxytetracycline dihydrate).

Pharmacopoeias. In *Eur.* (see p. vii) and *Int.*, which specify the dihydrate ($C_{22}H_{24}N_2O_9.2H_2O$ = 496.5);
US allows the anhydrous substance or the dihydrate.

Ph. Eur. 8: (Oxytetracycline Dihydrate). A substance produced by the growth of certain strains of *Streptomyces rimosus* or obtained by any other means. A yellow, crystalline powder. Very slightly soluble in water; dissolves in dilute acid and alkaline solutions. A 1% suspension in water has a pH of 4.5 to 7.5. Store in airtight containers. Protect from light.

USP 36: (Oxytetracycline). A pale yellow to tan, odourless crystalline powder, that darkens on exposure to strong sunlight. Soluble 1 in 4150 of water, 1 in 66 of dehydrated alcohol, and 1 in 6250 of ether; sparingly soluble in alcohol; practically insoluble in chloroform; freely soluble in 3N hydrochloric acid and in alkaline solutions. pH of a 1% suspension in water is between 4.5 and 7.0. It loses potency in solutions of pH below 2 and is rapidly destroyed by alkali hydroxide solutions. Store in airtight containers. Protect from light.

Oxytetracycline Calcium *(BANM, rINNM)*

Calcii Oxytetracyclinum; Oxitetraciclina cálcica; Oxytétracycline Calcique; Кальций Окситетрациклин.
$C_{44}H_{46}CaN_4O_{18}$=958.9
CAS — 15251-48-6 (xCa).
ATC — D06AA03; G01AA07; J01AA06; S01AA04.
ATC Vet — QD06AA03; QG01AA07; QJ01AA06; QS01AA04.
UNII — C8MRZ07FDV.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Oxytetracycline Calcium). A pale yellow to greenish-fawn, crystalline powder. Practically insoluble in water; soluble in dilute acids; dissolves slowly in dilute ammonia solution. A 2.5% suspension in water has a pH of 6.0 to 7.5. Store at a temperature of 2 degrees to 8 degrees. Protect from light.

USP 36: (Oxytetracycline Calcium). A yellow to light brown crystalline powder. Insoluble in water; soluble 1 in more than 1000 of alcohol, of chloroform, and of ether, and 1 in 15 of 0.1N sodium hydroxide. pH of a 2.5% suspension in water is between 6.0 and 8.0. Store in airtight containers at a temperature between 8 degrees and 15 degrees. Protect from light.

Oxytetracycline Hydrochloride *(BANM, rINNM)*

Hidrocloruro de oxitetraciclina; Oksitetraciklino hidrochloridas; Oksitetrasiklin Hidroklorür; Oksitetrasykliinihydrokloridi; Oksytetracykliny chlorowodorek; Oxitetraciclina, hidrocloruro de; Oxitetraciklin-hidroklorid; Oxitetracyklinhydroklorid; Oxytétracycline, Chlorhydrate d'; Oxytetracyclinhydrochlorid; Oxytetracyclini Hydrochloridum; Oxytetracyklin-hydroklorid; Окситетрациклина Гидрохлорид.
$C_{22}H_{24}N_2O_9HCl$=496.9
CAS — 2058-46-0.
ATC — D06AA03; G01AA07; J01AA06; S01AA04.
ATC Vet — QD06AA03; QG01AA07; QJ01AA06; QS01AA04.
UNII — 4U7K4N52ZM.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 8: (Oxytetracycline Hydrochloride). A yellow, hygroscopic, crystalline powder. Freely soluble in water; sparingly soluble in alcohol. Solutions in water become turbid on standing owing to the precipitation of oxytetracycline. A 1% solution in water has a pH of 2.3 to 2.9. Store in airtight containers. Protect from light.

USP 36: (Oxytetracycline Hydrochloride). A yellow, odourless, hygroscopic, crystalline powder. It decomposes at temperatures exceeding 180 degrees, and exposure to strong sunlight or temperatures exceeding 90 degrees in moist air causes it to darken. Its potency is diminished in solutions having a pH below 2, and it is rapidly destroyed by alkali hydroxide solutions. Freely soluble in water, but crystals of oxytetracycline separate as a result of partial hydrolysis of the hydrochloride; sparingly soluble in alcohol and in methyl alcohol, and even less soluble in dehydrated alcohol; insoluble in chloroform and in ether. pH of a 1% solution in water is between 2.0 and 3.0. Store in airtight containers. Protect from light.

Incompatibility. Oxytetracycline injections have an acid pH and incompatibility may reasonably be expected with alkaline preparations, or with drugs unstable at low pH. Tetracyclines can chelate metal cations to produce insoluble complexes, and incompatibility has been reported with solutions containing metallic salts.

Reports of incompatibility are not always consistent, and other factors, such as the strength and composition of the vehicles used, may play a role.

Uses and Administration

Oxytetracycline is a tetracycline derivative with actions and uses similar to those of tetracycline (p. 375.3).

Oxytetracycline dihydrate or hydrochloride are usually used in tablets, capsules, and injections, and the calcium salt in aqueous oral suspensions; all three are also used in topical preparations. Doses have been expressed as anhydrous oxytetracycline, the dihydrate, or the hydrochloride but in practice this appears to make little difference. Oxytetracycline dihydrate and oxytetracycline hydrochloride 269.8 mg, and oxytetracycline calcium 260.3 mg, are each equivalent to about 250 mg of oxytetracycline.

Oxytetracycline is usually given orally in adult doses of 250 to 500 mg four times daily, usually 1 hour before or 2 hours after food. Higher doses, up to 4 g daily, have occasionally been given to adults with severe infection, but increase the risk of adverse effects.

Doses of oxytetracycline 250 to 500 mg daily have been used in acne, although the *BNF* advocates a dose of 500 mg twice daily.

Oxytetracycline is sometimes given intramuscularly, in doses of 250 mg once daily or 300 mg daily in 2 or 3 divided doses, but this route may be painful and produces lower blood concentrations than recommended oral doses. As intramuscular injections are painful, lidocaine is usually included in the solution. Oxytetracycline has also been given intravenously.

For details of doses in children and adolescents, see p. 339.2.

Oxytetracycline and its salts have been applied topically, often with other agents, as a variety of eye and ear drops, ointments, creams, and sprays.

Administration in children. In children, the effects on teeth should be considered and tetracyclines only used when absolutely essential. In the UK, oxytetracycline is licensed for use in children aged 12 years and over; the usual adult dose (see above) may be given orally. However, in some other countries, it may be given to those over 8 years old in usual oral doses of 25 to 50 mg/kg (to a maximum of 1 g) daily in 4 divided doses or by intramuscular injection in usual doses of 15 to 25 mg/kg daily in 2 or 3 divided doses (maximum of 250 mg per dose).

Skin disorders. For reference to the use of oxytetracycline in the treatment of various skin disorders, see under Tetracycline, p. 376.3.

Adverse Effects and Precautions

As for Tetracycline, p. 377.1.

Oxytetracycline may produce less tooth discoloration than some other tetracyclines but gastrointestinal symptoms tend to be more severe.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies oxytetracycline as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 15/08/11)

Interactions

As for Tetracycline, p. 377.3.

Antimicrobial Action

As for Tetracycline, p. 377.3.

Oxytetracycline is somewhat less active against many organisms.

Pharmacokinetics

For the general pharmacokinetics of the tetracyclines, see Tetracycline, p. 378.2.

An oral dose of 500 mg every 6 hours is reported to produce steady-state plasma concentrations of 3 to 4 micrograms/mL. Plasma protein binding is reported to be about 20 to 40% and the half-life to be about 9 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Terramicina; ***Braz.***: Terramicina; ***Denm.***: Oxytetral†; ***Gr.***: Oxacycle; Terramycin; ***Hong Kong***: Oxylim; Syntermycin†; ***Hung.***: Tetran; ***India***: Oxter; Oxyteracin; Oxytetra; Terramycin; ***Indon.***: Chemotrex†; Corsamycin; Terramycin; ***Irl.***: Clinimycin†; ***Malaysia***: Oxylim; ***Mex.***: Metrecina; Oxitraklin; Terrados; Terramicina; ***Norw.***: Oxytetral†; ***Philipp.***: Noxebron; ***Port.***: Terricil; ***S.Afr.***: Acu-Oxytet†; Adco-Oxypan; Adco-Roxy; Be-Oxytet; Cotet†; Dynoxytet; Nucotet; O-4 Cycline; Oxymycin†; Pharmatet; Spectratet†; Tetracem; ***Singapore***: Oxylim; Syntermycin; ***Spain***: Terramicina; ***Swed.***: Oxytetral†; ***Thai.***: O-Tetra; Oxycide; Oxycline; Oxylim; Oxynutra; ***Turk.***: Neocol†; ***UK***: Oxymycin; ***Venez.***: Terramicina.

Multi-ingredient Preparations. ***Arg.***: Terra-Cortril; ***Austria***: Tetra-Gelomyrtol†; ***Belg.***: Terra-Cortril + Polymyxine B; Terra-Cortril; Terramycine + Polymyxine B; ***Braz.***: Terra-Cortril; Terramicina c/Polimixina; ***Denm.***: Hydrocortison med Terramycin og Polymyxin-B; Hydrocortison med Terramycin; Terramycin Polymyxin B; ***Fin.***: Terra-Cortril P; Terra-Cortril; ***Fr.***: Auricularum; Sterdex; ***Ger.***: Corti Biciron N; Tetra-Gelomyrtol; ***Gr.***: Auricularum; Oxacycle-P; Terra-Cortril; Terramycin w Polymyxin Otic; Terramycin with Polymyxin; ***Hong Kong***: Terramycin with Polymyxin B; ***Hung.***: Oxycort; Tetran-Hydrocortison; ***India***: Terramycin SF; ***Indon.***: Sancortmycin; Terra-Cortril; Terramycin Poly†; ***Israel***: Terramycin†; ***Ital.***: Cosmiciclina; ***Malaysia***: Terramycin; ***Mex.***: Terramicina; Terraxin; ***Neth.***: Terra-Cortril met polymyxine-B; ***Norw.***: Terra-Cortril Polymyxin B; Terra-Cortril; Terramycin Polymyxin B; ***Philipp.***: Terramycin; ***Pol.***: Atecortin; Oxycort; ***Rus.***: Gioxyson (Гиоксизон); Oxycort (Оксикорт); ***S.Afr.***: Terra-Cortril†; Terramycin†; ***Singapore***: Terramycin; ***Spain***: Terra-Cortril; Terra-Cortril; Terramicina; ***Swed.***: Terracortril med polymyxin B; Terracortril; Terramycin Polymyxin B†; ***Thai.***: Terramycin; ***Turk.***: Geotril†; Heksa; Polimisin; Sekamisin†; Terramycin; Vitacillin; ***UK***: Terra-Cortril; Trimovate; ***Ukr.***: Aprolat (Апролат); Oxycort (Оксикорт); ***USA***: Terak; Terra-Cortril; Terramycin with Polymyxin B; Urobiotic-250; ***Venez.***: Otterra; Terramicina con Polimixina B.

Pharmacopoeial Preparations

BP 2014: Oxytetracycline Capsules; Oxytetracycline Tablets;

USP 36: Oxytetracycline and Nystatin Capsules; Oxytetracycline and Nystatin for Oral Suspension; Oxytetracycline Calcium Oral Suspension; Oxytetracycline for Injection; Oxytetracycline Hydrochloride and Hydrocortisone Acetate Ophthalmic Suspension; Oxytetracycline Hydrochloride and Hydrocortisone Ointment; Oxytetracycline Hydrochloride and Polymyxin B Sulfate Ointment; Oxytetracycline Hydrochloride and Polymyxin B Sulfate Ophthalmic Ointment; Oxytetracycline Hydrochloride and Polymyxin B Sulfate Topical Powder; Oxytetracycline Hydrochloride and Polymyxin B Sulfate Vaginal Tablets; Oxytetracycline Hydrochloride Capsules; Oxytetracycline Injection; Oxytetracycline Tablets.

Panipenem *(rINN)*

CS-533; Panipenemi; Panipenemum; RS-533; Панипенем.
(+)-(5*R*,6*S*)-3-[[(*S*)-1-Acetimidoyl-3-pyrrolidinyl]thio]-6-[(*R*)-1-hydroxyethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid.
$C_{15}H_{21}N_3O_4S$=339.4

CAS — 87726-17-8.
UNII — W9769W09JF.

Pharmacopoeias. In *Jpn.*

Profile

Panipenem is a carbapenem beta-lactam antibacterial similar to imipenem (p. 309.2). It is given intravenously with betamipron (p. 231.1), which reduces its adverse renal effects.

References.

1. Goa KL, Noble S. Panipenem/betamipron. *Drugs* 2003; 63: 913–25.
2. Tajima N, *et al.* Population pharmacokinetic analysis of panipenem/betamipron in patients with various degrees of renal function. *Chemotherapy* 2006; 52: 245–53.
3. Kwon KT, *et al.* Panipenem versus cefepime as empirical monotherapy in adult cancer patients with febrile neutropenia: a prospective randomized trial. *Jpn J Clin Oncol* 2008; 38: 49–55.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *China*: Carbenin (克倍宁); *Jpn*: Carbenin.

Pazufloxacin Mesilate

Mesilato de pazufloxacino (rINNM); Mesilato de pazufloxacino; Pazufloxacine, Mésilate de; Pazufloxacini Mesilas; Pazufloxacino, mesilato de; T-3761 (pazufloxacin); T-3762; Пазуфлоксацина Мезилат.

(-)-(3*S*)-10-(1-Aminocyclopropyl)-9-fluoro-2,3-dihydro-3-methyl-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid methanesulfonate.

$C_{16}H_{15}FN_2O_4.CH_3SO_3H$=414.4

CAS — 127045-41-4 (pazufloxacin); 163680-77-1 (pazufloxacin mesilate).
ATC — J01MA18.
ATC Vet — QJ01MA18.
UNII — 2X1226J1HS.

Profile

Pazufloxacin is a fluoroquinolone antibacterial with properties similar to those of ciprofloxacin (p. 261.1). It is given by intravenous infusion as the mesilate in the treatment of susceptible infections in a usual dose equivalent to 1 g of pazufloxacin daily in 2 divided doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: An Ti (安替); Ao Er Man (奥尔曼); Ba Hong (巴红); BoXin (博信); Fa Duo Lin (法多琳); Fei Xun Qi (菲迅奇); Fengzhuxin (锋珠新); Fengzhuye (锋珠烨); Fu Li Te (伏立特); Heng Mu (恒沐); Jia Le Tong Xin (佳乐同欣); Jia Yi Ni (加易尼); Jun Ke Duo (君克多); Jun Pu (君普); Lai Mei Jing (莱美净); Mi Si Long (米斯龙); Min Xing (敏星); Ni Sai Xin (尼赛信); Nuo Jun Xin (诺君欣); Pa Di Xing (帕迪星); Pai Shu Ke (派抒可); Pai Si Xin (派斯欣); Qi Ruo Da (齐若达); Ren Ge Duo Na (仁格多那); Tong Qi (通琦); Wei Li Xian (威利仙); Wei Yu Qing (维予清); Xu Yuan (旭原); Xuan Bo (宣博); Ya Zheng Li (亚征利); Yanlei (严雷); *Jpn*: Pasil; Pazucross.

Pefloxacin Mesilate *(BANM, rINNM)*

EU-5306 (pefloxacin); Mesilato de pefloxacino; Pefloksacino mesilatas dihidratas; Pefloksacyny mezylan dwuwodny; Pefloksasiinimesilaattidihydraatti; Pefloxacin Mesilate Dihydrate; Pefloxacin mesylát dihydrát; Pefloxacin Mesylate; Pefloxacin Mesylate (USAN); Péfloxacine, Mésilate de; Péfloxacine (mésilate de) dihydraté; Pefloxacini Mesilas; Pefloxacini Mesilas Dihydricus; Pefloxacinmesilat-Dihydrat; Pefloxacinmesilatdihydrat; Pefloxacin-mezilát-dihidrát; Pefloxacino, mesilato de; 1589-RB (pefloxacin); 41982-RP; Пефлоксацина Мезилат.

1-Ethyl-6-fluoro-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid methanesulphonate dihydrate.

$C_{17}H_{20}FN_3O_3.CH_4O_3S.2H_2O$=465.5

CAS — 70458-92-3 (pefloxacin); 70458-95-6 (pefloxacin mesilate); 149676-40-4 (pefloxacin mesilate dihydrate).
ATC — J01MA03.
ATC Vet — QJ01MA03.
UNII — 5IAD0UV3FH.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Ph. Eur. 8: (Pefloxacin Mesilate Dihydrate). A fine, white or almost white powder. Freely soluble in water; slightly soluble in alcohol; very slightly soluble in dichloromethane. A 1% solution in water has a pH of 3.5 to 4.5. Store in airtight containers. Protect from light.

Profile

Pefloxacin is a fluoroquinolone antibacterial with actions and uses similar to those of ciprofloxacin (p. 261.1). It also has bactericidal activity against *Mycobacterium leprae* and has been tried in the treatment of leprosy (p. 188.3).

Pefloxacin has a longer plasma half-life than ciprofloxacin (about 8 to 13 hours) and is also extensively metabolised, the main metabolite being *N*-desmethylpefloxacin (norfloxacin, p. 333.3).

Pefloxacin is given orally or by intravenous infusion as the mesilate in the treatment of susceptible infections. Doses are expressed in terms of the base; pefloxacin mesilate 558.5 mg is equivalent to about 400 mg of pefloxacin. The usual dose is 400 mg twice daily; the first dose may be doubled if effective serum concentrations need to be attained quickly. A single oral dose of 800 mg may be used in the treatment of gonococcal urethritis in men and acute uncomplicated cystitis in women.

Fluoroquinolones have caused adverse effects on the musculoskeletal system (see under Adverse Effects of Ciprofloxacin, p. 263.2) and in the case of pefloxacin this has led to restrictions in some countries.

Adverse effects. References to adverse effects with pefloxacin.

1. Chevalier X, *et al.* A case of destructive polyarthropathy in a 17-year-old youth following pefloxacin treatment. *Drug Safety* 1992; 7: 310–14.
2. Al-Hedaithy MA. Noreddin AM. Hypersensitivity anaphylactoid reaction to pefloxacin in a patient with AIDS. *Ann Pharmacother* 1996; 30: 612–14.
3. Chang H, *et al.* Pefloxacin-induced arthropathy in an adolescent with brain abscess. *Scand J Infect Dis* 1996; 28: 641–3.

Pharmacokinetics. References to the pharmacokinetics of pefloxacin.

1. Bressolle F, *et al.* Pefloxacin clinical pharmacokinetics. *Clin Pharmacokinet* 1994; 27: 418–46.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Peflacin; *China*: Beining (倍宁); Da Fu Ming (达福明); Wei Li Ke (威力克); Wei Ning Jia (维宁佳); *Cz.*: Abaktal; *Fr.*: Peflacine; *Gr.*: Idrostamin; Labocton; Londoman; Obergan; Peflacine; *Hung.*: Abaktal†; Peflacine†; *India*: Cylox; Hinepox; Pefbid; Pelox; Proflox; Qucin; *Indon.*: Dexaflox; Felox; Noflexin; Oxaflox; Peflacine; *Ital.*: Peflacin; Peflox; *Malaysia*: Quilaxin; *Mex.*: Peflacina†; *Philipp.*: Floxin†; Floxol; Peraxin; *Pol.*: Abaktal; Peflacine; *Port.*: Peflacine†; *Rus.*: Abaktal (Абактал); Pefloxabol (Пефлоксабол); Pelox (Пелокс); Perti (Перти)†; Unikpef (Юникпеф); *Thai.*: Peflacine; *Turk.*: Peflacine; *Ukr.*: Abaktal (Абактал); Peflocin (Пефлоцин)†; Pelox (Пелокс)†.

Penethamate Hydriodide *(BAN)*

Diethylaminoethyl Penicillin G Hydroiodide; Penetamato, hidroioduro de; Pénéthamate, iodhydrate de; Penethamati hydroiodidum.

2-Diethylaminoethyl (6*R*)-6-(2-phenylacetamido)penicillanate hydriodide.

$C_{22}H_{31}N_3O_4S$,HI=561.5

CAS — 3689-73-4 (penethamate); 808-71-9 (penethamate hydriodide).
ATC Vet — QJ01CE90; QJ51CE90.
UNII — GA14AS9QOK.

Profile

Penethamate is a penicillin antibacterial used as the hydriodide in veterinary medicine.

Pheneticillin Potassium *(BANM, rINNM)*

Feneticilina potásica; Kalii Pheneticillinum; Penicillin B; Phenethicillin Potassium; Phénéticilline Potassique; Pheneticillinum Kalicum; Potassium α-Phenoxyethylpenicillin; Калия Фенетициллин.

A mixture of the D(+)- and L(-)-isomers of potassium (6*R*)-6-(2-phenoxypropionamido)penicillanate.

$C_{17}H_{19}KN_2O_5S$=402.5

CAS — 147-55-7 (pheneticillin); 132-93-4 (pheneticillin potassium).
ATC — J01CE05.
ATC Vet — QJ01CE05.
UNII — 70978WUK7C.

Pharmacopoeias. In *Jpn.*

Profile

Pheneticillin is a phenoxypenicillin with actions and uses similar to those of phenoxymethylpenicillin (p. 340.3). It is given orally in a usual dose of 250 mg three times daily, as the potassium salt, for the treatment of susceptible mild to moderate infections. Pheneticillin sodium has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Neth.*: Broxil.

Phenoxymethylpenicillin *(BAN, rINN)*

Fenoksimetilpenicilinas; Fenoksimetyylipenisilliini; Fenoksymetylopenicylina; Fenoximetilpenicilina; Fenoximetilpenicillin; Fenoximetylpenicillin; Fenoxymethylpenicilin; Penicillin, Phenoxymethyl; Penicillin V (USAN); Penisilin V; Phénomycilline; Phenoxymethyl Penicillin; Phénoxyméthylpénicilline; Phenoxymethylpenicillinum; Феноксиметилпенициллин.

(6*R*)-6-(2-Phenoxyacetamido)penicillanic acid.

$C_{16}H_{18}N_2O_5S$=350.4

CAS — 87-08-1.
ATC — J01CE02.
ATC Vet — QJ01CE02.
UNII — Z61I075U2W.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 8: (Phenoxymethylpenicillin). A substance produced by the growth of certain strains of *Penicillium notatum* or related organisms on a culture medium containing an appropriate precursor, or obtained by any other means. A white or almost white, slightly hygroscopic, crystalline powder. Very slightly soluble in water; soluble in alcohol. A 0.5% suspension in water has a pH of 2.4 to 4.0. Store in airtight containers.

USP 36: (Penicillin V). A white, odourless crystalline powder. Very slightly soluble in water; freely soluble in alcohol and in acetone; insoluble in fixed oils. pH of a 3% suspension in water is between 2.5 and 4.0. Store in airtight containers.

Phenoxymethylpenicillin Calcium

(BANM, rINNM)

Calcii Phenoxymethylpenicillinum; Fenoximetilpenicilina cálcica; Penicillin V Calcium; Phénoxyméthylpénicilline Calcique; Phenoxymethylpenicillinum Calcicum; Кальций Феноксиметилпенициллин.

$(C_{16}H_{17}N_2O_5S)_2Ca.2H_2O$=774.9

CAS — 147-48-8 (anhydrous phenoxymethylpenicillin calcium); 73368-74-8 (phenoxymethylpenicillin calcium dihydrate).
ATC — J01CE02.
ATC Vet — QJ01CE02.
UNII — 3750YH4NM7.

Pharmacopoeias. In *Int.*

Phenoxymethylpenicillin Potassium

(BANM, rINNM)

Fenoksimetil Penisilin Potasyum; Fenoksimetilpenicilino kalio druska; Fenoksimetyylipenisilliinikalium; Fenoksymetylopenicylina potasowa; Fenoximetilpenicilina potásica; Fenoximetilpenicilina Potássica; Fenoximetilpenicillinkálium; Fenoximetylpenicillin kalium; Fenoxymethylpenicilin draselná sůl; Kalii Phenoxymethylpenicillinum; Penicillin V Potassium (USAN); Phenoxymethylpenicillin-Kallum; Phénoxyméthylpénicilline Potassique; Phenoxymethylpenicillinum Kalicum; Калия Феноксиметилпенициллин.

$C_{16}H_{17}KN_2O_5S$=388.5

CAS — 132-98-9.
ATC — J01CE02.
ATC Vet — QJ01CE02.
UNII — 146T0TU1JB.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 8: (Phenoxymethylpenicillin Potassium). A white or almost white, crystalline powder. Freely soluble in water; practically insoluble in alcohol. A 0.5% solution in water has a pH of 5.5 to 7.5.

USP 36: (Penicillin V Potassium). A white, odourless crystalline powder. Very soluble in water; soluble 1 in 150 of alcohol; insoluble in acetone. pH of a 3% solution in water is between 4.0 and 7.5. Store in airtight containers.

Units

The first International Standard Preparation (1957) of phenoxymethylpenicillin contained 1695 units/mg but was withdrawn in 1968. Despite this, doses of phenoxymethylpenicillin are still expressed in units in some countries.

Phenoxymethylpenicillin 250 mg is equivalent to about 400 000 units.

Uses and Administration

Phenoxymethylpenicillin is used similarly to benzylpenicillin (p. 228.3) in the treatment or prophylaxis of infections caused by susceptible organisms, especially streptococci. It is used only for the treatment of mild to moderate infections, and not for chronic, severe, or deep-seated infections since absorption can be unpredictable. Patients treated initially with parenteral benzylpenicillin may continue treatment with oral phenoxymethylpenicillin once a satisfactory clinical response has been obtained. Specific indications for phenoxymethylpenicillin include anthrax (mild uncomplicated infections), Lyme disease (early stage in pregnant women or young children), pharyngitis or tonsillitis, rheumatic fever (primary and secondary prophylaxis), streptococcal skin infections, and spleen disorders (pneumococcal infection prophylaxis). For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Phenoxymethylpenicillin is given orally, usually as the potassium or calcium salt, preferably at least 30 minutes before, or 2 hours after, food. Benzathine phenoxymethylpenicillin (p. 228.1) is also used.

Doses are expressed in terms of the equivalent amount of phenoxymethylpenicillin; 1.1 g of phenoxymethylpenicillin calcium and 1.1 g of phenoxymethylpenicillin potassium are each equivalent to about 1 g of phenoxymethylpenicillin.

Usual adult doses have been 250 to 500 mg every 6 hours but in severe infections the *BNF* recommends up to 1 g every 6 hours. Dosage may need to be modified in severe renal impairment.

To prevent recurrences of rheumatic fever the *BNF* recommends 250 mg twice daily, while WHO suggests a dose of 500 mg twice daily. The *BNF* also recommends 250 to 500 mg every 6 hours for 10 days to prevent secondary cases of invasive group A streptococcal infection, and 250 mg every 12 hours for long-term prophylaxis of pneumococcal infection in asplenia, or in patients with sickle-cell disease.

For details of doses in children, see p. 341.1.

Administration in children. Phenoxymethylpenicillin may be given orally to children for the treatment of infections caused by susceptible bacteria, as well as for prevention of recurrent rheumatic fever and pneumococcal infection in some patient populations. It may also be used in neonates and children to prevent secondary group A streptococcal infection.

In the UK, the *BNFC* suggests the following doses:

For susceptible infections including **oral infections, tonsillitis, otitis media, erysipelas, and cellulitis**:

- children 1 month to 1 year of age: 62.5 mg 4 times daily
- children 1 to 6 years of age: 125 mg 4 times daily
- children 6 to 12 years of age: 250 mg 4 times daily

For **severe infection**, children should receive at least 12.5 mg/kg (maximum 1 g) 4 times daily.

For **prevention of pneumococcal infection** in asplenia or sickle-cell disease:

- children less than 1 year of age: 62.5 mg twice daily
- children 1 year to 5 years of age: 125 mg twice daily
- children from 5 years of age: 250 mg twice daily

To **prevent recurrence of rheumatic fever**:

- children 1 month to 6 years of age: 125 mg twice daily
- children from 6 years of age: 250 mg twice daily

To **prevent secondary cases of group A streptococcal infection, phenoxymethylpenicillin is given for 10 days in the following doses**:

- neonates: 12.5 mg/kg (maximum 62.5 mg) every 6 hours
- children 1 month to 1 year of age: 62.5 mg every 6 hours
- children 1 to 6 years of age: 125 mg every 6 hours
- children from 6 to 12 years of age: 250 mg every 6 hours

In the USA, the American Academy of Pediatrics (AAP)[1] makes the following alternative dosing recommendations for the treatment of **mild to moderate infections**:

- children from 1 month of age: 25 to 50 mg/kg daily, orally in 3 or 4 divided doses (maximum 2 g)

The AAP considers phenoxymethylpenicillin to be inappropriate for treatment of severe infections.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Adverse Effects and Precautions

As for Benzylpenicillin, p. 229.2.

Phenoxymethylpenicillin is usually well tolerated but may occasionally cause transient nausea and diarrhoea.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies phenoxymethylpenicillin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Potassium content. Each g of phenoxymethylpenicillin potassium contains about 2.6 mmol of potassium.

Interactions

As for Benzylpenicillin, p. 230.1.

Antibacterials. Reduced absorption was reported when phenoxymethylpenicillin was given after an oral course of *neomycin*.[1]

1. Cheng SH, White A. Effect of orally administered neomycin on the absorption of penicillin V. *N Engl J Med* 1962; 267: 1296–7.

Beta blockers. Fatal anaphylactic reactions to phenoxymethylpenicillin in 2 patients on *nadolol* and *propranolol* respectively, might have been potentiated by the beta blocker.[1]

1. Berkelman RL, *et al.* Beta-adrenergic antagonists and fatal anaphylactic reactions to oral penicillin. *Ann Intern Med* 1986; 104: 134.

Antimicrobial Action

Phenoxymethylpenicillin has a range of antimicrobial activity similar to that of benzylpenicillin (p. 230.1) and a similar mode of action. It may be less active against some susceptible organisms, particularly Gram-negative bacteria.

The mechanisms and patterns of resistance to phenoxymethylpenicillin are similar to those of benzylpenicillin.

Pharmacokinetics

Phenoxymethylpenicillin is more resistant to inactivation by gastric acid and is more completely absorbed than benzylpenicillin from the gastrointestinal tract. Absorption is usually rapid, although variable, with about 60% of an oral dose being absorbed. The calcium and potassium salts are better absorbed than the free acid. Peak plasma concentrations of 3 to 5 micrograms/mL occur 30 to 60 minutes after a dose of 500 mg. The effect of food on absorption appears to be slight. The plasma half-life of phenoxymethylpenicillin is about 30 to 60 minutes and may be increased to about 4 hours in severe renal impairment. About 80% is reported to be protein bound. The distribution and elimination of phenoxymethylpenicillin is similar to that of benzylpenicillin (p. 230.2). It is metabolised in the liver to a greater extent than benzylpenicillin; several metabolites have been identified including penicilloic acid. The unchanged drug and metabolites are excreted rapidly in the urine. Only small amounts are excreted in the bile.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Grampenil NF; Pen Oral; Penagrande†; Penfantil; Penicina†; ***Austral.***: Abbocillin-VK; Cilicaine VK; Cilopen VK; LPV; Penhexal VK†; ***Austria***: Ospen; Pen-V; Penbene; Penstad; Star-Pen†; ***Belg.***: Peni-Oral; ***Braz.***: Meracilina; Oracilin; Pen-V-Cil†; Pen-Ve-Oral; Pencilin-V; Penicigran; ***Canad.***: Apo-Pen-VK; Novo-Pen-VK; Nu-Pen-VK; ***China***: Bangning ShaJi (邦宁沙吉); Kai Lai Li Ke (凯莱立克); Li Te Er Xin (力特尔新); Weibaisi (维百斯); ***Cz.***: Ospen; Penbene; Pencid†; ***Denm.***: Pancillin; Primcillin; Rocilin†; Vepicombin; ***Fin.***: Medicillin; Milcopen; V-Pen; ***Fr.***: Oracilline; ***Ger.***: Arcasin; InfectoCillin; Isocillin; Ispenoral; Megacillin oral†; P-Mega-Tablinen; Pen Mega†; Penbeta†; Penhexal†; ***Gr.***: Ospen; ***Hung.***: Ospen; ***India***: Kaypen; ***Indon.***: Fenocin; Ospen; ***Irl.***: Calvepen; Kopen; ***Israel***: Pen-Rafa VK; Rafapen Mega; Rafapen V-K†; ***Malaysia***: Beapen; Ospen; ***Mex.***: Anapenil; Kavipen; Pen-Vi-K; Pota-Vi-Kin; ***Neth.***: Acipen†; ***Norw.***: Apocillin; Weifapenin; ***NZ***: Cilicaine VK; ***Philipp.***: Sumapen; ***Pol.***: Ospen; ***Rus.***: Star-Pen (Стар-Пен); ***S.Afr.***: Betapen; In Cil-Vk; Incil†; Len VK; Spec-Pen-V-K†; ***Singapore***: Ospen†; Penopen; ***Spain***: Penilevel; ***Swed.***: Kavepenin; Pecevе†; Tikacillin; ***Switz.***: Ospen; Phenocillin†; Stabicilline; ***Thai.***: Medic-V; Metro-V†; P-Cillin V; Pen-V; Pener; Penvedon; Penvelin; Penveno; Semicillin; Suveelin; ***Turk.***: Cilacil†; Cliacil; Penoksil; ***USA***: Pen-Vee K; Veetids†; ***Venez.***: Ospen.

Multi-ingredient Preparations. ***Spain***: Penilevel Retard.

Pharmacopoeial Preparations

BP 2014: Phenoxymethylpenicillin Oral Solution; Phenoxymethylpenicillin Tablets;

USP 36: Penicillin V for Oral Suspension; Penicillin V Potassium for Oral Solution; Penicillin V Potassium Tablets; Penicillin V Tablets.

Phthalylsulfacetamide *(BAN)*

Phthalylsulphacetamide; Sulfanilacetamidum Phthalylatum.

4′-(Acetylsulphamoyl)phthalanilic acid.

$C_{16}H_{14}N_2O_6S$=362.4

CAS — 131-69-1.

UNII — 24PUW23GRX.

Profile

Phthalylsulfacetamide is a sulfonamide antibacterial. It is poorly absorbed when given orally and has been used for gastrointestinal infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Chile***: Enterol Con Nifuroxacida; Enterol†; ***Mex.***: Facetin-D.

Phthalylsulfathiazole *(BAN, rINN)*

Ftalazol; Ftalilsulfatiazol; Ftalilsulfatiazolas; Ftalilszulfatiazol; Ftalylsulfathiazol; Ftalylsulfatiazol; Ftalyylisulfatiatsoli; Phtalylsulfathiazol; Phthalazol; Phthalazolum; Phthalylsulfathiazol; Phthalylsulfathiazolum; Phthalylsulphathiazole; Sulfaphtalylthiazol; Фталилсульфатиазол.

4′-(1,3-Thiazol-2-ylsulphamoyl)phthalanilic acid.

$C_{17}H_{13}N_3O_5S_2$=403.4

CAS — 85-73-4.

ATC — A07AB02.

ATC Vet — QA07AB02.

UNII — 6875L5852V.

Pharmacopoeias. In *Eur.* (see p. vii) and *Viet.*

Ph. Eur. 8: (Phthalylsulfathiazole). A white or yellowish-white crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in acetone; freely soluble in dimethylformamide. Protect from light.

Profile

Phthalylsulfathiazole is a sulfonamide with properties similar to those of sulfamethoxazole (p. 367.2). It is poorly absorbed, about 95% remaining in the intestine and only about 5% being slowly hydrolysed to sulfathiazole and absorbed.

It is given, with other antibacterials, for its antibacterial action in the gastrointestinal tract in the treatment of infections and for bowel decontamination before surgery.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Enterosulfa; ***Thai.***: Thalatex.

Multi-ingredient Preparations. ***Arg.***: Carbon Tabs; Colistop; Diarrocalmol; Estreptocarbocaftiazol; Estreptocarbocaftiazol; Opocarbon; ***Braz.***: Parenterin; ***Chile***: Esancol; Imecol; Liracol; Testisan; ***Gr.***: Enteromyk; ***Mex.***: Bontal; Ditayod; ***Thai.***: Chlorotracin†; Coccila; Diaropect; Disento; Endothalyl.

Pipemidic Acid *(BAN, rINN)*

Acide Pipémidique; Ácido pipemídico; Acidum Pipemidicum; Acidum pipemidicum trihydricum; Kyselina pipemidová trihydrát; Pipemídico, ácido; Pipemidihappo; Pipemidiinihappotrihydraatti; Pipemidinsav-trihidrát; Pipemidinsyratrihydrat; Pipémidique (acide) trihydraté; Pipemido rūgštis trihidratas; Pipemidsyra; Piperamic Acid; 1489-RB; Пипемидовая Кислота.

8-Ethyl-5,8-dihydro-5-oxo-2-(piperazin-1-yl)pyrido[2,3-*d*]pyrimidine-6-carboxylic acid.

$C_{14}H_{17}N_5O_3$=303.3

CAS — 51940-44-4 (anhydrous pipemidic acid); 72571-82-5 (pipemidic acid trihydrate).

ATC — J01MB04.

ATC Vet — QJ01MB04.

UNII — LT12J5HVR8.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn* (all as the trihydrate).

Ph. Eur. 8: (Pipemidic Acid Trihydrate). A pale yellow or yellow crystalline powder. Very slightly soluble in water and in dichloromethane; practically insoluble in alcohol. It dissolves in dilute solutions of acids and of alkali hydroxides. Protect from light.

Profile

Pipemidic acid is a 4-quinolone antibacterial with properties similar to those of nalidixic acid (p. 328.3), but is more active *in vitro* against some bacteria, including *Pseudomonas aeruginosa*. It is used (as the trihydrate) in the treatment of urinary-tract infections in oral doses equivalent to 400 mg of the anhydrous substance twice daily.

Interactions. For the effect of pipemidic acid on the clearance of xanthines, see under Caffeine, p. 1206.1, and Theophylline, p. 1234.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Pinuret; Memento; Priper; *Braz.*: Balurol; Elofuran; Pipram; Pipurol; Uroxina; *Chile*: Purid; Uropimide; *Fr.*: Pipram; *Ger.*: Deblaston†; *Gr.*: Diflogin; Pipram; *Hong Kong*: Urotractin; *Indon.*: Impresial; Urinter; Urixin; Urotractin; Utrex†; *Ital.*: Biosoviran†; Cistomid; Diperpen; Faremid; Pipefort; Pipemid; Pipram; Pipurin; Urodene†; Uropimid; Urosan; Urotractin; *Jpn*: Dolcol; *Malaysia*: Urotractin; *Mex.*: Uripiser; Uronovag; Uropipemid; *Neth.*: Pipram; *Philipp.*: Urixin†; *Pol.*: Palin; Urolin†; *Rus.*: Palin (Палин); Pilamin (Пиламин); Pimidel (Пимидель); Pipegal (Пипегал); Pipelin (Пипелин); Uropimid (Уропимид); Urotractin (Уротрактин); *S. Afr.*: Deblaston; *Singapore*: Urotractin; *Spain*: Galusan; Nuril; Urisan; Uropipedil†; *Thai.*: Pipedic; Urotractin; *Ukr.*: Palin (Палин); Pimidel (Пимидел); Pipemidin (Пипемидин).

Multi-ingredient Preparations. *Arg.*: Priper Plus.

Piperacillin *(BAN, rINN)*

Piperacilin monohydrát; Piperacilina; Piperacilinas; Pipéracilline; Piperacillinum; Piperacillinum Monohydricum; Piperasilliini; Пиперациллин.

(6*R*)-6-[*R*-2-(4-Ethyl-2,3-dioxopiperazine-1-carboxamido)-2-phenylacetamido]penicillanic acid monohydrate; 3-Dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid monohydrate.

$C_{23}H_{27}N_5O_7S,H_2O$=535.6

CAS — 61477-96-1 (anhydrous piperacillin); 66258-76-2 (piperacillin monohydrate).

ATC — J01CA12.

ATC Vet — QJ01CA12.

UNII — X00B0D5O0E (piperacillin); 91628532GX (anhydrous piperacillin).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Piperacillin). A white or almost white powder. Slightly soluble in water and in ethyl acetate; freely soluble in methyl alcohol.

USP 36: (Piperacillin). A white to off-white crystalline powder. Practically insoluble to very slightly soluble in water; very slightly soluble in ethyl acetate; slightly soluble in isopropyl alcohol; very soluble in methyl alcohol.

Piperacillin Sodium *(BANM, USAN, rINNM)*

CL-227193; Natril Piperacillinum; Piperacilin sodná sůl; Piperacilina sódica; Piperacilino natrio druska; Piperacillin-Natrium; Pipéracilline Sodique; Piperacillin-nátrium; Piperacillinnatrium natricum; Piperacilllnum; Piperacillinum natricum; Piperacylina sodowa; Piperasilin Sodyum; Piperasilliininatrium; T-1220; Натрий Пиперациллин.

$C_{23}H_{26}N_5NaO_7S$=539.5

CAS — 59703-84-3.

ATC — J01CA12.

ATC Vet — QJ01CA12.

UNII — M98T69Q7HP.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Piperacillin Sodium). A white or almost white, hygroscopic powder. Freely soluble in water and in methyl alcohol; practically insoluble in ethyl acetate. A 10% solution in water has a pH of 5.0 to 7.0. Store in airtight containers.

USP 36: (Piperacillin Sodium). A white to off-white solid. Freely soluble in water and in alcohol. pH of a 40% solution in water is between 5.5 and 7.5. Store in airtight containers.

Incompatibility. Piperacillin sodium has been reported to be incompatible with aminoglycosides and sodium bicarbonate.

A formulation of piperacillin plus tazobactam containing edetic and citric acids (*Tazocin, Zosyn*) is considered compatible with lactated Ringer's solution, as well as some aminoglycosides at specific concentrations, whereas formulations without these additives are not compatible.

Stability. References.

1. Zhang Y, Trissel LA. Stability of piperacillin and ticarcillin in AutoDose Infusion System bags. *Ann Pharmacother* 2001; 35: 1360–3.

Uses and Administration

Piperacillin is a ureidopenicillin that is used similarly to ticarcillin (p. 380.2) for the treatment of infections caused by *Pseudomonas aeruginosa*, and also infections due to other susceptible bacteria. It has been used particularly in immunocompromised patients (neutropenic patients) and for biliary-tract infections (cholangitis). Other indications have included uncomplicated gonorrhoea due to penicillin-sensitive gonococci, and urinary-tract infections. It has also been used for surgical infection prophylaxis. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2. For the treatment of serious infections piperacillin is commonly used with an aminoglycoside, but they should be given separately because of possible incompatibility.

Piperacillin is given by injection as the sodium salt. Doses are expressed in terms of the equivalent amount of piperacillin; 1.04 g of piperacillin sodium is equivalent to about 1 g of piperacillin. Doses should generally be reduced in moderate to severe renal impairment (see p. 342.3).

Piperacillin may be given by slow intravenous injection over 3 to 5 minutes, by intravenous infusion over 20 to 30 minutes, or by deep intramuscular injection. Single doses of more than 2 g should not be given by the intramuscular route. For information on extended infusions of piperacillin with tazobactam see p. 342.2.

For the treatment of serious or complicated infections, piperacillin 200 to 300 mg/kg daily may be given in divided doses intravenously; the usual dose is 3 to 4 g every 4 or 6 hours. In life-threatening infections, particularly those caused by *Pseudomonas* or *Klebsiella* spp., it should be given in a dose of not less than 16 g daily. The usual maximum daily dose is 24 g, although this has been exceeded.

For mild or uncomplicated infections, 100 to 125 mg/kg daily may be given; usual doses are 2 g every 6 or 8 hours, or 4 g every 12 hours, intravenously, or 2 g every 8 or 12 hours intramuscularly.

Uncomplicated gonorrhoea may be treated by a single intramuscular dose of 2 g. Probenecid 1 g may be given orally 30 minutes before the injection.

For the prophylaxis of infection during surgery, 2 g just before the procedure, or when the umbilical cord is clamped in caesarean section, followed by at least 2 doses of 2 g at intervals of 4 or 6 hours within 24 hours of the procedure, may be given.

Piperacillin with tazobactam. Piperacillin is frequently used with tazobactam (p. 371.3), a beta-lactamase inhibitor, to widen its antibacterial spectrum to organisms usually resistant because of the production of beta-lactamases. The combination is given intravenously in a ratio of piperacillin (as the sodium salt) 8 parts to 1 part of tazobactam (as the sodium salt). The usual recommended dose (expressed as the combined amount of piperacillin and tazobactam) is 4.5 g given every 8 hours or 3.375 g given every 6 hours. For nosocomial pneumonia, bacterial infections in neutropenic patients, and other severe infections a dose of 4.5 g may be given every 6 hours.

For details of dosing in children for both piperacillin and piperacillin plus tazobactam, see p. 342.2.

References.

1. Greenwood D, Finch RG, eds. Piperacillin/tazobactam: a new β -lactam/β -lactamase inhibitor combination. *J Antimicrob Chemother* 1993; 31 (suppl A): 1–124.
2. Schoonover LL, *et al.* Piperacillin/tazobactam: a new beta-lactam/beta-lactamase inhibitor combination. *Ann Pharmacother* 1995; 29: 501–14.
3. Perry CM, Markham A. Piperacillin/tazobactam: an updated review of its use in the treatment of bacterial infections. *Drugs* 1999; 57: 805–43.
4. Kotapati S, *et al.* The clinical and economic benefits of administering piperacillin-tazobactam by continuous infusion. *Intensive Crit Care Nurs* 2005; 21: 87–93.
5. Gin A, *et al.* Piperacillin-tazobactam: a beta-lactam/beta-lactamase inhibitor combination. *Expert Rev Anti Infect Ther* 2007; 5: 365–83.

Administration. There is evidence from *in-vitro*, *animal*, and some small clinical studies that intravenous infusions of piperacillin-tazobactam given over extended periods (4 hours instead of the recommended 30 minutes) enhances the pharmacodynamic profile of piperacillin-tazobactam, by extending the time the free drug level remains above the minimum inhibitory concentration. For these studies a dose regimen of 3.375 g every 8 hours as a 4-hour infusion was commonly given.[1] This dose may, however, not be adequate for isolates with minimum inhibitory concentrations of ≥32 micrograms/mL (such as *Pseudomonas aeruginosa*), and for these organisms a dose of 4.5 g given every 6 hours as a 3-hour infusion has been suggested.[1]

1. Kaufman SE, *et al.* Rationale and evidence for extended infusion of piperacillin-tazobactam. *Am J Health-Syst Pharm* 2011; 68: 1521–6.

Administration in children. Piperacillin has been given alone, or with tazobactam to neonates and children for the treatment of infections caused by susceptible organisms.

Piperacillin. Although it is not licensed for use in children under 12 years of age in the USA, the American Academy of Pediatrics (AAP)[1] suggests intramuscular or intravenous doses of 200 mg/kg daily in 3 or 4 divided doses for mild to moderate infections in children 1 month of age and older; for severe infections, the dose may be increased to 300 to 400 mg/kg daily in 4 to 6 divided doses.

Piperacillin plus tazobactam. Piperacillin has also been given with tazobactam to paediatric patients.[2] In the UK, the combination of piperacillin plus tazobactam is not licensed for use in children under 12 years of age *except* for those with neutropenia or complicated intra-abdominal infections. Despite this, it has been used for a number of other indications. The *BNFC* recommends the following doses (expressed as the combined amount of piperacillin and tazobactam) by intravenous infusion over 30 minutes.

For hospital-acquired pneumonia, septicaemia, complicated infections involving the urinary-tract or skin and soft tissues:

- neonates: 90 mg/kg every 8 hours
- children 1 month to 12 years of age: 90 mg/kg every 6 to 8 hours (maximum 4.5 g every 6 hours)
- children from 12 years of age: 4.5 g every 8 hours, increased to 4.5 g every 6 hours in severe infection

For infections in children with **neutropenia:**

- children from 1 month of age: 90 mg/kg (maximum 4.5 g) every 6 hours

For complicated intra-abdominal infections:

- children from 2 to 12 years of age: 112.5 mg/kg (maximum 4.5 g) every 8 hours
- children from 12 years of age: 4.5 g every 8 hours, increased to 4.5 g every 6 hours in severe infection

Alternatively, the AAP[1] recommends the following intravenous doses [based on piperacillin component]:

- for neonates aged 7 days or less: 100 mg/kg every 12 hours
- for neonates aged 8 to 28 days: 100 mg/kg every 8 hours; a dosing interval of 12 hours may be used until 2 weeks of life in extremely low birth-weight neonates (weighing less than 1 kg)
- for children beyond the newborn period: 300 mg/kg daily in 3 divided doses; a lower daily dose of 240 mg/kg is recommended for those 2 to 9 months of age.

The AAP[1] does not recommend the use of piperacillin plus tazobactam in mild to moderate infection.

Doses of piperacillin plus tazobactam may need to be adjusted in children with renal impairment; for further information see p. 342.3.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases.* 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.
2. Wolf MP, Simon A. The use of piperacillin-tazobactam in neonatal and paediatric patients. *Expert Opin Drug Metab Toxicol* 2009; 5: 57–69.

Administration in renal impairment. Doses of *piperacillin* should be reduced in moderate to severe renal impairment; for serious infections in adults, the following maximum doses for intravenous or intramuscular use have been recommended based on creatinine clearance (CC):

- CC 20 to 40 mL/min: 4 g every 8 hours
- CC less than 20 mL/min: 4 g every 12 hours
- haemodialysis patients: 2 g every 8 hours, with an additional dose of 1 g given after each haemodialysis run

For *piperacillin plus tazobactam*, UK licensed product information recommends the following maximum intravenous doses (expressed as the combined amount of piperacillin and tazobactam) in renal impairment, based on CC:

Adults:

- CC 20 to 40 mL/min: 4.5 g every 8 hours
- CC less than 20 mL/min: 4.5 g every 12 hours
- haemodialysis patients: an additional 2.25-g dose should be given after each dialysis run

Children:

- CC ≤ 50 mL/min: 78.75 mg/kg every 8 hours
- haemodialysis patients: an additional 45-mg/kg dose should be given after each dialysis run

In a review,[1] the following doses, expressed as the combined amount of piperacillin and tazobactam, were recommended for critically ill adults undergoing different types of renal replacement therapy:

- continuous venovenous haemofiltration (CVVH): 2.25 to 3.375 g every 6 to 8 hours
- continuous venovenous haemodialysis (CVVHD): 2.25 to 3.375 g every 6 hours
- continuous venovenous haemodiafiltration (CVVHDF): 3.375 g every 6 hours
- intermittent haemodialysis: 2.25 g every 8 to 12 hours

1. Heintz BH, *et al.* Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy* 2009; 29: 562–77.

Adverse Effects and Precautions

As for Carbenicillin Sodium, p. 232.1.

Prolongation of bleeding time has been less frequent and less severe with piperacillin than with carbenicillin. Like other penicillins, piperacillin may interfere with some diagnostic tests (see Precautions for Benzylpenicillin, p. 229.3); additionally, false-positive tests for *Aspergillus* infection have been reported in patients given piperacillin plus tazobactam.

Effects on the blood. References.

1. Peralta FG, *et al.* Incidence of neutropenia during treatment of bone-related infections with piperacillin-tazobactam. *Clin Infect Dis* 2003; 37: 1568–72.
2. Scheetz MH, *et al.* Systematic review of piperacillin-induced neutropenia. *Drug Safety* 2007; 30: 295–306.
3. Garcia Gala JM, *et al.* Immune hemolysis due to piperacillin/tazobactam. *Transfus Apher Sci* 2009; 40: 97–8.

4. Mayer B, *et al.* Piperacillin-induced immune hemolysis: new cases and a concise review of the literature. *Transfusion* 2010; 50: 1135–8.

Hypersensitivity. In the mid 1980s there were reports of a relatively high incidence of adverse reactions to piperacillin, especially fever, in patients with cystic fibrosis.[1-3] However, the manufacturers[4] considered such patients to be particularly prone to allergy and cited reactions with other semisynthetic penicillins including carbenicillin and azlocillin.

Similar apparent hypersensitivity reactions have been reported in patients taking high doses of piperacillin and other ureidopenicillins, over long periods for other indications,[5] and with other penicillins in patients with cystic fibrosis,[6] although piperacillin does appear to be most frequently implicated.[6]

1. Stead RJ, *et al.* Adverse reactions to piperacillin in cystic fibrosis. *Lancet* 1984; i: 857–8.
2. Strandvik B. Adverse reactions to piperacillin in patients with cystic fibrosis. *Lancet* 1984; i: 1362.
3. Stead RJ, *et al.* Adverse reactions to piperacillin in adults with cystic fibrosis. *Thorax* 1985; 40: 184–6.
4. Brock PG, Roach M. Adverse reactions to piperacillin in cystic fibrosis. *Lancet* 1984; i: 1070–1.
5. Lang R, *et al.* Adverse reactions to prolonged treatment with high doses of carbenicillin and ureidopenicillins. *Rev Infect Dis* 1991; 13: 68–72.
6. Pleasants RA, *et al.* Allergic reactions to parenteral beta-lactam antibiotics in patients with cystic fibrosis. *Chest* 1994; 106: 1124–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies piperacillin as not porphyrinogenic and the combination of piperacillin with tazobactam as probably not porphyrinogenic; both may be used as drugs of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Sodium content. Each g of piperacillin sodium contains about 1.85 mmol of sodium. As piperacillin sodium has a lower sodium content than carbenicillin sodium, hypernatraemia and hypokalaemia are less likely to occur.

Products containing piperacillin plus tazobactam contain about 2.36 mmol of sodium for each g of the piperacillin component; when the product is formulated with edetic acid the sodium content is higher (about 2.36 mmol sodium per g).

Interactions

As for Benzylpenicillin, p. 230.1.

Antibacterials. For the effect of piperacillin on *flucloxacillin*, see p. 300.1.

Neuromuscular blockers. Piperacillin and other ureidopenicillins are reported to prolong the action of competitive muscle relaxants such as *vecuronium* (see Atracurium, p. 2032.1).

Antimicrobial Action

Piperacillin has a similar antimicrobial action to carbenicillin (p. 232.1) and ticarcillin (p. 381.1), but is active against a wider range of Gram-negative organisms, including *Klebsiella pneumoniae*. It is also generally more active *in vitro*, especially against *Pseudomonas aeruginosa* and the Enterobacteriaceae, against Gram-positive *Enterococcus faecalis*, and possibly against *Bacteroides fragilis*. There is, however, an inoculum effect, i.e. minimum inhibitory concentrations of piperacillin increase with the size of the inoculum.

Combinations of piperacillin and aminoglycosides have been shown to be synergistic *in vitro* against *Ps. aeruginosa* and Enterobacteriaceae. The effect of using piperacillin with other beta lactams has been less predictable.

The activity of piperacillin against some organisms, resistant because of the production of beta-lactamases, may be restored by tazobactam, a beta-lactamase inhibitor. Such organisms include beta-lactamase-producing strains of staphylococci, *Escherichia coli*, *Haemophilus influenzae*, and *Bacteroides* spp.; the activity of piperacillin against *Ps. aeruginosa* is not enhanced by tazobactam.

Resistance has developed in *Ps. aeruginosa* during treatment with piperacillin, especially when used alone. There may be some cross-resistance with other antipseudomonal penicillins.

References.

1. Higashitani F, *et al.* Inhibition of β-lactamases by tazobactam and in-vitro antibacterial activity of tazobactam combined with piperacillin. *J Antimicrob Chemother* 1990; 25: 567–74.
2. Mehtar S, *et al.* The in-vitro activity of piperacillin/tazobactam, ciprofloxacin, ceftazidime and imipenem against multiple resistant Gram-negative bacteria. *J Antimicrob Chemother* 1990; 25: 915–19.
3. Kempers J, MacLaren DM. Piperacillin/tazobactam and ticarcillin/clavulanic acid against resistant Enterobacteriaceae. *J Antimicrob Chemother* 1990; 26: 598–9.
4. Kadima TA, Weiner JH. Mechanism of suppression of piperacillin resistance in enterobacteria by tazobactam. *Antimicrob Agents Chemother* 1997; 41: 2177–83.
5. Klepser ME, *et al.* Comparison of the bactericidal activities of piperacillin-tazobactam, ticarcillin-clavulanate, and ampicillin-sulbactam against clinical isolates of Bacteroides fragilis, Enterococcus faecalis, Escherichia coli, and Pseudomonas aeruginosa. *Antimicrob Agents Chemother* 1997; 41: 435–9.
6. Peterson LR. Antibiotic policy and prescribing strategies for therapy of extended-spectrum beta-lactamase-producing Enterobacteriaceae: the role of piperacillin-tazobactam. *Clin Microbiol Infect* 2008; 14 (suppl 1): 181–4. Correction. *ibid.*: (suppl 5): 21–4.

Pharmacokinetics

Piperacillin is not absorbed from the gastrointestinal tract. It is well absorbed after intramuscular use and peak plasma concentrations of 30 to 40 micrograms/mL occur 30 to 50 minutes after a 2-g dose. The pharmacokinetics of piperacillin are reported to be nonlinear and dose-dependent. The plasma half-life is about 1 hour, but is prolonged in neonates. In patients with severe renal impairment there may be a threefold increase in half-life; in those with end-stage renal failure half-lives of 4 to 6 hours have been reported, and in those with both renal and hepatic impairment much longer half-lives may result. About 20% of piperacillin in the circulation is bound to plasma proteins.

Piperacillin is widely distributed in body tissues and fluids. It crosses the placenta into the fetal circulation and small amounts are distributed into breast milk. There is little diffusion into the CSF except when the meninges are inflamed.

About 60 to 80% of a dose is excreted unchanged in the urine by glomerular filtration and tubular secretion within 24 hours, achieving high concentrations. High concentrations also occur in the bile and up to 20% of a dose may be excreted by this route.

Plasma concentrations are enhanced by probenecid.

Piperacillin is removed by haemodialysis.

Piperacillin with tazobactam. The pharmacokinetics of piperacillin do not appear to be altered by tazobactam, but piperacillin reduces the renal clearance of tazobactam.

References.

1. Heikkilä A, Erkkola R. Pharmacokinetics of piperacillin during pregnancy. *J Antimicrob Chemother* 1991; 28: 419–23.
2. Wise R, *et al.* Pharmacokinetics and tissue penetration of tazobactam administered alone and with piperacillin. *Antimicrob Agents Chemother* 1991; 35: 1081–4.
3. Johnson CA, *et al.* Single-dose pharmacokinetics of piperacillin and tazobactam in patients with renal disease. *Clin Pharmacol Ther* 1992; 51: 32–41.
4. Dupon M, *et al.* Plasma levels of piperacillin and vancomycin used as prophylaxis in liver transplant patients. *Eur J Clin Pharmacol* 1993; 45: 529–34.
5. Sörgel F, Kinzig M. The chemistry, pharmacokinetics and tissue distribution of piperacillin/tazobactam. *J Antimicrob Chemother* 1993; 31 (suppl A): 39–60.
6. Reed MD, *et al.* Single-dose pharmacokinetics of piperacillin and tazobactam in infants and children. *Antimicrob Agents Chemother* 1994; 38: 2817–26.
7. Bourget P, *et al.* Clinical pharmacokinetics of piperacillin-tazobactam combination in patients with major burns and signs of infection. *Antimicrob Agents Chemother* 1996; 40: 139–45.
8. Occhipinti DJ, *et al.* Pharmacokinetics and pharmacodynamics of two multiple-dose piperacillin-tazobactam regimens. *Antimicrob Agents Chemother* 1997; 41: 2511–17.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Petezam; ***Gr.***: Pipril; Zobactam; Zoracilin; ***India***: Pipracil; ***Israel***: Pipracin; ***Ital.***: Cilpier; Ecosette; Farecillin; Peracil; Picillin; Piperital; Pipersal; Pipertex; Reparcillin; Semipenil; ***Jpn***: Pentcillin; ***Thai.***: Peracin†; Pipracil; ***Turk.***: Pipraks.

Multi-ingredient Preparations. ***Arg.***: Pipetexina; Tazonam; Vredian; ***Austral.***: PiperTaz; Tazocin; Tazopip; ***Austria***: Pipitaz; Tazonam; ***Belg.***: Tazocin; ***Braz.***: Tazocilina; Tazocin; ***Canad.***: Tazocin; ***Chile***: Aurotaz-P; Tazonam; ***China***: An Di Tai (安迪泰); Bai Ding (百定); Bang Da (邦达); Caryn (凯伦); Fengtailing (锋泰灵); Haitaxin (海他欣); Kang De Li (康得力); Li Ke Duo (力可多); Pai Shu (派舒); Tazocin (特治星); Xintemie (新特灭); Yi Jun (一君); Yi Tan (益坦); ***Cz.***: Tazabax; Tazip; Tazocin; Tazopet; Tazoratio; Tebranic; ***Denm.***: Tazocin; ***Fin.***: Tazocin; ***Fr.***: Tazocilline; ***Ger.***: Tazobac; ***Gr.***: Bactalin; Gramenox; Oliten; Tavoctame; Tazepen; Tazidron; Tazobion; Tazocin; Tazorex; ***Hong Kong***: Tazocin; ***Hung.***: Tazocin; ***India***: Adzopip; Ampip-T; Badin; Boxter; Cadipip; Cidal; Cinpip-TZ; Combiwin; Cureact; Durataz; Elzox; Europep-T; Everpip-TZ; Forpep; Gotaz; Gramotaz; Hoslin; Infocer; Inforcer; Ip-Taz; Jope; Kombat; KPT; Lazocin Forte; Lazopip; Lintaz; Lupitaz; Matlin; Medipip; Megacillin; Mezobact-P; Microtaz; Monal; Olin; Pactum; Tazact; Tazofast; Tazopen; Zosyn; ***Indon.***: Tazocin; ***Irl.***: Pipercin; Piperin; Tazocin; ***Israel***: Tazocillin; Tazocin; Tazopip; Tazorex; ***Ital.***: Ibitazina; Limerick; Tazobac; Tazocin; Tazopenil; ***Jpn***: Zosyn; ***Malaysia***: Tazocin; ***Mex.***: Tasovak; Tazocin; Tazpen; ***Neth.***: Tazocin; ***Norw.***: Piptazira; Tazocin; ***NZ***: Tazocin; ***Philipp.***: Bactaz; Peprasan-T; Piptaz; Pizobac; Pletzolyn; Tanzo; Tapimycin; Tazobak; Tazocin; Tazolin†; Tazopen; Tazotaz; Tebranic; Vigocid; ***Pol.***: Tazacylin; Tazocin; Tazoratio; ***Port.***: Tazobac; ***Rus.***: Tacillin-J (Тациллин ДК); Tazocin (Тазоцин); ***S.Afr.***: Curitaz; Tazobax; Tazocin; ***Singapore***: Tazocin; Tazpen; ***Spain***: Tazocel; ***Swed.***: Tazocin†; ***Switz.***: Tazobac; ***Thai.***: Astaz-P; Pipertaz; Tazocin; Tazrobida; Tebranic; ***Turk.***: Tazocin; Tazoper; ***UK***: Tazocin; ***Ukr.***: Tazar (Тазар); Zopercin (Зоперцин); ***USA***: Zosyn; ***Venez.***: Tazopril; Tazpen.

Pharmacopoeial Preparations

BP 2014: Piperacillin Infusion;
USP 36: Piperacillin and Tazobactam for Injection; Piperacillin for Injection.

Pirlimycin Hydrochloride *(USAN, rINNM)*

Hidrocloruro de pirlimicina; Pirlimicina, hidrocloruro de; Pirlimycine, Chlorhydrate de; Pirlimycinhydroklorid; Pirlimycini Hydrochloridum; Pirlimysiinihydrokloridi; U-57930E; Пирлимицина Гидрохлорид.

Methyl 7-chloro-6,7,8-trideoxy-6-(*cis*-4-ethyl-L-pipecolamido)-1-thio-L-*threo*-α-D-*galacto*-octopyranoside monohydrochloride monohydrate.

$C_{17}H_{31}ClN_2O_5S,HCl,H_2O$=465.4

CAS — 79548-73-5 (pirlimycin); 77495-92-2 (pirlimycin hydrochloride).

UNII — 8S09O559AQ.

NOTE. The name Pirsue has been used as a trade mark for pirlimycin hydrochloride.

Profile

Pirlimycin is a lincosamide antibacterial used in veterinary medicine.

Piromidic Acid *(rINN)*

Acide Piromidique; Ácido piromídico; Acidum Piromidicum; PD-93; Piromídico, ácido; Piromidihappo; Piromidsyra; Пиромидовая Кислота.

8-Ethyl-5,8-dihydro-5-oxo-2-(pyrrolidin-1-yl)pyrido[2,3-*d*]pyrimidine-6-carboxylic acid.

$C_{14}H_{16}N_4O_3$=288.3

CAS — 19562-30-2.

ATC — J01MB03.

ATC Vet — QJ01MB03.

UNII — 3I12WH4EWF.

Profile

Piromidic acid is a 4-quinolone antibacterial with properties similar to those of nalidixic acid (p. 328.3). It has been used in the treatment of susceptible infections. There have been several reports of acute renal failure associated with piromidic acid.

Pivampicillin *(BAN, rINN)*

MK-191; Pivampicilin; Pivampicilina; Pivampicilinas; Pivampicilline; Pivampicillinum; Pivampisilliini; Пивампициллин.

Pivaloyloxymethyl (6*R*)-6-(α-D-phenylglycylamino)penicillanate.

$C_{22}H_{29}N_3O_6S$=463.5

CAS — 33817-20-8.

ATC — J01CA02.

ATC Vet — QJ01CA02.

UNII — 0HLM346LL7.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Pivampicillin). A white or almost white crystalline powder. Practically insoluble in water; soluble in dehydrated alcohol; freely soluble in methyl alcohol. It dissolves in dilute acids. Store in airtight containers.

Pivampicillin Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de pivampicilina; Pivampicilina, hidrocloruro de; Pivampicilline, Chlorhydrate de; Pivampicillini Hydrochloridum; Пивампициллина Гидрохлорид.

$C_{22}H_{29}N_3O_6S,HCl$=500.0

CAS — 26309-95-5.

ATC — J01CA02.

ATC Vet — QJ01CA02.

UNII — V9HOC53L7L.

Uses and Administration

Pivampicillin is the pivaloyloxymethyl ester of ampicillin (p. 218.3) and has similar uses; 1.3 g of pivampicillin and 1.43 g of pivampicillin hydrochloride are each equivalent to about 1 g of ampicillin. Pivampicillin is given in usual oral doses of 350 to 700 mg 3 or 4 times daily; if necessary, the dose may be increased to 1 g orally 3 times daily.

In areas where gonococci remain sensitive a single dose of 1.4 g is given for gonorrhoea, with probenecid 1 g.

For details of doses in children, see p. 344.1.

Pivampicillin hydrochloride has been used in some countries.

Pivampicillin has also been given with pivmecillinam (p. 344.1).

Administration in children. Pivampicillin may be used orally in children for the treatment of susceptible infections. An oral dose of 35 to 70 mg/kg daily in 3 divided doses has been suggested for children up to 6 years of age; those older than 6 years may be dosed as for adults (see p. 341.3).

Adverse Effects and Precautions

As for Ampicillin, p. 219.2. Pivampicillin is reported to cause a lower incidence of diarrhoea than ampicillin. Upper gastrointestinal discomfort may be more frequent when pivampicillin is taken on an empty stomach.

Pivaloyloxymethyl esters such as pivampicillin have been associated with the induction of carnitine deficiency (see p. 344.1).

Carnitine deficiency. Carnitine deficiency (see p. 2053.3) has been reported after the use of pivampicillin and pivmecillinam.[1] It is thought that the pivalic acid liberated on hydrolysis of these pivaloyloxymethyl esters *in vivo* is excreted as pivaloyl-carnitine with a consequent depletion in plasma and muscle concentrations of carnitine.[2] Low plasma-carnitine concentrations persisted in a patient after stopping pivampicillin, despite 6 weeks of replacement therapy with oral carnitine 1g daily. She had originally presented with skeletal myopathy when given pivampicillin for 3 months. A more intensive carnitine replacement regimen might be necessary in such patients.[3]

1. Holme E, *et al.* Carnitine deficiency induced by pivampicillin and pivmecillinam therapy. *Lancet* 1989; ii: 469–73.
2. Anonymous. Carnitine deficiency. *Lancet* 1990; 335: 631–3.
3. Rose SJ, *et al.* Carnitine deficiency associated with long-term pivampicillin treatment: the effect of a replacement therapy regime. *Postgrad Med J* 1992; 68: 932–4.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pivampicillin as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Interactions

As for Benzylpenicillin, p. 230.1.

There is a theoretical possibility that carnitine deficiency may be increased in patients receiving pivampicillin (or pivmecillinam) and valproate; use of either antibacterial with valproate or medications that liberate pivalic acid should be avoided.

Antimicrobial Action

Pivampicillin has the antimicrobial activity of ampicillin to which it is hydrolysed *in vivo* (p. 219.3).

Pharmacokinetics

Pivampicillin is acid-stable and is readily absorbed from the gastrointestinal tract. On absorption it is rapidly and almost completely hydrolysed to ampicillin, pivalic acid, and formaldehyde. Plasma-ampicillin concentrations 1 hour after a dose are 2 to 3 times those attained after an equivalent dose of ampicillin. The absorption of pivampicillin is generally not significantly affected by food. About 70% of a dose is excreted in the urine as ampicillin within 6 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Denm.*: Pondocillin; *Fr.*: Proampi†.

Pivmecillinam *(BAN, rINN)*

Amdinocillin Pivoxil (USAN); FL-1039; Pivamdinocillin; Pivmecilinam; Pivmécillinam; Pivmecillinamum; Pivmesillinaami; Ro-10-9071; Пивмециллинам.

Pivaloyloxymethyl (6*R*)-6-(perhydroazepin-1-ylmethyleneamino)penicillanate.

$C_{21}H_{33}N_3O_5S$=439.6

CAS — 32886-97-8.

ATC — J01CA08.

ATC Vet — QJ01CA08.

UNII — 1WAM1OQ30B.

Pivmecillinam Hydrochloride *(BANM, rINNM)*

Hidrocloruro de pivmecilinam; Pivmecilinam, hidrocloruro de; Pivmecilnam-hydrochlorid; Pivmecllinamo hidrochloridas; Pivmécillinam, Chlorhydrate de; Pivmecillinám-hidroklorid; Pivmecillinamhydrochlorid; Pivmecillinamhydroklorid; Pivmecillinami Hydrochloridum; Pivmesillinaamihydrokloridi; Пивмециллинама Гидрохлорид.

$C_{21}H_{33}N_3O_5S.HCl$=476.0

CAS — 32887-03-9.

ATC — J01CA08.

ATC Vet — QJ01CA08.

UNII — 48FX7N21H2.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.*

Ph. Eur. 8: (Pivmecillinam Hydrochloride). A white or almost white crystalline powder. Freely soluble in water, in dehydrated alcohol, and in methyl alcohol; slightly soluble in acetone. A 10% solution in water has a pH of 2.8 to 3.8. Store at a temperature of 2 degrees to 8 degrees. Protect from light.

Uses and Administration

Pivmecillinam is the pivaloyloxymethyl ester of mecillinam (p. 321.1), to which it is hydrolysed after oral dosage. It is used in the treatment of urinary-tract infections (p. 213.1).

Doses of pivmecillinam have often been expressed in a confusing manner since no differentiation has been made between the hydrochloride, used in tablets, and the base, used in suspensions for oral use. Pivmecillinam 1.35 g and pivmecillinam hydrochloride 1.46 g are each equivalent to about 1 g of mecillinam.

Pivmecillinam should preferably be taken with food (see also Administration, under Adverse Effects and Precautions, p. 344.2).

In acute uncomplicated cystitis, the initial dose is 400 mg orally followed by 200 mg three times daily for 8 doses. In chronic or recurrent bacteriuria, 400 mg may be given 3 or 4 times daily.

For details of doses in children, see p. 344.2.

Pivmecillinam has been given with other beta lactams, particularly pivampicillin (p. 341.3), to extend the spectrum of antimicrobial activity to Gram-positive organisms and because of reported synergism against Gram-negative bacteria *in vitro*.

For parenteral use, mecillinam is given.

References.

1. Nicolle LE. Pivmecillinam in the treatment of urinary tract infections. *J Antimicrob Chemother* 2000; 46 (suppl S1): 35–9.

Administration in children. Pivmecillinam may be used orally in children 3 months of age and older for the treatment of urinary-tract infections. In the UK, the *BNFC* recommends that for all urinary-tract infections in children weighing less than 40 kg, a dose of 5 to 10 mg/kg every 6 hours may be used; alternatively the total daily dose may be given in 3 divided doses. Children weighing more than 40 kg may be treated as for adults (see Uses and Administration, above).

Adverse Effects and Precautions

As for Benzylpenicillin, p. 229.2.

Pivaloyloxymethyl esters such as pivmecillinam have been associated with the induction of carnitine deficiency (see Pivampicillin, above).

Administration. Oesophageal injury has been associated rarely with pivmecillinam tablets.[1,2] Patients are advised to take them during a meal, while sitting or standing, and with at least half a glass of water.[3]

1. CSM. Pivmecillinam and oesophageal injury. *Current Problems* 19 1987. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024426&RevisionSelectionMethod=LatestReleased (accessed 22/07/08)
2. Mortimer Ö, Wiholm B-E. Oesophageal injury associated with pivmecillinam tablets. *Eur J Clin Pharmacol* 1989; 37: 605–7.
3. Anonymous. CSM warning on pivmecillinam. *Pharm J* 1987; 238: 443.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pivmecillinam as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Interactions

As for Pivampicillin, above.

Antimicrobial Action

Pivmecillinam has the antimicrobial activity of mecillinam (p. 321.1) to which it is hydrolysed *in vivo*.

Pharmacokinetics

Pivmecillinam is well absorbed from the gastrointestinal tract and is rapidly hydrolysed to the active drug mecillinam (p. 321.2), pivalic acid, and formaldehyde. The presence of food in the stomach does not appear to have a significant effect on absorption. Peak plasma concentrations of mecillinam of 5 micrograms/mL have been achieved 1 to 2 hours after a 400-mg dose of pivmecillinam.

About 45% of a dose may be excreted in the urine as mecillinam, mainly within the first 6 hours.

References.

1. Heikkilä A, *et al.* The pharmacokinetics of mecillinam and pivmecillinam in pregnant and non-pregnant women. *Br J Clin Pharmacol* 1992; 33: 629–33.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Selexid; *Canad.*: Selexid†; *Denm.*: Penomax; Selexid; *Fin.*: Penomax; Selexid; *Fr.*: Selexid; *Gr.*: Selexid; *Norw.*: Penomax; Selexid; *NZ*: Selexid; *Port.*: Selexid; *Swed.*: Penomax; Selexid; *UK*: Selexid.

Polymyxin B Sulfate *(BANM, rINNM)*

Polimiksin B Sülfat; Polimiksino B sulfatas; Polimixin-B-szulfát; Polimixina B, sulfato de; Polimyksyny B siarczan; Polimyxini b sulfas; Polymyksiini-B-sulfaatti; Polymyxin B sulfat; Polymyxin B Sulphate; Polymyxin-B-sulfat; Polymyxin-B-sulfát; Polymyxine B, Sulfate de; Polymyxini B Sulfas; Polymyxinum B Sulfas; Sulfato de polimixina B; Полимиксина В Сульфат.

CAS — 1404-26-8 (polymyxin B); 1405-20-5 (polymyxin B sulfate); 4135-11-9 (polymyxin B1); 34503-87-2 (polymyxin B2); 71140-58-4 (polymyxin B3).

ATC — A07AA05; J01XB02; S01AA18; S02AA11; S03AA03.

ATC Vet — QA07AA05; QJ01XB02; QS01AA18; QS02AA11; QS03AA03.

UNII — 19371312D4 (polymyxin B sulfate); 57VAB21ZLF (polymyxin B1 sulfate); WTC2W6JDTU (polymyxin B2 sulfate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Polymyxin B Sulfate). A mixture of the sulfates of polypeptides produced by the growth of certain strains of *Bacillus polymyxa* or obtained by any other means. A white or almost white, hygroscopic powder. Soluble in water; slightly soluble in alcohol. A 2% solution in water has a pH of 5.0 to 7.0. Store in airtight containers. Protect from light.

USP 36: (Polymyxin B Sulfate). The sulfate salt of a kind of polymyxin, a substance produced by the growth of *Bacillus polymyxa* (Bacillaceae), or a mixture of two or more such salts. A white to buff-coloured, powder, odourless or has a faint odour. It has a potency of not less than 6000 Polymyxin B units/mg, calculated on the dried substance. Freely soluble in water; slightly soluble in alcohol. pH of a 0.5% solution in water is between 5.0 and 7.5. Store in airtight containers. Protect from light.

Incompatibility. Incompatibility has been reported with many other drugs including antibacterials. Polymyxin B sulfate is rapidly inactivated by strong acids and alkalis.

Units

The second International Standard Preparation (1969) of polymyxin B sulfate contains 8403 units/mg.

NOTE. The available forms of polymyxin B sulfate are generally less pure than the International Standard Preparation. Doses have sometimes been stated in terms of pure polymyxin base; 100 mg of pure polymyxin B is considered to be equivalent to 1 million units (1 mega unit).

Uses and Administration

Polymyxin B sulfate is used topically, often with other drugs, in the treatment of skin, ear, and eye infections due to susceptible organisms. Eye drops containing polymyxin B with neomycin and gramicidin have been used for the prophylaxis of infection in patients undergoing ocular surgery and, with propamidine isetionate, for the treatment of acanthamoeba keratitis (p. 921.2). Polymyxin B has been given orally with other drugs in regimens for selective digestive-tract decontamination (SDD) in patients at high risk of endogenous infections (see under Intensive Care, p. 187.3). Polymyxin B is also used parenterally for the treatment of infections due to susceptible Gram-negative bacteria, especially *Pseudomonas aeruginosa;* other drugs have generally been preferred but its use is increasing due to the emergence of multidrug resistant Gram-negative organisms. Polymyxin B has been given intrathecally in meningeal infection, by subconjunctival injection for eye infections, and by inhalation for the treatment of pneumonia.

For topical application polymyxin B is usually available as a 0.1% solution or ointment (10 000 units per mL or per g respectively) combined with other drugs. Intravenous doses

range from 15 000 to 25 000 units/kg daily, by infusion and may be given every 12 hours. The intramuscular route has also been used despite the severe pain which may be associated with it; doses range from 25 000 to 30 000 units/kg daily, and may be given every 4 or 6 hours.

Doses should be reduced in patients with renal impairment (see p. 345.1).

Intrathecal doses of 50 000 units may be given once daily for 3 to 4 days, then on alternate days for at least 2 weeks after the CSF cultures become negative.

For details of doses in children, see p. 345.1.

For subconjunctival injection, doses of up to 100 000 units daily may be used for infections of the cornea and conjunctiva.

References.
1. Evans ME, *et al.* Polymyxin B sulfate and colistin: old antibiotics for emerging multiresistant Gram-negative bacteria. *Ann Pharmacother* 1999; 33: 960–7.
2. Falagas ME, *et al.* The use of intravenous and aerosolized polymyxins for the treatment of infections in critically ill patients: a review of the recent literature. *Clin Med Res* 2006; 4: 138–46.
3. Arnold TM, *et al.* Polymyxin antibiotics for gram-negative infections. *Am J Health-Syst Pharm* 2007; 64: 819–26.
4. Zavascki AP, *et al.* Polymyxin B for the treatment of multidrug-resistant pathogens: a critical review. *J Antimicrob Chemother* 2007; 60: 1206–15.
5. Kwa A, *et al.* Polymyxin B: similarities to and differences from colistin (polymyxin E). *Expert Rev Anti Infect Ther* 2007; 5: 811–21.
6. Nation RL, Li J. Optimizing use of colistin and polymyxin B in the critically ill. *Semin Respir Crit Care Med* 2007; 28: 604–14.
7. Michalopoulos A, Falagas ME. Colistin and polymyxin B in critical care. *Crit Care Clin* 2008; 24: 377–91.
8. Yuan Z, Tam VH. Polymyxin B: a new strategy for multidrug-resistant Gram-negative organisms. *Expert Opin Invest Drugs* 2008; 17: 661–8.
9. Molina J, *et al.* New information about the polymyxin/colistin class of antibiotics. *Expert Opin Pharmacother* 2009; 10: 2811–28.
10. Velkov T, *et al.* Structure-activity relationships of polymyxin antibiotics. *J Med Chem* 2010; 53: 1898–916.

Administration in children. Polymyxin B may be used parenterally in neonates and children for the treatment of infections caused by susceptible bacteria, particularly *Pseudomonas aeruginosa*, and intrathecally for the treatment of meningitis. Up to 40 000 units/kg daily of polymyxin sulfate may be given to infants with normal renal function by intravenous infusion or by intramuscular injection, although the latter is not recommended routinely because of severe pain at injection sites. Doses as high as 45 000 units/kg daily have been tried in premature and full-term neonates. For suggested doses in children with renal impairment see p. 345.1.

In children under 2 years of age, intrathecal doses of 20 000 units once daily for 3 to 4 days or 25 000 units on alternate days may be given, followed by the latter dose for at least 2 weeks after the CSF cultures become negative.

Older children may be given the usual adult dose (see Uses and Administration, p. 342.3).

Administration in renal impairment. Licensed product information recommends that parenteral doses of polymyxin sulfate should be reduced in adults and children with renal impairment; a maximum intravenous dose of 15 000 units/kg daily has been suggested. However, a small study[1] of 8 critically ill patients reported that polymyxin B given intravenously was eliminated mainly by non-renal pathways, and that total body clearance appears to be relatively insensitive to renal function. Others have suggested that the dose and/or frequency of intravenous polymyxin B do not need to be adjusted in patients with renal impairment.[2]

1. Zavascki AP, *et al.* Pharmacokinetics of intravenous polymyxin B in critically ill patients. *Clin Infect Dis* 2008; 47: 1298–1304.
2. Kwa AL, *et al.* Pharmacokinetics of polymyxin B in a patient with renal insufficiency: a case report. *Clin Infect Dis* 2011; 52: 1280–1.

Adverse Effects, Treatment, and Precautions

When given parenterally, the major adverse effects of the polymyxins are dose-related neurotoxicity and nephrotoxicity. Hypersensitivity reactions are rare, although rashes and fever have been reported, and polymyxins cause histamine release, which may lead to bronchoconstriction and other anaphylactoid symptoms. Polymyxins should be avoided in patients with a history of hypersensitivity to any of the group.

Neurotoxic reactions can occur in up to 7% of patients with normal renal function and include peripheral effects such as circumoral and 'stocking-glove' pattern paraesthesias, visual disturbances, and dizziness, ataxia, confusion, drowsiness, and other CNS effects. The polymyxins are potent neuromuscular blockers, and respiratory paralysis and apnoea may result, especially in overdosage and in patients with renal impairment or pre-existing disorders of neuromuscular transmission such as myasthenia gravis, in whom particular care is needed; certain medications may also increase the risk (see Interactions, p. 345.2). Neostigmine or calcium salts are usually of little value in reversing neuromuscular blockade and artificial ventilation may be required if it develops.

Nephrotoxicity may occur in up to 20% of patients after parenteral use and may be marked by nitrogen retention, haematuria, proteinuria, and tubular necrosis. Electrolyte disturbances are common. Baseline renal function levels should be established before starting parenteral polymyxin B therapy and renal function and blood concentrations of polymyxins should be monitored frequently during therapy. Patients with pre-existing renal impairment and nitrogen retention are at particular risk and require dosage reduction. Signs of decreasing urine output and increasing nitrogen retention are an indication for stopping the drug in all patients. Although polymyxin B is said to be more nephrotoxic than colistin on a weight-for-weight basis, their effects on the kidney seem to be similar at therapeutically equivalent doses.

Polymyxin B is irritant; pain after intramuscular injection may be severe and thrombophlebitis can occur after intravenous injection. Meningeal irritation, manifest as fever, headache, stiff neck, and increased cell count and protein levels in the CSF, may follow intrathecal doses.

Ear drops containing polymyxins should not be used in patients with perforated ear drums, due to the increased risk of ototoxicity. Topical application to large areas of skin should be avoided because of the risk of systemic absorption resulting in neurotoxicity and nephrotoxicity, particularly in children, the elderly, and patients with renal impairment.

References.
1. Falagas ME, Kastakou SK. Toxicity of polymyxins: a systematic review of the evidence from old and recent studies. *Crit Care* 2006; 10: R27.
2. Wunsch H, *et al.* Polymyxin use associated with respiratory arrest. *Chest* 2012; 141: 515–17.

Interactions

Polymyxins may enhance the action of neuromuscular blockers (p. 2032.1) possibly resulting in respiratory depression and apnoea, and concurrent use should be avoided. Additive neurotoxicity and/or nephrotoxicity may occur if polymyxins are given with other potentially neurotoxic and/or nephrotoxic drugs including aminoglycosides; concurrent use should also be avoided.

Antimicrobial Action

Polymyxin B and the other polymyxin antibacterials act primarily by binding to membrane phospholipids and disrupting the bacterial cytoplasmic membrane. Polymyxin B has a bactericidal action on most Gram-negative bacilli except *Proteus* spp. It is particularly effective against *Pseudomonas aeruginosa*. Of the other Gram-negative organisms, *Acinetobacter*spp., *Escherichia coli*, *Enterobacter* and *Klebsiella* spp., *Haemophilus influenzae*, *Bordetella pertussis*, *Salmonella*, and *Shigella* spp. are sensitive. Classical *Vibrio cholerae* 01 is sensitive but the El Tor and O139 biotypes are resistant. *Serratia*, *Burkholderia*, and *Providencia* spp., and *Bacteroides fragilis* are usually resistant. It is not active against *Neisseria* spp., obligate anaerobes, and Gram-positive bacteria. Some fungi such as *Coccidioides immitis* are susceptible but most are resistant.

Antimicrobial synergy has been reported with other drugs, including chloramphenicol, tetracyclines, and the sulfonamides and trimethoprim.

The action of polymyxin B is reduced by divalent cations such as calcium and magnesium, and so activity *in vivo* is less marked than *in vitro*.

Acquired resistance to polymyxin B is uncommon, although adaptive resistance may develop in enterobacteria exposed to sublethal concentrations. There is complete cross-resistance between polymyxin B and colistin.

Pharmacokinetics

Polymyxin B sulfate is not absorbed from the gastrointestinal tract, except in infants who may absorb up to 10% of a dose. It is not absorbed through mucous membranes, or intact or denuded skin.

Peak plasma concentrations after intramuscular injection usually occur within 2 hours, but are variable and polymyxin B sulfate is partially inactivated by serum. It is widely distributed and extensively bound to cell membranes in the tissues; it does not appear to be highly bound to serum proteins. Accumulation may occur after repeated doses. There is no diffusion into the CSF and it does not cross the placenta. Polymyxin B is reported to have a serum half-life of about 6 hours but this is prolonged in renal impairment; values of 2 to 3 days have been reported in patients with a creatinine clearance of less than 10 mL/minute.

Polymyxin B sulfate is excreted mainly by the kidneys by glomerular filtration, about 60% of a dose being recovered unchanged in the urine, but there is a time lag of 12 to 24 hours before polymyxin B is recovered in the urine.

Polymyxin B is not removed to an appreciable extent by peritoneal dialysis or haemodialysis.

References.
1. Zavascki AP, *et al.* Pharmacokinetics of intravenous polymyxin B in critically ill patients. *Clin Infect Dis* 2008; 47: 1298–304.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Aerosporin; *Philipp.*: Aerosporin; *Port.*: Oto-Synalar N.

Multi-ingredient Preparations. *Arg.*: Belbar; Cristalomicina NF; Fangan Plus; Ginal Cent; Ginkan; Irix Biotic; Isoptomax; Linfol Cicatrizante; Mailen; Mini O; Neo Pelvicillin; Neoftalm Dexa; Neoftalm; Neolag; O-Biol P†; Otosporin L; Otosporin; Ovufem; Ovumix; Pantometil†; Pentol; Poenbioptal NF; Polygynax; Polyplex; Septigyn; Sincerum Biotic L; Trimepol D†; Trimepol†; Vagicural Plus; *Austral.*: Neosporin†; *Austria*: Otosporin; *Belg.*: Dexa-Polyspectran New†; Maxitrol; Neobacitracine; Panotile; Polydexa; Polyspectran Gramicidine†; Polytrim; Predmycin P; Statrol†; Synalar Bi-Otic; Terra-Cortril + Polymyxine B; Terramycine + Polymyxine B; *Braz.*: Anaseptil; Colpolase†; Elotin; Ginec; Lidosporin; Maxinom; Maxitrol; Nepodex; Otomixyn; Otosporin; Otosynalar; Panotil; Poliginax; Polipred; Polysporin†; Predmicin; Terramicina c/Polimixina; *Canad.*: Ak Spor; Ak Trol; Antibiotic Cold Sore Ointment†; Antibiotic Cream; Antibiotic Ointment; Antibiotic Plus; Antibiotique Onguent†; Bacimyxin; Band-Aid Antibiotic Adhesive Bandages plus Antibiotic Bioderm; Complete Antibiotic Ointment; Cortimyxin; Cortimyxin; Cortisporin; Cortisporin; Dioptrol; Diosporin†; Diosporin; Lidomyxin; Maxitrol; Neosporin; Neosporin; Neosporin; Optimyxin Plus; Optimyxin; Optimyxin; Ozonol Antibiotic Plus; PMS-Polytrimethoprim; Polyderm; Polysporin Complete; Polysporin For Kids; Polysporin Plus Pain Relief; Polysporin Plus Pain Relief; Polysporin Triple Antibiotic; Polysporin; Polysporin; Polytopic; Polytopic; Polytrim; Spor-HC; Triple Antibiotic Ointment; *Chile*: Dermabiotico; Gotalgic; Grifotal-D†; Maxitrol†; Oftabiotico; Oftabiotico; Oticum; Otolisan; Otoseptil; *China*: Poly Pred (帕利百); *Cz.*: Maxitrol; Otosporin†; Polygynax; Pulpomixine†; *Denm.*: Hydrocortison med Terramycin og Polymyxin-B; Terramycin Polymyxin B; *Fin.*: Maxitrol; Polysporin†; Terra-Cortril P; *Fr.*: Antibio-Synalar; Atebemyxine; Auricularum; Cebemyxine; Framyxone; Maxidrol; Panotile; Polydexa; Polyfra†; Polygynax Virgo; Polygynax; Pulpomixine; *Ger.*: Dexa Polyspectran; Isopto Max; Polyspectran HC; Polyspectran; Polyspectran; *Gr.*: Auricularum; Fotocollyre; Isopto Maxitrol; Neo-Dexacanol; Neopolymyx; Neosporin; Oxacycle-P; Paroticin; Polypictine; Statrol; Synalar; Terramycin w Polymyxin Otic; Terramycin with Polymyxin; Thilodexine-N; *Hong Kong*: Aplosyn-Otic; Bacimyxin†; Cebemyxine; Maxitrol; Neosporin; Otosporin; Otozambon; Polycin†; Polydex-N; Polydexa; Polygynax; Polyneospin†; Polyoph; Polyspectran†; Terramycin with Polymyxin B; *Hung.*: Otosporin; Polysport†; *India*: Cadiprim; Chlormixin†; Decol-P; Derbec-N; Dexosyn Plus†; Eydor-Dexa; Eydor; Mycin; Neosporin-H; Neosporin-H; Neosporin; Neosporin; Ocupol-D; Ocupol; Oriprim-P; *Indon.*: Inmatrol; Isotic Enpigi; Isotic Neolyson; Isotic Nepafrin†; Kenetrol†; Kloramixin D; Kloramixin; Liposin; Maxitrol; Nelicort; Neocortic; Neofen; Neosyd; Oregan; Osatrol†; Otilon; Otolin; Otopain; Otopraf; Otozambon; Polidemisin; Polifrisin; Terramycin Poly†; Tigalin; Ximex Optixitrol; *Irl.*: Maxitrol; Otosporin; Polyfax; Predmycin-P; *Israel*: Barnyxin; Desoren; Dex-Otic; Maxitrol; Phenimixin; Tarocidin D; Tarocidin; Terramycin†; *Ital.*: Anauran; Cicatrene; Mixotone; *Malaysia*: Bacitracin-N; Maxitrol; Oftalmotrim; Pocin G†; Pocin H; Terramycin; *Mex.*: Alosol; Biodexan; Biofrin; Biotriamin†; Cortisporin; Dexsul; Hidropolicin†; Maxitrol; Neobacigrin; Neosporin; Neosporin; Polixin; Polixin; Poly-Micron; Rinadex Compuesto; Septilisin; Soperil; Soxaron; Sulned; Synalar N; Synalar O; Synalar Oftalmico†; Terramicina; Terraxin; Tribiot; *Neth.*: Maxitrol†; Otosporin; Panotile; Polytrim; Synalar; Terra-Cortril met polymyxine-B; *Norw.*: Maxitrol; Terra-Cortril Polymyxin B; Terramycin Polymyxin B; *NZ*: Maxitrol; *Philipp.*: Aceflo; Aplosyn-Otic; BNP Ointment; Cortisporin; Hydrospor; Ipodex; Iporam; Ircos; Isonep H; Isonep; Isore; Maxirap; Maxitrol; Maxoptic; Neodex-V; Neosporin; Novasorin; Postop; Postotic; Predmycin-P; Rapidax; Statrol†; Supravis; Synalar Otic; Syntemax; Terramycin Plus; Terramycin; Trimycin-H; Trimycin; Trispec; Vistacom; *Pol.*: Atecortin; Dexadent; Maxibiotic; Maxitrol; Multibiotic; Neotopic†; Tribiotic; *Port.*: Conjunctilone-S; Conjunctilone; Oftalmotrim; Otosporin; Polisulfade; Polydexa; *Rus.*: Anauran (Ануаран); Maxitrol (Макситрол); Polydexa (Полидекса); Polydexa with Phenylephrine (Полидекса С Фенилефрином); Polygynax (Полижинакс); *S.Afr.*: Maxitrol; Otosporin; Polysporin†; Terra-Cortril†; Terramycin†; *Singapore*: Maxitrol; Otosporin; Polybamycin; Polydexa; Polygynax; Predmycin-P†; Terramycin; *Spain*: Bacisporin†; Blastoestimulina; Creanolona; Dermisone Tri Antibiotic; Liquipom Dexa Antibiotico†; Maxitrol; Oftalmotrim; Oftalmowell; Otix; Panotile†; Phonal; Poly Pred; Pomada Antibiotica; Synalar Nasal; Synalar Otico; Terra-Cortril; Terramicina; Tivitis†; Tulgrasum Antibiotico; Vinciseptil Otico; *Swed.*: Terracortril med polymyxin B; Terramycin Polymyxin B†; *Switz.*: Baneopol†; Maxitrol; Mycinopred†; Neosporin; Otosporin†; Panotile; Polydexa; Spersapolymyxin; *Thai.*: Banocin; Maxitrol; My-B; Otosamthong†; Polyoph; Predmycin P; SM Oto; Spersapolymyxin†; Terramydn; Xanalin; *Turk.*: Cebemyxine; Geotril†; Heksa; Neosporin; Oftalmotrim†; Polimisin; Polycilline†; Polytrim; Sekamisin†; Terramycin; Vitacillin; *UK*: Maxitrol; Neosporin†; Otosporin†; Polyfax; *Ukr.*: Aproiat (Апроіат); Maxitrol (Макситрол); Neladex (Неладекс); Polydexa (Полидекса); Polydexa with Phenylephrine (Полидекса С Фенилэфрином); Polygynax (Полижинакс); *USA*: Ak-Poly-Bac; Cortatrigen; Cortimycin; Cortimycin; Cortisporin; Dexasporin†; Ear-Eze†; LazerSporin-C; Maxitrol; Neocin; Neopolydex; Neosporin + Pain Relief; Neosporin + Pain Relief; Neosporin GU; Neosporin; Neotricin HC†; Ocu-Spor-B; Ocu-Spor-G; Ocu-Trol; Ocutricin;

Ocutricin; Otic-Care; OtiTricin; Otobiotic; Otocort; Otomycin-HPN; Otosporin; Pediotic†; Poly-Dex; Poly-Pred†; Polycin-B; Polymycin; Polymycin; Polysporin; Polytracin; Polytrim; ProCo-Mycin; Terak; Terramycin with Polymyxin B; Tri-Biozene; UAD-Otic; *Venez.*: Dermabiotic; Maxicort; Maxitrol; Oflerra; Otocort; Poli-Otico; Terramicina con Polimixina B.

Pharmacopoeial Preparations

BP 2014: Polymyxin and Bacitracin Eye Ointment; Polymyxin and Bacitracin Ointment;

USP 36: Bacitracin and Polymyxin B Sulfate Topical Aerosol; Bacitracin Zinc and Polymyxin B Sulfate Ointment; Bacitracin Zinc and Polymyxin B Sulfate Ophthalmic Ointment; Chloramphenicol and Polymyxin B Sulfate Ophthalmic Ointment; Chloramphenicol, Polymyxin B Sulfate, and Hydrocortisone Acetate Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates and Bacitracin Ointment; Neomycin and Polymyxin B Sulfates and Bacitracin Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates and Bacitracin Zinc Ointment; Neomycin and Polymyxin B Sulfates and Bacitracin Zinc Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates and Dexamethasone Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates and Dexamethasone Ophthalmic Suspension; Neomycin and Polymyxin B Sulfates and Gramicidin Cream; Neomycin and Polymyxin B Sulfates and Gramicidin Ophthalmic Solution; Neomycin and Polymyxin B Sulfates and Hydrocortisone Acetate Cream; Neomycin and Polymyxin B Sulfates and Hydrocortisone Acetate Ophthalmic Suspension; Neomycin and Polymyxin B Sulfates and Hydrocortisone Ophthalmic Suspension; Neomycin and Polymyxin B Sulfates and Hydrocortisone Otic Solution; Neomycin and Polymyxin B Sulfates and Hydrocortisone Otic Suspension; Neomycin and Polymyxin B Sulfates and Lidocaine Cream; Neomycin and Polymyxin B Sulfates and Pramoxine Hydrochloride Cream; Neomycin and Polymyxin B Sulfates and Prednisolone Acetate Ophthalmic Suspension; Neomycin and Polymyxin B Sulfates Cream; Neomycin and Polymyxin B Sulfates Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates Ophthalmic Solution; Neomycin and Polymyxin B Sulfates Solution for Irrigation; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Acetate Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Lidocaine Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin, and Hydrocortisone Acetate Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin, and Hydrocortisone Acetate Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin, and Lidocaine Ointment; Neomycin and Polymyxin B Sulfates, Gramicidin, and Hydrocortisone Acetate Cream; Oxytetracycline Hydrochloride and Polymyxin B Sulfate Ointment; Oxytetracycline Hydrochloride and Polymyxin B Sulfate Ophthalmic Ointment; Oxytetracycline Hydrochloride and Polymyxin B Sulfate Topical Powder; Oxytetracycline Hydrochloride and Polymyxin B Sulfate Vaginal Tablets; Polymyxin B for Injection; Polymyxin B Sulfate and Bacitracin Zinc Topical Aerosol; Polymyxin B Sulfate and Bacitracin Zinc Topical Powder; Polymyxin B Sulfate and Hydrocortisone Otic Solution; Polymyxin B Sulfate and Trimethoprim Ophthalmic Solution.

Pristinamycin *(BAN, rINN)*

Pristinamicina; Pristinamycine; Pristinamycinum; RP-7293; Пристинамицин.

CAS — 270076-60-3.
ATC — J01FG01.
ATC Vet — QJ01FG01.

Profile

Pristinamycin is a streptogramin antibacterial produced by the growth of *Streptomyces pristina spiralis*, with actions and uses similar to those of virginiamycin (p. 389.3). It is given orally in the treatment of susceptible infections, particularly staphylococcal infections, in a dose of 2 to 4 g daily in divided doses.

Pristinamycin is a naturally occurring mixture of two synergistic components, pristinamycin I which is a macrolide, and pristinamycin II which is a depsipeptide.[1] It has been available for many years as an oral antistaphylococcal drug, and also acts against streptococci. It is effective against strains showing resistance to erythromycin; resistance to pristinamycin is rare,[2,3] although resistance in staphylococci has been reported in the past.[4,5] It is effective against meticillin-resistant *Staphylococcus aureus* (MRSA)[6,7] and other multidrug-resistant Gram-positive organisms,[8] but its usefulness in severe infection is limited by its poor solubility, which prevents development of an intravenous formulation. Oral pristinamycin has been shown to be as effective as standard therapy with intravenous then oral penicillin in the treatment of erysipelas.[9]

Mixtures of water-soluble derivatives of pristinamycins I and II, such as quinupristin/dalfopristin (p. 349.1), are in clinical use or under investigation.

1. Hamilton-Miller JMT. From foreign pharmacopoeias: 'new' antibiotics from old? *J Antimicrob Chemother* 1991; 27: 702–5.
2. Weber P. Streptococcus pneumoniae: absence d'émergence de résistance à la pristinamycine. *Pathol Biol (Paris)* 2001; 49: 840–5.
3. Leclercq R, *et al.* Activité in vitro de la pristinamycine vis-àvis des staphylocoques isolés dans les hôpitaux français en 1999-2000. *Pathol Biol (Paris)* 2003; 51: 400–4.
4. Loncle V, *et al.* Analysis of pristinamycin-resistant Staphylococcus epidermidis isolates responsible for an outbreak in a Parisian hospital. *Antimicrob Agents Chemother* 1993; 37: 2159–65.
5. Allignet J, *et al.* Distribution of genes encoding resistance to streptogramin A and related compounds among staphylococci resistant to these antibiotics. *Antimicrob Agents Chemother* 1996; 40: 2523–8.
6. Dancer SJ, *et al.* Oral streptogramins in the management of patients with methicillin-resistant Staphylococcus aureus (MRSA) infections. *J Antimicrob Chemother* 2003; 51: 731–5.
7. Ng J, Gosbell IB. Successful oral pristinamycin therapy for osteoarticular infections due to methicillin-resistant Staphylococcus aureus (MRSA) and other Staphylococcus spp. *J Antimicrob Chemother* 2005; 55: 1008–12.
8. Ruparelia N, *et al.* Pristinamycin as adjunctive therapy in the management of Gram-positive multi-drug resistant organism (MDRO) osteoarticular infection. *J Infect* 2008; 57: 191–7.
9. Bernard P, *et al.* Oral pristinamycin versus standard penicillin regimen to treat erysipelas in adults: randomised, non-inferiority, open trial. *BMJ* 2002; 325: 864–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Pyostacine.

Procaine Benzylpenicillin *(BAN, rINNM)*

Benzylpenicillinprokain; Bentsyylipenisilliiniprokaiini; Benzilpenicilinas prokainas; Benzilpenicillin-prokain; Benzylopenicylina prokainowa; Benzylpenicillin Novocaine; Benzylpénicilline Procaïne; Benzylpenicillinum Procainum; Penicillin G Procaine; Procaína bencilpenicilina; Procaína penicilina; Procaine Benzylpénicilline; Procaine Penicillin; Procaine Penicillin G; Procaini Benzylpenicillinum; Procainum Benzylpenicillinum; Prokain Benzilpenisilin; Prokain Penisilin G; Prokain-benzylpenicilin; Прокаин Бензилпенициллин.

2-(4-Aminobenzoyloxy)ethyldiethylammonium (6*R*)-6-(2-phenylacetamido)penicillanate monohydrate.

$C_{13}H_{20}N_2O_2.C_{16}H_{18}N_2O_4S.H_2O$=588.7

CAS — 54-35-3 (anhydrous procaine benzylpenicillin); 6130-64-9 (procaine benzylpenicillin monohydrate).
ATC — J01CE09.
ATC Vet — QJ01CE09; QJ51CE09.
UNII — 17R794ESYN.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US*.

Ph. Eur. 8: (Benzylpenicillin, Procaine). A white or almost white, crystalline powder. Slightly soluble in water; sparingly soluble in alcohol. A 0.33% solution in water has a pH of 5.0 to 7.5. Store in airtight containers.

USP 36: (Penicillin G Procaine). White crystals or white, very fine, microcrystalline powder, odourless or practically odourless. Slightly soluble in water; soluble in alcohol and in chloroform. It is rapidly inactivated by acids, by alkali hydroxides, and by oxidising agents. pH of a saturated solution in water is between 5.0 and 7.5.

Uses and Administration

Procaine benzylpenicillin has the same antimicrobial action as benzylpenicillin (p. 230.1) to which it is hydrolysed gradually after deep intramuscular injection. This results in a prolonged effect, but because of the relatively low blood concentrations produced, its use should be restricted to infections caused by micro-organisms that are highly sensitive to penicillin. Procaine benzylpenicillin should not be used as the sole treatment for severe acute infections, or when bacteraemia is present.

Procaine benzylpenicillin is used mainly in the treatment of syphilis; other indications have included pneumonia (in children in developing countries), and Whipple's disease. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Doses of procaine benzylpenicillin may sometimes be expressed in terms of equivalent units of benzylpenicillin. Procaine benzylpenicillin 600 mg is equivalent to about 360 mg of benzylpenicillin (600 000 units). Procaine benzylpenicillin is given by deep intramuscular injection in usual doses of 0.6 to 1.2 g daily. For dosing regimens used in the treatment of syphilis, see p. 205.2.

Procaine benzylpenicillin is also used in combined preparations with other penicillins, including benzylpenicillin and benzathine benzylpenicillin.

For details of doses in children, see p. 346.2.

Administration in children. Procaine benzylpenicillin may be given by deep intramuscular injection to infants and children for the treatment of susceptible bacterial infections, including pneumonia and congenital syphilis.

If used for the treatment of **pneumonia**, WHO suggests a dose of 50 mg/kg daily for 10 days.

For doses used to treat **congenital syphilis** in infants, see p. 205.2.

Adverse Effects and Precautions

As for Benzylpenicillin, p. 229.2.

Procaine benzylpenicillin should not be given to patients known to be hypersensitive to either of its components. Procaine benzylpenicillin should not be injected intravascularly since ischaemic reactions may occur.

Severe, usually transient, reactions with symptoms of severe anxiety and agitation, confusion, psychotic reactions including visual and auditory hallucinations, seizures, tachycardia and hypertension, cyanosis, and a sensation of impending death have occasionally been reported with procaine benzylpenicillin and may be due to accidental intravascular injection. Since similar reactions have also occurred with other depot penicillin preparations that do not contain procaine, its presence is unlikely to be the major cause of such reactions, but may be a contributory factor, especially after injection of high doses. These reactions have been termed non-allergic, pseudoallergic, pseudoanaphylactic, or Hoigné's syndrome; the term 'embolic-toxic reaction' has also been proposed.

Interactions

As for Benzylpenicillin, p. 230.1.

Pharmacokinetics

When procaine benzylpenicillin is given by intramuscular injection, it forms a depot from which it is slowly released and hydrolysed to benzylpenicillin. Peak plasma concentrations are produced in 1 to 4 hours, and effective concentrations of benzylpenicillin are usually maintained for 12 to 24 hours. However, plasma concentrations are lower than those after an equivalent dose of benzylpenicillin potassium or sodium.

Distribution into the CSF is reported to be poor.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Cilicaine Syringe; *Cz.*: Pendepon Compositum; *Hung.*: Retardillin; *Mex.*: Benzotripen; Farmabep; Promizol; Sodilin†; Unicil 3/1; Unicil 6:3:3; *NZ*: Cilicaine; *S.Afr.*: Bio-Cillin; Procillin; *Spain*: Farmaproina; *Turk.*: Benzapen 6.3.3; Deposilin 6.3.3; Devapen; Iecilline; Penadur 6.3.3; Penkain-K†; Procillin†; *USA*: Crysticillin.

Multi-ingredient Preparations. *Austria*: Retarpen compositum; *Braz.*: Benapen; Benzapen G; Despacilina; Pencil 400†; Penkaron; Wycillin; *Ger.*: Retacillin compositum; *Hong Kong*: Pan-Fort Procaine†; Penicillin G Procaine Fortified†; *Hung.*: Promptcillin Forte; *India*: Bistrepen; Fortified PP; Fortified Procaine Peni; FPP; *Malaysia*: Procaine Penicillin; *Mex.*: Bencelin Combinado; Benzanil Compuesto†; Benzetacil Combinado; Hidrocilina; Lugaxil; Pecivax; Pendiben Compuesto†; Penicil; Penipot; Penisodina; Penprocilina†; Procilin†; Respicil; Robencaxil; Suipen; *Port.*: Atralcilina†; Lentocilin; *Rus.*: Benzycillin 3 (Бензициллин 3); Benzycillin 5 (Бензициллин 5); Bicillin-3 (Бициллин-3); Bicillin-5 (Бициллин-5); *S.Afr.*: Ultracillin†; *Spain*: Benzetacil Compuesta; Cepacilina 633†; *Turk.*: Pencain K; Pronapen; *Ukr.*: Bicillin-3 (Бициллин-3); Bicillin-5 (Бициллин-5); *USA*: Bicillin C-R; *Venez.*: Benzetacil 3-3; Benzetacil 6-3-3; Pronapen.

Pharmacopoeial Preparations

USP 36: Penicillin G Benzathine and Penicillin G Procaine Injectable Suspension; Penicillin G Procaine for Injectable Suspension; Penicillin G Procaine Injectable Suspension.

Propicillin Potassium *(BANM, pINNM)*

Kalii Propicillinum; Potassium α-Phenoxypropylpenicillin; Propicilina potásica; Propicilline Potassique; Propicillinum Kalicum; Калия Пропициллин.

A mixture of the D(+)- and L(-)-isomers of potassium (6*R*)-6-(2-phenoxybutyramido)penicillanate.

$C_{18}H_{21}KN_2O_5S$=416.5

CAS — 551-27-9 (propicillin); 1245-44-9 (propicillin potassium).
ATC — J01CE03.
ATC Vet — QJ01CE03.
UNII — 75RXW2P83Y.

Profile

Propicillin is a phenoxypenicillin with actions and uses similar to those of phenoxymethylpenicillin (p. 338.3). Propicillin potassium is given orally for the treatment of susceptible mild to moderate infections in a usual dose of 700 mg three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Baycillin†.

Protionamide (BAN, rINN)

Prothionamide; Protionamid; Protionamida; Protionamidi; Protionamidum; RP-9778; TH-1321; Протионамид.

2-Propylpyridine-4-carbothioamide.

$C_9H_{12}N_2S$=180.3

CAS — 14222-60-7.

ATC — J04AD01.

ATC Vet — QJ04AD01.

UNII — 76YOO33643.

Pharmacopoeias. In *Chin.*, *Int.*, and *Jpn.*

Uses and Administration

Protionamide is a thioamide derivative considered to be interchangeable with ethionamide (p. 297.3) and is used as a second-line drug in the treatment of multidrug-resistant tuberculosis (p. 210.2). It has also been used, as a substitute for clofazimine, in regimens for the treatment of leprosy (p. 188.3) but less toxic alternatives are now preferred. Complete cross-resistance occurs between the two drugs. In the treatment of resistant tuberculosis, adults may be given 15 to 20 mg/kg daily (maximum 1 g daily) orally; typically treatment in such patients is given in divided doses with meals, or as a single daily dose. It has also been given as rectal suppositories; protionamide hydrochloride has been given intravenously. Like ethionamide, it has generally been replaced by less toxic antimycobacterials.

References.

1. Anonymous. Prothionamide. *Tuberculosis (Edinb)* 2008; **88**: 139–40.

Adverse Effects, Precautions, and Antimicrobial Action

As for Ethionamide, p. 297.3.

Pharmacokinetics

Protionamide is readily absorbed from the gastrointestinal tract and produces peak plasma concentrations about 2 hours after an oral dose. It is widely distributed throughout body tissues and fluids, including the CSF. Protionamide is metabolised to the active sulfoxide and other inactive metabolites and less than 1% of a dose appears in the urine as unchanged drug.

References.

1. Lee HW, *et al.* Pharmacokinetics of prothionamide in patients with multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2009; **13**: 1161–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: ektebin†; Peteha; *Hong Kong*: Peteha; *India*: MDPride; Mycotuf P; Prothicid; *Rus.*: Peteha (Петеха); Pronicid (Проницид); *Turk.*: Promid†; Tionamid.

Multi-ingredient Preparations. *Austria*: Isoprodian†; *Rus.*: Combitub-Neo (Комбитуб-Нео); Protiocomb (Протиоком6); Protub-5 (Протуб-5).

Prulifloxacin (rINN)

NM-441; Prulifloxacine; Prulifloxacino; Prulifloxacinum; Прулифлоксацин.

(±)-7-{4-[(*Z*)-2,3-Dihydroxy-2-butenyl]-1-piperazinyl}-6-fluoro-1-methyl-4-oxo-1*H*,4*H*-[1,3]thiazeto[3,2-*a*]quinoline-3-carboxylic acid cyclic carbonate.

$C_{21}H_{20}FN_3O_6S$=461.5

CAS — 123447-62-1.

ATC — J01MA17.

ATC Vet — QJ01MA17.

UNII — J42298IESW.

Profile

Prulifloxacin is the prodrug of ulifloxacin (AF-3013; NM-394), a fluoroquinolone antibacterial. It is given for the treatment of susceptible infections in a usual oral dose of 600 mg daily.

Reviews.

1. Keam SJ, Perry CM. Prulifloxacin. *Drugs* 2004; **64**: 2221–34.
2. Prats G, *et al.* Prulifloxacin: a new antibacterial fluoroquinolone. *Expert Rev Anti Infect Ther* 2006; **4**: 27–41.
3. Blasi F, *et al.* Prulifloxacin: a brief review of its potential in the treatment of acute exacerbation of chronic bronchitis. *Int J Chron Obstruct Pulmon Dis* 2007; **2**: 27–31.
4. Giannarini G, *et al.* Prulifloxacin: clinical studies of a broad-spectrum quinolone agent. *Future Microbiol* 2009; **4**: 13–24.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Unidrox; *China*: Aifude (艾弗德); Jiaxin (加欣); Tian Zan (天赞); Xun Ao (迅奥); Yi Qi Di (易启迪); *Cz.*: Unidrox; *Gr.*: Chinoplus; Glimbax; Prixina; *Hung.*: Unidrox; *Ital.*: Chinoplus; Keraflox; Unidrox; *Pol.*: Chinoplus; Prixina; *Port.*: Keraflox; Oliflox; Unidrox; *Thai.*: Darflox.

Pyrazinamide (BAN, rINN)

Pirazinamid; Pirazinamida; Pirazinamidas; Pirazynamid; Pyratsiiniamidi; Pyrazinamid; Pyrazinamidum; Pyrazinoic Acid Amide; Пиразинамид.

Pyrazine-2-carboxamide.

$C_5H_5N_3O$=123.1

CAS — 98-96-4.

ATC — J04AK01.

ATC Vet — QJ04AK01.

UNII — 2KNI5N06TI.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Pyrazinamide). A white or almost white, crystalline powder. It shows polymorphism. Sparingly soluble in water, slightly soluble in alcohol and in dichloromethane.

USP 36: (Pyrazinamide). A white to practically white, odourless or practically odourless, crystalline powder. Soluble 1 in 67 of water, 1 in 175 of dehydrated alcohol, 1 in 135 of chloroform, 1 in 1000 of ether, and 1 in 72 of methyl alcohol; slightly soluble in alcohol.

Uses and Administration

Pyrazinamide is used as part of multidrug regimens for the treatment of tuberculosis (p. 210.2), mainly in the initial 8-week phase of short-course treatment. Pyrazinamide is usually given daily or 3 times weekly. In the UK, usual recommended oral doses for adults under 50 kg are 1.5 g daily, or 2 g three times weekly. The usual dose for those 50 kg or more is 2 g daily, or 2.5 g three times weekly. The recommended doses in the USA are 20 to 25 mg/kg daily (maximum 2 g) or 1.5 to 3 g three times weekly or 2 to 4 g twice weekly. WHO recommends 25 mg/kg daily or 35 mg/kg three times weekly.

For details of doses in children, see p. 347.2.

Pyrazinamide has also been used in the chemoprophylaxis of tuberculosis (see p. 347.3).

Fixed-dose combination products have been developed in order to improve patient compliance and avoid monotherapy; thereby decreasing the risk of acquired drug resistance. Combination products containing pyrazinamide with isoniazid, isoniazid and rifampicin, or isoniazid, rifampicin, and ethambutol are available in some countries.

References.

1. Anonymous. Pyrazinamide. *Tuberculosis (Edinb)* 2008; **88**: 141–4.

Administration in children. For the treatment of tuberculosis in infants, children, and adolescents the American Academy of Pediatrics[1] suggests an oral dose of pyrazinamide of 30 to 40 mg/kg daily or 50 mg/kg (to a maximum of 2 g) twice weekly, for the initial treatment phase. For children 1 month and older the *BNFC* suggests a dose of 35 mg/kg (to a maximum of 1.5 g in those under 50 kg and 2 g in those over 50 kg) once daily or 50 mg/kg (to a maximum of 2 g in those under 50 kg and 2.5 g in those over 50 kg) three times a week. WHO now recommends[2] 30 to 40 mg/kg once daily; in children weighing between 5 and 30 kg, specific guidance has been issued on achieving this using available fixed dose combination products. Heavier children are treated as adults (see Uses and Administration, above).

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*. 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.
2. WHO. Dosing instructions for the use of currently available fixed-dose combination TB medicines for children. Available at: http://www.who.int/entity/tb/challenges/interim_paediatric_fdc_dosing_instructions_sept09.pdf (accessed 19/01/11)

Administration in hepatic impairment. See Precautions, p. 348.2.

Administration in renal impairment. Oral pyrazinamide is mainly metabolised in the liver, but its metabolites are excreted in the urine, therefore the CDC[1] suggests that the dose may need to be reduced in patients with renal impairment; alternatively, WHO[2] recommends a dose of 25 mg/kg be given three times a week. The Joint Tuberculosis Committee of the British Thoracic Society[3] consider that standard dosage may be used in such patients. Dialysis affects the clearance of pyrazinamide and CDC recommends reducing the dose to 25 to 35 mg/kg three times a week after dialysis.

In a study[4] of 6 patients on haemodialysis, the average amount of pyrazinamide and its metabolites removed during a dialysis session was 926 mg after an oral dose of 1700 mg. It was recommended that the usual pyrazinamide dose be given to patients on dialysis as the risk of accumulation was negligible, and that the dose on dialysis days be given after the procedure.

1. American Thoracic Society, CDC, and the Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; **52** (RR-11): 1–77. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf (accessed 03/10/07) Correction. *ibid.* 2005; **53**: 1203. [dose]
2. WHO. *Treatment of tuberculosis: guidelines—4th edition*. Geneva: WHO, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf (accessed 06/12/10)
3. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; **53**: 536–48.[Although these guidelines were replaced by ones issued by NICE in 2006 the latter do not *"explain tuberculosis or its treatment in detail"* and therefore reference to the earlier guidelines has been retained] Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Tuberculosis/Guidelines/Chemotherapy.pdf (accessed 29/07/08)
4. Lacroix C, *et al.* Haemodialysis of pyrazinamide in uraemic patients. *Eur J Clin Pharmacol* 1989; **37**: 309–11.

Tuberculosis chemoprophylaxis. In the USA, the American Thoracic Society and the CDC recommended an oral dose of pyrazinamide 15 to 20 mg/kg daily (maximum 2 g daily) with rifampicin 600 mg daily as an alternative to isoniazid monotherapy for the treatment of latent tuberculosis infection.[1] (In those unable to take rifampicin, it was substituted with rifabutin 300 mg daily.) However, owing to reports of serious and fatal liver damage (see Effects on the Liver, under Adverse Effects, p. 347.3) the CDC and the American Thoracic Society now recommend that the combination of pyrazinamide with rifampicin should not be offered to persons with latent tuberculosis.[2]

1. American Thoracic Society. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000; **49**: 1–51. Also published in *Am J Respir Crit Care Med* 2000; **161**: S221–S247. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4906a1.htm (accessed 07/06/10)
2. CDC. Update: adverse event data and revised American Thoracic Society/CDC recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection—United States, 2003. *MMWR* 2003; **52**: 735–9. Also available at: http://www.cdc.gov/mmwr/PDF/wk/mm5231.pdf (accessed 05/10/07)

Adverse Effects and Treatment

Hepatotoxicity is the most serious adverse effect of pyrazinamide therapy and its frequency appears to be dose related. However, in currently recommended doses, when given with isoniazid and rifampicin, the incidence of hepatitis has been reported to be less than 3%. Patients may have a transient increase in liver enzyme values; more seriously hepatomegaly, splenomegaly, and jaundice may develop and on rare occasions death has occurred.

Hyperuricaemia commonly occurs and may lead to attacks of gout.

Other adverse effects are anorexia, nausea, vomiting, aggravation of peptic ulcer, arthralgia, malaise, fever, sideroblastic anaemia, thrombocytopenia, and dysuria. Photosensitivity, pellagra, and rashes have been reported on rare occasions.

Effects on the cardiovascular system. Acute hypertension was associated with pyrazinamide in a previously normotensive woman.[1]

1. Goldberg J, *et al.* Acute hypertension as an adverse effect of pyrazinamide. *JAMA* 1997; **277**: 1356.

Effects on the liver. Transient abnormalities in liver function are common during the early stages of antituberculous therapy with pyrazinamide and other first-line antituberculous drugs, but sometimes hepatotoxicity may be more serious and require a change of treatment. Drug-induced hepatitis usually occurs within the first few weeks of treatment and it may not be possible to identify which drug or drugs are responsible. Pyrazinamide and isoniazid are thought to have a greater potential for hepatotoxicity than rifampicin.[1]

The risk of hepatitis with antituberculous regimens containing pyrazinamide may be lower than suggested by early studies, in which large doses were used, often for long periods (the influence of dose on hepatotoxicity has, however, been questioned[2]). The incidence of hepatitis in studies[3] of short-course regimens containing pyrazinamide has ranged from 0.2% in Africa, to 0.6% in Hong Kong, to 2.8% in Singapore. These and later studies[4-6] have shown that hepatotoxicity is not increased when pyrazinamide is added to the *initial phase* of short-term chemotherapy containing rifampicin and isoniazid. Nevertheless, a report[7] of 4 cases of fulminant hepatic failure in patients given triple therapy with the potentially hepatotoxic drugs rifampicin, isoniazid, and pyrazinamide (1 patient also received ethambutol) highlighted the importance of strict liver function monitoring and this was reinforced by others. The addition of pyrazinamide to a *continuation-phase* regimen of isoniazid and/or rifampicin was found to considerably increase the risk of hepatotoxicity; after 12 weeks or more of treatment, the estimated risk of hepatotoxicity was 2.6% for regimens with pyrazinamide plus isoniazid and/or rifampicin compared with 0.8% for isoniazid plus rifampicin.[8]

The incidence of severe hepatotoxicity was found to be lower in patients receiving isoniazid, rifampicin, and pyrazinamide for initial treatment of active disease, than in those receiving rifampicin and pyrazinamide for 2 months for latent tuberculosis infection. For further information on hepatotoxicity caused by rifampicin and pyrazinamide for the management of latent tuberculosis infection see Effects on the Liver, under Rifampicin, p. 354.1.

The Joint Tuberculosis Committee of the British Thoracic Society has produced recommendations[9] for initial measurement of liver function in all patients and regular **monitoring** in patients with pre-existing liver disease, as well as the response to deteriorating liver function; prompt re-introduction of appropriate antituberculosis therapy is recommended once normal liver function is restored. Similar guidelines have been produced for the USA.[10,11] For further information on hepatotoxicity caused by antituberculous drugs see Effects on the Liver, under Isoniazid, p. 312.1.

1. Yew WW, Leung CC. Antituberculosis drugs and hepatotoxicity. *Respirology* 2006; 11: 699–707.
2. Pasipanodya JG, Gumbo T. Clinical and toxicodynamic evidence that high-dose pyrazinamide is not more hepatotoxic than the low doses currently used. *Antimicrob Agents Chemother* 2010; 54: 2847–54.
3. Girling DJ. The role of pyrazinamide in primary chemotherapy for pulmonary tuberculosis. *Tubercle* 1984; 65: 1–4.
4. Parthasarathy R, *et al.* Hepatic toxicity in South Indian patients during treatment of tuberculosis with short-course regimens containing isoniazid, rifampicin and pyrazinamide. *Tubercle* 1986; 67: 99–108.
5. Combs DL, *et al.* USPHS tuberculosis short-course chemotherapy trial 21: effectiveness, toxicity, and acceptability: the report of final results. *Ann Intern Med* 1990; 112: 397–406.
6. le Bourgeois M, *et al.* Good tolerance of pyrazinamide in children with pulmonary tuberculosis. *Arch Dis Child* 1989; 64: 177–8.
7. Mitchell I, *et al.* Anti-tuberculous therapy and acute liver failure. *Lancet* 1995; 345: 555–6.
8. Chang KC, *et al.* Hepatotoxicity of pyrazinamide: cohort and case-control analyses. *Am J Respir Crit Care Med* 2008; 177: 1391–6.
9. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; 53: 536–48.[Although these guidelines were replaced by ones issued by NICE in 2006 the latter do not *"explain tuberculosis or its treatment in detail"* and therefore reference to the earlier guidelines has been retained] Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Tuberculosis/Guidelines/Chemotherapy.pdf (accessed 29/07/08)
10. American Thoracic Society, CDC, and the Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; 52 (RR-11): 1–77. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf (accessed 03/10/07) Correction. *ibid.* 2005; 53: 1203. [dose]
11. Saukkonen JJ, *et al.* American Thoracic Society. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med* 2006; 174: 935–52. Also available at: http://www.thoracic.org/statements/resources/mtpi/hepatotoxicity-of-antituberculosis-therapy.pdf (accessed 16/07/10)

Effects on the nervous system. Convulsions that developed in a 2-year-old child receiving antituberculous therapy appeared to be due to pyrazinamide, given in a dose of 250 mg daily.[1]

1. Herlevsen P, *et al.* Convulsions after treatment with pyrazinamide. *Tubercle* 1987; 68: 145–6.

Hyperuricaemia. Hyperuricaemia in patients taking pyrazinamide may be due to pyrazinoic acid, the main metabolite of pyrazinamide, inhibiting uric acid excretion.[1]

In a large multicentre study,[2] the incidence of elevated serum concentrations of uric acid for patients taking rifampicin, isoniazid, and pyrazinamide was 52.2% at 8 weeks while the incidence for patients given rifampicin and isoniazid was 5.4%. Arthralgia was reported in 6 of 617 patients taking rifampicin, isoniazid, and pyrazinamide, but in none of 445 patients given rifampicin and isoniazid.

Slight increases in plasma concentrations of uric acid occurred in 9 of 43 children after one month's treatment with rifampicin, isoniazid, ethambutol, and pyrazinamide. Arthralgias and gout did not occur. Uric acid concentrations were normal on completion of treatment with pyrazinamide.[3] Some studies[4] have suggested a relationship between elevated serum uric acid levels and arthralgia, but this has not been confirmed.[5]

1. Ellard GA, Haslam RM. Observations on the reduction of the renal elimination of urate in man caused by the administration of pyrazinamide. *Tubercle* 1976; 57: 97–103.
2. Combs DL, *et al.* USPHS tuberculosis short-course chemotherapy trial 21: effectiveness, toxicity, and acceptability: the report of final results. *Ann Intern Med* 1990; 112: 397–406.
3. le Bourgeois M, *et al.* Good tolerance of pyrazinamide in children with pulmonary tuberculosis. *Arch Dis Child* 1989; 64: 177–8.
4. Hong Kong Tuberculosis Treatment Services/British MRC. Adverse reactions to short-course regimens containing streptomycin, isoniazid, pyrazinamide and rifampicin in Hong Kong. *Tubercle* 1976; 57: 81–95.
5. Jenner PJ, *et al.* Serum uric acid concentrations and arthralgia among patients treated with pyrazinamide-containing regimens in Hong Kong and Singapore. *Tubercle* 1981; 62: 175–9.

Pellagra. Pellagra, probably due to pyrazinamide, developed in a 26-year-old woman receiving antituberculous therapy.[1] Symptoms regressed, despite continued therapy, on giving nicotinamide.

1. Jørgensen J. Pellagra probably due to pyrazinamide: development during combined chemotherapy of tuberculosis. *Int J Dermatol* 1983; 22: 44–5.

Precautions

Pyrazinamide should be used with caution in patients with liver disorders and is contra-indicated in established chronic or severe liver disease. In patients with liver disorders, liver function should be assessed before and regularly during treatment. The British Thoracic Society has recommended that pyrazinamide treatment should be suspended if serum aminotransferase concentrations are elevated to 5 times the normal upper limit or if the bilirubin concentration rises. They allow cautious sequential re-introduction of antimycobacterial drugs once liver function has returned to normal: first isoniazid, then rifampicin, and then pyrazinamide. WHO recommends that pyrazinamide not be reintroduced if the hepatitis produced a clinical jaundice.

Pyrazinamide should not be given to patients with acute gout or hyperuricaemia and should be used with caution in patients with a history of gout. Caution should also be observed in patients with renal impairment. Increased difficulty has been reported in controlling diabetes mellitus when diabetics are given pyrazinamide.

Porphyria. Pyrazinamide has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Pregnancy. Although detailed teratogenicity data are not available, WHO,[1] the IUATLD,[2] the British Thoracic Society,[3] and the CDC[4] do not contra-indicate pyrazinamide in pregnant patients.

1. WHO. *Treatment of tuberculosis: guidelines—4th edition.* Geneva: WHO, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf (accessed 08/06/10)
2. Caminero Luna JA. *A tuberculosis guide for specialist physicians.* Paris: International Union Against Tuberculosis and Lung Disease (IUATLD). 2004. Available at: http://www.tbrieder.org/publications/specialists_en.pdf (accessed 03/10/07)
3. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; 53: 536–48.[Although these guidelines were replaced by ones issued by NICE in 2006 the latter do not *"explain tuberculosis or its treatment in detail"* and therefore reference to the earlier guidelines has been retained] Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Tuberculosis/Guidelines/Chemotherapy.pdf (accessed 29/07/08)
4. American Thoracic Society, CDC, and the Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; 52 (RR-11): 1–77. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf (accessed 03/10/07) Correction. *ibid.* 2005; 53: 1203. [dose]

Interactions

Antigout drugs. The complex interactions occurring when pyrazinamide and *probenecid* are given to patients with gout have been studied.[1] Urinary excretion of urate depends on the relative size and timing of doses of the two drugs. Probenecid is known to block the excretion of pyrazinamide. A pharmacokinetic study[2] in 6 healthy subjects found that *allopurinol*, a xanthine oxidase inhibitor, increases concentrations of pyrazinoic acid (the main metabolite of pyrazinamide) thereby worsening pyrazinamide-induced hyperuricaemia. Allopurinol would therefore also appear to be unsuitable for treating pyrazinamide-induced hyperuricaemia.

1. Yü TF, *et al.* The effect of the interaction of pyrazinamide and probenecid on urinary uric acid excretion in man. *Am J Med* 1977; 63: 723–8.
2. Lacroix C, *et al.* Interaction between allopurinol and pyrazinamide. *Eur Respir J* 1988; 1: 807–11.

Antiretrovirals. Concentrations of pyrazinamide were low or undetectable in 4 patients also taking *zidovudine*.[1] In the same study, 6 of 7 patients with HIV infection taking pyrazinamide without zidovudine had normal serum pyrazinamide concentrations.

1. Peloquin CA, *et al.* Low antituberculosis drug concentrations in patients with AIDS. *Ann Pharmacother* 1996; 30: 919–25.

Antimicrobial Action

Pyrazinamide has a bactericidal effect on *Mycobacterium tuberculosis* but appears to have no activity against other mycobacteria or micro-organisms *in vitro*. It is almost completely inactive at a neutral pH, but is effective against persisting tubercle bacilli within the acidic intracellular environment of the macrophages. The initial inflammatory response to chemotherapy increases the number of organisms in the acidic environment. As inflammation subsides and pH increases, the sterilising activity of pyrazinamide decreases. This pH-dependent activity explains the clinical efficacy of pyrazinamide as part of the initial 8-week phase in short-course treatment regimens.

Resistance to pyrazinamide rapidly develops when it is used alone.

Action. Although the antimicrobial activity of pyrazinamide has been recognised since the 1950s, the mode of action is still unclear. One proposal is that pyrazinoic acid is the active moiety. Pyrazinamidase produced by the tubercle bacilli is known to convert pyrazinamide to pyrazinoic acid. A further proposal[1] is that the pyrazinoic acid formed within the macrophage would be trapped, thereby lowering intracellular pH to levels toxic to tubercle bacilli.

A review[2] has suggested that pyrazinoic acid depends on pH-based passive diffusion to enter the mycobacterial cell whereas its removal from the cell via an efflux pump requires energy; under conditions of dormancy, when bacterial metabolism decreases, pyrazinoic acid tends to accumulate in the bacterium, accounting for the value of pyrazinamide in preferentially killing dormant organisms and thus its role in combination therapy. Because relatively small changes in local pH could affect this accumulation, it was hypothesised that adjunctive inhalation of pyrazinoic acid might greatly enhance the efficacy of oral pyrazinamide therapy.

1. Salfinger M, *et al.* Pyrazinamide and pyrazinoic acid activity against tubercle bacilli in cultured human macrophages and in the BACTEC system. *J Infect Dis* 1990; 162: 201–7.
2. Mitchison DA, Pourie PB. The near future: improving the activity of rifamycins and pyrazinamide. *Tuberculosis (Edinb)* 2010; 90: 177–81.

Activity with other antimicrobials. Synergistic activity against *Mycobacterium tuberculosis* has been reported with pyrazinamide and clarithromycin.[1]

1. Mor N, Esfandiari A. Synergistic activities of clarithromycin and pyrazinamide against Mycobacterium tuberculosis in human macrophages. *Antimicrob Agents Chemother* 1997; 41: 2035–6.

Pharmacokinetics

Pyrazinamide is readily absorbed from the gastrointestinal tract. Peak serum concentrations occur about 2 hours after an oral dose and have been reported to be about 33 micrograms/mL after 1.5 g, and 59 micrograms/mL after 3 g. Pyrazinamide is widely distributed in body fluids and tissues and diffuses into the CSF. The half-life has been reported to be about 9 to 10 hours. It is metabolised mainly in the liver by hydrolysis to the major active metabolite pyrazinoic acid, which is subsequently hydroxylated to the major excretory product 5-hydroxypyrazinoic acid. It is excreted via the kidneys mainly by glomerular filtration. About 70% of a dose appears in the urine within 24 hours mainly as metabolites and about 4% as unchanged drug. Pyrazinamide is removed by dialysis. Pyrazinamide is distributed into breast milk.

A short distribution phase and an elimination phase of 9.6 hours in healthy subjects after a single oral dose of pyrazinamide 27 mg/kg has been reported;[1] the half-life for the major metabolite pyrazinoic acid was 11.8 hours.

In the major metabolic pathway, pyrazinamide was deaminated to pyrazinoic acid which was hydroxylated to hydroxypyrazinoic acid; in the minor pathway, pyrazinamide was hydroxylated to hydroxypyrazinamide which was then deaminated to hydroxypyrazinoic acid. The limiting step was deamination; oxidation by xanthine oxidase occurred very quickly.

1. Lacroix C, *et al.* Pharmacokinetics of pyrazinamide and its metabolites in healthy subjects. *Eur J Clin Pharmacol* 1989; 36: 395–400.

Bioavailability. The oral bioavailability of rifampicin and isoniazid, but not of pyrazinamide, was decreased by food in a study.[1] However, another report[2] showed slightly reduced peak serum concentrations when pyrazinamide was given with a high-fat meal, and the authors suggested that pyrazinamide should preferably be given on an empty stomach.

1. Zent C, Smith P. Study of the effect of concomitant food on the bioavailability of rifampicin, isoniazid and pyrazinamide. *Tubercle Lung Dis* 1995; 76: 109–13.
2. Peloquin CA, *et al.* Pharmacokinetics of pyrazinamide under fasting conditions, with food, and with antacids. *Pharmacotherapy* 1998; 18: 1205–11.

Breast feeding. The peak concentration of pyrazinamide in breast milk of a 29-year-old woman was 1.5 micrograms/mL 3 hours after a 1-g dose.[1] The peak plasma concentration was 42 micrograms/mL after 2 hours.

1. Holdiness MR. Antituberculosis drugs and breast-feeding. *Arch Intern Med* 1984; 144: 1888.

Distribution. Pyrazinamide was given to 28 patients with suspected tuberculous meningitis in doses of 34 to 41 mg/kg. The mean concentration of pyrazinamide in the CSF after 2 hours was 38.6 micrograms/mL and represented about 75% of that in serum; concentrations at 5 and 8 hours were 44.5 and 31.0 micrograms/mL respectively and were about 10% higher than those in serum.[1] The use of corticosteroids appeared to have no influence on penetration of pyrazinamide into the CSF of patients with tuberculous meningitis.[2]

1. Ellard GA, *et al.* Penetration of pyrazinamide into the cerebrospinal fluid in tuberculous meningitis. *BMJ* 1987; 294: 284–5.
2. Woo J, *et al.* Cerebrospinal fluid and serum levels of pyrazinamide and rifampicin in patients with tuberculous meningitis. *Curr Ther Res* 1987; 42: 235–42.

Hepatic impairment. A study[1] of the pharmacokinetics of pyrazinamide was carried out in 10 patients with cirrhosis of the liver. After a dose of about 19.3 mg/kg, the elimina-

tion phase was about 15 hours for pyrazinamide and 24 hours for the major metabolite pyrazinoic acid.

1. Lacroix C, *et al.* Pharmacokinetics of pyrazinamide and its metabolites in patients with hepatic cirrhotic insufficiency. *Arzneimittelforschung* 1990; 40: 76–9.

HIV-infected patients. Malabsorption of pyrazinamide and other antituberculous drugs may occur in patients with HIV infection and tuberculosis, and may contribute to acquired drug resistance and reduced efficacy of tuberculosis treatment. For further information on the absorption of antituberculous drugs in HIV-infected patients see Pharmacokinetics, under Rifampicin, p. 356.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Zinamide†; ***Austria***: Pyrafat; ***Belg.***: Tebrazid; ***Braz.***: Pirazinon†; ***Canad.***: Tebrazid; ***Fin.***: Tisamid; ***Fr.***: Pirilene; ***Ger.***: Pyrafat; ***Hong Kong***: Pyrafat; ***India***: Actizid; Antizide; Copyrazin; Eumide; Isomide; Macrozide; Montozin; P-Zide; Parazid; Pyzina; PZA-Ciba; Rifacom-EZ; ***Indon.***: Corsazinamid; Neotibi; Pezeta-Ciba; Prazina; Sanazet; Siramid; TB ZET; ***Ital.***: Piraldina; ***Malaysia***: PZA; ***Mex.***: Nizamyl; ***NZ***: Zinamide†; ***Philipp.***: Midazen; Pyramin; Pyrasol†; Pyrazin; PZA-Ciba; Zapedia†; Zcure; Zinaplex; Zinaprim; ***Port.***: Pramide; ***Rus.***: Lynamid (Линамид); Macrozide (Макрозид); Pyrafat (Пирафат); Pyzina (Пизина); ***S.Afr.***: Pyrazide; ***Singapore***: PZA; ***Thai.***: Myrin-P†; Pyramide; PZA†; TZM†; ***Turk.***: Pirazinid; ***UK***: Zinamide.

Multi-ingredient Preparations. ***Austria***: Rifater; ***Canad.***: Rifater; ***China***: Chang Wei Rui Da Xin (长威瑞达欣); Dai Fei Lin (戴菲林); Fei Ning (费宁); Fei Su (菲苏); Hu Fei Te (护菲特); Ke Lao Er Kang (克劳尔康); Pi Lv (匹律); Rui Fu An Kang (瑞福安康); Rui Qing (瑞清); Wei Bao (维葆); Yi Bi Fu (依比福); Yi Nuo Ni Kang (怡诺尼康); Yi Ti Bi (伊提碧); ***Denm.***: Rimcure; Rimstar; ***Fin.***: Rimstar; ***Fr.***: Rifater; ***Ger.***: Rifater†; tebesium Trio; ***Gr.***: Rifater; ***Hong Kong***: Rifater; ***India***: AFB4; Akt-4; Akt-FD; Akurit-4; Akurit-Z; Becox Forte Kit; Binex Z; Binex ZE; Cavirip; Caviter FD; Caviter; Coxina-4; Coxter-3; Coxter-4; Cx-5; Emrif Kit; Eufacin Plus; Eufazid; Faminex Forte; Forecox; Gocox-3; Infez-4; Macox-ZH; Monto-4; Montorip; Mycocox-4; Mycocox-Z; Mycodot-4; Mycodot-Z; Mycurit-4; Mycurit-Z; R-Cinex Z; RHZ Plus; RHZ; Rimactazid + Z; Tricox; Wokex-4; Xeed 4; ***Indon.***: Rimcure; Rimstar; ***Irl.***: Rifater; Rimcure†; Rimstar; ***Ital.***: Rifater; Rimcure; Rimstar; ***Malaysia***: Rimcure; ***Mex.***: Arpisen†; Dotbal; Finateramida†; Rifater; ***Neth.***: Rimcure†; Rimstar†; ***Norw.***: Rimcure; Rimstar; ***Philipp.***: 4D; AKurIT-4; CombiKids†; CombiPack; Econofix; Econokit-MDR; Econokit; Econopack; Fixcom 4; HRZ Pedia Kit; Kidz Kit 3; Myrin-P; Quadmax; Quadtab; Refam Pedia Kit†; Rifater; Rimcure; Rimstar; SVM-Polypac-A†; Triofix; Viper†; ***Port.***: Rifater; ***Rus.***: Combitub (Комбитуб); Combitub-Neo (Комбитуб-Нео); Forecox (Форкокс); Isocomb (Изокомб); Laslonvita (Ласловита); Lomecomb (Ломекомб); Phthizopiram (Фтизопирам); Protiocomb (Протиокомб); Protub-3 (Протуб-3); Protub-4 (Протуб-4); Protub-5 (Протуб-5); Protub-Lome (Протуб-Ломе); Protubpira (Протубпира); Protubvita (Протубвита); Repin B_4 (Репин B_4); Rifacomb Plus (Рифакомб Плюс)†; Rimecure 3-FDC (Римкур 3-ФДС)†; Rimstar 4-FDC (Римстар 4-ФДС)†; ***S.Afr.***: Rifafour; Rifater†; Rimcure; Rimstar; ***Singapore***: Merip; ***Spain***: Rifater; Rimcure†; Rimstar; ***Swed.***: Rimcure; Rimstar; ***Switz.***: Rifater; Rimstar; ***Thai.***: Rifafour; Rifampyzid; Rifater; Rimcure 3-FDC; Rimstar†; ***UK***: Rifater; Rimstar; Voractiv; ***USA***: Rifater; ***Venez.***: Rimcure.

Pharmacopoeial Preparations

BP 2014: Pyrazinamide Oral Suspension; Pyrazinamide Tablets; **USP 36:** Pyrazinamide Oral Suspension; Pyrazinamide Tablets; Rifampin, Isoniazid, and Pyrazinamide Tablets; Rifampin, Isoniazid, Pyrazinamide, and Ethambutol Hydrochloride Tablets.

Quinupristin/Dalfopristin

Dalfopristin (rINN); Dalfopristin (USAN); Dalfopristin (BAN); Kinupristiini/dalfopristiini; Kinupristin/dalfopristin; Quinupristin (BAN); Quinupristin (rINN); Quinupristin (USAN); Quinupristina/dalfopristina; Quinupristine/dalfopristine; Quinupristinum/Dalfopristinum; RP-59500; Хинупристин/Дальфопристин.

CAS — 126602-89-9 (quinupristin/dalfopristin); 176861-85-1 (quinupristin/dalfopristin).
ATC — J01FG02.
ATC Vet — QJ01FG02.
UNII — R9M4FJE48E (dalfopristin); 23OW28RS7P (quinupristin).

Dalfopristin Mesilate *(BANM, rINNM)*

Dalfopristin Mesylate; Dalfopristina, mesilato de; Dalfopristine, Mésilate de; Dalfopristini Mesilas; Mesilato de dalfopristina; RP-54476 (dalfopristin); Дальфопристина Мезилат.

(3*R*,4*R*,5*E*,10*E*,12*E*,14*S*,26*R*,26a*S*)-26-[[2-(Diethylamino)ethyl]sulfonyl]-8,9,14,15,24,25,26,26a-octahydro-14-hydroxy-3-isopropyl-4,12-dimethyl-3*H*-21,18-nitrilo-1*H*,22*H*-pyrrolo[2,1-*c*][1,8,4,19]dioxadiazacyclotetracosine-1,7,16,22(4*H*,17*H*)-tetrone methanesulphonate; (26*R*,27*S*)-26-[[2-(Diethylamino)-ethyl]sulfonyl]-26,27-dihydrovirginiamycin M_1 methanesulphonate.

$C_{34}H_{50}N_4O_9S,CH_4O_3S$=787.0
CAS — 112362-50-2 (dalfopristin).
UNII — R9M4FJE48E (dalfopristin).

Quinupristin Mesilate *(BANM, rINNM)*

Mesilato de quinupristina; Quinupristin Mesylate; Quinupristina, mesilato de; Quinupristine, Mésilate de; Quinupristini Mesilas; RP-57669 (quinupristin); Хинупристина Мезилат.

N-[(6*R*,9*S*,10*R*,13*S*,15a*S*,18*R*,22*S*,24a*S*)-22-[*p*-(Dimethylamino)benzyl]-6-ethyldocosahydro-10,23-dimethyl-5,8,12,15,17,21,24-heptaoxo-13-phenyl-18-[[(3*S*)-3-quinuclidinylthio]methyl]-1*H*-pyrido[2,1-*f*]pyrrolo[2,1-*f*][1,4,7,10,13,16]-oxapentaazacyclononadecin-9-yl]-3-hydroxypicolinamide methanesulphonate; 4-[4-(Dimethylamino)-*N*-methyl-L-phenylalamine]-5-(*cis*-5-[[(*S*)-1-azabicyclo[2.2.2]oct-3-ylthio]methyl]-4-oxo-L-2-piperidinecarboxylic acid)-virginiamycin S_1 methanesulphonate.

$C_{53}H_{67}N_9O_{10}S,CH_4O_3S$=1118.3
CAS — 120138-50-3 (quinupristin).
UNII — 23OW28RS7P (quinupristin).

Uses and Administration

Quinupristin/dalfopristin is a streptogramin antibacterial related to pristinamycin. Quinupristin and dalfopristin are semisynthetic derivatives of pristinamycin I and pristinamycin IIA respectively, and are used in the ratio 3:7. Quinupristin/dalfopristin is active against a range of Gram-positive and some Gram-negative organisms, but it is reserved for the treatment of serious infections with multidrug-resistant Gram-positive bacteria, specifically MRSA and vancomycin-resistant *Enterococcus faecium*.

Quinupristin/dalfopristin is given as the mesilate salts by intravenous infusion, in glucose 5% over 60 minutes, in a dose of 7.5 mg/kg (equivalent to quinupristin 2.25 mg/kg and dalfopristin 5.25 mg/kg) every 8 or 12 hours for at least 7 days. To minimise venous irritation, the vein should be flushed with glucose 5% after each infusion; alternatively, the infusion may be given through a central venous catheter. The injection should not be diluted with saline solutions since it is incompatible with sodium chloride.

Doses may need to be reduced in patients with hepatic impairment (see p. 349.2).

References.

1. Bayston R, *et al.* , eds. Quinupristin/dalfopristin—update on the first injectable streptogramin. *J Antimicrob Chemother* 1997; 39 (suppl A): 1–151.
2. Wood MJ (ed). Quinupristin/dalfopristin–a novel approach for the treatment of serious Gram-positive infections. *J Antimicrob Chemother* 1999; 44 (suppl A): 1–46.
3. Lamb HM, *et al.* Quinupristin/dalfopristin: a review of its use in the management of serious Gram-positive infections. *Drugs* 1999; 58: 1061–97.
4. Drew RH, *et al.* Treatment of methicillin-resistant Staphylococcus aureus infections with quinupristin-dalfopristin in patients intolerant of or failing prior therapy: for the Synercid Emergency-Use Study Group. *J Antimicrob Chemother* 2000; 46: 775–84.
5. Allington DR, Rivey MP. Quinupristin/dalfopristin: a therapeutic review. *Clin Ther* 2001; 23: 24–44.
6. Linden PK, *et al.* Treatment of vancomycin-resistant Enterococcus faecium infections with quinupristin/dalfopristin. *Clin Infect Dis* 2001; 33: 1816–23.
7. Goff DA, Sierawski SJ. Clinical experience of quinupristin-dalfopristin for the treatment of antimicrobial-resistant gram-positive infections. *Pharmacotherapy* 2002; 748–58.
8. Eliopoulos GM. Quinupristin-dalfopristin and linezolid: evidence and opinion. *Clin Infect Dis* 2003; 36: 473–81.
9. Brown J, Freeman BB. Combining quinupristin/dalfopristin with other agents for resistant infections. *Ann Pharmacother* 2004; 38: 677–85.
10. Manfredi R. A re-emerging class of antimicrobial agents: streptogramins (quinupristin/dalfopristin) in the management of multiresistant gram-positive nosocomial cocci in hospital setting. *Mini Rev Med Chem* 2005; 5: 1075–81.

Administration in hepatic impairment. Licensed product information states that in clinical studies of quinupristin/dalfopristin the incidence of adverse effects in patients with chronic liver impairment or cirrhosis was similar to that in patients with normal liver function. However, pharmacokinetic studies have shown that systemic exposure to quinupristin/dalfopristin and their metabolites may be increased in those with hepatic impairment. In some countries it has therefore been recommended that quinupristin/dalfopristin should be avoided in patients with severe hepatic impairment, and that for those with moderate impairment a dose reduction to 5 mg/kg intravenously (equivalent to quinupristin 1.5 mg/kg and dalfopristin 3.5 mg/kg) should be considered if 7.5 mg/kg is not tolerated.

Adverse Effects and Treatment

The adverse effects most frequently reported in patients receiving quinupristin/dalfopristin include nausea and vomiting, diarrhoea, skin rash, pruritus, headache, and pain. Myalgia and arthralgia have occurred and may be severe; symptoms may be improved by decreasing the dose frequency. Eosinophilia, anaemia, leucopenia, and neutropenia are also common. Individual cases of severe thrombocytopenia and pancytopenia have been reported. Pseudomembranous colitis has also been reported.

Hyperbilirubinaemia and raised liver enzyme values may occur.

Pain and inflammation at the injection site is common, and thrombophlebitis has occurred.

Quinupristin/dalfopristin is not removed by peritoneal dialysis, and removal by haemodialysis is considered unlikely.

Effects on the musculoskeletal system. References.

1. Olsen KM, *et al.* Arthralgias and myalgias related to quinupristin-dalfopristin administration. Abstract: *Clin Infect Dis* 2001; 32: 674. Full version: http://www.journals.uchicago.edu/doi/pdf/10.1086/318702 (accessed 12/08/08)
2. Carver PL, *et al.* Risk factors for arthralgias or myalgias associated with quinupristin-dalfopristin therapy. *Pharmacotherapy* 2003; 23: 159–64.
3. Raad I, *et al.* Relationship between myalgias/arthralgias occurring in patients receiving quinupristin/dalfopristin and biliary dysfunction. *J Antimicrob Chemother* 2004; 53: 1105–8.
4. Gupte G, *et al.* Quinupristin-dalfopristin use in children is associated with arthralgias and myalgias. *Pediatr Infect Dis J* 2006; 25: 281.

Precautions

Quinupristin/dalfopristin should be used with caution in patients with hepatic impairment and avoided in severe impairment, as elevated plasma concentrations of quinupristin and dalfopristin and their metabolites have been found in patients with hepatic dysfunction, and elevated concentrations of quinupristin metabolites have occurred in patients with hyperbilirubinaemia. The combination is contra-indicated in patients who have plasma-bilirubin concentrations greater than 3 times the normal upper limit.

Prolongation of the QT interval has been seen in *animals* given quinupristin/dalfopristin; therefore caution is advised in patients at risk of cardiac arrhythmias.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies quinupristin/dalfopristin as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

Quinupristin/dalfopristin inhibits the cytochrome P450 isoenzyme CYP3A4 and it may therefore inhibit the metabolism of several drugs. In particular, there is a theoretical possibility of serious ventricular arrhythmias when given with drugs that prolong the QT interval, such as astemizole, cisapride, and terfenadine. Quinupristin/dalfopristin has been shown to increase plasma concentrations of ciclosporin, midazolam, nifedipine, and tacrolimus. The use of ergot alkaloids with quinupristin/dalfopristin should be avoided.

Antimicrobial Action

Quinupristin/dalfopristin is a semisynthetic streptogramin antibacterial. Quinupristin and dalfopristin each have bacteriostatic activity and in combination usually act synergistically to produce bactericidal activity. The streptogramins act on the ribosome to block protein synthesis.

Quinupristin/dalfopristin is active against a range of Gram-positive bacteria including meticillin- and multidrug-resistant strains of *Staphylococcus aureus* and *S. epidermidis*, vancomycin-resistant *Enterococcus faecium* (but not *E. faecalis*), and penicillin- and macrolide-resistant *Streptococcus pneumoniae*. It is also active against the anaerobe *Clostridium perfringens*, and Gram-negative bacteria *Legionella pneumophila*, *Moraxella catarrhalis* (*Branhamella catarrhalis*), *Mycoplasma pneumoniae*, and *Neisseria meningitidis*.

References.

1. Schouten MA, Hoogkamp-Korstanje JAA. Comparative in-vitro activities of quinupristin-dalfopristin against Gram-positive bloodstream isolates. *J Antimicrob Chemother* 1997; 40: 213–19.
2. Pankuch GA, *et al.* Postantibiotic effect and postantibiotic sub-MIC effect of quinupristin-dalfopristin against Gram-positive and negative organisms. *Antimicrob Agents Chemother* 1998; 42: 3028–31.
3. Johnson AP, *et al.* Susceptibility to quinupristin/dalfopristin and other antibiotics of vancomycin-resistant enterococci from the UK, 1997 to mid-1999. *J Antimicrob Chemother* 2000; 46: 125–8.
4. Ling TK, *et al.* In vitro activity and post-antibiotic effect of quinupristin/dalfopristin (Synercid). *Chemotherapy* 2001; 47: 243–9.
5. Eliopoulos GM, Wennersten CB. Antimicrobial activity of quinupristin-dalfopristin combined with other antibiotics against vancomycin-resistant enterococci. *Antimicrob Agents Chemother* 2002; 46: 1319–24.
6. Hancock RE. Mechanisms of action of newer antibiotics for Gram-positive pathogens. *Lancet Infect Dis* 2005; 5: 209–18.

Resistance. Although uncommon, isolated reports of *E. faecium* resistant to quinupristin/dalfopristin have

emerged,[1-8] and have included a link to the use of the streptogramin virginiamycin as an animal food additive.[3,4]

1. Eliopoulos GM, *et al.* Characterization of vancomycin-resistant Enterococcus faecium isolates from the United States and their susceptibility in vitro to dalfopristin-quinupristin. *Antimicrob Agents Chemother* 1998; **42**: 1088–92.
2. Bozdogan B, *et al.* Plasmid-mediated coresistance to streptogramins and vancomycin in Enterococcus faecium HM1032. *Antimicrob Agents Chemother* 1999; **43**: 2097–8.
3. Werner G, *et al.* Association between quinupristin/dalfopristin resistance in glycopeptide-resistant Enterococcus faecium and the use of additives in animal feed. *Eur J Clin Microbiol Infect Dis* 1998; **17**: 401–2.
4. Hershberger E, *et al.* Quinupristin-dalfopristin resistance in gram-positive bacteria: mechanism of resistance and epidemiology. *Clin Infect Dis* 2004; **38**: 92–8.
5. Oh WS, *et al.* High rate of resistance to quinupristin-dalfopristin in Enterococcus faecium clinical isolates from Korea. *Antimicrob Agents Chemother* 2005; **49**: 5176–8.
6. Donabedian SM, *et al.* Quinupristin-dalfopristin resistance in Enterococcus faecium isolates from humans, farm animals, and grocery store meat in the United States. *J Clin Microbiol* 2006; **44**: 3361–5.
7. Karanika M, *et al.* Reduced susceptibility to quinupristin/dalfopristin in Enterococcus faecium in Greece without prior exposure to the agent. *Int J Antimicrob Agents* 2008; **31**: 55–7.
8. Chong YP, *et al.* Quinupristin-dalfopristin versus linezolid for the treatment of vancomycin-resistant Enterococcus faecium bacteraemia: efficacy and development of resistance. *Scand J Infect Dis* 2010; **42**: 491–9.

Pharmacokinetics

After parenteral doses, quinupristin and dalfopristin are rapidly metabolised. At steady state, the half-life of quinupristin and its metabolites is about 3 hours and that of dalfopristin and its metabolites about 1 hour. Elimination half-lives of unchanged quinupristin and dalfopristin are 0.9 and 0.75 hours, respectively. Protein binding ranges from 55 to 78% for quinupristin and 11 to 26% for dalfopristin. The main route of excretion is biliary, with 75 to 77% of a dose detectable in the faeces. Urinary excretion accounts for 15% of the quinupristin and 19% of the dalfopristin dose. Negligible amounts are removed by peritoneal dialysis and probably also by haemodialysis.

Distribution into milk has been found in studies in *rats*.

References.

1. Bearden DT. Clinical pharmacokinetics of quinupristin/dalfopristin. *Clin Pharmacokinet* 2004; **43**: 239–52.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Synercid†; *Braz.*: Synercid; *Cz.*: Synercid†; *Fr.*: Synercid†; *Gr.*: Synercid; *Hung.*: Synercid†; *Irl.*: Synercid†; *Ital.*: Synercid; *Neth.*: Synercid; *NZ*: Synercid; *Pol.*: Synercid†; *Port.*: Synercid†; *UK*: Synercid; *USA*: Synercid.

Ramoplanin *(USAN, rINN)*

A-16686; MDL-62198; Ramoplanina; Ramoplanine; Ramoplaninum; Рамопланин.

CAS — 76168-82-6.
UNII — 0WX9996O2G.

Profile

Ramoplanin is a lipoglycodepsipeptide antibacterial with a spectrum of activity *in vitro* similar to that of vancomycin (p. 389.1) but considerably more potent. It is also active against *Bacteroides* spp. It is under investigation, notably for the treatment of *Clostridium difficile*-associated diarrhoea. It has also been investigated for use in the prevention of systemic infection in patients colonised with vancomycin-resistant enterococci.

Reviews.

1. Farver DK, *et al.* Ramoplanin: a lipoglycodepsipeptide antibiotic. *Ann Pharmacother* 2005; **39**: 863–8.
2. Fulco P, Wenzel RP. Ramoplanin: a topical lipoglycodepsipeptide antibacterial agent. *Expert Rev Anti Infect Ther* 2006; **4**: 939–45.

Retapamulin *(BAN, USAN, rINN)*

Retapamulina; Rétapamuline; Retapamulinum; SB-275833; Ретапамулин.

(3a*S*,4*R*,5*S*,6*S*,8*R*,9*R*,9a*R*,10*R*)-6-Ethenyl-5-hydroxy-4,6,9,10-tetramethyl-1-oxodecahydro-3a,9-propanocyclopenta[8]annulen-8-yl [[(1*R*,3*s*,5*S*)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl] sulfanyl]acetate.

$C_{30}H_{47}NO_4S$=517.8

CAS — 224452-66-8.
ATC — D06AX13.
ATC Vet — QD06AX13.
UNII — 4MG6O8991R.

Uses and Administration

Retapamulin is a pleuromutilin antibacterial isolated from the fungus *Clitopilus passeckerianus*. It is applied topically as a 1% ointment in the treatment of impetigo and other bacterial skin infections due to meticillin-susceptible *Staphylococcus aureus* and *Streptococcus pyogenes*. The preparation should be applied twice daily for 5 days; treatment should be re-evaluated if there is no response within about 3 days. It is not suitable for application to mucous membranes.

For further details of skin infections and staphylococcal infections and their treatment, see p. 207.1 and p. 208.2 respectively.

References.

1. Parish LC, *et al.* Topical retapamulin ointment (1%, wt/wt) twice daily for 5 days versus oral cephalexin twice daily for 10 days in the treatment of secondarily infected dermatitis: results of a randomized controlled trial. *J Am Acad Dermatol* 2006; **55**: 1003–1013.
2. Oranje AP, *et al.* Topical retapamulin ointment, 1%, versus sodium fusidate ointment, 2%, for impetigo: a randomized, observer-blinded, noninferiority study. *Dermatology* 2007; **215**: 331–40.
3. Yang LPH, Keam SJ. Retapamulin: a review of its use in the management of impetigo and other uncomplicated superficial skin infections. *Drugs* 2008; **68**: 855–73.
4. Anonymous. Retapamulin for impetigo and other infections. *Drug Ther Bull* 2008; **46**: 76–9. Correction. *ibid.*; 88.
5. Yang LP, Keam SJ. Spotlight on retapamulin in impetigo and other uncomplicated superficial skin infections. *Am J Clin Dermatol* 2008; **9**: 411–13.
6. Shawar R, *et al.* Topical retapamulin in the management of infected traumatic skin lesions. *Ther Clin Risk Manag* 2009; **5**: 41–9.

Adverse Effects and Precautions

Retapamulin is usually well tolerated; the most common reported adverse effect is application site irritation. Other local reactions such as erythema, pain, and pruritus occur rarely. Retapamulin ointment contains butylated hydroxytoluene (p. 1742.1), which may cause local adverse effects such as contact dermatitis, or irritation to the eyes and mucous membranes. It should not be applied to abscesses.

Retapamulin has proved ineffective in infections caused by meticillin-resistant *Staphylococcus aureus*, and should not be used in their treatment.

Antimicrobial Action

Retapamulin is an antibacterial that selectively inhibits bacterial protein synthesis by binding to the 50S subunit of the ribosome. It is mainly bacteriostatic against meticillin-susceptible *Staphylococcus aureus*, and streptococci such as *Strep. pyogenes*. Although *in vitro* activity has been shown against meticillin-resistant *Staph. aureus*, the *in vivo* efficacy of retapamulin was found to be inadequate in clinical studies.

References.

1. Pankuch GA, *et al.* Activity of retapamulin against Streptococcus pyogenes and Staphylococcus aureus evaluated by agar dilution, microdilution, E-test, and disk diffusion methodologies. *Antimicrob Agents Chemother* 2006; **50**: 1727–30.
2. Jones RN, *et al.* Activity of retapamulin (SB-275833), a novel pleuromutilin, against selected resistant Gram-positive cocci. *Antimicrob Agents Chemother* 2006; **50**: 2583–6.
3. Rittenhouse S, *et al.* Selection of retapamulin, a novel pleuromutilin for topical use. *Antimicrob Agents Chemother* 2006; **50**: 3882–5.
4. Champney WS, Rodgers WK. Retapamulin inhibition of translation and 50S ribosomal subunit formation in Staphylococcus aureus cells. *Antimicrob Agents Chemother* 2007; **51**: 3385–7.
5. Woodford N, *et al.* In vitro activity of retapamulin against Staphylococcus aureus isolates resistant to fusidic acid and mupirocin. *J Antimicrob Chemother* 2008; **62**: 766–8.

Pharmacokinetics

Only very small amounts of topically applied retapamulin are absorbed into the systemic circulation. It is about 94% bound to plasma proteins and has been shown to be metabolised by mono-oxygenation and N-demethylation *in vitro*.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Altargo; *Austria*: Altargo; *Belg.*: Altargo; *Braz.*: Altargo; *Chile*: Altargo; *Cz.*: Altargo; *Denm.*: Altargo; *Ger.*: Altargo; *Gr.*: Altargo; *Hung.*: Altargo; *Irl.*: Altargo; *Ital.*: Altargo; *Neth.*: Altargo; *Norw.*: Altargo; *Pol.*: Altargo; *Port.*: Altargo; *Singapore*: Altargo; *Spain*: Altargo; *Swed.*: Altargo; *UK*: Altargo; *USA*: Altabax.

Ribostamycin Sulfate *(BANM, rINNM)*

Ribostamycin Sulphate; Ribostamycine, Sulfate de; Ribostamycini Sulfas; SF-733 (ribostamycin); Sulfato de ribostamicina; Рибостамицина Сульфат.

2-Deoxy-4-*O*-(2,6-diamino-2,6-dideoxy-α-D-glucopyranosyl)-5-*O*-(β-D-ribofuranosyl)-streptamine sulphate.

$C_{17}H_{34}N_4O_{10}xH_2SO_4$

CAS — 25546-65-0 (ribostamycin); 53797-35-6 (ribostamycin sulfate).
ATC — J01GB10.
ATC Vet — QJ01GB10.

Pharmacopoeias. In *Chin.* and *Jpn*.

Profile

Ribostamycin is an aminoglycoside with actions and use similar to those of gentamicin (p. 304.2). It is given as th sulfate by intramuscular injection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Vistamycin.

Rifabutin *(BAN, USAN, rINN)*

Ansamicin; Ansamycin; Ansamycinum; Ansamysiini; LM-427 Rifabutiini; Rifabutina; Rifabutinas; Rifabutine; Rifabutinum Рифабутин.

(9*S*,12*E*,14*S*,15*R*,16*S*,17*R*,18*R*,19*R*,20*S*,21*S*,22*E*,24*Z*)-6,16,18,20-Tetrahydroxy-1′-isobutyl-14-methoxy-7,9,15,17,19,21,25-heptamethylspiro[9,4-(epoxypentadeca[1,11,13]trienimino)-2*H*-furo-[2′,3′:7,8]naphth[1,2-*d*]imidazole-2,4′-piperidine]-5,10,26-(3*H*,9*H*)-trione-16-acetate.

$C_{46}H_{62}N_4O_{11}$=847.0

CAS — 72559-06-9.
ATC — J04AB04.
ATC Vet — QJ04AB04.
UNII — 1W306TDA6S.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Rifabutin). A reddish-violet amorphou powder. Slightly soluble in water and in alcohol; solubl in methyl alcohol.

USP 36: (Rifabutin). An amorphous red-violet powde Very slightly soluble in water; sparingly soluble in alcohol soluble in chloroform and in methyl alcohol. Store at temperature not exceeding 40 degrees. Protect from light.

Stability. Study of the stability of two extemporaneou oral liquid preparations of rifabutin.[1]

1. Haslam JL, *et al.* Stability of rifabutin in two extemporaneous compounded oral liquids. *Am J Health-Syst Pharm* 1999; **56**: 333–6.

Uses and Administration

Rifabutin is a rifamycin antibacterial used as an alternativ to the macrolides for the prophylaxis of *Mycobacterium aviun* complex (MAC) infection in immunocompromised patients It is also used for the treatment of other nontuberculou mycobacterial infections (including those due to MAC (p. 194.1) and tuberculosis (p. 210.2). When used fo treatment rifabutin, like rifampicin, should be used with other antibacterials to prevent the emergence of resistan organisms.

Rifabutin is given as a single oral daily dose. The dose fo the prophylaxis of MAC infection is 300 mg daily. For th treatment of nontuberculous mycobacterial infections th dose is 450 to 600 mg daily in a multidrug regimen for up t 6 months after negative cultures are obtained. Fo pulmonary tuberculosis the usual dose is 300 mg daily fo at least 6 months as part of a multidrug regimen; it can als be given intermittently (usually 3 times each week) as a alternative to daily use.

For details of doses in children, see p. 350.3.

Doses should be reduced to 300 mg daily in patients als receiving macrolides or azole antifungals (see under Adverse Effects, Effects on the Eyes, p. 351.2). Dosag alterations may also be necessary in patients receiving HIV protease inhibitors (see under Tuberculosis, p. 351.1) and i those with severe renal impairment (see p. 351.1).

Reviews.

1. Brogden RN, Fitton A. Rifabutin: a review of its antimicrobial activity pharmacokinetic properties and therapeutic efficacy. *Drugs* 1994; **47** 983–1009.
2. Anonymous. Rifabutin. *Tuberculosis (Edinb)* 2008; **88**: 145–7.

Administration in children. For the prophylaxis of MAC i HIV-infected infants and children with low CD4+ counts the American Academy of Pediatrics (AAP)[1] suggests a oral dose of rifabutin 5 mg/kg daily in those older than 6 years; the *BNFC* suggests the same dose may be given from 1 year of age and those 12 years of age and olde may be given the usual adult dose (see Uses and Administration, above). The maximum oral dose of rifabutin is 300 mg daily.

For the treatment of nontuberculous mycobacterial disease in children aged 1 month to 12 years the *BNFC* suggests a dose of 5 mg/kg once daily as part of a multidrug regimen for up to 6 months after negative cultures are obtained; those 12 years of age and older may be given the usual adult dose.

For the treatment of pulmonary tuberculosis in those 12 years of age and older the *BNFC* suggests a dose of 150 to

450 mg once daily for at least 6 months as part of a multidrug regimen.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Administration in renal impairment. Oral doses of rifabutin should be reduced by 50% in patients with severe renal impairment (creatinine clearance less than 30 mL/minute).

Cryptosporidiosis. Rifabutin may have a potential prophylactic effect against cryptosporidiosis (p. 923.1).

Mycobacterium avium complex infections. Alterations in rifabutin dosage may be necessary in patients receiving antiretrovirals for the management of HIV infection; further details are given under Tuberculosis, p. 351.1.

Peptic ulcer disease. For mention of the use of rifabutin in eradication regimens for *Helicobacter pylori* see p. 1816.2.

References.

1. Borody TJ, *et al.* Efficacy and safety of rifabutin-containing 'rescue therapy' for resistant Helicobacter pylori infection. *Aliment Pharmacol Ther* 2006; **23**: 481–8. Correction. *ibid.*; **24**: 439.
2. Miehlke S, *et al.* Randomized trial of rifabutin-based triple therapy and high-dose dual therapy for rescue treatment of Helicobacter pylori resistant to both metronidazole and clarithromycin. *Aliment Pharmacol Ther* 2006; **24**: 395–403.
3. González Carro P, *et al.* Efficacy of rifabutin-based triple therapy in Helicobacter pylori infected patients after two standard treatments. *J Gastroenterol Hepatol* 2007; **22**: 60–3.
4. Navarro-Jarabo JM, *et al.* Efficacy of rifabutin-based triple therapy as second-line treatment to eradicate helicobacter pylori infection. *BMC Gastroenterol* 2007; **7**: 31. Available at: http://www.biomedcentral.com/1471-230X/7/31 (accessed 12/11/07)

Toxoplasmosis. A beneficial response to rifabutin used with pyrimethamine was reported in a patient with AIDS-related *Toxoplasma gondii* encephalitis.[1] The patient was allergic to sulfonamides and clindamycin, which are commonly used (see p. 926.1).

1. Schürmann D, *et al.* Rifabutin appears to be a promising agent for combination treatment of AIDS-related toxoplasma encephalitis. *J Infect* 1998; **36**: 352–3.

Tuberculosis and HIV infection. A systematic review[1] noted that although there was no evidence to support a general replacement of rifampicin by rifabutin in regimens for tuberculosis, persons with HIV were the most likely to benefit from such an alternative because of the reduced risk of interactions with antiretroviral therapy, and had been underrepresented in studies. Rifabutin has nonetheless been used in place of rifampicin in short-course therapy for tuberculosis in patients given antiretroviral drugs for HIV infection and may be preferred for patients unable to take efavirenz.[2,3] However, dose modifications are often necessary; additionally, some combinations, notably rifabutin with delavirdine, or saquinavir alone, should not be used, although rifabutin may be given with ritonavir-boosted saquinavir.

- In patients taking ritonavir-boosted HIV-protease inhibitors the dose of rifabutin should be substantially reduced from 300 mg daily or intermittently to 150 mg every other day or three times each week.[2,3] It should be noted, however, that there have been reports of inadequate serum-rifabutin concentrations (leading to rifamycin resistance) with the three times weekly regimen among patients taking ritonavir-boosted lopinavir; serum-rifabutin concentration monitoring should be considered[4]
- In patients taking unboosted atazanavir the dose of rifabutin should be substantially reduced from 300 mg daily or intermittently to 150 mg every other day or three times each week[2,3]
- In those taking unboosted amprenavir, fosamprenavir, indinavir, or nelfinavir the daily dose of rifabutin should be decreased from 300 mg to 150 mg, and the dose for intermittent therapy should be 300 mg three times weekly. The dose of indinavir may need to be increased[5]
- In patients taking efavirenz (without a coadministered HIV-protease inhibitor), the dose of rifabutin should be increased from 300 mg daily or intermittently to 450 to 600 mg daily or 600 mg three times each week[2,3]
- In patients taking nevirapine the usual dose of rifabutin is given (300 mg daily or 300 mg three times each week)
- Rifabutin should not be used in patients taking etravirine plus a ritonavir-boosted HIV-protease inhibitor; if etravirine is given without a ritonavir-boosted HIV-protease inhibitor, rifabutin may be given at a dose of 300 mg once daily[3]
- Delavirdine plasma concentrations are significantly decreased by rifabutin and therefore its use with rifabutin is not recommended.

1. Davies GR, *et al.* Rifabutin for treating pulmonary tuberculosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 08/07/09).
2. Pozniak AL, *et al.* British HIV Association. BHIVA treatment guidelines for TB/HIV infection, February 2005. Available at: http://www.bhiva.org/documents/Guidelines/TB/TB_HIV_FINAL2005.pdf (accessed 16/07/10)
3. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. January 2011. Available at: http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf (accessed 11/04/11)
4. Boulanger C, *et al.* Pharmacokinetic evaluation of rifabutin in combination with lopinavir-ritonavir in patients with HIV infection and active tuberculosis. *Clin Infect Dis* 2009; **49**: 1305–11.
5. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 2009. accessed 07/12/10.

Adverse Effects and Precautions

As for Rifampicin, p. 353.3.

Rifabutin is usually well tolerated. The most common adverse effects include rash, gastrointestinal disturbances, and neutropenia. It produces a syndrome of polyarthralgia-arthritis at doses greater than 1 g daily. Uveitis has been reported, especially in patients also receiving clarithromycin or other macrolides and possibly also with fluconazole. Asymptomatic corneal opacities have been reported after long-term use.

Rifabutin should be used with caution in patients with severe hepatic or renal impairment.

An orange-tan skin pigmentation has been reported to occur in most patients taking rifabutin.[1] Urine may also be discoloured.[2] A flu-like syndrome has been reported in 2 of 12 patients given 300 mg daily for Crohn's disease,[3] in 8 of 15 HIV-infected patients given increasing doses of rifabutin,[2] and in 1 of 16 HIV-infected patients on continuous rifabutin.[1]

Other reported adverse effects include hepatitis,[1] leucopenia[2] (including neutropenia[4]), epigastric pain,[3] rash,[3] erythema,[2] and ageusia.[5]

Rash, fever, and vomiting occurred in 1 of 2 children receiving 6.5 mg/kg daily.[6]

1. Siegal FP, *et al.* Dose-limiting toxicity of rifabutin in AIDS-related complex: syndrome of arthralgia/arthritis. *AIDS* 1990; **4**: 433–41.
2. Torseth J, *et al.* Evaluation of the antiviral effect of rifabutin in AIDS-related complex. *J Infect Dis* 1989; **159**: 1115–18.
3. Basilisco G, *et al.* Controlled trial of rifabutin in Crohn's disease. *Curr Ther Res* 1989; **46**: 245–50.
4. Apseloff G, *et al.* Severe neutropenia caused by recommended prophylactic doses of rifabutin. *Lancet* 1996; **348**: 685.
5. Morris JT, Kelly JW. Rifabutin-induced ageusia. *Ann Intern Med* 1993; **119**: 171–2.
6. Levin RH, Bolinger AM. Treatment of nontuberculous mycobacterial infections in pediatric patients. *Clin Pharm* 1988; **7**: 545–51.

Effects on the eyes. Uveitis may occur a few weeks or months after starting rifabutin, and generally necessitates withdrawal of the drug and treatment with topical or systemic corticosteroids and cycloplegics.[1] In 1994, the UK CSM was aware of 48 reports of uveitis in patients taking rifabutin.[2] Most patients were also receiving clarithromycin for treatment of AIDS-related *Mycobacterium avium* complex (MAC) infection and many were also receiving fluconazole (see Interactions, p. 351.3). A dosage reduction to 300 mg rifabutin daily is now recommended in patients also receiving macrolides or triazole antifungals[2,3] and is reported to produce a satisfactory response in MAC infections.[4] Panuveitis and retinal vasculitis has been reported[5] in 4 patients with active tuberculosis given rifabutin, and was thought to be a result of activation of the immune system by *Mycobacterium tuberculosis* and the very low weight of the patients.

Rifabutin-associated uveitis in children is less commonly reported probably because they may not notice or complain about visual changes, therefore monitoring of their vision while on treatment is advised.[6]

Persistent corneal deposits have been reported[7] in patients given rifabutin for Crohn's disease.

1. Tseng AL, Walmsley SL. Rifabutin-associated uveitis. *Ann Pharmacother* 1995; **29**: 1149–55.
2. CSM. Rifabutin (Mycobutin)—uveitis. *Current Problems* 1994; **20**: 4. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON20244576&RevisionSelectionMethod=LatestReleased (accessed 05/10/07)
3. CSM. Revised indications and drug interactions of rifabutin. *Current Problems* 1997; **23**: 14. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON20232386&RevisionSelectionMethod=LatestReleased (accessed 05/10/07)
4. Shafran SD, *et al.* A comparison of two regimens for the treatment of Mycobacterium avium complex bacteremia in AIDS: rifabutin, ethambutol, and clarithromycin versus rifampin, ethambutol, clofazimine, and ciprofloxacin. *N Engl J Med* 1996; **335**: 377–83.
5. Skolik S, *et al.* Rifabutin-associated panuveitis with retinal vasculitis in pulmonary tuberculosis. *Ocul Immunol Inflamm* 2005; **13**: 483–5.
6. Olesen HH, Krag S. Rifabutin-associated uveitis in a child. *Pediatr Infect Dis J* 2005; **24**: 1023–5.
7. Williams K, Ilari L. Persistent corneal endothelial deposits associated with rifabutin therapy for Crohn's disease. *Cornea* 2010; **29**: 706–7.

Effects on the joints. A polyarthralgia-arthritis syndrome was reported in an initial dose finding study[1] in 9 of 10 patients taking rifabutin, as monotherapy, at doses greater than 1 g. The syndrome did not occur in patients given less than 1 g daily and disappeared on drug withdrawal. Two patients with polyarthralgia-arthritis symptoms developed uveitis (see also under Effects on the Eyes, above) and aphthous stomatitis at doses of about 1.8 g daily. However, a later study[2] and case reports[3] have reported polyarthralgia-arthritis syndrome when rifabutin was given at doses of 300 to 600 mg daily as part of a multidrug regimen, including a macrolide (azithromycin or clarithromycin), for the treatment of *Mycobacterium avium* complex infection. Concentrations of rifabutin were increased as a result of inhibition of cytochrome P450 isoenzymes by the macrolide and some have suggested a maximum dose of rifabutin of 300 mg daily when used with a macrolide.[2] Higher doses of 450 to 600 mg daily may be considered for large patients or those who have failed to respond to initial treatment with a lower dose.

1. Siegal FP, *et al.* Dose-limiting toxicity of rifabutin in AIDS-related complex: syndrome of arthralgia/arthritis. *AIDS* 1990; **4**: 433–41.
2. Griffith DE, *et al.* Adverse events associated with high-dose rifabutin in macrolide-containing regimens for the treatment of Mycobacterium avium complex lung disease. *Clin Infect Dis* 1995; **21**: 594–8.
3. Le Gars L, *et al.* Polyarthralgia-arthritis syndrome induced by low doses of rifabutin. *J Rheumatol* 1999; **26**: 1201–2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies rifabutin as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 08/07/11)

Interactions

As for Rifampicin, p. 355.1.

Rifabutin accelerates the metabolism of many drugs by inducing microsomal liver enzymes (in particular the cytochrome P450 isoenzyme CYP3A4). It is a less potent inducer of cytochrome P450 isoenzymes than rifampicin, but similar interactions should nevertheless be anticipated. Use with other drugs that induce or inhibit these isoenzymes may result in changes in plasma concentrations of rifabutin, and possibly adverse effects.

Plasma concentrations of rifabutin are increased by clarithromycin (and possibly other macrolides) or fluconazole, resulting in increased rifabutin toxicity, in particular uveitis, (see Effects on the Eyes, above), neutropenia, and polyarthralgia-arthritis syndrome (see Effects on the Joints, above).

Some other interactions affecting the activity of rifabutin are discussed below.

General references.

1. Baciewicz AM, *et al.* Update on rifampin and rifabutin drug interactions. *Am J Med Sci* 2008; **335**: 126–36.

Antibacterials. As discussed under Effects on the Eyes, above, most patients developing uveitis during rifabutin treatment are also receiving *clarithromycin* and it may also be implicated in the polyarthralgia-arthritis syndrome (see Effects on the Joints, above). In a study[1] of the treatment of *Mycobacterium avium* complex infection in AIDS patients, uveitis or pseudojaundice or both were noted in those receiving rifabutin, ethambutol, and clarithromycin, but not in those receiving rifabutin, ethambutol, ciprofloxacin, and clofazimine. A retrospective study[2] after an outbreak of uveitis in a similar patient population also found clarithromycin to be a risk factor, with a trend towards greater risk at higher rifabutin doses, although patient numbers were small. In 26 patients taking rifabutin with either clarithromycin or *azithromycin*,[3] the incidence and severity of adverse effects in general was similar, although the 2 patients who developed uveitis were both receiving clarithromycin.

Pharmacokinetic studies have found increased rifabutin concentrations when clarithromycin is also used. A study in healthy subjects[4] was terminated prematurely because of the high incidence of adverse effects, including neutropenia, fevers, and myalgia, particularly in subjects receiving rifabutin with azithromycin or clarithromycin. Mean serum concentrations of rifabutin and its 25-*O*-deacetyl metabolite in subjects also receiving clarithromycin were more than 4 times and 37 times those in subjects receiving rifabutin alone. Plasma concentrations were unaffected by azithromycin. Similar effects on rifabutin concentrations were found in HIV-infected subjects receiving clarithromycin[5] and reductions in clarithromycin concentrations were also noted. A study[6] to determine the tolerance and pharmacokinetic interactions of rifabutin and azithromycin in subjects with or without HIV infection found no significant drug interaction; however, the combination was poorly tolerated, mainly because of a high incidence of gastrointestinal symptoms and neutropenia.

1. Shafran SD, *et al.* Uveitis and pseudojaundice during a 3-regimen of clarithromycin, rifabutin, and ethambutol. *N Engl J Med* 1994; **330**: 438–9.
2. Kelleher P, *et al.* Uveitis associated with rifabutin and macrolide therapy for Mycobacterium avium intracellulare infection in AIDS patients. *Genitourin Med* 1996; **72**: 419–21.

3. Griffith DE, *et al.* Adverse events associated with high-dose rifabutin in macrolide-containing regimens for the treatment of Mycobacterium avium complex lung disease. *Clin Infect Dis* 1995; 21: 594–8.
4. Apseloff G, *et al.* Comparison of azithromycin and clarithromycin in their interactions with rifabutin in healthy volunteers. *J Clin Pharmacol* 1998; 38: 830–5.
5. Hafner R, *et al.* Tolerance and pharmacokinetic interactions of rifabutin and clarithromycin in human immunodeficiency virus-infected volunteers. *Antimicrob Agents Chemother* 1998; 42: 631–9.
6. Hafner R, *et al.* Tolerance and pharmacokinetic interactions of rifabutin and azithromycin. *Antimicrob Agents Chemother* 2001; 45: 1572–7.

Antifungals. Rifabutin concentrations are increased by triazole antifungals and patients are at increased risk of rifabutin toxicity, specifically uveitis (see under Effects on the Eyes, p. 349.2). Rifabutin also markedly reduces the plasma concentrations of *itraconazole, posaconazole,* and *voriconazole,* but does not affect the metabolism of *fluconazole.*

The area under the concentration-time curve (AUC) for rifabutin and its active 25-deacetyl metabolite were increased by 82% and 216% respectively when fluconazole was given to 12 HIV-infected patients.[1] Another study[2] in 10 patients with HIV infection, found that fluconazole increased the AUC of rifabutin by 76% and by 152% when the patients were also given clarithromycin. Raised plasma-rifabutin concentrations were reported in a patient who developed uveitis while also receiving itraconazole.[3] The mechanism of the interaction remains uncertain but could involve microsomal cytochrome P450 isoenzyme CYP3A4 (see Metabolism under Pharmacokinetics, p. 352.3).

1. Trapnell CB, *et al.* Increased plasma rifabutin levels with concomitant fluconazole therapy in HIV-infected patients. *Ann Intern Med* 1996; 124: 573–6.
2. Jordan MK, *et al.* Effects of fluconazole and clarithromycin on rifabutin and 25-O-desacetylrifabutin pharmacokinetics. *Antimicrob Agents Chemother* 2000; 44: 2170–2.
3. Lefort A, *et al.* Uveitis associated with rifabutin prophylaxis and itraconazole therapy. *Ann Intern Med* 1996; 125: 939–40.

Antiretrovirals. Rifabutin may be used as a substitute for rifampicin in the treatment of tuberculosis.[1,2] It has little effect on the serum concentrations of unboosted *HIV-protease inhibitors* (except indinavir, nelfinavir, and saquinavir) and ritonavir-boosted HIV-protease inhibitors, although it has been reported to *increase* plasma concentrations of ritonavir-boosted lopinavir (see p. 1005.1). However, HIV-protease inhibitors, particularly if boosted with ritonavir, significantly increase serum concentrations and toxicity of rifabutin. The dose of rifabutin is therefore usually substantially decreased when given with HIV-protease inhibitors (see Tuberculosis and HIV infection under Uses, p. 349.1). Rifabutin should not be given with unboosted saquinavir; but saquinavir may be given with rifabutin if boosted with ritonavir.[2] Increases in the dose of indinavir are also required.[2]

Serum concentrations of rifabutin may be increased or decreased in those taking *NNRTIs,* however, rifabutin may usually be given to patients taking nevirapine without the need for any dose modifications. US licensed product information advises that etravirine should not be used with rifabutin if combined with ritonavir-boosted darunavir, ritonavir-boosted lopinavir, or ritonavir-boosted saquinavir; however, US guidelines[3] advise avoiding combination with any ritonavir-boosted HIV-protease inhibitor. Rifabutin is not recommended in patients taking delavirdine. In patients taking efavirenz, the dose of rifabutin should be increased by at least 50% (see Tuberculosis and HIV infection under Uses, p. 349.1).

No clinically significant interactions are expected with the integrase inhibitor *raltegravir* or the CCR-5 receptor antagonist *maraviroc.*[2]

Although rifabutin is reported to reduce the plasma concentrations of *zidovudine,* studies have shown that the effect is not marked (see p. 1026.2), and licensed product information for rifabutin suggests that the reduction may not be clinically relevant.

1. Pozniak AL, *et al.* British HIV Association. BHIVA treatment guidelines for TB/HIV infection, February 2005. Available at: http://www.bhiva.org/documents/Guidelines/TB/TB_HIV_FINAL2005.pdf (accessed 16/07/10)
2. CDC. Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis (issued December 2007). Available at: http://www.cdc.gov/tb/publications/guidelines/TB_HIV_Drugs/PDF/tbhiv.pdf (accessed 16/07/10)
3. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. January 2011. Available at: http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf (accessed 11/04/11)

Antimicrobial Action

Rifabutin possesses a spectrum of antibacterial activity similar to that of rifampicin (p. 355.3). However, most investigations have concentrated on its action against mycobacteria. Cross-resistance with rifampicin is common.

Antimycobacterial action. Rifabutin possesses activity against most species of mycobacteria. It may be more active *in vivo* than *in vitro* studies suggest, as a result of its favourable pharmacokinetic profile and prolonged postantibiotic effect.[1]

Rifabutin has been reported to be active in *animal* assays against *Mycobacterium leprae,*[2] including a rifampicin-resistant strain.[3] Synergistic activity against *M. leprae* has been reported[4] *in vitro* for rifabutin with sparfloxacin.

1. Kunin CM. Antimicrobial activity of rifabutin. *Clin Infect Dis* 1996; 22 (suppl 1): S3–S14.
2. Hastings RC, Jacobson RR. Activity of ansamycin against Mycobacterium leprae in mice. *Lancet* 1983; ii: 1079–80. Correction. *ibid.*: 1210.
3. Hastings RC, *et al.* Ansamycin activity against rifampicin-resistant Mycobacterium leprae. *Lancet* 1984; i: 1130.
4. Dhople AM, Ibanez MA. In-vitro activity of three new fluoroquinolones and synergy with ansamycins against Mycobacterium leprae. *J Antimicrob Chemother* 1993; 32: 445–51.

Resistance. Rifampicin-resistant strains of *Mycobacterium tuberculosis* have been identified in 2 patients receiving rifabutin alone as prophylaxis against *M. avium* complex.[1,2] It is therefore important to exclude *M. tuberculosis* infection before beginning rifabutin prophylaxis.

Rifampicin-resistant *M. kansasii* has also been reported in a patient receiving rifabutin.[3]

Acquired resistance has been reported in HIV-infected persons receiving highly intermittent regimens (once- or twice-weekly) of rifabutin for the treatment of active tuberculosis,[4,5] and the CDC has advised that such patients receive daily treatment during the intensive phase of therapy and daily or 3 times-weekly treatment during the continuation phase.

1. Weltman AC, *et al.* Rifampicin-resistant Mycobacterium tuberculosis. *Lancet* 1995; 345: 1513.
2. Bishai WR, *et al.* Brief report: rifampin-resistant tuberculosis in a patient receiving rifabutin prophylaxis. *N Engl J Med* 1996; 334: 1573–6.
3. Meynard JL, *et al.* Rifampin-resistant Mycobacterium kansasii infection in a patient with AIDS who was receiving rifabutin. *Clin Infect Dis* 1997; 24: 1262–3.
4. CDC. Notice to readers: acquired rifamycin resistance in persons with advanced HIV disease being treated for active tuberculosis with intermittent rifamycin-based regimens. *MMWR* 2002; 51: 214–15.
5. Burman W, *et al.* Acquired rifamycin resistance with twice-weekly treatment of HIV-related tuberculosis. *Am J Respir Crit Care Med* 2006; 173: 350–6.

Pharmacokinetics

Rifabutin is readily but incompletely absorbed from the gastrointestinal tract and peak plasma concentrations of about 250 to 600 nanograms/mL have been reported 2 to 4 hours after an oral dose of 300 mg; doubling the dose increases the peak plasma concentration. Food may delay absorption but does not affect the extent of absorption. Rifabutin is about 70% bound to plasma proteins. Rifabutin is lipophilic and therefore is widely distributed in body tissues and fluids.

Rifabutin is rapidly metabolised in the liver by the cytochrome P450 isoenzyme CYP3A4 mainly to active 25-O-deacetyl and 31-hydroxy metabolites. Rifabutin induces its own metabolism resulting in a lower area under the curve after 4 weeks of continuous treatment than after the first few doses.

About 53% of a dose is found in the urine, mainly as metabolites and about 30% of a dose is excreted in the faeces. The mean half-life for rifabutin is reported to be about 40 hours, with a range of 16 to 69 hours.

References.
1. Skinner MH, *et al.* Pharmacokinetics of rifabutin. *Antimicrob Agents Chemother* 1989; 33: 1237–41.

HIV-infected patients. Malabsorption of rifabutin and other antituberculous drugs may occur in patients with HIV infection and tuberculosis, and may contribute to acquired drug resistance and reduced efficacy of tuberculosis treatment. For further information on the absorption of antituberculous drugs in HIV-infected patients see Pharmacokinetics, under Rifampicin, p. 356.1.

The pharmacokinetics of rifabutin were studied in HIV-infected patients with normal renal and hepatic function.[1] A two-compartment open pharmacokinetic model was proposed. Rifabutin was rapidly but incompletely absorbed from the gastrointestinal tract and bioavailability was poor, being 20% on day 1 of the study and 12% on day 28. Mean peak plasma concentrations occurred 2 to 3 hours after oral doses and were about 350, 500, and 900 nanograms/mL after doses of 300, 600, and 900 mg respectively. The peak and trough concentrations after 600 mg twice daily were about 900 and 200 nanograms/mL respectively. Rifabutin was about 70% bound to plasma proteins. The area under the curve showed a decrease on repeated dosage which might be explained by the induction of drug-metabolising liver enzymes. A large volume of distribution of 8 to 9 litres/kg, indicative of extensive tissue distribution, and a mean terminal half-life of 32 to 38 hours were reported.

This study[1] also showed that the peak plasma concentration of the major metabolite, 25-deacetylrifabutin, was 10% of the parent compound. Only 4% of unchanged rifabutin was excreted in the urine after oral use and between 6 to 14% after intravenous use. Total urinary excretion of rifabutin and metabolite 72 hours after intravenous use was 44%; total faecal excretion was between 30 and 49%.

Peak and trough concentrations at steady state were reported as 900 and 200 nanograms/mL respectively in a patient with tuberculosis given rifabutin 450 mg daily.[2] While these figures were the same as those previously reported with 600 mg twice daily,[1] the earlier study showed that there was considerable interpatient variability.

CSF concentrations in 5 patients with AIDS on rifabutin 450 mg daily ranged from 36 to 70% of serum concentrations.[3]

1. Skinner MH, *et al.* Pharmacokinetics of rifabutin. *Antimicrob Agent Chemother* 1989; 33: 1237–41.
2. Gillespie SH, *et al.* The serum rifabutin concentrations in a patien successfully treated for multi-resistant mycobacterium tuberculosi infection. *J Antimicrob Chemother* 1990; 25: 490–1. Correction. *ibid.* 1991 27: 877.
3. Siegal FP, *et al.* Dose-limiting toxicity of rifabutin in AIDS-relate complex: syndrome of arthralgia/arthritis. *AIDS* 1990; 4: 433–41.

Metabolism. Five metabolites of rifabutin were identifiec in an *in-vitro* study[1] using human hepatic and enterocyte microsomes. Cytochrome P450 isoenzyme CYP3A4 wa involved in the formation of all metabolites except 25-O deacetylrifabutin. Deacetylation of rifabutin was appar ently mediated by microsomal cholinesterase,[1] although another study[2] showed that further metabolism of 25-O deacetylrifabutin is dependent on CYP3A4. The results also suggested that metabolism by intestinal CYP3A4 con tributes significantly to presystemic metabolism of rifabu tin (and consequently its low bioavailability) and to drug interactions with azole antifungals (see above) and with macrolides (see p. 349.3).

1. Iatsimirskaia E, *et al.* Metabolism of rifabutin in human enterocyte and liver microsomes: kinetic parameters, identification of enzyme systems and drug interactions with macrolides and antifungal agents. *Clin Pharmacol Ther* 1997; 61: 554–62.
2. Trapnell CB, *et al.* Metabolism of rifabutin and its 25-desacety metabolite, LM565, by human liver microsomes and recombinan human cytochrome P-450 3A4: relevance to clinical interaction with fluconazole. *Antimicrob Agents Chemother* 1997; 41: 924–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Mycobutin; ***Austria*** Mycobutin; ***Belg.***: Mycobutin; ***Canad.***: Mycobutin; ***Cz.***: Mycobutin; ***Fin.***: Ansatipin; ***Fr.***: Ansatipine; ***Gr.***: Ansatipin; Mycobutin; ***Hong Kong***: Mycobutin; ***Irl.***: Mycobutin; ***Israel***: Mycobutin. ***Ital.***: Mycobutin; ***Neth.***: Mycobutin; ***NZ***: Mycobutin; ***Port.***: Mycobutin; ***Rus.***: Mycobutin (Микобутин); ***S.Afr.***: Mycobutin; ***Spain***: Ansatipin; ***Swed.***: Ansatipin; ***Switz.***: Mycobutin; ***Turk.***: Mycobutin; ***UK***: Mycobutin; ***Ukr.***: Mycobutin (Микобутин); ***USA***: Mycobutin.

Pharmacopoeial Preparations
USP 36: Rifabutin Capsules; Rifabutin Oral Suspension.

Rifampicin *(BAN, rINN)*

Ba-41166/E; L-5103; NSC-113926; Rifaldazine; Rifampicina; Rifampicinas; Rifampicine; Rifampicinum; Rifampin (USAN); Rifampisilini; Rifampisin; Rifamycin AMP; Ryfampicyna; Рифампицин.

3-(4-Methylpiperazin-1-yliminomethyl)rifamycin SV; (12*Z*,14*E*,24*E*)-(2*S*,16*S*,17*S*,18*R*,19*R*,20*R*,21*S*,22*R*,23*S*)-1,2-Dihydro-5,6,9,17,19-pentahydroxy-23-methoxy-2,4,12,16,18,20,22-heptamethyl-8-(4-methylpiperazin-1-yliminomethyl)-1,11-dioxo-2,7-(epoxypentadeca[1,11,13]trienimino)naphtho[2,1-*b*]furan-21-yl acetate.

$C_{43}H_{58}N_4O_{12}$=823.0

CAS — 13292-46-1.

ATC — J04AB02.

ATC Vet — QJ04AB02; QJ54AB02.

UNII — VJT6J7R4TR.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Rifampicin). A reddish-brown or brownish-red, crystalline powder. Slightly soluble in water, in alcohol, and in acetone; soluble in methyl alcohol. A 1% suspension has a pH of 4.5 to 6.5. Store at a temperature not exceeding 25 degrees in an atmosphere of nitrogen in airtight containers. Protect from light.

USP 36: (Rifampin). A red-brown crystalline powder. Very slightly soluble in water; freely soluble in chloroform; soluble in ethyl acetate and in methyl alcohol. A 1% suspension in water has a pH of 4.5 to 6.5. Store at a temperature not exceeding 40 degrees in airtight containers. Protect from light.

Uses and Administration

Rifampicin belongs to the rifamycin group of antimycobacterials (p. 169.1) and is used in the treatment of various infections due to mycobacteria and other susceptible organisms (see Antimicrobial Action, p. 355.3). It is usually

given with other antibacterials to prevent the emergence of resistant organisms.

Rifampicin is used, mainly with isoniazid and pyrazinamide, as a component of multidrug regimens for the treatment of tuberculosis, and with dapsone and clofazimine in the treatment of leprosy. For the treatment of nontuberculous mycobacterial infections it is usually used with clarithromycin and ethambutol as part of a multidrug regimen.

Other uses include the treatment of brucellosis, Legionnaires' disease, mycetoma, penicillin-resistant pneumococcal meningitis, Q-fever, and various staphylococcal infections, including endocarditis. Rifampicin is used for the prophylaxis of epiglottitis and meningitis due to *Haemophilus influenzae* and for meningococcal meningitis. It is also used for the eradication of pharyngeal streptococcal carriage in pharyngitis, to reduce staphylococcal carriage, and to eliminate the carrier states for meningococcal and *H. influenzae* meningitis. It may be used as part of a multidrug regimen for the treatment of inhalation and gastrointestinal anthrax. For discussions of all these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

The usual oral adult dose of rifampicin is 8 to 12 mg/kg (to a maximum of 600 mg) daily, preferably on an empty stomach, or the same dose by intravenous infusion as the base or the sodium salt; higher doses are sometimes used (see below).

Rifampicin is given in the initial and continuation phases of short-course **tuberculosis** regimens (p. 210.2) with other antimycobacterials. Rifampicin is given orally on an empty stomach in adult doses of 10 mg/kg (maximum 600 mg) daily or two or three times weekly. (WHO does not recommend twice-weekly regimens as there is an increased risk of treatment failure if a dose is missed.) Alternatively, doses may be expressed as follows: with daily use, adults weighing less than 50 kg receive 450 mg and those over 50 kg receive 600 mg; with intermittent use, adults receive 600 to 900 mg three times weekly. The maximum recommended dose is considered to be 900 mg because a greater incidence of adverse effects may occur with doses above 900 mg.

For the treatment of latent tuberculosis oral rifampicin 10 mg/kg (to a maximum dose of 600 mg) may be given once daily with isoniazid for 3 months. If the contact is infected with isoniazid-resistant tuberculosis then rifampicin monotherapy may be given daily for 4 to 6 months.

In **leprosy** regimens (p. 188.3), rifampicin is usually given with dapsone for paucibacillary leprosy, and with dapsone and clofazimine for multibacillary leprosy. WHO recommends that rifampicin is given once monthly in a usual oral adult dose of 600 mg. Single-dose treatment with rifampicin, ofloxacin, and minocycline may be an alternative in patients with single-lesion paucibacillary leprosy.

In the treatment of **brucellosis, Legionnaires' disease,** and serious **staphylococcal infections** a dose of 600 to 1200 mg daily, orally or by intravenous infusion, in divided doses has been recommended in combination with other antibacterials.

For **prophylaxis** against meningococcal meningitis and the treatment of meningococcal carriers, rifampicin is usually given in an oral dose of 600 mg twice daily for 2 days. For prophylaxis against meningitis due to *Haemophilus influenzae*, an oral dose of 20 mg/kg once daily (to a maximum dose of 600 mg daily) for 4 days is given to adults.

For details of doses in children see p. 353.1.

Fixed-dose combination products for antimycobacterial therapy have been developed in order to improve patient compliance and avoid monotherapy, thereby decreasing the risk of acquired drug resistance. Combination products containing rifampicin with isoniazid, isoniazid and pyrazinamide, isoniazid and ethambutol, or isoniazid, ethambutol, and pyrazinamide are available in some countries.

Doses of rifampicin should be reduced in patients with hepatic impairment (see p. 353.2).

References.
1. Anonymous. Rifampin. *Tuberculosis (Edinb)* 2008; **88**: 151–4.
2. Forrest GN, Tamura K. Rifampin combination therapy for nonmycobacterial infections. *Clin Microbiol Rev* 2010; **23**: 14–34.

Administration in children. For the treatment of **tuberculosis** in infants, children, and adolescents the American Academy of Pediatrics (AAP)[1] suggests an oral dose of rifampicin of 10 to 20 mg/kg (to a maximum of 600 mg) daily or twice weekly, for both the initial and continuation phases. For children 1 month and older the *BNFC* suggests an oral dose of 15 mg/kg once daily (to a maximum of 450 mg in those under 50 kg or 600 mg in those over 50 kg); alternatively, 15 mg/kg (to a maximum of 900 mg) three times a week. WHO now recommends 10 to 20 mg/kg once daily in children weighing between 5 and 30 kg; specific recommendations have been issued on achieving this using available fixed dose combination products. Heavier children are treated as adults (see Uses and Administration, p. 350.3).[2]

For the treatment of *latent* tuberculosis the *BNFC* suggests that children 1 month and older are given oral rifampicin 15 mg/kg (to a maximum of 450 mg in those under 50 kg or 600 mg in those over 50 kg) once daily with isoniazid for 3 months. If the contact is infected with isoniazid-resistant tuberculosis then rifampicin monotherapy should be given daily for 6 months. The AAP, however, suggest oral rifampicin 10 to 20 mg/kg daily for 6 months; if daily treatment is not possible the same dose may be given twice a week for 6 months.

In **leprosy** regimens rifampicin is usually given with dapsone for the treatment of paucibacillary leprosy, and with dapsone and clofazimine for the treatment of multibacillary leprosy. WHO recommends that rifampicin is given once monthly in an oral dose of 450 mg to children 10 years of age and older.

In the treatment of **brucellosis, Legionnaires' disease,** and serious **staphylococcal infections** doses recommended by the *BNFC* are 5 to 10 mg/kg twice daily in neonates and infants up to 12 months of age, and 10 mg/kg (maximum 600 mg) twice daily in those older than one year of age. Doses are given orally or by intravenous infusion and in combination with other antibacterials.

For doses used in the treatment of human granulocytic anaplasmosis, see Ehrlichiosis, p. 353.2.

For prophylaxis against meningococcal **meningitis** the AAP recommends infants less then 1 month old are given 5 mg/kg, while infants and children aged 1 month or more are given 10 mg/kg (to a maximum of 600 mg), both given orally twice daily for 2 days. The *BNFC* recommends doses of 5 mg/kg for neonates and infants up to 12 months of age and 10 mg/kg (maximum 600 mg) for children between 1 and 12 years of age, each given orally twice daily for 2 days.

For prophylaxis against meningitis due to *Haemophilus influenzae* the AAP suggests that infants less than 1 month old may be given 10 mg/kg once daily orally for 4 days, while the *BNFC* suggests that this dose should be given to infants aged 1 to 3 months. For older infants and children both the AAP and the *BNFC* recommend an oral dose of 20 mg/kg (to a maximum of 600 mg) once daily for 4 days.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.
2. WHO. Dosing instructions for the use of currently available fixed-dose combination TB medicines for children. Available at: http://www.who.int/entity/tb/challenges/interim_paediatric_fdc_dosing_instructions_sept09.pdf (accessed 19/01/11)

Administration in hepatic impairment. Reduced oral and intravenous doses of rifampicin are recommended for patients with hepatic impairment and a maximum of 8 mg/kg daily has been suggested. See also Precautions, p. 354.3.

Ehrlichiosis. Beneficial responses to rifampicin were reported[1] in 2 women with human granulocytic anaplasmosis (see Ehrlichiosis, p. 179.1), who were pregnant and in whom the usual treatment (a tetracycline) was contra-indicated.

US guidelines[2] recommend rifampicin as a treatment alternative for patients with mild human granulocytic ehrlichiosis in whom doxycycline is contra-indicated; a dose of 300 mg orally twice daily for 7 to 10 days is recommended. Children may be given 10 mg/kg (to a maximum of 300 mg) twice daily for the same duration.

1. Buitrago ML, *et al.* Human granulocytic ehrlichiosis during pregnancy treated successfully with rifampin. *Clin Infect Dis* 1998; **27**: 213–15.
2. Wormser GP, *et al.* The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2006; **43**: 1089–1134. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/508667 (accessed 09/12/10)

Meningitis prophylaxis. *HAEMOPHILUS INFLUENZAE MENINGITIS PROPHYLAXIS.* Meningeal infection with *Haemophilus influenzae* type b (Hib) in children is associated with substantial morbidity, but the incidence has decreased since the introduction of immunisation with *H. influenzae* type b vaccine. Although a worldwide problem, the disease (p. 191.1) and its prophylaxis has been studied mainly in the USA, where it was shown that children under 4 years of age formed the highest risk group for primary infection while children under 2 years of age formed the highest risk group for secondary infection.[1] The goal of prophylaxis in close contacts is to eliminate carriage of the organism to prevent spread to young children. Risk of infection to young children with recent household contact to the primary case of infection with *H. influenzae* type b is increased 600- to 800-fold,[1,2] but only increased 20-fold[3] from day-care or school contact. The risk may be higher when more than 1 index patient is identified.

Rifampicin given orally in doses of 20 mg/kg once daily for 4 days (maximum dose 600 mg) has been shown to eradicate Hib nasopharyngeal carriage in at least 95% of contacts of the primary case.[4] There is some evidence from a study involving 68 families of patients with Hib infection that rifampicin 20 mg/kg daily for 2 days may be as effective as a 4-day course in eradicating Hib pharyngeal colonisation.[5] Rifampicin prophylaxis appears to be successful in preventing infection in household contacts, but benefit in school settings where there has been a single index case has not been established.[3]

Recommendations have been made for rifampicin prophylaxis.[4,7] The American Academy of Pediatrics (AAP) recommends[6] that all household contacts be given rifampicin prophylaxis where there is at least 1 vulnerable contact person (considered to be a child younger than 4 years of age who is not or incompletely immunised against Hib, an incompletely immunised child younger than 12 months of age, or an immunocompromised child, regardless of vaccine status) in the household. Similar recommendations have been made in the UK (although a vulnerable contact is considered to be a child under 10 years old, or any immunocompromised person, regardless of age).[7] The AAP[6] also recommends rifampicin prophylaxis when 2 or more cases of Hib disease have occurred within 60 days in a day-care or school. In the UK,[7] prophylaxis has been recommended for all room contacts when 2 or more cases of disease have occurred within 120 days. Rifampicin prophylaxis is not recommended for pregnant women.[6]

For recommended *doses* see Uses and Administration (p. 350.3) and Administration in Children, above.

Rifampicin should also be given to the primary case since treatment of the infection does not eradicate nasopharyngeal carriage.[2,4,7]

1. Casto DT, Edwards DL. Preventing Haemophilus influenzae type b disease. *Clin Pharm* 1985; **4**: 637–48.
2. Cartwright KAV, *et al.* Chemoprophylaxis for Haemophilus influenzae type b: rifampicin should be given to close contacts. *BMJ* 1991; **302**: 546–7.
3. ASHP Commission on Therapeutics. ASHP therapeutic guidelines on nonsurgical antimicrobial prophylaxis. *Clin Pharm* 1990; **9**: 423–45.
4. Band JD, *et al.* Prevention of Hemophilus influenzae type b disease. *JAMA* 1984; **251**: 2381–6.
5. Green M, *et al.* Duration of rifampin chemoprophylaxis for contacts of patients infected with Haemophilus influenzae type B. *Antimicrob Agents Chemother* 1992; **36**: 545–7.
6. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.
7. DoH, Public Health England. Revised recommendations for the prevention of secondary Haemophilus influenzae type b (Hib) disease (updated 1 July, 2013). Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/231009/ Revised_recommendations_for_the_preventions_of_secondary_Haemophilus_influenzae_type_b_disease.pdf (accessed 11/09/13)

MENINGOCOCCAL MENINGITIS PROPHYLAXIS. Neisseria meningitidis is an important cause of bacterial meningitis (p. 191.1); all age groups are at risk during epidemics but children are usually at highest risk during endemic outbreaks. Vaccines are available for meningococci groups A, C, Y, and W135 but not usually for group B, therefore antimicrobial prophylaxis remains important in preventing the spread of the disease. The aim of prophylaxis is to eliminate nasopharyngeal carriage of the organism. Sulfadiazine and minocycline are no longer used because of resistance and adverse effects. A 2-day course of oral rifampicin (for doses see Uses and Administration (p. 350.3) and Administration in Children, above) is one of the recommended regimens for prophylaxis (although ciprofloxacin is usually preferred).[1] Antibacterial prophylaxis should be given as soon as possible to close contacts (ideally within 24 hours of diagnosis of the index case). It is also recommended for child care or nursery school contacts in the USA,[2] but is not usually advised for this group in the UK after a single case.[1] The index patient should also receive antibacterial prophylaxis for 2 days before hospital discharge since treatment with penicillin does not eliminate nasopharyngeal carriage.

1. Health Protection Agency. Guidance for public health management of meningococcal disease in the UK (updated January 2011). Available at: http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1194947389261 (accessed 12/05/11)
2. CDC. Recommendations of the Advisory Committee on Immunization Practices (ACIP): prevention and control of meningococcal disease. *MMWR* 2005; **54** (RR-7): 1–21. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5407.pdf (accessed 05/10/07)

Naegleria infections. For mention of the use of rifampicin in primary amoebic meningoencephalitis, see p. 922.1.

Adverse Effects

Rifampicin is usually well tolerated. Adverse effects are more common during intermittent therapy or after restarting interrupted treatment.

Some patients may have a cutaneous syndrome that presents 2 to 3 hours after a daily or intermittent dose as facial flushing and itching, with or without a rash, or rarely eye irritation and visual disturbances. A flu-like syndrome characterised by episodes of fever, chills, headache, dizziness, bone pain, shortness of breath, and malaise has been associated with intermittent use. It usually occurs after 3 to 6 months of intermittent treatment and has a higher incidence with doses of 25 mg/kg or more given once weekly than with more frequent dosage regimens. Anaphylaxis or shock has occurred rarely.

Gastrointestinal adverse effects include nausea, vomiting, anorexia, diarrhoea, and epigastric distress. Taking doses on an empty stomach is recommended for maximal absorption, but dosage after a meal will minimise gastrointestinal intolerance. Pseudomembranous colitis has been reported. Rifampicin produces transient abnormalities in liver function and hepatitis. Fatalities due to hepatotoxicity have been reported occasionally (see Effects on the Liver, p. 354.1).

Rifampicin can cause thrombocytopenia and purpura, usually when given as an intermittent regimen, and if this occurs further use of rifampicin is contra-indicated. Other haematological adverse effects include eosinophilia, leucopenia, and haemolytic anaemia.

Alterations in kidney function and renal failure have occurred, particularly during intermittent therapy. Menstrual disturbances have been reported.

Nervous system adverse effects include headache, drowsiness, ataxia, dizziness, and numbness.

Oedema, myopathy, and muscular weakness have been reported.

Thrombophlebitis has occurred after prolonged intravenous infusion. Extravasation during intravenous infusion may cause local irritation and inflammation.

Rifampicin causes a harmless orange-red discoloration of the urine, faeces, sweat, saliva, sputum, tears, and other body fluids. Soft contact lenses may become permanently stained.

Effects on the blood. Thrombocytopenia may occur in patients taking rifampicin, most commonly as intermittent therapy, and probably has an immunological basis. The platelet count may fall within 3 hours of a dose and return to normal within 36 hours, if additional doses are not given.[1] There may also be a risk of thrombocytopenia when re-introducing rifampicin to patients who have interrupted their treatment.[2] Thrombocytopenia has also been reported in a patient taking rifampicin for the first time for meningococcal prophylaxis.[3] Thrombotic thrombocytopenic purpura has been reported in a patient after two weeks of treatment with oral rifampicin and intravenous vancomycin for an infection with MRSA.[4] Fatalities have occurred when rifampicin was not withdrawn once thrombocytopenic purpura had developed or when treatment with rifampicin was resumed in patients who had experienced purpura.[1] However, there is a report of the successful re-introduction of rifampicin in a patient who developed thrombocytopenia without rifampicin-dependent antibodies.[5]

Bleeding from the oral cavity not associated with thrombocytopenia has been reported in a patient taking rifampicin.[6] Leucopenia,[7,8] haemolysis or haemolytic anaemia,[9] and red cell aplasia[10] have occurred. Disseminated intravascular coagulation has been reported in a patient receiving intermittent rifampicin therapy.[11] The incidence of deep-vein thrombosis increased in one group of hospitalised tuberculosis patients when rifampicin was introduced as standard therapy,[12] but data from others have not supported a causal relationship.[13]

1. Girling DJ. Adverse effects of antituberculosis drugs. *Drugs* 1982; 23: 56–74.
2. Burnette FK, *et al.* Rifampin-associated thrombocytopenia secondary to poor compliance. *Drug Intell Clin Pharm* 1989; 23: 382–4.
3. Hall AP, *et al.* New hazard of meningococcal chemoprophylaxis. *J Antimicrob Chemother* 1993; 31: 451.
4. Gupta R, Wargo KA. Rifampin-induced thrombotic thrombocytopenic purpura. *Ann Pharmacother* 2005; 39: 1761–2.
5. Bhasin DK, *et al.* Can rifampicin be restarted in patients with rifampicin-induced thrombocytopenia? *Tubercle* 1991; 72: 306–7.
6. Sule RR. An unusual reaction to rifampicin in a once monthly dose. *Lepr Rev* 1996; 67: 227–33.
7. Van Assendelft AHW. Leucopenia in rifampicin chemotherapy. *J Antimicrob Chemother* 1985; 16: 407–8.
8. Vijayakumaran P, *et al.* Leucocytopenia after rifampicin and ofloxacin therapy in leprosy. *Lepr Rev* 1997; 68: 10–15.
9. Lakshminarayan S, *et al.* Massive haemolysis caused by rifampicin. *BMJ* 1973; 2: 282–3.
10. Mariette X, *et al.* Rifampicin-induced pure red cell aplasia. *Am J Med* 1989; 87: 459–60.
11. Souza CS, *et al.* Disseminated intravascular coagulopathy as an adverse reaction to intermittent rifampin schedule in the treatment of leprosy. *Int J Lepr* 1997; 65: 366–71.
12. White NW. Venous thrombosis and rifampicin. *Lancet* 1989; ii: 434–5.
13. Cowie RL, *et al.* Deep-vein thrombosis and pulmonary tuberculosis. *Lancet* 1989; ii: 1397.

Effects on the gastrointestinal tract. In addition to symptoms of gastrointestinal intolerance, there have been reports of gastrointestinal bleeding and erosive gastritis,[1] ulcerative colitis,[2] and eosinophilic colitis[3] in patients receiving rifampicin.

1. Zargar SA, *et al.* Rifampicin-induced upper gastrointestinal bleeding. *Postgrad Med J* 1990; 66: 310–11.
2. Tajima A, *et al.* Rifampicin-associated ulcerative colitis. *Ann Intern Med* 1992; 116: 778–9.
3. Lange P, *et al.* Eosinophilic colitis due to rifampicin. *Lancet* 1994; 344: 1296–7.

Effects on the liver. Transient abnormalities in liver function are common during the early stages of antituberculous therapy with rifampicin and other first-line antituberculous drugs, but sometimes the **hepatotoxicity** may be more serious and require a change of treatment. Drug-induced hepatitis usually occurs within the first few weeks of treatment and it may not be possible to identify which drug or drugs are responsible. Rifampicin is thought to have a lower potential for hepatotoxicity than isoniazid or pyrazinamide.[1]

Risk factors for hepatotoxicity include alcoholism, old age, female gender, malnutrition, HIV infection, and chronic hepatitis B and C infections.[1]

The **incidence** of severe hepatotoxicity was found to be lower in patients taking isoniazid, rifampicin, and pyrazinamide for initial treatment of active tuberculosis, than in those given rifampicin and pyrazinamide for 2 months for latent infection. Management of latent disease with the rifampicin plus pyrazinamide regimen was also associated with a higher incidence of severe hepatotoxicity than was isoniazid monotherapy for 6 months.[2] Severe and sometimes fatal hepatotoxicity has been associated with a regimen of rifampicin and pyrazinamide for the treatment of latent tuberculosis in a mainly HIV-negative study population.[2-6] In the USA, the CDC and the American Thoracic Society[7] now recommend that a regimen of rifampicin with pyrazinamide should not generally be offered to persons with latent tuberculosis. However, an evaluation of studies[8] for the prevention of tuberculosis, involving HIV-infected patients, reported very little evidence of hepatotoxicity among patients taking rifampicin plus pyrazinamide and among those taking isoniazid.

The Joint Tuberculosis Committee of the British Thoracic Society has published recommendations[9] for initial measurement of liver function in all patients and regular **monitoring** in patients with pre-existing liver disease. Details are given concerning the response to deteriorating liver function and guidelines included for prompt re-introduction of appropriate antituberculosis therapy once normal liver function is restored. Similar guidelines have been produced for the USA.[10,11]

For further information on hepatotoxicity caused by antituberculous drugs see Effects on the Liver, under Isoniazid, p. 312.1 and Pyrazinamide, p. 345.3.

Hepatitis and liver dysfunction have also been reported in patients taking rifampicin, in the absence of other hepatotoxic drugs, for the treatment of pruritus associated with primary biliary cirrhosis.[12]

1. Yew WW, Leung CC. Antituberculosis drugs and hepatotoxicity. *Respirology* 2006; 11: 699–707.
2. van Hest R, *et al.* Hepatotoxicity of rifampin-pyrazinamide and isoniazid preventive therapy and tuberculosis treatment. *Clin Infect Dis* 2004; 39: 488–96.
3. CDC. Update: fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infection, and revisions in American Thoracic Society/CDC recommendations—United States, 2001. *MMWR* 2001; 50: 733–5. Also available at http://www.cdc.gov/mmwr/PDF/wk/mm5034.pdf (accessed 05/10/07)
4. CDC. Update: fatal and severe liver injuries associated with rifampin and pyrazinamide treatment for latent tuberculosis infection. *MMWR* 2002; 51: 998–9. Also available at http://www.cdc.gov/mmwr/PDF/wk/mm5144.pdf (accessed 05/10/07)
5. Jasmer RM, *et al.* Short-course rifampin and pyrazinamide compared with isoniazid for latent tuberculosis infection: a multicenter clinical trial. *Ann Intern Med* 2002; 137: 640–7.
6. Ijaz K, *et al.* Severe or fatal liver injury in 50 patients in the United States taking rifampin and pyrazinamide for latent tuberculosis infection. *Clin Infect Dis* 2006; 42: 346–55.
7. CDC. Update: adverse event data and revised American Thoracic Society/CDC recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection—United States, 2003. *MMWR* 2003; 52: 735–9. Also available at: http://www.cdc.gov/mmwr/PDF/wk/mm5231.pdf (accessed 05/10/07)
8. Gordin FM, *et al.* Hepatotoxicity of rifampin and pyrazinamide in the treatment of latent tuberculosis infection in HIV-infected persons: is it different than in HIV-uninfected persons? *Clin Infect Dis* 2004; 39: 561–5.
9. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; 53: 536–48.[Although these guidelines were replaced by ones issued by NICE in 2006 the latter do not *"explain tuberculosis or its treatment in detail"* and therefore reference to the earlier guidelines has been retained] Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Tuberculosis/Guidelines/Chemotherapy.pdf (accessed 29/07/08)
10. American Thoracic Society, CDC, and the Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; 52 (RR-11): 1–77. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf (accessed 05/10/07) Correction. *ibid.* 2005; 53: 1203. [dose]
11. Saukkonen JJ, *et al.* American Thoracic Society. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med* 2006; 174: 935–52. Also available at: http://www.thoracic.org/statements/resources/mtpi/hepatotoxicity-of-antituberculosis-therapy.pdf (accessed 16/07/10)
12. Prince MI, *et al.* Hepatitis and liver dysfunction with rifampicin therapy for pruritus in primary biliary cirrhosis. *Gut* 2002; 50: 436–9.

Effects on the lungs. Pulmonary fibrosis[1] in one elderly man and pneumonitis[2] in another were attributed to rifampicin.

1. Umeki S. Rifampicin and pulmonary fibrosis. *Arch Intern Med* 1988; 148: 1663, 7.
2. Kunichika N, *et al.* Pneumonitis induced by rifampicin. *Thorax* 2002; 57: 1000–1001.

Effects on the pancreas. Chronic pancreatic insufficiency has been reported in a patient after use of rifampicin, isoniazid, ethambutol, and pyrazinamide.[1]

1. Liu BA, *et al.* Pancreatic insufficiency due to antituberculosis therapy. *Ann Pharmacother* 1997; 31: 724–6.

Effects on the skin. Skin reactions to rifampicin are usually mild, irrespective of it being given daily or intermittently.[1] However, there have been a few isolated reports of severe reactions such as toxic epidermal necrolysis, exfoliative dermatitis,[3] fixed drug eruptions,[4,5] and acute generalised exanthematous pustulosis.[6] Contact dermatitis has been seen after handling rifampicin powder.[7]

1. Girling DJ. Adverse reactions to rifampicin in antituberculosis regimens. *J Antimicrob Chemother* 1977; 3: 115–32.
2. Okano M, *et al.* Toxic epidermal necrolysis due to rifampicin. *J Am Acad Dermatol* 1987; 17: 303–4.
3. Goldin HM, *et al.* Rifampin and exfoliative dermatitis. *Ann Intern Med* 1987; 107: 789.
4. Mimouni A, *et al.* Fixed drug eruption following rifampin treatment. *DICP Ann Pharmacother* 1990; 24: 947–8.
5. John SS. Fixed drug eruption due to rifampin. *Lepr Rev* 1998; 69: 397–9.
6. Azad A, Connelly N. Case of rifampicin-induced acute generalized exanthematous pustulosis. *Intern Med J* 2006; 36: 619–20.
7. Anker N, Da Gunha Bang F. Long-term intravenous rifampicin treatment: advantages and disadvantages. *Eur J Respir Dis* 1981; 62: 84–6.

Hypersensitivity. References.

1. Girling DJ. Adverse reactions to rifampicin in antituberculosis regimens. *J Antimicrob Chemother* 1977; 3: 115–32.
2. Wurtz RM, *et al.* Anaphylactoid drug reactions to ciprofloxacin and rifampicin in HIV-infected patients. *Lancet* 1989; i: 955–6.
3. Harland RW, *et al.* Anaphylaxis from rifampin. *Am J Med* 1992; 92: 581–2.
4. Cnudde F, Leynadier F. The diagnosis of allergy to rifampicin confirmed by skin test. *Am J Med* 1994; 97: 403–4.
5. Sharma VK, *et al.* Rifampicin-induced urticaria in leprosy. *Lepr Rev* 1997; 68: 331–2.
6. Martínez E, *et al.* Shock and cerebral infarct after rifampin re-exposure in a patient infected with human immunodeficiency virus. *Clin Infect Dis* 1998; 27: 1329–30.

Lupus. Symptoms including malaise, arthralgia, arthritis and oedema of the extremities, occurring in 4 patients taking rifampicin and 3 taking rifabutin, were considered to be due to drug-induced lupus syndrome.[1] Cutaneous lupus erythematosus was reported in a patient receiving rifampicin with clarithromycin and ethambutol.[2] All patients had positive anti-nuclear antibody titres.[1,2]

1. Berning SE, Iseman MD. Rifamycin-induced lupus syndrome. *Lancet* 1997; 349: 1521–2.
2. Patel GK, Anstey AV. Rifampicin-induced lupus erythematosus. *Clin Exp Dermatol* 2001; 26: 260–2.

Overdosage. Cases of skin pigmentation induced by rifampicin overdose have been reviewed.[1] Reddish-orange discoloration of the skin appeared within a few hours of taking the drug; urine, mucous membranes, and sclerae were also discoloured. Periorbital or facial oedema, pruritus, and gastrointestinal intolerance occurred in most patients. Treatment was supportive and clinical symptoms resolved in most patients over 3 to 4 days, although fatalities occurred with doses over 14 g.

1. Holdiness MR. A review of the redman syndrome and rifampicin overdosage. *Med Toxicol Adverse Drug Exp* 1989; 4: 444–51.

Precautions

Liver function should be checked before treatment with rifampicin and special care should be taken in alcoholics, patients or those with pre-existing liver disease who require regular monitoring during therapy. UK licensed product information states that use is contra-indicated in patients with jaundice. A self-limiting hyperbilirubinaemia may occur in the first 2 or 3 weeks of treatment. Alkaline phosphatase values may be raised moderately due to rifampicin's enzyme-inducing capacity. Isolated results showing hyperbilirubinaemia in the first few weeks and/or moderately elevated transaminase values are not indications to withdraw rifampicin. However, dose adjustment is necessary when there is other evidence of hepatic impairment and treatment should be suspended when there is evidence of more serious liver toxicity.

Blood counts should be monitored during prolonged treatment and in patients with hepatic disorders. Should thrombocytopenia or purpura occur then rifampicin should be withdrawn permanently. UK product information also recommends such withdrawal in patients who develop haemolytic anaemia or renal failure.

Use of rifampicin after interruption of treatment has been associated with increased risk of serious adverse effects.

The enzyme-inducing properties of rifampicin (see Interactions, p. 355.1) can enhance the metabolism of endogenous substrates including adrenal hormones, thyroid hormone, and vitamin D. Management of diabetes mellitus may be more difficult, and rifampicin should be used with caution in diabetic patients.

Patients should be advised that rifampicin may colour faeces, saliva, sputum, sweat, tears, urine, and other body-

fluids orange-red. Soft contact lenses may become permanently stained.

Rifampicin should not be given by the intramuscular or subcutaneous route. When given by intravenous infusion care should be taken to avoid extravasation.

Adrenocortical insufficiency. Adrenal insufficiency has been associated with tuberculosis and induction of microsomal enzymes by rifampicin may accelerate the metabolism of cortisol and precipitate an acute adrenal crisis in such patients.[1] Induction of microsomal enzymes may be enough to compromise even patients with mildly impaired cortisol production. Critical hypotension has also developed in non-Addisonian patients within a week to 10 days of starting rifampicin therapy. However, it has not been necessary to suspend the use of rifampicin if patients are treated with corticosteroids.[2] The efficacy of corticosteroid therapy can be reduced by rifampicin.

1. Elansary EH, Earis JE. Rifampicin and adrenal crisis. *BMJ* 1983; 286: 1861–2.
2. Boss G. Rifampicin and adrenal crisis. *BMJ* 1983; 287: 62.

Breast feeding. Rifampicin is excreted into breast milk. No adverse effects have been seen in breast-fed infants whose mothers were taking rifampicin, and the last available guidance from the American Academy of Pediatrics considered[1] that it was therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 05/10/07)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies rifampicin as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 08/07/11)

Pregnancy. Guidelines produced by WHO,[1] by an expert group in the UK,[2] and by the CDC in the USA[3] have recommended treatment of pregnant patients with the same rifampicin-containing multidrug regimens as would be used in non-pregnant patients. While use of rifampicin in pregnant patients is generally considered to be safe, the drug does cross into the fetus[4] and malformations and bleeding tendencies have been reported.[5] A literature review[5] revealed 386 normal term infants and 29 elective terminations out of 446 pregnancies in patients who took rifampicin with other antimycobacterial drugs. A variety of malformations were reported; there were 14 abnormal infants or fetuses, 2 premature births, 9 still-births and 7 spontaneous abortions. It was considered that rifampicin did not increase the overall risk of congenital malformations.

Rifampicin treatment can increase the metabolism of vitamin K, resulting in clotting disorders associated with vitamin K deficiency. Bleeding disorders in 2 mothers shortly after delivery, and scalp haemorrhage, anaemia, and shock in one of the infants have been reported.[6] The authors recommended blood coagulation monitoring and giving prophylactic vitamin K to mothers and neonates when the mother has received rifampicin during pregnancy.

1. WHO. *Treatment of tuberculosis: guidelines—4th edition.* Geneva: WHO. 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf (accessed 08/12/10)
2. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; 53: 536–48. [Although these guidelines were replaced by ones issued by NICE in 2006 the latter do not *"explain tuberculosis or its treatment in detail"* and therefore reference to the earlier guidelines has been retained] Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Tuberculosis/Guidelines/Chemotherapy.pdf (accessed 29/07/08)
3. American Thoracic Society, CDC, and the Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; 52 (RR-11): 1–77. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf (accessed 05/10/07) Correction. *ibid.* 2005; 53: 1203. [dose]
4. Holdiness MR. Transplacental pharmacokinetics of the antituberculosis drugs. *Clin Pharmacokinet* 1987; 13: 125–9.
5. Snider DE, *et al.* Treatment of tuberculosis during pregnancy. *Am Rev Respir Dis* 1980; 122: 65–79.
6. Chouraqui JP, *et al.* Hémorragie par avitaminose K chez la femme enceinte et le nouveau-né: rôle éventuel de la rifampicine: a propos de 2 observations. *Therapie* 1982; 37: 447–50.

Interactions

Rifampicin accelerates the metabolism of many drugs by inducing microsomal liver enzymes (in particular the cytochrome P450 isoenzyme family CYP3A) or drug transporter proteins (such as p-glycoprotein). Drugs so affected may require an increase in dosage to maintain efficacy and patients should be monitored closely when starting or stopping concurrent rifampicin treatment. Women taking oral contraceptives should use additional precautions or change to a non-hormonal form of contraception (see Rifamycins, p. 2243.1).

The absorption of rifampicin may be reduced by antacids, but this interaction can be overcome by giving rifampicin an hour before any antacid. Similarly, rifampicin and preparations containing bentonite (for example some aminosalicylic acid preparations) should be given 8 hours apart. Isoniazid and halothane may increase the potential for hepatotoxicity when given with rifampicin. Atovaquone may increase the concentration of rifampicin, while rifampicin decreases the concentration of atovaquone. Some other interactions affecting the activity of rifampicin are discussed below.

Reviews.

1. Yew WW. Clinically significant interactions with drugs used in the treatment of tuberculosis. *Drug Safety* 2002; 25: 111–33.
2. Niemi M, *et al.* Pharmacokinetic interactions with rifampicin: clinical relevance. *Clin Pharmacokinet* 2003; 42: 819–50.
3. Baciewicz AM, *et al.* Update on rifampin and rifabutin drug interactions. *Am J Med Sci* 2008; 335: 126–36.

Antibacterials. Use of *clofazimine* in leprosy patients receiving rifampicin with or without dapsone may decrease the rate of absorption of rifampicin and increase the time to peak plasma concentration.[1] In patients receiving clofazimine, rifampicin, and dapsone, the area under the curve for rifampicin was reduced.[1] However, a multiple dose study[2] showed that the pharmacokinetics of rifampicin were similar after 7 days of treatment with rifampicin and dapsone or rifampicin, dapsone, and clofazimine.

In 15 patients receiving therapy including rifampicin for tuberculosis, a course of *co-trimoxazole* resulted in increases in peak plasma concentrations and in the area under the concentration-time curve for rifampicin.[3] No adverse effects were seen and the clinical implications of this observation remain unclear. In another study,[4] significant reductions in the area under the plasma concentration-time curves for trimethoprim and sulfamethoxazole occurred after therapy including rifampicin was given to 10 HIV-infected patients on co-trimoxazole prophylaxis. Again, the clinical significance of this interaction is unclear.

There is little significant pharmacokinetic interaction between rifampicin and *isoniazid*.[5] Although lower blood concentrations of rifampicin have been reported with isoniazid, the effect is not considered clinically significant.[6] Since both drugs are hepatotoxic, there could be an increased incidence of hepatic damage, although the benefits of using this combination are considered to outweigh any potential risks.

1. Mehta J, *et al.* Effect of clofazimine and dapsone on rifampicin (Lositril) pharmacokinetics in multibacillary and paucibacillary leprosy cases. *Lepr Rev* 1986; 57 (suppl 3): 67–76.
2. Venkatesan K, *et al.* The effect of clofazimine on the pharmacokinetics of rifampicin and dapsone in leprosy. *J Antimicrob Chemother* 1986; 18: 715–18.
3. Bhatia RS, *et al.* Drug interaction between rifampicin and cotrimoxazole in patients with tuberculosis. *Hum Exp Toxicol* 1991; 10: 419–21.
4. Ribera E, *et al.* Rifampin reduces concentrations of trimethoprim and sulfamethoxazole in serum in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother* 2001; 45: 3238–41.
5. Acocella G, *et al.* Kinetics of rifampicin and isoniazid administered alone and in combination to normal subjects and patients with liver disease. *Gut* 1972; 13: 47–53.
6. Mouton RP, *et al.* Blood levels of rifampicin, desacetylrifampicin and isoniazid during combined therapy. *J Antimicrob Chemother* 1979; 5: 447–54.

Antifungals. Giving rifampicin, *ketoconazole*, and isoniazid together has produced low serum concentrations of each drug resulting in failure of antifungal treatment.[1] Rifampicin serum concentrations are reduced when rifampicin is given with ketoconazole;[2] separation of the doses by 30 minutes[3] to 12 hours[2] may result in similar rifampicin concentrations to those attained when rifampicin is given alone, although serum concentrations of ketoconazole remain depressed regardless of the timing of doses.

1. Abadie-Kemmerly S, *et al.* Failure of ketoconazole treatment of Blastomyces dermatitidis due to interaction of isoniazid and rifampin. *Ann Intern Med* 1988; 109: 844–5. Correction. *ibid.* 1989; 111: 96.
2. Engelhard D, *et al.* Interaction of ketoconazole with rifampin and isoniazid. *N Engl J Med* 1984; 311: 1681–3.
3. Doble N, *et al.* Pharmacokinetic study of the interaction between rifampicin and ketoconazole. *J Antimicrob Chemother* 1988; 21: 633–5.

Antigout drugs. Although a study[1] showed that *probenecid* could increase serum-rifampicin concentrations, another[2] subsequently found that the effect was uncommon and inconsistent and concluded that probenecid had no place as an adjunct to routine rifampicin therapy.

1. Kenwright S, Levi AJ. Impairment of hepatic uptake of rifamycin antibiotics by probenecid and its therapeutic implications. *Lancet* 1973; ii: 1401–5.
2. Fallon RJ, *et al.* Probenecid and rifampicin serum levels. *Lancet* 1975; ii: 792–4.

Antiretrovirals. Rifamycins can induce the metabolism of *zidovudine*, the NNRTIs delavirdine, efavirenz, etravirine, and nevirapine, and *HIV-protease inhibitors*, resulting in potentially subtherapeutic plasma concentrations. In addition HIV-protease inhibitors inhibit the metabolism of rifamycins resulting in elevated plasma-rifamycin concentrations and an increased incidence of adverse effects.[1,2]

Guidelines in the UK[3] and the USA[2] recommend that rifampicin should not be used with the *NNRTIs* delavirdine and etravirine but opinion varies on whether it should be used with nevirapine. Patients taking rifampicin-based tuberculosis treatment when antiretroviral therapy (ART) was started were found to have a higher probability of an elevated viral load or virological failure in the first 2 years if they started treatment with a nevirapine-based regimen compared with those who started efavirenz-based ART.[4] However, virological outcomes for those given a nevirapine-based regimen were good, with 80% of them being virologically suppressed after 18 months of ART. Similarly, a prospective, controlled study of 142 HIV and tuberculosis co-infected Thai patients[5] found plasma-efavirenz concentrations to be less compromised by rifampicin than plasma-nevirapine concentrations; low NNRTI concentrations were predictive of HAART failure. Based on these data, the authors suggested that efavirenz-based ART should be preferred for HIV-infected patients who require treatment with rifampicin. Licensed product information for nevirapine and etravirine advise against the use of either drug with rifampicin. Rifampicin decreases the serum concentration of efavirenz and if they are used together, consideration should be given to increasing the dose of the antiretroviral (see Uses and Administration of Efavirenz, p. 977.1); no dose modification is needed for rifampicin.

It is also recommended that rifampicin should not be used with unboosted or low-dose ritonavir-boosted *HIV-protease inhibitor* regimens.

Rifampicin significantly decreases the serum concentration of the CCR-5 receptor antagonist, *maraviroc*, and it is recommended that the dose of maraviroc be increased (see Uses and Administration of Maraviroc, p. 1005.2); no dose modification is needed for rifampicin. Similarly, a dose increase should be considered for the integrase inhibitor *raltegravir* if coadministration with rifampicin cannot be avoided (see Uses and Administration of Raltegravir, p. 1011.3). No clinically significant interactions are expected with the HIV fusion inhibitor *enfuvirtide*.[6] See also p. 350.1 for comment on the interaction of antiretrovirals with rifabutin.

1. Anonymous. Clinical update: impact of HIV protease inhibitors on the treatment of HIV-infected tuberculosis patients with rifampin. *MMWR* 1996; 45: 921–5.
2. CDC. Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis (issued December 2007). Available at: http://www.cdc.gov/tb/publications/guidelines/TB_HIV_Drugs/PDF/tbhiv.pdf (accessed 16/07/10)
3. Pozniak AL, *et al.* British HIV Association. BHIVA treatment guidelines for TB/HIV infection, February 2005. Available at: http://www.bhiva.org/documents/Guidelines/TB/TB_HIV_FINAL2005.pdf (accessed 16/07/10)
4. Boulle A, *et al.* Outcomes of nevirapine- and efavirenz-based antiretroviral therapy when coadministered with rifampicin-based antitubercular therapy. *JAMA* 2008; 300: 530–9.
5. Manosuthi W, *et al.* A randomized trial comparing plasma drug concentrations and efficacies between 2 nonnucleoside reverse-transcriptase inhibitor-based regimens in HIV-infected patients receiving rifampicin: the N_2R Study. *Clin Infect Dis* 2009; 48: 1752–9.
6. Boyd MA, *et al.* Lack of enzyme-inducing effect of rifampicin on the pharmacokinetics of enfuvirtide. *J Clin Pharmacol* 2003; 43: 1382–91.

Antimicrobial Action

Rifampicin is bactericidal against a wide range of microorganisms and interferes with their synthesis of nucleic acids by inhibiting DNA-dependent RNA polymerase. It has the ability to kill intracellular organisms. It is active against mycobacteria, including *Mycobacterium tuberculosis*, *M. avium*, and *M. leprae* and, having high sterilising activity against these organisms, it possesses the ability to eliminate semi-dormant or persisting organisms.

Rifampicin is also active against Gram-positive bacteria, especially staphylococci, but less active against Gram-negative organisms. The most sensitive Gram-negative bacteria include *Neisseria meningitidis*, *N. gonorrhoeae*, *Haemophilus influenzae*, and *Legionella* spp. Rifampicin also has activity against *Chlamydia trachomatis* and some anaerobic bacteria. At high concentrations it is active against some viruses.

Strains of *M. tuberculosis*, *M. leprae*, and other susceptible bacteria (such as *N. meningitidis*) have shown resistance, both initially and during treatment. Acquired resistance to rifampicin develops rapidly if it is used alone in the treatment of clinical infection, and resistance is thought to be due to a single-step mutation of the DNA-dependent RNA polymerase. Thus in tuberculosis and leprosy treatment regimens, rifampicin is used with other antimycobacterials to delay or prevent the development of rifampicin resistance. Resistance does not appear to be a problem when rifampicin is used alone in the management of latent tuberculosis, probably because the bacillary load is low. Cross-resistance has been shown between rifampicin and other rifamycins. Strains of *M. tuberculosis* resistant to both rifampicin and isoniazid (termed multidrug-resistant tuberculosis) are increasingly being reported; some strains are also resistant to second-line antimycobacterials (termed extensively drug-resistant tuberculosis).

Pharmacokinetics

Rifampicin is readily absorbed from the gastrointestinal tract and peak plasma concentrations varying from 4 to 32 micrograms/mL (average 7 micrograms/mL) have been reported after a dose of 600 mg. Food may reduce and delay absorption. Rifampicin is about 80% bound to plasma proteins. It is widely distributed in body tissues and fluids and diffusion into the CSF is increased when the meninges are inflamed. Rifampicin is distributed into breast milk and crosses the placenta (see Breast Feeding, p. 353.1, and Pregnancy, p. 353.1, under Precautions). Half-lives for rifampicin have been reported to range initially from 2 to 5 hours, the longest elimination times occurring after the largest doses. However, as rifampicin induces its own metabolism, elimination time may decrease by up to 40% during the first 2 weeks, resulting in half-lives of about 2 to 3 hours. The half-life is prolonged in patients with severe hepatic impairment.

Rifampicin is rapidly metabolised in the liver mainly to active 25-*O*-deacetylrifampicin and excreted in the bile. Deacetylation diminishes intestinal reabsorption and increases faecal excretion, although significant enterohepatic circulation still takes place. About 60% of a dose eventually appears in the faeces. The amount excreted in the urine increases with increasing doses and up to 30% of a dose may be excreted in the urine, about half of it being unchanged drug. The metabolite formylrifampicin is also excreted in the urine. In patients with renal impairment the half-life of rifampicin is not prolonged at doses of 600 mg or less.

Distribution. Rifampicin is widely distributed in most body tissues and fluids after oral or intravenous use.[1] Rifampicin is also able to penetrate into polymorphonuclear leucocytes to kill intracellular pathogens.[2] Rifampicin does not appear to diffuse well through the uninflamed meninges[3] but therapeutic concentrations have been attained in the CSF after daily doses of 600 and 900 mg when the meninges are inflamed;[4] concentrations in the CSF are about 10 to 20% of simultaneous serum concentrations, and approximately represent the fraction unbound to plasma proteins. Corticosteroids do not appear to influence the penetration of rifampicin into the CSF of patients with tuberculous meningitis.[5]

1. Holdiness MR. Clinical pharmacokinetics of the antituberculosis drugs. *Clin Pharmacokinet* 1984; 9: 511–44.
2. Prokesch RC, Rand WL. Antibiotic entry into human polymorphonuclear leukocytes. *Antimicrob Agents Chemother* 1982; 21: 373–80.
3. Sippel JE, *et al.* Rifampin concentrations in cerebrospinal fluid of patients with tuberculous meningitis. *Am Rev Respir Dis* 1974; 109: 579–80.
4. D'Oliveira JJG. Cerebrospinal fluid concentrations of rifampin in meningeal tuberculosis. *Am Rev Respir Dis* 1972; 106: 432–7.
5. Woo J, *et al.* Cerebrospinal fluid and serum levels of pyrazinamide and rifampicin in patients with tuberculous meningitis. *Curr Ther Res* 1987; 42: 235–42.

HIV-infected patients. Malabsorption of rifampicin and other antituberculous drugs has been reported in some patients with HIV infection and tuberculosis,[1-6] and may contribute to acquired drug resistance and reduced efficacy of tuberculosis treatment. It is not clear whether this is related to the HIV infection itself or associated diarrhoea. A pilot study[2] in 26 HIV-positive patients undergoing multidrug antituberculosis treatment found that serum concentrations of isoniazid were generally regarded as adequate; serum concentrations of rifampicin and ethambutol were low. A study[3] in patients with HIV infection but not co-infected with tuberculosis reported reduced absorption for rifampicin and pyrazinamide compared with healthy subjects; isoniazid was generally well absorbed. A pharmacokinetic study[4] reported malabsorption of all first-line antituberculous drugs in patients who had advanced HIV infection with diarrhoea and cryptosporidial infection. A further pharmacokinetic study,[5] in a similar subject population, found a significant degree of malabsorption of rifampicin and isoniazid in HIV-infected patients with or without diarrhoea. Low serum concentrations of rifabutin were reported in HIV-infected patients co-infected with tuberculosis treated with an intermittent (twice-weekly) tuberculosis regimen.[6] However, others found that HIV infection either did not affect[7,8] or uncommonly affected[9] the pharmacokinetics of antituberculous drugs.

Some authorities[10,11] consider that HIV-infected patients (including children) with tuberculosis have a similar response to short-course multidrug therapy as HIV-negative tuberculosis patients, and that most can be treated with the standard 6-month regimen. US[11,12] and UK[13] guidelines recommend that highly intermittent (once or twice weekly) tuberculosis regimens should not be used for co-infected patients with CD4+ cell counts less than 100 cells/microlitre.

1. Patel KB, *et al.* Drug malabsorption and resistant tuberculosis in HIV-infected patients. *N Engl J Med* 1995; 332: 336–7.
2. Peloquin CA, *et al.* Low antituberculosis drug concentrations in patients with AIDS. *Ann Pharmacother* 1996; 30: 919–25.
3. Sahai J, *et al.* Reduced plasma concentrations of antituberculosis drugs in patients with HIV infection. *Ann Intern Med* 1997; 127: 289–93.
4. Gurumurthy P, *et al.* Decreased bioavailability of rifampin and other antituberculosis drugs in patients with advanced human immunodeficiency virus disease. *Antimicrob Agents Chemother* 2004; 48: 4473–5.
5. Gurumurthy P, *et al.* Malabsorption of rifampin and isoniazid in HIV-infected patients with and without tuberculosis. *Clin Infect Dis* 2004; 38: 280–3.
6. Weiner M, *et al.* Association between acquired rifamycin resistance and the pharmacokinetics of rifabutin and isoniazid among patients with HIV and tuberculosis. *Clin Infect Dis* 2005; 40: 1481–91.
7. Choudhri SH, *et al.* Pharmacokinetics of antimycobacterial drugs in patients with tuberculosis, AIDS, and diarrhea. *Clin Infect Dis* 1997; 25: 104–11.
8. Taylor B, Smith PJ. Does AIDS impair the absorption of antituberculosis agents? *Int J Tuberc Lung Dis* 1998; 2: 670–5.
9. Perlman DC, *et al.* The clinical pharmacokinetics of pyrazinamide in HIV-infected persons with tuberculosis. *Clin Infect Dis* 2004; 38: 556–64.
10. WHO. *TB/HIV. A clinical manual.* 2nd ed. Geneva: WHO, 2004. Available at: http://whqlibdoc.who.int/publications/2004/9241546344.pdf (accessed 05/10/07)
11. CDC. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR* 2009; 58 (RR-4): 1 207. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5804.pdf (accessed 01/07/09)
12. CDC. Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. *MMWR* 2009; 58 (RR-11): 1–166. Available at http://aidsinfo.nih.gov/contentfiles/Pediatric_OI.pdf (accessed 16/07/10)
13. Pozniak AL, *et al.* British HIV Association. BHIVA treatment guidelines for TB/HIV infection, February 2005. Available at: http://www.bhiva.org/documents/Guidelines/TB/TB_HIV_FINAL2005.pdf (accessed 16/07/10)

Intravenous administration. Mean peak plasma concentrations of 10 micrograms/mL have been reported after rifampicin 600 mg by intravenous infusion over 3 hours. Peak plasma concentrations declined with repeated doses but to a less marked extent than occurs with oral use.[1] Mean peak plasma concentrations of 27 micrograms/mL have been reported in children after doses of 11.5 mg/kg infused over 30 minutes. Mean concentrations of 1.9 micrograms/mL were reported 8 hours after the dose.[2]

1. Acocella G, *et al.* Serum and urine concentrations of rifampicin administered by intravenous infusion in man. *Arzneimittelforschung* 1977; 27: 1221–6.
2. Koup JR, *et al.* Pharmacokinetics of rifampin in children I. Multiple dose intravenous infusion. *Ther Drug Monit* 1986; 8: 11–16.

Oral administration. Gastrointestinal absorption of rifampicin is considered good. However, analysis of serum-rifampicin concentrations in children indicated that only 50 ± 22% of a freshly prepared oral suspension was absorbed.[1] Varying oral bioavailability from capsule formulations has also been reported and could result in ineffective therapy[2] or higher than needed serum concentrations.[3]

The oral bioavailability of rifampicin and isoniazid, but not of pyrazinamide, was decreased by food in a study.[4] Another report[5] also showed reduced peak serum concentrations when rifampicin was given with a high-fat meal, and it was suggested that rifampicin should preferably be given on an empty stomach.

1. Koup JR, *et al.* Pharmacokinetics of rifampin in children II. Oral bioavailability. *Ther Drug Monit* 1986; 8: 17–22.
2. Holdiness MR. Clinical pharmacokinetics of the antituberculosis drugs. *Clin Pharmacokinet* 1984; 9: 511–44.
3. Ganiswarna SG, *et al.* Bioavailability of rifampicin caplets (600 mg and 450 mg) in healthy Indonesian subjects. *Int J Clin Pharmacol Ther Toxicol* 1986; 24: 60–4.
4. Zent C, Smith P. Study of the effect of concomitant food on the bioavailability of rifampicin, isoniazid and pyrazinamide. *Tubercle Lung Dis* 1995; 76: 109–13.
5. Peloquin CA, *et al.* Pharmacokinetics of rifampin under fasting conditions, with food, and with antacids. *Chest* 1999; 115: 12–18. Correction. *ibid.*; 1485.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Moxina†; Rifadin; Rifalep; *Austral.*: Rifadin; Rimycin; *Austria*: Eremfat; Rifoldin; Rimactan; *Belg.*: Rifadine; *Braz.*: Monicil†; Rifaldin; Rifamp; *Canad.*: Rifadin; Rofact; *Chile*: Rifadin; Rifaldin†; *China*: Fuhe (复和); Pi Jin (匹金); Shu Lan Xin (舒兰新); Wei Fu Xin (维夫欣); *Cz.*: Arficin; Benemicin; Eremfat; *Denm.*: Rimactan; *Fin.*: Rimapen; *Fr.*: Rifadine; Rimactan; *Ger.*: Eremfat; Rifa†; *Gr.*: Decloblotic; Maximicetin; Rifadin; Rifaldin; *Hong Kong*: Ricin; Rifacap†; Rifadin; Rifasynt; Rimactane†; Rimycin†; *Hung.*: Rifamed; *India*: Coxid; Eufacin; Famcin; Iso-Rifa; Kemorifa; LS Rif; Macox; Monocin; Montomycin; R-Cin; Rifacilin; Rifacom-EZ; Rifamycin; Rimactane; Siticox†; *Indon.*: Corifam; Famri; Lanarif; Medirif†; Merimac Prolung†; Ramicin†; RIF; Rifablotic†; Rifacin†; Rifamtibi; Rimactane; *Irl.*: Rifadin; Rimactane†; *Israel*: Rimactan; *Ital.*: Rifadin; *Malaysia*: Rifasynt; Rimactane; *Mex.*: Alfiral; Eurifam; Finamicina†; Pestarin†; Rifadin; Rimactan; Turifam; *Neth.*: Rifadin; *Norw.*: Rimactan; *NZ*: Rifadin; *Philipp.*: Crisarfam; Fampisec; Framacin†; Medifam; Natricin; Odifam†; Refam†; Rexilan; Ricyn†; Rifacin; Rifadin; Rifamax; Rifanid; Rimactane; Rimaped; Riprocin; *Port.*: Rifadin; Rifex†; *Rus.*: Benemicin (Бенемицин)†; Eremfat (Эремфат); Farbutin (Фарбутин); Macox (Макокс); Rimactane (Римактан); Rimpin (Римпин); *S.Afr.*: Rifadin; Rimactane; *Singapore*: Rifaren; Rimactane†; *Spain*: Rifaldin; Rimactan; *Swed.*: Rifadin; Rimactan; *Switz.*: Rimactan; *Thai.*: Manorifcin; Myrin-P†; Ricin; Rifacin-A; Rifadin; Rifagen; Rifam-P; Rifam; Rifamcin; Rimaccin; Rimactane†; Rimecin; Ripin; *Turk.*: Rifadin; Rifcap; Rifex†; *UK*: Rifadin; Rimactane; *USA*: Rifadin; Rimactane; *Venez.*: Rifadin; Rimactan.

Multi-ingredient Preparations. *Arg.*: Bacifim†; Rifaprim; Rifinah; *Austria*: Rifater; Rifoldin mit INH; *Braz.*: Isoniaton†; *Canad.* Rifater; *China*: An Si Nuo Kang (安斯诺康); Chang Wei Rui Da Xin (长威瑞达欣); Dai Fei Lin (戴菲林); Fei An (费安); Fei Lu De (菲路得); Fei Ning (费宁); Fei Su (菲苏); Fei Ting (菲亭); Hu Fei Te (护菲特); Ke Lao Er Kang (克劳尔康); Pi Lv (匹律); Rui Fu An Kang (瑞福安康); Rui Qing (瑞清); Ti Bi (缇碧); Wei Bao (维葆); Wei Fei (维菲); Yi Bi Fu (依比福); Yi Nuo Ni Kang (怡诺尼康); Yi Ti Bi (伊缇碧); *Denm.*: Rimactazid; Rimcure; Rimstar; *Fin.*: Rimactazid; Rimstar; *Fr.*: Rifater; Rifinah; *Ger.*: Iso-Eremfat; Rifater†; Rifinah†; tebesium Duo; tebesium Trio; *Gr.*: Oboliz; Rifater; Rifinah; Rimactazid; *Hong Kong*: Rifater; Rifinah; *Hung.*: Rifazid; *India*: AFB3; AFB4; Akt-2; Akt-3; Akt-4; Akt-FD; Akurit-3; Akurit-4; Akurit-Z; Akurit; Antibin; Arzade; Azide†; Becox Forte Kit; Becox RH; Bicox Kid; Bicox-E; Bicox; Binex DT; Binex E; Binex Kid; Binex Z; Binex ZE; Binex; Cavidin INH; Cavirip; Cavitar RHE; Caviter FD; Caviter; Confez-3; Coxina-3; Coxina-4; Coxinex; Coxkit-3; Coxpic; Coxter-2; Coxter-3; Coxter-4; Cx-3; Cx-4; Cx-5; Emrif Kit; Emrif; Eufacin Inh; Eufacin Plus; Eufazid; Famcin H; Faminex Forte; Faminex; Forecox; Gocox Compound; Gocox-3; Infez-4; Ipcacin Kid†; Ipcacin; Iso-Ripharmed; Isorifam; Macox Plus; Macox-ZH; Monto-2; Monto-3; Monto-4; Montonex Forte; Montorip; Mycocox-4; Mycocox-E; Mycocox-Z; Mycocox; Mycodot Kit; Mycodot-4; Mycodot-E; Mycodot-Z; Mycurit-3; Mycurit-4; Mycurit-Z; Optirifa Plus; R-Cinex 2; R-Cinex; RHZ Plus; RHZ; Rifa E; Rifa; Rimactazid + Z; Rimpazid; Siticox-INH†; Tibirim INH; Tricox; Wokex-2; Wokex-3; Wokex-4; Xeed 2; Xeed 3E; Xeed 4; *Indon.*: Ramicin-ISO†; Rimactazid; Rimcure; Rimstar; *Irl.*: Rifater; Rifinah; Rimactazid; Rimcure†; Rimstar; *Ital.*: Rifater; Rifinah; Rimactazid; Rimcure; Rimstar; *Malaysia*: Rimactazid; Rimcure; *Mex.*: Arpisen†; Dotbal-S; Dotbal; Finater†; Finateramida†; Rifaprim; Rifater; Rifinah; *Neth.*: Rifinah; Rimactazid†; Rimcure†; Rimstar†; *Norw.*: Rimactazid; Rimcure; Rimstar; *NZ*: Rifinah; *Philipp.*: 4D; AKurit-4; AKurit; Bifix; CombiKids†; CombiPack; Continukit Plus†; Continukit; Continupack†; Duomax; Econofix; Econokit-MDR; Econokit; Econopack; Fixcom 3; Fixcom 4; HR Pedia Kit; HRZ Pedia Kit; Kidz Kit 2; Kidz Kit 3; Myrin-P; Myrin; Quadmax; Quadtab; Refam Duo†; Refam Pedia Kit†; Rifater; Rifinah; Rifzin; Rimactazid; Rimcure; Rimstar; SVM-Polypac-A†; Tres; Triofix; Tritab; Viper†; *Pol.*: Rifamazid; *Port.*: Rifater; Rifinah; *Rus.*: Combitub (Комбитуб); Forecox (Форкокс); Iso-Eremfat (Изо-Эремфат); Isocomb (Изокомб); Laslonvita (Ласлонвита); Protub-2 (Протуб-2); Protub-3 (Протуб-3); Protub-4 (Протуб-4); Protubvita (Протубвита); Repin B_6 (Репин B_6); Rifacomb (Рифакомб); Rifacomb Plus (Рифакомб Плюс)†; Rimactazid (Римактазид)†; Rimecure 3-FDC (Римкур 3-ФДС)†; Rimstar 4-FDC (Римстар 4-ФДС)†; Tubavit (Тубавит); *S.Afr.*: Rifafour; Rifater†; Rifinah; Rimactazid; Rimcure; Rimstar; *Singapore*: Merip; Rimactazid; *Spain*: Rifater; Rifinah; Rimactazid†; Rimcure†; Rimstar; Tisobrif†; *Swed.*: Rimactazid; Rimcure; Rimstar; *Switz.*: Rifater; Rifinah; Rimactazid; Rimstar; *Thai.*: Lepromix MB; Lepromix PB; Rifafour; Rifampyzid; Rifater; Rifinah; Rimactazid†; Rimcure 3-FDC; Rimstar†; *UK*: Rifater; Rifinah; Rimstar; Voractiv; *USA*: IsonaRif; Rifamate; Rifater; *Venez.*: Rimactazid; Rimcure.

Pharmacopoeial Preparations

BP 2014: Rifampicin Capsules; Rifampicin Oral Suspension;
USP 36: Rifampin and Isoniazid Capsules; Rifampin Capsules; Rifampin for Injection; Rifampin Oral Suspension; Rifampin, Isoniazid, and Pyrazinamide Tablets; Rifampin, Isoniazid, Pyrazinamide, and Ethambutol Hydrochloride Tablets.

Rifamycin Sodium *(BANM, USAN, rINNM)*

CB-01-11; M-14 (rifamycin); Natrii Rifamycinum; Rifamicina sódica; Rifamicin-nátrium; Rifamicino natrio druska; Rifamycin-Natrium; Rifamycin sodná sůl; Rifamycin SV; Rifamycin SV Sodium; Rifamycine sodique; Rifamycinnatrium; Rifamycinum Natricum; Rifamysininatrium; Ryfamycinum Natricum; Ryfamycyna sodowa; Натрий Рифамицин.

Sodium (12*Z*,14*E*,24*E*)-(2*S*,16*S*,17*S*,18*R*,19*R*,20*R*,21*S*,22*R*,23*S*)-21-acetoxy-1,2-dihydro-6,9,17,19-tetrahydroxy-23-methoxy-2,4,12,16,18,20,22-heptamethyl-1,11-dioxo-2,7-(epoxypentadeca-1,11,13-trienimino)-naphtho[2,1-*b*]furan-5-olate.

$C_{37}H_{46}NNaO_{12}$=719.8

CAS — 6998-60-3 (rifamycin); 14897-39-3 (rifamycin sodium); 15105-92-7 (rifamycin sodium).

ATC — J04AB03; S01AA16; S02AA12.

ATC Vet — QJ04AB03; QS01AA16; QS02AA12.

UNII — 32086GS35Z.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Rifamycin Sodium). The monosodium salt of rifamycin SV, a substance obtained by chemical transformation of rifamycin B which is produced during growth of certain strains of *Amycolatopsis mediterranei*. Rifamycin SV may also be obtained directly from certain mutants of *A. mediterranei*. The potency is not less than 900 units/mg calculated with reference to the anhydrous substance. A red, fine or slightly granular powder. Soluble in water; freely soluble in dehydrated alcohol. A 5% solution in water

has a pH of 6.5 to 8.0. Store in airtight containers at a temperature of 2 degrees to 8 degrees. Protect from light.

Uses and Administration

Rifamycin is a rifamycin antibacterial that has been used in the treatment of infections caused by susceptible organisms including Gram-positive organisms such as staphylococci. It has been given as the sodium salt by intramuscular injection and by slow intravenous infusion and is also given by local instillation and topical application.

Adverse Effects and Precautions

Some gastrointestinal adverse effects have occurred after injections of rifamycin. High doses may produce alterations in liver function. Hypersensitivity reactions including rashes, pruritus, and anaphylaxis have occurred rarely, but prolonged use increases the risk of sensitisation. A reddish coloration of the urine and other body fluids has been reported. Rifamycin should be used with care in patients with hepatic dysfunction.

Antimicrobial Action

Rifamycin has similar antimicrobial actions to those of rifampicin (p. 353.3).

Pharmacokinetics

Rifamycin is not effectively absorbed from the gastrointestinal tract. Plasma concentrations of 2 micrograms/mL occur 2 hours after a dose of 250 mg by intramuscular injection; concentrations of about 11 micrograms/mL have been achieved 2 hours after an intravenous dose of 500 mg. Rifamycin is about 80% bound to plasma proteins and has a plasma half-life of about 1 hour.

Rifamycin is excreted mainly in the bile and only small amounts appear in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Rifocina: *Austria*: Rifocin; *Belg.*: Rifocine; *Braz.*: Arrif; Rifan; Rifasan; Rifocina; *China*: De Ji Jin Fei Ke (德济金菲克); Feng Li Fu (锋立复); Fu An Er (夫安尔); Lan Qi (澜琪); Sai Rui Chen (赛瑞辰); Xing Suo Ning (星索宁); *Fr.*: Otofa; *Ital.*: Rifocin; *Mex.*: Rifocyna; *Port.*: Rifocina; *Rus.*: Otofa (Отофа); *Switz.*: Otofa; *Turk.*: Rif; Rifateral; Rifocin; *Ukr.*: Otofa (Отофа); Rifonat (Рифонат); *Venez.*: Rifocina.

Multi-ingredient Preparations. *Braz.*: Rifocort.

Rifapentine *(BAN, USAN, rINN)*

DL-473; DL-473-IT; L-11473; MDL-473; Rifapentina; Rifapentinum; Рифапентин.

3-[*N*-(4-Cycloperityl-1-piperazinyl)formimidoyl]rifamycin.

$C_{47}H_{64}N_4O_{12}$=877.0

CAS — 61379-65-5.

ATC — J04AB05.

ATC Vet — QJ04AB05.

UNII — XJM390A33U.

Uses and Administration

Rifapentine is a rifamycin antibacterial (see Rifampicin, p. 350.3) that is used, with other antimycobacterials, for the treatment of tuberculosis (p. 210.2).

For drug-susceptible organisms rifapentine is given orally in a dose of 600 mg twice weekly during the initial intensive phase of short-course tuberculosis regimens, then once weekly during the continuation phase.

General references.

1. Jarvis B, Lamb HM. Rifapentine. *Drugs* 1998; 56: 607–16.
2. Munsiff SS, *et al.* Rifapentine for the treatment of pulmonary tuberculosis. *Clin Infect Dis* 2006; 43: 1468–75.
3. Anonymous. Rifapentine. *Tuberculosis (Edinb)* 2008; 88: 155–8.

Adverse Effects

As for Rifampicin, p. 351.3.

A higher incidence of hyperuricaemia has been reported with rifapentine than with rifampicin.

Precautions

As for Rifampicin, p. 352.3.

Rifapentine is only licensed for use in once- or twice-weekly regimens, and should not be given to HIV-infected patients because of potential interactions with HIV-protease inhibitors; an increased risk of developing resistance to rifamycins with highly intermittent (once- or twice-weekly) dosing regimens may occur in these patients.

Rifapentine is teratogenic in *animals*.

Interactions

As for Rifampicin, p. 353.1.

Enzyme induction studies have suggested that rifapentine is a more potent inducer of cytochrome P450 isoenzymes than rifabutin, but less potent than rifampicin. It should not be used with HIV-protease inhibitors because of the risk of developing resistance, see Precautions, above.

Antimicrobial Action

As for Rifampicin, p. 353.3.

Cross-resistance is common between rifapentine and rifampicin in *Mycobacterium tuberculosis*.

Antimycobacterial action. References.

1. Mor N, *et al.* Comparison of activities of rifapentine and rifampin against Mycobacterium tuberculosis residing in human macrophages. *Antimicrob Agents Chemother* 1995; 39: 2073–7.
2. Vernon A, *et al.* Acquired rifamycin monoresistance in patients with HIV-related tuberculosis treated with once-weekly rifapentine and isoniazid. *Lancet* 1999; 353: 1843–7.

Pharmacokinetics

Rifapentine is absorbed after oral doses. Absorption is enhanced by between about 35 and 85% when rifapentine is taken with food. Peak plasma concentrations occur 5 to 6 hours after a single dose of 600 mg and steady-state concentrations are reached by day 10 during daily use. A half-life of about 13 hours has been reported. Rifapentine undergoes nonoxidative metabolism and does not induce its own metabolism. Rifapentine and its active metabolite 25-deacetylrifapentine are 98% and 93% bound to plasma proteins, respectively.

Rifapentine and 25-deacetylrifapentine are excreted mainly in the faeces with a small amount appearing in the urine.

References.

1. Keung ACF, *et al.* Pharmacokinetics of rifapentine in patients with varying degrees of hepatic dysfunction. *J Clin Pharmacol* 1998; 38: 517–24.
2. Keung AC-F, *et al.* Pharmacokinetics of rifapentine in subjects seropositive for the human immunodeficiency virus: a phase I study. *Antimicrob Agents Chemother* 1999; 43: 1230–3.
3. Conte JE, *et al.* Single-dose intrapulmonary pharmacokinetics of rifapentine in normal subjects. *Antimicrob Agents Chemother* 2000; 44: 985–90.
4. Weiner M, *et al.* Pharmacokinetics of rifapentine at 600, 900, and 1,200 mg during once-weekly tuberculosis therapy. *Am J Respir Crit Care Med* 2004; 169: 1191–7.
5. Langdon G, *et al.* Population pharmacokinetics of rifapentine and its primary desacetyl metabolite in South African tuberculosis patients. *Antimicrob Agents Chemother* 2005; 49: 4429–36.
6. Blake MJ, *et al.* Pharmacokinetics of rifapentine in children. *Pediatr Infect Dis J* 2006; 25: 405–9.
7. Zvada SP, *et al.* Effects of four different meal types on the population pharmacokinetics of single-dose rifapentine in healthy male volunteers. *Antimicrob Agents Chemother* 2010; 54: 3390–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Ming Jia Xin (明佳欣); *Rus.*: Rifapex (Рифапекс); *USA*: Priftin.

Rifaximin *(BAN, USAN, rINN)*

L-105; Rifaxidin; Rifaximina; Rifaximine; Rifaximinum; Рифаксимин.

(2*S*,16*Z*,18*E*,20*S*,21*S*,22*R*,23*R*,24*R*,25*S*,26*S*,27*S*,28*E*)-5,6,21,23,25-Pentahydroxy-27-methoxy-2,4,11,16,20,22,24,26-octamethyl-2,7-(epoxypentadeca[1,11,13]trienimino)benzofuro[4,5-*e*]pyrido[1,2-*a*]benzimidazole-1,15(2*H*)-dione 25-acetate.

$C_{43}H_{51}N_3O_{11}$=785.9

CAS — 80621-81-4.

ATC — A07AA11; D06AX11.

ATC Vet — QA07AA11; QD06AX11; QG51AA06; QJ51XX01.

UNII — L36O5T016N.

NOTE. The code L-105 has also been applied to the cephalosporin cefuzonam.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Rifaximin). A semisynthetic product derived from a fermentation product. A red-orange, crystalline, hygroscopic powder. It exhibits polymorphism. Practically insoluble in water; soluble in acetone and in methyl alcohol. Store in airtight containers. Protect from light.

Uses and Administration

Rifaximin is a synthetic, nonabsorbed, derivative of rifamycin used orally for the treatment of travellers' diarrhoea (see Gastro-enteritis, p. 182.2) caused by noninvasive strains of *Escherichia coli* and to reduce the risk of recurrence of hepatic encephalopathy (see p. 1811.2). It has also been tried for other infectious diarrhoea in nontravellers, abdominal distension, bloating, and flatulence, small bowel bacterial overgrowth, and for surgical infection prophylaxis, as well as in some of those conditions discussed under Gastrointestinal Disorders (p. 1807.2), including diverticulitis, Crohn's disease, and non-constipation irritable bowel syndrome.

For the treatment of travellers' diarrhoea in those 12 years of age and older, the recommended oral dose is 200 mg three times daily for 3 days. A dose of 550 mg orally twice daily is recommended to reduce the risk of overt hepatic encephalopathy recurrence among patients 18 years of age and older. Doses given for other indications range from 400 to 1200 mg daily, in 2 to 4 divided doses.

Rifaximin has also been used topically as a 5% ointment.

General references.

1. Gillis JC, Brogden RN. Rifaximin: a review of its antibacterial activity, pharmacokinetic properties and therapeutic potential in conditions mediated by gastrointestinal bacteria. *Drugs* 1995; 49: 467–84.
2. Ojetti V, *et al.* Rifaximin pharmacology and clinical implications. *Expert Opin Drug Metab Toxicol* 2009; 5: 675–82.
3. Bajaj JS, Riggio O. Drug therapy: rifaximin. *Hepatology* 2010; 52: 1484–8.
4. Dupont HL. Biologic properties and clinical uses of rifaximin. *Expert Opin Pharmacother* 2011; 12: 293–302.

Gastrointestinal disorders. References.

1. DuPont HL, *et al.* Rifaximin versus ciprofloxacin for the treatment of traveler's diarrhea: a randomized, double-blind clinical trial. *Clin Infect Dis* 2001; 33: 1807–15.
2. Pakyz AL. Rifaximin: a new treatment for travelers' diarrhea. *Ann Pharmacother* 2005; 39: 284–9.
3. Robins GW, Wellington K. Rifaximin: a review of its use in the management of traveller's diarrhoea. *Drugs* 2005; 65: 1697–1713.
4. Adachi JA, DuPont HL. Rifaximin: a novel nonabsorbed rifamycin for gastrointestinal disorders. *Clin Infect Dis* 2006; 42: 541–7. Correction. *ibid.*; 896. [dose frequency]
5. Pimentel M, *et al.* The effect of a nonabsorbed oral antibiotic (rifaximin) on the symptoms of the irritable bowel syndrome: a randomized trial. *Ann Intern Med* 2006; 145: 557–63.
6. Fumi AL, Trexler K. Rifaximin treatment for symptoms of irritable bowel syndrome. *Ann Pharmacother* 2008; 42: 408–12.
7. Shafran I, Burgunder P. Rifaximin for the treatment of newly diagnosed Crohn's disease: a case series. *Am J Gastroenterol* 2008; 103: 2158–60.
8. Jiang Q, *et al.* Rifaximin versus nonabsorbable disaccharides in the management of hepatic encephalopathy: a meta-analysis. *Eur J Gastroenterol Hepatol* 2008; 20: 1064–70.
9. Lauritano EC, *et al.* Antibiotic therapy in small intestinal bacterial overgrowth: rifaximin versus metronidazole. *Eur Rev Med Pharmacol Sci* 2009; 13: 111–16.
10. Peralta S, *et al.* Small intestine bacterial overgrowth and irritable bowel syndrome-related symptoms: experience with rifaximin. *World J Gastroenterol* 2009; 15: 2628–31.
11. Maclayton DO, Eaton-Maxwell A. Rifaximin for treatment of hepatic encephalopathy. *Ann Pharmacother* 2009; 43: 77–84.
12. Bass NM, *et al.* Rifaximin treatment in hepatic encephalopathy. *N Engl J Med* 2010; 362: 1071–81.
13. Hong KS, *et al.* Efficacy of rifaximin compared with ciprofloxacin for the treatment of acute infectious diarrhea: a randomized controlled multicenter study. *Gut Liver* 2010; 4: 357–62.
14. Tannous G, *et al.* Therapeutic success of rifaximin for *Clostridium difficile* infection refractory to metronidazole and vancomycin. *Case Rep Gastroenterol* 2010; 4: 404–409.
15. Patrick Basu P, *et al.* Rifaximin therapy for metronidazole-unresponsive *Clostridium difficile* infection: a prospective pilot trial. *Therap Adv Gastroenterol* 2010; 3: 221–5.
16. Pimentel M, *et al.* TARGET Study Group. Rifaximin therapy for patients with irritable bowel syndrome without constipation. *N Engl J Med* 2011; 364: 22–32.

Diverticular disease. Rifaximin may be used in the management of diverticular disease (p. 1809.2); for reference to its use with mesalazine see p. 1862.3.

Adverse Effects and Precautions

Since rifaximin is poorly absorbed from the gastrointestinal tract, adverse effects have generally been restricted to gastrointestinal disturbances such as abdominal pain, diarrhoea, and nausea. Headache may also occur. Hypersensitivity reactions, including exfoliative dermatitis and angioedema have been reported.

Because of its poor systemic absorption (see p. 357.3) rifaximin should not be used to treat systemic bacterial infections. It should not be given to patients with travellers' diarrhoea complicated by fever or blood in the stool and should be used with caution in patients with severe (Child-Pugh Class C) hepatic impairment because of the risk of increased systemic exposure.

References.

1. Ericsson CD. Safety and tolerability of the antibacterial rifaximin in the treatment of travellers' diarrhoea. *Drug Safety* 2006; 29: 201–7.

Antimicrobial Action

Rifaximin has a mechanism of action and spectrum of antibacterial activity similar to that of rifampicin (see p. 353.3). Among Gram-negative bacteria, it is particularly active against the Enterobacteriaceae, and has good activity against *Vibrio cholera*. It also has pH-dependent activity against *Helicobacter pylori* (including clarithromycin-resistant strains); activity is improved at basic pH.

Rifaximin also appears to have activity against some protozoa, such as *Blastocystis hominis* and *Cryptosporidium parvum*.

Pharmacokinetics

Rifaximin is essentially nonabsorbed from the gastrointestinal tract, having a bioavailability of less than 0.4%. After a

single 400-mg oral dose serum concentrations up to 5.3 nanograms/mL have been found at 4 hours. Rifaximin is moderately bound to human plasma proteins. No excretion in breast milk has been noted.

Systemically available rifaximin is believed to be metabolised in the liver, similarly to other rifamycin derivatives; the systemic exposure of rifaximin is markedly elevated in patients with hepatic impairment; after the same dosing regimen, AUCs were 10-, 13-, and 20-fold higher in those with Child-Pugh Class A, B, and C hepatic impairment, respectively, than in healthy patients.

Rifaximin concentrates, and is mainly excreted unchanged in the faeces; less than 1% of a dose is recovered in the urine within the first 24 hours, mostly as metabolites.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Coloximina; Rifadom; *Austria*: Colidimin; *China*: Bang Yi (邦益); Fu Jie Ting (弗皆亭); Fu Te (抚特); Ji Li Qing (及利晴); Jinxili (金喜利); Lai Li Qing (莱利青); Ou Ke Shuang (欧克双); Qian Er Fen (倩儿芬); Sa Fen (萨芬); Xi Jie (希捷); Xifushen (昔服申); Zi Jun (紫军); *Cz.*: Normix; *Denm.*: Faxinorm; Saftra; Xifaxan; *Fin.*: Targaxan; *Ger.*: Xifaxan; *Gr.*: Lormyx; Rifacol; *Hung.*: Normix; *Ital.*: Colrifax; Diamixin; Normix; Redactiv; Rifacol; Sanecol; *Mex.*: Flonorm; *Neth.*: Xifaxan; *Pol.*: Xifaxan; *Port.*: Xifaxan; *Rus.*: Alfa Normix (Альфа Нормикс); *Spain*: Spiraxin; Zaxine†; *Turk.*: Colidur; Normix; *UK*: Targaxan; Xifaxanta; *USA*: Xifaxan.

Rokitamycin *(rINN)*

M-19-Q; Rikamycin; Rokitamicina; Rokitamycine; Rokitamycinum; TMS-19Q; Рокитамицин; 3''-Propionyl-leucomycin A_5.

[(4*R*,5*S*,6*S*,7*R*,9*R*,10*R*,11*E*,13*E*,16*R*)-7-(Formylmethyl)-4,10-dihydroxy-5-methoxy-9,16-dimethyl-2-oxooxacyclohexadeca-11,13-dien-6-yl]-3,6-dideoxy-4-*O*-(2,6-dideoxy-3-*C*-methyl-α-L-*ribo*-hexopyranosyl)-3-(dimethylamino)-β-D-glucopyranoside 4''-butyrate 3''-propionate.

$C_{42}H_{69}NO_{15}$=828.0

CAS — 74014-51-0.

ATC — J01FA12.

ATC Vet — QJ01FA12.

UNII — ZPT03UEM0E.

Pharmacopoeias. In *Jpn*.

Profile

Rokitamycin is a macrolide antibacterial with actions and uses similar to those of erythromycin (p. 291.2). It has been given orally in usual doses of 400 mg twice daily in the treatment of susceptible infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Paidocin; Rokital; *Jpn*: Ricamycin.

Rolitetracycline *(BAN, USAN, rINN)*

PMT; Pyrrolidinomethyltetracycline; Rolitetraciclina; Rolitétracycline; Rolitetracyclinum; Rolitetracyklin; Rolitetrasykliini; SQ-15659; Ролитетрациклин.

N^2-(Pyrrolidin-1-ylmethyl)tetracycline.

$C_{27}H_{33}N_3O_8$=527.6

CAS — 751-97-3.

ATC — J01AA09.

ATC Vet — QJ01AA09.

UNII — GH9IW85221.

Profile

Rolitetracycline is a tetracycline derivative with general properties similar to those of tetracycline (p. 375.1). It is included in some topical eye preparations used for the treatment of susceptible infections. It has also been given by injection, when it has been associated with shivering and, more rarely, rigor, due to a Jarisch-Herxheimer reaction. Injection has also been followed by a peculiar taste sensation, often similar to ether.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Ital.*: Colbiocin; Eubetal Antibiotico; *Rus.*: Colbiocin (Колбиоцин).

Rosoxacin *(BAN, USAN, rINN)*

Acrosoxacin; Rosoksasiini; Rosoxacine; Rosoxacino; Rosoxacinum; Win-35213; Розоксацин.

1-Ethyl-1,4-dihydro-4-oxo-7-(4-pyridyl)quinoline-3-carboxylic acid.

$C_{17}H_{14}N_2O_3$=294.3

CAS — 40034-42-2.

ATC — J01MB01.

ATC Vet — QJ01MB01.

UNII — 3Y1OT3J4NW.

Uses and Administration

Rosoxacin is a 4-quinolone antibacterial with actions similar to those of nalidixic acid (p. 328.3). It is active against *Neisseria gonorrhoeae* and has been given as single-dose oral treatment for gonorrhoea. It has also been used in the treatment of urinary-tract infections.

Adverse Effects and Precautions

As for Nalidixic Acid, p. 329.1.

Dizziness, drowsiness, and visual disturbances occur relatively frequently, and patients should be advised not to drive or operate machinery if affected.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Eradacil; *Mex.*: Eradacil†.

Roxithromycin *(BAN, USAN, rINN)*

Roksitromicinas; Roksitromisin; Roksitromysiini; Roxithromycine; Roxithromycinum; Roxitromicin; Roxitromicina; Roxitromycin; RU-965; RU-28965; Рокситромицин.

Erythromycin 9-[*O*-[(2-methoxyethoxy)methyl]oxime].

$C_{41}H_{76}N_2O_{15}$=837.1

CAS — 80214-83-1.

ATC — J01FA06.

ATC Vet — QJ01FA06.

UNII — 21KOF230FA.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn*.

Ph. Eur. 8: (Roxithromycin). A white or almost white, crystalline powder. It exhibits polymorphism. Very slightly soluble in water; freely soluble in alcohol, in acetone, and in dichloromethane; slightly soluble in dilute hydrochloric acid. Store in airtight containers.

Uses and Administration

Roxithromycin is a macrolide antibacterial given for the treatment of susceptible infections; its actions and uses are similar to those of erythromycin (p. 292.1). It is given orally to adults in a usual dose of 150 mg twice daily or sometimes 300 mg once daily, at least 15 minutes before meals, for 5 to 10 days.

Dosage may need to be modified in patients with hepatic or renal impairment (see p. 358.2).

For doses in infants and children, see p. 358.2.

References.
1. Williams JD, Sefton AM. Comparison of macrolide antibiotics. *J Antimicrob Chemother* 1993; **31** (suppl C): 11–26.
2. Markham A, Faulds D. Roxithromycin: an update of its antimicrobial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1994; **48**: 297–326.
3. Young LS, Lode H, eds. Roxithromycin: first of a new generation of macrolides: update and perspectives. *Infection* 1995; **23** (suppl 1): S1–S52.
4. Lovering AM, *et al.*, eds. Roxithromycin—additional therapeutic potential. *J Antimicrob Chemother* 1998; **41** (suppl B): 1–97.

Administration in children. Roxithromycin may be given orally to children for the treatment of susceptible infections. In those weighing from 6 to 40 kg, a dose of 5 to 8 mg/kg daily may be used.

Administration in hepatic impairment. The licensed product information for roxithromycin notes that safety in hepatic impairment has not been established and advises halving the usual daily oral dose (see above) if used.

Administration in renal impairment. The licensed product information for roxithromycin notes that safety in renal impairment has not been established and dosage adjustment details are not specified.

A pharmacokinetic study[1] in 20 subjects (10 with normal renal function and 10 with severely impaired function) suggested that doubling the dosage interval of oral roxithromycin would be suitable in those with a creatinine clearance of less than 15 mL/minute.

1. Halstenson CE, *et al.* Disposition of roxithromycin in patients with normal and severely impaired renal function. *Antimicrob Agents Chemother* 1990; **34**: 385–9.

Alopecia. Results of a study *in vitro* and *in vivo*[1] suggested that topical roxithromycin might be of benefit in restoring hair loss in individuals with androgenetic alopecia.

1. Ito T, *et al.* Roxithromycin antagonizes catagen induction in murine and human hair follicles: implication of topical roxithromycin as hair restoration reagent. *Arch Dermatol Res* 2009; **301**: 347–55.

Hyperplasia. Gingival hyperplasia is a well recognised adverse effect of ciclosporin treatment; a small study[1] indicated that roxithromycin could reduce overgrowth, possibly by an effect on transforming growth factor-β. For the use of another macrolide, azithromycin, for this indication see Hyperplasia, p. 1954.3.

1. Condé SAP, *et al.* Roxithromycin reduces cyclosporine-induced gingival hyperplasia in renal transplant patients. *Transplant Proc* 2008; **40**: 1435–8.

Ischaemic heart disease. For mention of studies investigating roxithromycin in the prevention of ischaemic heart disease, see under Azithromycin, p. 222.1.

Respiratory disorders. For reference to the use of roxithromycin in the management of respiratory disorders, see under Erythromycin, p. 292.3.

Adverse Effects and Precautions

As for Erythromycin, p. 293.1.

Gastrointestinal disturbances are the most frequent adverse effect, but are less frequent than with erythromycin.

The dose of roxithromycin may need to be reduced in patients with hepatic or renal impairment.

Effects on the kidneys. Acute interstitial nephritis has been reported[1] in a patient given roxithromycin; renal function improved over several days after the drug was stopped.

1. Akcay A, *et al.* Acute renal failure and hepatotoxicity associated with roxithromycin. *Ann Pharmacother* 2004; **38**: 721–2.

Effects on the lungs. Acute eosinophilic pneumonia was attributed in a patient to the use of roxithromycin.[1] The condition resolved after treatment with methylprednisolone.

1. Pérez-Castrillón JL, *et al.* Roxithromycin-induced eosinophilic pneumonia. *Ann Pharmacother* 2002; **36**: 1808–9.

Effects on the pancreas. Acute pancreatitis, with duodenal inflammation, pain, pancreatic enlargement, and raised serum-amylase developed in a patient within 24 hours of substituting roxithromycin for erythromycin ethyl succinate.[1] Symptoms resolved rapidly once roxithromycin was stopped.

1. Souweine B, *et al.* Acute pancreatitis associated with roxithromycin therapy. *DICP Ann Pharmacother* 1991; **25**: 1137.

Hypersensitivity. For a report of an eosinophilic syndrome in a patient after treatment with azithromycin or roxithromycin, see Azithromycin, p. 222.3. See also under Effects on the Lungs, above.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies roxithromycin as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

For a discussion of drug interactions of macrolide antibacterials, see Erythromycin, p. 294.2.

Roxithromycin has a much lower affinity for cytochrome P450 isoenzymes than erythromycin and therefore has fewer interactions. It does not appear to interact with antacids, carbamazepine, oral contraceptives, prednisolone, or ranitidine.

Antimicrobial Action

As for Erythromycin, p. 295.1. It is reported to be as active or slightly less active than erythromycin.

Pharmacokinetics

Roxithromycin is absorbed after oral doses with a bioavailability of about 50%. Peak plasma concentrations of about 6 to 8 micrograms/mL occur around 2 hours after a single 150-mg dose. The mean peak plasma concentration at steady state after a dose of 150 mg twice daily is 9.3 micrograms/mL. Absorption is reduced when taken after a meal. It is widely distributed into tissues and body fluids; high concentrations are taken up into white blood cells. Small amounts of roxithromycin are distributed into breast milk. It is about 96% bound to plasma proteins

(mainly α_1-acid glycoprotein) at trough concentrations, but binding is saturable, and only about 87% is bound at usual peak concentrations. Small amounts of roxithromycin are metabolised in the liver, and the majority of a dose is excreted in the faeces as unchanged drug and metabolites; about 7 to 10% is excreted in urine, and up to 15% via the lungs. The elimination half-life is reported to range from about 8 to 13 hours, but may be more prolonged in patients with hepatic or renal impairment and in children. It has been reported that roxithromycin is not substantially removed by peritoneal dialysis.

References.
1. Puri SK, Lassman HB. Roxithromycin: a pharmacokinetic review of a macrolide. *J Antimicrob Chemother* 1987; **20** (suppl B): 89–100.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Delos; Klomicina; Rulid†; ***Austral.***: Biaxsig; Roxar; Roxide†; Roximycin; Rulide; ***Austria***: Roxithrostad; Rulide; ***Belg.***: Rulid; ***Braz.***: Floxid; Rotram; Roxina; Roxitran; Roxitrom; Rulid; ***Chile***: Ramivan; ***China***: Ai Luo Xin (爱罗欣); Ao Ge Shen (奥格申); Bei Ke (蓓克); Bei Sha (倍沙); Bi Ai Di (毕埃帝); Fu Xin (芙欣); Heng Te (恒特); Lang Su (朗素); Le Er Tai (乐尔泰); Le Xi Qing (乐喜清); Li Fu (力弗); Lizhuxing (丽珠星); Luo Jun Qing (罗君青); Luo Li Sa (罗立萨); Luo Shi Li (逻施立); Luo Si Mei (洛司美); Pinsheng (品圣); Pu Hong (浦虹); Qi Wei (齐威); Ren Su (仁苏); Romycin (罗迈新); Rulide (罗力得); Sai Le Lin (赛乐林); Tai Luo (泰罗); Techne (德依); Tian Kai (天凯); Wei Man (维曼); Xi Shi Ning (西适宁); Xin Mei Luo (欣美罗); Xinhong (悄虹); Ya Li Xi (亚力希); Yan Di (严迪); ***Denm.***: Roximstad; Surlid; ***Fin.***: Surlid; ***Fr.***: Claramid; Rulid; Subroxine†; ***Ger.***: Infectoroxit†; Roxi-Puren†; Roxi-Q†; Roxi-saar†; Roxi†; Roxibeta; Roxigamma†; Roxigrun†; RoxiHexal†; Roxithro-Lich†; Rulid†; ***Gr.***: Acevor; Anti-Bio; Aristomycin; Asmetic; Azuril; Bazuctril; Bicofen; Delitroxin; Erybros; Hobatmycine; Macrolid-S; Neo-Suxigal; Nirox; Oxetine; Redotrin; Roxibron; Roxicillin; Roxicur; Roximin; Roxitazon; Roxivinol; Roxuril; Roxy-Due; Roxyspes; Rulid; Seide; Siguon; Thriostaxil; Tirabicin; Toscamycin-R; Uramilon; Vaselpin; Vomitoran; ***Hong Kong***: Roxicin; Roxinox†; Rudin; Rulid; Ruxitex; Uonin; ***Hung.***: Renicin†; Rulid; ***India***: Actirox; Arbid; Artirox; Atrox; Aurox 150; Aurox-Kid; Avirox; Bd-Rox; Bio-Throx; Biorox; C-Rox; Canrox; Curox; Cyrox; Derox; E-Rox; Emrox; Entrox-P; Geerox; Hirox; Hycin; Inrox; Kevrox; Leolide; Luprex; Maclong; Mactox; Medirox; MGrox; Myrox; N-Rox; Nuroxy; Odirox; Roxee; Roxem; Roxeptin; Roxibid; Roxid; Roxivista; Roxyrol; Unorox; ***Indon.***: Anbiolid; Biostatik; Ixor; Rolexit; Rulid; Ruxcine†; Simacron; Sitro; Uplores; Xorin; ***Israel***: Roxo; Rulid; ***Ital.***: Assoral; Overal; Rossitrol; Rulid; ***Malaysia***: Roxcin; Roxinox; Rulid; Uonin; ***Mex.***: Crolix; Kensodic†; Rulid; Sertrom; ***Neth.***: Rulide†; ***NZ***: Romicin†; ***Philipp.***: Dorolid; Guamil; Macrol; Marulide; Plethirox; Rocin; Roxid; Roxil; Roximed; Roxitaz†; Roxithro; Roxl; Rulid; Ruthison; Thromyn; Trodex; Troxolid; Xithrom; ***Pol.***: Renicin; Rolicyn; Roxiratio; Roxitron; Rulid; Xitrocin; ***Port.***: Inferoxin; Odonticina; Roxitron; Rulide; ***Rus.***: Elrox (Элрокс); Remora (Ремора); Roksolit (Роксолит); Romyk (Ромик); Rovenal (Ровенал); Roxeptin (Роксептин); Roxihexal (Роксигексал); Roxybel (Роксибел); Roxylor (Роксилор); Rulicin (Рулицин); Rulid (Рулид); ***S.Afr.***: Roxulide†; Roxxibid; Rulide; Throsyn; ***Singapore***: Roxid; Uplores; ***Spain***: Rulide; ***Swed.***: Surlid; ***Switz.***: Rulid†; ***Thai.***: Ammirox; Coroxin; Eroxade; I-Throcin; Manroxin; Neolid†; Poliroxin; Rocitro; Romed; Rothricin; Roxamycin; Roxcin; Roxicin; Roxifect; Roxilan; Roximed; Roximin; Roxino; Roxinox; Roxinpac; Roxithro; Roxithroxyl; Roxitin; Roxitop; Roxitron; Roxlecon; Roxomycin†; Roxthomed; Roxthrin; Roxto; Roxtrocin; Roxxo†; Roxy; Roxydin†; Rucin; Rulid; Rulosone; Ruxitex; Saroxxo; Uonin; Utolid; V-Rox; Vesthromycin; ***Turk.***: Remora; Ritosin; Roksimin; Roksolit; Rulid; ***Ukr.***: Renicin (Реніцин)†; Roxid (Роксид); Roxihexal (Роксигексал)†; Roxilid (Роксилид); Xitrocin (Ксітроцин); ***Venez.***: Roxicure; Roxitrol; Rulid.

Multi-ingredient Preparations. ***India***: Ambroxit; Arbid-A; Artirox-SP; Aurox 50; Avirox-AM; Avirox-ST; Canrox-A; Flanzen-RX; Kevrox-S; Kevrox-SA; Medirox-A; Roxeptin-ME.

Rufloxacin Hydrochloride *(BANM, rINNM)*

Hidrocloruro de rufloxacino; MF-934 (rufloxacin); Rufloxacine, Chlorhydrate de; Rufloxacini Hydrochloridum; Rufloxacino, hidrocloruro de; Руфлоксацина Гидрохлорид.

9-Fluoro-2,3-dihydro-10-[4-methylpiperazin-1-yl]-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzothiazine-6-carboxylic acid hydrochloride.

$C_{17}H_{18}FN_3O_3S,HCl=399.9$

CAS — 101363-10-4 (rufloxacin); 106017-08-7 (rufloxacin hydrochloride).

ATC — J01MA10.

ATC Vet — QJ01MA10.

UNII — 1643374N6L.

Profile

Rufloxacin is a fluoroquinolone antibacterial with properties similar to those of ciprofloxacin (p. 261.1). It is given orally as the hydrochloride in the treatment of susceptible infections in a usual initial dose of 400 mg on the first day followed by 200 mg daily thereafter. A plasma half-life of 30 hours or more has been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Kang Zan (康赞); Qari (卡力); ***Ital.***: Monos; Qari; Tebraxin†; ***Mex.***: Uroflox; ***Philipp.***: Uroclar; ***Thai.***: Uroflox.

Sarafloxacin Hydrochloride

(BANM, USAN, rINNM)

A-56620 (sarafloxacin or sarafloxacin hydrochloride); A-57135 (sarafloxacin); Abbott-56620 (sarafloxacin or sarafloxacin hydrochloride); Hidrocloruro de sarafloxacino; Sarafloxacine, Chlorhydrate de; Sarafloxacini Hydrochloridum; Sarafloxacino, hidrocloruro de; Сарафлоксацина Гидрохлорид.

6-Fluoro-1-(*p*-fluorophenyl)-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid monohydrochloride.

$C_{20}H_{17}F_2N_3O_3,HCl=421.8$

CAS — 98105-99-8 (sarafloxacin); 91296-87-6 (sarafloxacin hydrochloride).

UNII — I36JP4Q9DF.

Profile

Sarafloxacin is a fluoroquinolone antibacterial that has been used as the hydrochloride in veterinary medicine.

Sisomicin Sulfate *(BANM, USAN, rINNM)*

Antibiotic 6640 (sisomicin); Rickamicin Sulphate; Sch-13475 (sisomicin); Sisomicin Sulphate; Sisomicina, sulfato de; Sisomicine, Sulfate de; Sisomicini Sulfas; Sissomicin Sulphate; Sulfato de sisomicina; Сизомицина Сульфат.

4-*O*-[(2*R*,3*R*)-*cis*-3-Amino-6-aminomethyl-3,4-dihydro-2*H*-pyran-2-yl]-2-deoxy-6-*O*-(3-deoxy-4-*C*-methyl-3-methylamino-β-L-arabinopyranosyl)streptamine sulphate; 2-Deoxy-6-*O*-(3-deoxy-4-*C*-methyl-3-methylamino-β-L-arabinopyranosyl)-4-*O*-(2,6-diamino-2,3,4,6-tetradeoxy-D-*glycero*-hex-4-enopyranosyl)streptamine sulphate.

$(C_{19}H_{37}N_5O_7)_2,5H_2SO_4=1385.4$

CAS — 32385-11-8 (sisomicin); 53179-09-2 (sisomicin sulfate).

ATC — J01GB08.

ATC Vet — QJ01GB08.

UNII — K14444371C.

Pharmacopoeias. In *Chin.*, *Jpn*, and *US*.

USP 36: (Sisomicin Sulfate). It loses not more than 15% of its weight on drying. 1 mg of sisomicin sulfate has a potency equivalent to not less than 580 micrograms of sisomicin calculated on the dried basis. A 4% solution in water of sisomicin has a pH of 3.5 to 5.5. Store in airtight containers.

Profile

Sisomicin, an antibacterial produced by *Micromonospora inyoensis* and closely related to gentamicin C_{1A}, is an aminoglycoside with general properties similar to those of gentamicin (p. 304.2). It is given as the sulfate but doses are expressed in terms of the base; 1.5 g of sisomicin sulfate is equivalent to about 1 g of sisomicin. The usual dose for adults is 3 mg/kg daily given intramuscularly in 2 or 3 divided doses. It may be given by intravenous infusion if necessary.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Ao Jia Xi (奥加西); De Bao Yi (德宝益); Lai Sai (莱赛); Li Sui (利岁); Luo Li (洛利); ***Gr.***: Geonyn; Somazinal; Sosialon; Udolin; ***India***: Ensamycin; Sisoptin.

Pharmacopoeial Preparations

USP 36: Sisomicin Sulfate Injection.

Sitafloxacin *(USAN, rINN)*

DU-6859 (anhydrous sitafloxacin); DU-6859a (sitafloxacin sesquihydrate); Sitafloxacine; Sitafloxacino; Sitafloxacinum; Ситафлоксацин.

(-)-7-[(7*S*)-7-Amino-5-azaspiro[2.4]hept-5-yl]-8-chloro-6-fluoro-1-[(1*R*,2*S*)-2-fluorocyclopropyl]-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid.

$C_{19}H_{18}ClF_2N_3O_3=409.8$

CAS — 127254-12-0 (anhydrous sitafloxacin); 163253-37-0 (sitafloxacin monohydrate); 163253-35-8 (sitafloxacin sesquihydrate).

ATC — J01MA21.

ATC Vet — QJ01MA21.

UNII — 9TD681796G (sitafloxacin); 3GJC60U4Q8 (sitafloxacin anhydrous).

NOTE. Sitafloxacin exists in several hydration states; the name sitafloxacin has been used to refer to both the anhydrous substance and the sesquihydrate ($C_{19}H_{18}ClF_2N_3O_3,1½H_2O=436.8$); the latter is known in Japan as sitafloxacin hydrate.

Profile

Sitafloxacin is a fluoroquinolone that is given orally in the treatment of susceptible infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Jpn***: Gracevit; ***Thai.***: Gracevit.

Sparfloxacin *(BAN, USAN, rINN)*

AT-4140; CI-978; Esparfloxacino; PD-131501; RP-64206; Sparfloksasiini; Sparfloxacine; Sparfloxacinum; Спарфлоксацин.

5-Amino-1-cyclopropyl-7-(*cis*-3,5-dimethylpiperazin-1-yl)-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid.

$C_{19}H_{22}F_2N_4O_3=392.4$

CAS — 110871-86-8.

ATC — J01MA09.

ATC Vet — QJ01MA09.

UNII — Q90AGA7B7L.

Pharmacopoeias. In *Chin.*

Uses and Administration

Sparfloxacin is a fluoroquinolone antibacterial with actions and uses similar to those of ciprofloxacin (p. 261.2). It is given orally for the treatment of susceptible infections in a usual dose of 100 to 300 mg in 1 or 2 divided doses daily. It has also been tried in tuberculosis. For further information on the use of other fluoroquinolones in the treatment of tuberculosis, see under Uses and Administration of Ciprofloxacin, p. 262.2.

General references.

1. Pinch RG, *et al.*, eds. Sparfloxacin: focus on clinical performance. *J Antimicrob Chemother* 1996; **37** (suppl A): 1–167.
2. Goa KL, *et al.* Sparfloxacin: a review of its antibacterial activity, pharmacokinetic properties, clinical efficacy and tolerability in lower respiratory tract infections. *Drugs* 1997; **53**: 700–25.
3. Martin SJ, *et al.* Levofloxacin and sparfloxacin: new quinolone antibiotics. *Ann Pharmacother* 1998; **32**: 320–36.
4. Schentag JJ. Sparfloxacin: a review. *Clin Ther* 2000; **22**: 372–87.

Adverse Effects and Precautions

As for Ciprofloxacin, p. 262.2.

Concern over phototoxicity associated with sparfloxacin has led to restriction of its use in some countries; patients should be advised to avoid exposure to sunlight during, and for a few days after, sparfloxacin therapy, and to stop the drug immediately if phototoxicity occurs.

Photosensitivity. In a survey[1] of the reporting rate for phototoxicity associated with sparfloxacin in France, the manufacturer or the French Pharmacovigilance System received 371 reports of severe phototoxic reactions during the first 9 months after marketing of the drug; this approximated to between 4 and 25 times the rate reported for other fluoroquinolones. In addition to photodermatitis, photo-onycholysis has also been reported with sparfloxacin.[2]

1. Pierfitte C, *et al.* The link between sunshine and phototoxicity of sparfloxacin. *Br J Clin Pharmacol* 2000; **49**: 609–12.
2. Mahajan VK, Sharma NL. Photo-onycholysis due to sparfloxacin. *Australas J Dermatol* 2005; **46**: 104–5.

Interactions

As for Ciprofloxacin, p. 264.3.

Sparfloxacin does not appear to interact with theophylline or caffeine, nor with warfarin or cimetidine. Probenecid does not alter the pharmacokinetics of sparfloxacin.

Antimicrobial Action

As for Ciprofloxacin, p. 265.2.

Sparfloxacin is reported to be more active *in vitro* than ciprofloxacin against mycobacteria and against Gram-positive bacteria, including *Streptococcus pneumoniae*, and other streptococci and staphylococci.

Pharmacokinetics

Sparfloxacin is well absorbed from the gastrointestinal tract with a bioavailability of about 90%. Peak plasma

concentrations occur 3 to 6 hours after a dose. Sparfloxacin is widely distributed into body tissues and fluids, including respiratory tissues, but is only about 45% bound to plasma proteins. It is metabolised in the liver by glucuronidation and has an elimination half-life of about 20 hours. It is excreted in equal amounts in the faeces and urine as unchanged drug and as the glucuronide metabolite.

References.
1. Shimada J, *et al.* Clinical pharmacokinetics of sparfloxacin. *Clin Pharmacokinet* 1993; 25: 358–69.
2. Montay G. Pharmacokinetics of sparfloxacin in healthy volunteers and patients: a review. *J Antimicrob Chemother* 1996; 37 (suppl A): 27–39.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Ba Sha (巴沙); Lang Rui (朗瑞); Sen Ao Xin (森奥欣); SenAoXin (森澳欣); Shi Bao Fu (世保扶); Spara (司巴乐); Sparca (立特); *India*: Actiflox; Acuspar; Alps; Artispar; Aspar; Atospar; Bal-Spar; Bluspar; Canspar; Cinospar; Dinor; E-Spar; Efospar; Flotome; Floxpar; Guspar; Inspar; Jugam; Kespar; Klaspar; Novospar; Onespar; Ospar; Paar; Parcy; Scat; Sparbact; Sparcip; Spardac; Spardrops; Sparquin; Sparvista; Sparx; *Indon.*: Newspar; Resflok; Sparos; *Jpn*: Spara†; *Rus.*: Respara (Респара); Sparbact (Спарбакт); Sparflo (Спарфло); *Ukr.*: Sparflo (Спарфло).

Spectinomycin *(BAN, rINN)*

Actinospectacin; Espectinomicina; Spectinomycine; Spectinomycinum; Spektinomycin; Spektinomyslini; Спектиномицин.

Perhydro-4a,7,9-trihydroxy-2-methyl-6,8-bis(methylamino) pyrano[2,3-*b*][1,4]benzodioxin-4-one.

$C_{14}H_{24}N_2O_7$=332.4

CAS — 1695-77-8.

ATC — J01XX04.

ATC Vet — QJ01XX04.

UNII — 93AK1U6QF.

Description. Spectinomycin is an antimicrobial substance produced by the growth of *Streptomyces spectabilis* or by any other means.

Spectinomycin Hydrochloride

(BANM, USAN, rINNM)

Espectinomicina, hidrocloruro de; Hidrocloruro de espectinomicina; M-141; Spectinomycine, Chlorhydrate de; Spectinomycine (dichlorhydrate de) pentahydraté; Spectinomycini dihydrochloridum pentahydricum; Spectinomycini Hydrochloridum; Spektinomicin-hidroklorid; Spektinomicino hidrochloridas; Spektinomycin hydrochlorid; Spektinomycindihydrokloridpentahydrat; Spektinomysiinidihydrokloridipentahydraatti; Spektynomycyny chlorowodorek; Spektynomycyny dichlorowodorek pięciowodny; U-18409AE; Спектиномицина Гидрохлорид.

Spectinomycin dihydrochloride pentahydrate.

$C_{14}H_{24}N_2O_7.2HCl.5H_2O$=495.3

CAS — 21736-83-4 (anhydrous spectinomycin hydrochloride); 22189-32-8 (spectinomycin hydrochloride pentahydrate).

ATC — J01XX04.

ATC Vet — QJ01XX04.

UNII — HWT06H303Z (spectinomycin hydrochloride pentahydrate); 296JEI210Z (anhydrous spectinomycin hydrochloride).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Spectinomycin Dihydrochloride Pentahydrate). A substance produced by *Streptomyces spectabilis* or by any other means. A white or almost white, slightly hygroscopic, powder. Freely soluble in water; very slightly soluble in alcohol. A 10% solution in water has a pH of 3.8 to 5.6. Store in airtight containers.

USP 36: (Spectinomycin Hydrochloride). A white to pale buff crystalline powder. 1 mg of monograph substance has a potency equivalent to not less than 603 micrograms of spectinomycin. Freely soluble in water; practically insoluble in alcohol, in chloroform, and in ether. A 1% solution in water has a pH of 3.8 to 5.6. Store in airtight containers.

Uses and Administration

Spectinomycin is used as an alternative to cephalosporins or fluoroquinolones in the treatment of gonorrhoea (p. 204.2) although poor distribution into saliva limits its usefulness in pharyngeal infections. It has also been used in the treatment of chancroid (p. 204.2).

Spectinomycin is given as the hydrochloride but doses are expressed in terms of the base. Spectinomycin hydrochloride 1.5 g is equivalent to about 1 g of spectinomycin. In the treatment of gonorrhoea it is given by deep intramuscular injection as a single dose equivalent to 2 g of spectinomycin, although a dose of 4 g may sometimes be required, divided between two injection sites. Multiple-dose courses have been used for the treatment of disseminated infections.

Spectinomycin is not effective against syphilis or chlamydial infections and additional therapy for these infections may also be needed.

For details of doses in children, see p. 360.2.

Administration in children. Parenteral spectinomycin is generally not recommended in neonates because of the presence of benzyl alcohol, a preservative that has been associated with fatalities in neonates due to the 'gasping syndrome' (see Neonates, p. 1741.1).

For prophylaxis in neonates born to mothers with gonorrhoea WHO permits a single intramuscular dose of spectinomycin 25 mg/kg (maximum 75 mg) as an alternative to ceftriaxone. The CDC recommends spectinomycin as an alternative to cephalosporins in the treatment of uncomplicated gonorrhoea (p. 204.2) in children beyond the newborn period and weighing under 45 kg; a single intramuscular dose equivalent to 40 mg/kg of spectinomycin may be given.

Adverse Effects and Precautions

Nausea, dizziness, fever and chills, insomnia, and urticaria have occasionally occurred with single doses of spectinomycin. Anaphylaxis has occurred rarely. Mild to moderate pain has been reported after intramuscular injections. Alterations in kidney and liver function and a decrease in haemoglobin and haematocrit have occasionally been seen with repeated doses. Although a reduction in urine output has been seen after single and multiple doses, spectinomycin has not been noted to produce functional changes indicative of nephrotoxicity.

Spectinomycin is ineffective in the treatment of syphilis and patients being treated for gonorrhoea should be observed for evidence of syphilis.

Interactions

Lithium. For the effect of spectinomycin in patients receiving lithium, see Antimicrobials, under Interactions of Lithium, p. 433.3.

Antimicrobial Action

Spectinomycin is an aminocyclitol antibacterial that acts by binding to the 30S subunit of the bacterial ribosome and inhibiting protein synthesis. Its activity is generally modest, particularly against Gram-positive organisms. Anaerobic organisms are mostly resistant. Various Gram-negative organisms are sensitive, including many enterobacteria and also *Haemophilus ducreyi*, and it is particularly effective against *Neisseria gonorrhoeae*. Although generally bacteriostatic, spectinomycin is bactericidal against susceptible gonococci at concentrations not much above the MIC.

Resistance may develop by chromosomal mutation or may be plasmid-mediated in some organisms; resistant gonococci have been reported clinically, notably in the Far East, but in most parts of the world resistant neisserial strains have been uncommon to date.

Pharmacokinetics

Spectinomycin is poorly absorbed orally but is rapidly absorbed after the intramuscular injection of the hydrochloride. A 2-g dose produces peak plasma concentrations of about 100 micrograms/mL at 1 hour while a 4-g dose produces peak concentrations of about 160 micrograms/mL at 2 hours. Therapeutic plasma concentrations are maintained for up to 8 hours. Distribution into saliva is poor (which limits its value in pharyngeal gonorrhoea). It is poorly bound to plasma proteins. Spectinomycin is excreted in an active form in the urine and up to 100% of a dose has been recovered within 48 hours. A half-life of about 1 to 3 hours has been reported; it is prolonged in patients with renal impairment. Spectinomycin is partially removed by dialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Trobicin†; *Belg.*: Trobicin; *China*: Shubeitinuo (舒贝替诺); Trobicin (曲必星); Zhuo Qing (卓青); *Fr.*: Trobicine; *Gr.*: Trobicin; *Hong Kong*: Kirin; Trobicin; *India*: Myspec; Spectin; Trobicin; *Mex.*: Trobicin; *Rus.*: Kirin (Кирин); Trobicin (Тробицин); *S.Afr.*: Trobicin†; *Singapore*: Trobicin; *Spain*: Kempi†; *Thai.*: Trobicin; Vabicin†.

Pharmacopoeial Preparations

USP 36: Spectinomycin for Injectable Suspension.

Spiramycin *(BAN, USAN, rINN)*

Espiramicina; IL-5902; NSC-55926; NSC-64393 (spiramycin hydrochloride); RP-5337; Spiramicin; Spiramicinas; Spiramisin; Spiramycine; Spiramycinum; Spiramyslini; Спирамицин.

A mixture comprised principally of (4*R*,5*S*,6*S*,7*R*,9*R*,10*R*,16*R*-(11*E*,13*E*)-6-[(*O*-2,6-dideoxy-3-*C*-methyl-α-L-*ribo*-hexopyranosyl)-(1→4)-(3,6-dideoxy-3-dimethylamino-β-D-glucopyranosyl)oxy]-7-formylmethyl-4-hydroxy-5-methoxy-9,16-dimethyl-10-[(2,3,4,6-tetradeoxy-4-dimethylamino-D-*erythro*-hexopyranosyl)oxy]oxacyclohexadeca-11,13-dien-2-one (Spiramycin I).

$C_{43}H_{74}N_2O_{14}$=843.1

CAS — 8025-81-8.

ATC — J01FA02.

ATC Vet — QJ01FA02; QJ51FA02.

UNII — 71ODY0V87H (spiramycin); 033ECH6IFG (spiramycin I); 05298J5WMU (spiramycin II); 0NHE9TRJ93 (spiramycin III).

Pharmacopoeias. In *Eur.* (see p. vii). Also in *BP(Vet)*. *Jpn* includes Acetylspiramycin.

Ph. Eur. 8: (Spiramycin). A macrolide antibiotic produced by the growth of certain strains of *Streptomyces ambofaciens* or obtained by any other means. The potency is not less than 4100 units/mg, calculated with reference to the dried substance. A white or slightly yellowish, slightly hygroscopic powder. Slightly soluble in water; freely soluble in alcohol, in acetone, and in methyl alcohol. A 0.5% solution in methyl alcohol and water has a pH of 8.5 to 10.5. Store in airtight containers.

Uses and Administration

Spiramycin is a macrolide antibacterial that is used similarly to erythromycin (p. 292.1) in the treatment of susceptible bacterial infections. It has also been used in the protozoal infections cryptosporidiosis (p. 923.1) and toxoplasmosis (p. 926.1).

Spiramycin is given orally as the base or intravenously as the adipate; it has also been given rectally as the adipate. The usual oral adult dose is 6 to 9 million units daily, in 2 or 3 divided doses. Doses of up to 15 million units have been given daily in divided doses for severe infections. A dose of 1.5 million units of spiramycin may be given by slow intravenous infusion every 8 hours; in severe infection the dose may be doubled.

Spiramycin is available in combination preparations with metronidazole in some countries.

Acetylspiramycin is also used.

Reviews.
1. Rubinstein E, Keller N. Spiramycin renaissance. *J Antimicrob Chemother* 1998; 42: 572–6.

Adverse Effects and Precautions

As for Erythromycin, p. 293.1.

The most frequent adverse effects are gastrointestinal disturbances. Transient paraesthesia has been reported during parenteral use.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies spiramycin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

For a discussion of drug interactions of macrolide antibacterials, see Erythromycin, p. 294.2.

Spiramycin is reported to have little or no effect on hepatic cytochrome P450 isoenzymes and may therefore produce fewer interactions than erythromycin with other drugs metabolised by this enzyme system (see Mechanism, under Interactions of Erythromycin, p. 294.2). The lack of interactions between spiramycin and theophylline and ciclosporin would appear to support this. Nevertheless, a report of torsade de pointes in a patient with a congenital long QT syndrome during treatment with spiramycin and *mequitazine*[1] suggests that caution is still needed.

Reduced plasma concentrations of *levodopa* have been reported when given with spiramycin (see p. 908.1).

1. Verdun P, *et al.* Torsades de pointes sous traitement par spiramycine et méquitazine: à propos d'un cas. *Arch Mal Coeur Vaiss* 1997; 90: 103–6.

Antimicrobial Action

As for Erythromycin, p. 295.1, although it is somewhat less active *in vitro* against many species. It is active against *Toxoplasma gondii*.

Pharmacokinetics

Spiramycin is incompletely absorbed from the gastrointestinal tract and absorption is reduced by food. It is widely distributed into tissues, although it does not cross the blood-brain barrier. Spiramycin crosses the placenta and is distributed into breast milk. Plasma protein binding ranges from 10 to 25%. An oral dose of 6 million units produces peak blood concentrations of 3.3 micrograms/mL after 1.5 to 3 hours; the half-life is about 5 to 8 hours. High tissue concentrations occur and persist long after the plasma concentration has fallen to low levels.

Spiramycin is metabolised in the liver to active metabolites; substantial amounts are excreted in the bile and about 10% in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Rovamycine; ***Austria***: Rovamycin; ***Belg.***: Rovamycine; ***Braz.***: Rovamicina; ***Canad.***: Rovamycine; ***China***: Fa Luo (法罗); Fuluxian (芙露仙); Yi Nuo Xin (伊诺欣); ***Cz.***: Rovamycine; ***Fr.***: Rovamycine; ***Ger.***: Rovamycine; Selectomycin; ***Gr.***: Rovamycine; ***Hong Kong***: Rovamycine; ***Hung.***: Rovamycine; ***India***: Rovamycin; ***Indon.***: Ethirov; Hypermycin†; Ismacrol; Medirov†; Osmycin; Provamed; Rofacin; Rovadin; Rovamycine; Sorov; Spirabiotic; Spiradan; Spiranter; Spirasin; Varoc; Vipram; ***Israel***: Rovamycine; ***Ital.***: Rovamicina; Spiromix†; ***Malaysia***: Rovamycine; ***Mex.***: Provamicina; ***Neth.***: Rovamycine; ***Norw.***: Rovamycin; ***Philipp.***: Rovamax; ***Pol.***: Rovamycine; ***Port.***: Rovamycine; ***Rus.***: Rovamycine (Ровамицин); ***Singapore***: Rovamycine; ***Spain***: Dicorvin; Rovamycine; ***Switz.***: Rovamycine†; ***Thai.***: Rovamycine; Spiracin†; ***Turk.***: Rovagyl; Rovamycine; ***Ukr.***: Rovacid (Ровацид)†; Rovamycine (Ровамицин); Starket (Старкет); ***Venez.***: Provamicina.

Multi-ingredient Preparations. ***Arg.***: Estilomicin; ***Braz.***: Periodontil; ***Fr.***: Bi Missilor; Birodogyl; Missilor; Rodogyl; ***Malaysia***: Rodogyl; ***Mex.***: Rodogyl; ***Spain***: Rhodogil.

Streptomycin *(BAN, rINN)*

Estreptomicina; Streptomisin; Streptomycine; Streptomycinum; Streptomyslini; Стрептомицин.

O-2-Deoxy-2-methylamino-α-L-glucopyranosyl-(1→2)-O-5-deoxy-3-C-formyl-α-L-lyxofuranosyl-(1→4)-N^3,N^3-diamidino-D-streptamine.

$C_{21}H_{39}N_7O_{12}$=581.6

CAS — 57-92-1.

ATC — A07AA04; J01GA01.

ATC Vet — QA07AA04; QJ01GA01.

UNII — Y45QSO73OB.

Description. An antimicrobial organic base produced by the growth of certain strains of *Streptomyces griseus*, or by any other means.

Streptomycin Hydrochloride *(BANM, rINNM)*

Hidrocloruro de estreptomicina; Streptomycine, Chlorhydrate de; Streptomycini Hydrochloridum; Стрептомицина Гидрохлорид.

$C_{21}H_{39}N_7O_{12}$,3HCl=691.0

CAS — 6160-32-3.

ATC — A07AA04; J01GA01.

ATC Vet — QA07AA04; QJ01GA01.

UNII — 8P331B9592.

Streptomycin Sulfate *(BANM, rINNM)*

Estreptomicina, sulfato de; Streptomicino sulfatas; Streptomycin Sesquisulphate; Streptomycyn sulfát; Streptomycin Sulphate; Streptomycine, Sulfate de; Streptomycini sulfas; Streptomycinsulfat; Streptomycyny siarczan; Streptomysiini-sulfaatti; Sulfato de estreptomicina; Sztreptomicin-szulfát; Стрептомицина Сульфат.

$(C_{21}H_{39}N_7O_{12})_2$,$3H_2SO_4$=1457.4

CAS — 3810-74-0.

ATC — A07AA04; J01GA01.

ATC Vet — QA07AA04; QJ01GA01.

UNII — CW25IKJ202.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Streptomycin Sulfate). A white or almost white, hygroscopic powder. The potency is not less than 720 units/mg, calculated with reference to the dried substance. Very soluble in water; practically insoluble in dehydrated alcohol. A 25% solution in water has a pH of 4.5 to 7.0. Store in airtight containers.

USP 36: (Streptomycin Sulfate). A white or practically white, hygroscopic powder; odourless or with not more than a faint odour. It has a potency equivalent to not less than 650 micrograms and not more than 850 micrograms of streptomycin per mg. Freely soluble in water; very slightly soluble in alcohol; practically insoluble in chloroform. A solution in water containing the equivalent of streptomycin 20% has a pH of 4.5 to 7.0. Store in airtight containers.

Incompatibility. Streptomycin sulfate is incompatible with acids and alkalis.

Uses and Administration

Streptomycin is an aminoglycoside antibacterial mainly used with other antimycobacterials, in the treatment of nontuberculous mycobacterial infections and tuberculosis. It is given during the initial phase of treatment in those with tuberculous meningitis and in those previously treated for tuberculosis. Streptomycin has been used, with a penicillin, as an alternative to gentamicin in the treatment of bacterial endocarditis. Streptomycin is effective in the treatment of plague, tularaemia, and, with a tetracycline, in brucellosis. It has also been used, with other drugs, in various other infections including mycetoma and Whipple's disease. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Streptomycin is mostly used as the sulfate but doses are expressed in terms of the base; 1.25 g of streptomycin sulfate is equivalent to about 1 g of streptomycin. It is given by intramuscular injection.

In the treatment of **tuberculosis**, streptomycin is given in usual adult doses of 15 mg/kg daily, up to a maximum of 1 g daily. The maximum daily dose should be reduced to 500 to 750 mg in adults aged over 40 years, and in those weighing less than 50 kg. Dosage should also be reduced in those with renal impairment, in whom plasma-drug concentration should be monitored. Streptomycin may also be given at the same dose as part of an intermittent regimen 2 or 3 times weekly. It has been given by the intrathecal route, together with intramuscular dosage, for tuberculous meningitis, but this is no longer recommended.

In the treatment of **other infections**, streptomycin has been given in usual adult doses of 1 to 2 g daily in divided doses, depending on the susceptibility and severity of infection.

For details of doses in children, see p. 361.2.

In all patients dosage should preferably be adjusted according to plasma-streptomycin concentrations, and particularly where factors such as age, renal impairment, or prolonged therapy may predispose to toxicity. The course of treatment (other than in tuberculosis) should usually be limited to 7 to 14 days, and peak plasma concentrations should be between 15 and 40 micrograms/mL and trough concentrations below 3 to 5 micrograms/mL or below 1 microgram/mL in renal impairment or in those over 50 years of age. For discussion of the methods used to calculate aminoglycoside dosage requirements, see Administration and Dosage under Gentamicin Sulfate, p. 305.2.

Streptomycin has also been used as the hydrochloride, the pantothenate, and as a complex with calcium chloride.

Administration in children. For the treatment of *tuberculosis* in children from 1 month of age, streptomycin is given by intramuscular injection and with other antimycobacterial drugs. The American Academy of Pediatrics[1] suggests a dose of streptomycin of 20 to 40 mg/kg (to a maximum of 1 g) daily, while the *BNFC* suggests a dose of 15 mg/kg (also to a maximum of 1 g) once daily. WHO recommends a dose of streptomycin of 12 to 18 mg/kg once daily or three times a week.

Streptomycin is given with doxycycline for the treatment of *brucellosis*. In children aged 1 month and older the *BNFC* suggests a dose of streptomycin of 5 to 10 mg/kg every 6 hours or the total daily dose may be given in 2 or 3 divided doses.

Streptomycin is given by intramuscular injection for the treatment of *other infections* in children in doses of up to 40 mg/kg daily (to a maximum of 1 g daily) in divided doses for 3 to 7 days, depending on the susceptibility and severity of infection.

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases.* 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Ménière's disease. Streptomycin and gentamicin have been used for medical ablation in advanced Ménière's disease (p. 611.2). Systemic treatment has generally been limited by the development of chronic ataxia and oscillopsia (oscillating vision). However, streptomycin sulfate 1 g twice daily by intramuscular injection on 5 days each week for 2 weeks, repeated as necessary to a total dose of up to 60 g,[1,2] or 1 g twice daily for 5 days, followed if necessary by a further 3 days of treatment in the second week,[3] has produced improvements in vestibular symptoms without hearing loss in patients with Ménière's disease. Local (intratympanic) injections have also been tried,[4] but gentamicin is considered to be less toxic and is now generally preferred.

1. Shea JJ, *et al.* Long-term results of low dose intramuscular streptomycin for Ménière's disease. *Am J Otol* 1994; 15: 540–4.
2. Balyan FR, *et al.* Titration streptomycin therapy in Meniere's disease: long-term results. *Otolaryngol Head Neck Surg* 1998; 118: 261–6.
3. Graham MD. Bilateral Meniere's disease: treatment with intramuscular titration streptomycin sulfate. *Otolaryngol Clin North Am* 1997; 30: 1097–1100.
4. Beck C, Schmidt CL. 10 Years of experience with intratympanally applied streptomycin (gentamycin) in the therapy of Morbus Menière. *Arch Otorhinolaryngol* 1978; 221: 149–52.

Adverse Effects, Treatment, and Precautions

As for Gentamicin Sulfate, p. 306.2. Like gentamicin the ototoxic effects of streptomycin are mainly vestibular rather than auditory. Ototoxicity has been seen in infants whose mothers had been given streptomycin during pregnancy. However, streptomycin is reported to be somewhat less nephrotoxic than the other aminoglycosides.

Paraesthesia in and around the mouth is not uncommon after intramuscular injection of streptomycin, and other neurological symptoms, including peripheral neuropathies, optic neuritis, and scotoma have occasionally occurred. Intrathecal use has resulted in symptoms of meningeal inflammation including radiculitis, arachnoiditis, nerve root pain, and paraplegia, and some recommend that it be avoided. The risk of neurotoxic reactions is greater in patients with renal impairment or pre-renal azotaemia.

Hypersensitivity skin reactions are reported in about 5% of patients, and eosinophilia may occur. There have been reports of Stevens-Johnson syndrome, toxic epidermal necrolysis, severe exfoliative dermatitis, and anaphylaxis. Sensitisation is common among those who handle streptomycin occupationally. Topical and inhalational use of streptomycin should be avoided. If necessary, hypersensitivity can usually be overcome by desensitisation. Aplastic anaemia and agranulocytosis have been reported rarely.

Although sources differ, it is usually suggested that peak plasma concentrations should be between 15 and 40 micrograms/mL, and trough concentrations below 3 to 5 micrograms/mL; in the UK the *BNF* recommends that trough concentrations in excess of 1 microgram/mL should be avoided in those over 50 years of age or those with renal impairment. A total cumulative dose in excess of 100 g may be associated with a higher incidence of adverse effects and should only be exceeded in exceptional circumstances.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving streptomycin, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/05/04)

Handling. Streptomycin may cause severe dermatitis in sensitised persons, and pharmacists, nurses, and others who handle the drug frequently should wear masks and rubber gloves.

Interactions

As for Gentamicin Sulfate, p. 307.2.

Antimicrobial Action

Streptomycin has a mode of action and antimicrobial spectrum similar to that of gentamicin (p. 307.2), although most strains of *Pseudomonas aeruginosa* are resistant. It is effective against *Yersinia pestis*, *Francisella tularensis*, and *Brucella* spp. Streptomycin has particular activity against *Mycobacterium tuberculosis*.

Resistance to streptomycin has often been reported and may develop in strains which are initially sensitive within a few days or weeks of beginning therapy. The widespread emergence of resistance has largely halted its use in infections due to the common Gram-negative aerobes. Primary resistance in *M. tuberculosis* is relatively uncommon in the UK and USA but may be seen in a third or more of cases in the Far East.

Both low-level and high-level resistance have been reported; the latter is thought to be due to mutation of the ribosomal binding site of the antibiotic and cannot be overcome by the synergistic use of another drug such as a beta lactam, whereas strains with moderate resistance due to decreased uptake or permeability of streptomycin may respond to combined use.

Organisms resistant to framycetin, kanamycin, neomycin, and paromomycin usually show cross-resistance to streptomycin, although streptomycin-resistant strains sometimes respond to one of these drugs.

References.

1. Cooksey RC, *et al.* Characterization of streptomycin resistance mechanisms among Mycobacterium tuberculosis isolates from patients in New York City. *Antimicrob Agents Chemother* 1996; 40: 1186–8.
2. Ho YH, *et al.* In-vitro activities of aminoglycoside-aminocyclitols against mycobacteria. *J Antimicrob Chemother* 1997; 40: 27–32.

Pharmacokinetics

As for Gentamicin Sulfate, p. 307.3. After intramuscular injection of streptomycin, peak plasma concentrations occur in 0.5 to 2 hours but the time taken and the concentration attained, which may be as high as about 50 micrograms/mL after a dose of 1 g, vary considerably. The half-life of streptomycin is about 2.5 hours. About one-third of streptomycin in the circulation is bound to plasma proteins. It is rapidly excreted by glomerular filtration and the concentration of streptomycin in the urine is often very high, with about 30 to 90% of a dose usually being excreted within 24 hours. It is distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Strepto-Fatol; *Ger.*: Strepto-Fatol†; Strepto-Hefa†; *India*: Ambistryn-S; Cipstryn; Isos; *Mex.*: Bucomicina†; Sulfestrep; *S.Afr.*: Bio-Strep; Solustrep; *Thai.*: Strepto.

Multi-ingredient Preparations. *Arg.*: Estreptocarbocaftiazol; Estreptocarbocaftiazol; *Gr.*: Polypictine; *Mex.*: Aguipental; *Port.*: Bientericot.

Pharmacopoeial Preparations
BP 2014: Streptomycin Injection;
USP 36: Streptomycin for Injection; Streptomycin Injection.

Succinylsulfathiazole *(BAN, rINN)*

Succinilsolfatiazolo; Succinilsulfatiazol; Succinylsulfathiazol; Succinylsulfathiazolum; Succinylsulfathiazolum Monohydricum; Succinylsulfatiazol; Succinylsulphathiazole; Sukcinilsulfatiazolas; Sukcinylsulfathiazol monohydrát; Suksinyylisulfatiatsoli; Szukcinilszulfatiazol; Сукцинилсульфатиазол.

4′-(1,3-Thiazol-2-ylsulphamoyl)succinanilic acid monohydrate.

$C_{13}H_{13}N_3O_5S_2,H_2O$=373.4

CAS — 116-43-8 (anhydrous succinylsulfathiazole).

ATC — A07AB04.

ATC Vet — QA07AB04.

UNII — RSS8647O4S (succinylsulfathiazole); HM7K18OJZ9 (succinylsulfathiazole monohydrate).

Profile

Succinylsulfathiazole is a sulfonamide with properties similar to those of sulfamethoxazole (p. 367.2). It is poorly absorbed and has been given for its antibacterial activity in the gastrointestinal tract.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Venez.*: Guanicar.

Sulbactam *(BAN, rINN)*

CP-45899; Sulbactamum; Sulbaktaami; Sulbaktam; Сульбактам.

Penicillanic acid 1,1-dioxide; (2*S*,5*R*)-3,3-Dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid 4,4-dioxide.

$C_8H_{11}NO_5S$=233.2

CAS — 68373-14-8.

ATC — J01CG01.

ATC Vet — QJ01CG01.

UNII — S4TF6I2330.

Pivsulbactam *(BAN)*

CP-47904; Sulbactam Pivoxil (USAN); Пивсульбактам.

Pivaloyloxymethyl penicillanate 1,1-dioxide.

$C_{14}H_{21}NO_5S$=347.4

CAS — 69388-79-0.

UNII — 2X0WTA96KX.

Sulbactam Sodium *(BANM, USAN, rINNM)*

CP-45899-2; Natrii Sulbactamum; Sulbactam-Natrium; Sulbactam sódico; Sulbactam Sodique; Sulbactamum natricum; Sulbaktaaminatrium; Sulbaktam sodná sůl; Sulbaktam sodowy; Sulbaktamnatrium; Натрий Сульбактам.

$C_8H_{10}NNaO_5S$=255.2

CAS — 69388-84-7.

ATC — J01CG01.

ATC Vet — QJ01CG01.

UNII — DKQ4T82YE6.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Sulbactam Sodium). A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; very slightly soluble in alcohol; sparingly soluble in ethyl acetate. It is freely soluble in diluted acids. A 5.0% solution in water has a pH of 4.5 to 7.2; if the substance is sterile: 5.2 to 7.2. Store in airtight containers.

USP 36: (Sulbactam Sodium). A white to off-white crystalline powder. It contains not less than 886 micrograms and not more than 941 microgram of sulbactam per mg, calculated on the anhydrous basis. Freely soluble in water and in dilute acid; sparingly soluble in acetone, in chloroform, and in ethyl acetate. Store in airtight containers.

Profile

Sulbactam is a penicillanic acid sulfone with beta-lactamase inhibitory properties. It is active against Neisseriaceae and *Acinetobacter baumanii*, but generally has only weak antibacterial activity against other organisms. It is an irreversible inhibitor of many plasmid-mediated and some chromosomal beta-lactamases and has a similar spectrum of beta-lactamase inhibition to clavulanic acid (p. 268.3), although it is regarded as less potent. Sulbactam can therefore enhance the activity of penicillins and cephalosporins against many resistant strains of bacteria.

It is given with ampicillin (p. 218.2) in the treatment of infections where beta-lactamase production is suspected. Sulbactam is poorly absorbed from the gastrointestinal tract and is given by injection as the sodium salt. The pharmacokinetics of parenteral sulbactam and ampicillin are similar. For oral use the mutual prodrug sultamicillin (p. 371.1) is available in some countries. Sulbactam is also given orally as the pivoxil derivative, pivsulbactam, with amoxicillin. Sulbactam has also been given with cefoperazone.

References.

1. Lee NLS, *et al.* β-Lactam antibiotic and β-lactamase inhibitor combinations. *JAMA* 2001; 285: 386–8.
2. Lode H. Role of sultamicillin and ampicillin/sulbactam in the treatment of upper and lower bacterial respiratory tract infections. *Int J Antimicrob Agents* 2001; 18: 199–209.
3. Kanra G. Experience with ampicillin/sulbactam in severe infections. *J Int Med Res* 2002; 30 (suppl 1): 20A–30A.
4. Lee N, *et al.* Clinical role of β-lactam/β-lactamase inhibitor combinations. *Drugs* 2003; 63: 1511–24.
5. Rafailidis PI, *et al.* Ampicillin/sulbactam: current status in severe bacterial infections. *Drugs* 2007; 67: 1829–49.
6. Akova M. Sulbactam-containing beta-lactamase inhibitor combinations. *Clin Microbiol Infect* 2008; 14 (suppl 1): 185–8.

Breast feeding. Although sulbactam is distributed into breast milk in small amounts,[1] no adverse effects have been seen in breast-fed infants and the American Academy of Pediatrics considers that it is usually compatible with breast feeding.[2]

1. Foulds G, *et al.* Sulbactam kinetics and excretion into breast milk in postpartum women. *Clin Pharmacol Ther* 1985; 38: 692–6.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/05/04)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Combactam; *China*: Lianke (联可); *Ger.*: Combactam; *India*: Cefritz-S; *Indon.*: Cefoject; *Spain*: Betamaz; *Turk.*: Ampisid; B-Laktam.

Multi-ingredient Preparations. *Arg.*: Aminoxidin Sulbactam; Ampi-Bis Plus; Ampigen SB; Darzitil SB; Prixin; Trifamox IBL Duo; Trifamox IBL; Unasyna†; *Austria*: Unasyn; *Braz.*: Combactan; Sulbamox; Trifamox; Unasyn; *Chile*: Auropennz; Sulbamox; Sulperazon; Unasyn; *China*: Bai Ding (百定); Bei Shu Lin (倍舒林); Dalipaitan (达力唏坦); Dexiao (得消); Fanlin (凡林); Fengpaixin (锋派新); Fumaixin (孚麦欣); Haishubi (海舒必); Han Guang (汉光); Jia Luo Tan (佳洛坦); Kai Wei Ke (凯韦可); KaiLin (开林); Kaisheng (凯生); Kang Li Shu (康力舒); Lai Qie Li (来切利); Li Ke Duo (力可多); Lijunpaishu (利君派舒); Linglanxin (铃兰欣); Litan (力坦); Pai Shu (派纾); Pu Shu (普舒); Ruipuxin (瑞普欣); Shu An Xin (舒氨新); Shu Sa Lin (舒萨林); Shuanxilin (舒氧西林); Shudi (舒敌); Shutabituo (舒他必妥); Stanyn (施坦宁); Sulperazon (舒普深); Trifamox IBL (特福猛); Unasyn (优立新); Wei Qi Da (威奇达); Xi Lin (悉林); Xian Qiang (先强); Xianjie (先捷); Xianpu (先普); Xianshu (先舒); Xidilin (西迪林); Xin An Lin (欣安林); Xin Junbizhi (新君必治); Xinkuaixin (新快欣); Xinruipuxin (新瑞普欣); Xinternie (新特灭); Xinzhijun (新治君); Yi Jun (一君); Yi Tan (益坦); Zetong (泽同); *Cz.*: Bitammon; Sulperazon; Unasyn; *Fr.*: Unacim; *Ger.*: Ampicillin comp†; Unacid; *Gr.*: Begalin-P; Demotine; *Hong Kong*: Sulperazon; Unasyn; *Hung.*: Unasyn; *India*: Acticef-SB; Adesul; Afzone-S; Alitax-S; Alkaceff-S; Alnacef-S; Amceft-S; Amisul; Ampitum; Ampy S; Ampysul; Apozone-S; Arifzon-SB; Arixon-SB; Atozon-S; Augtax; Avcef-S; Avicef-S; Axocare-S; Axon-SB; Axone-SB; Axtrum-S; Bacticid-CS; Bactocef; Bactonis; Bactorus; Bactosul; Bahutcef-SL; Betamp; Big-Tum; Broadcef-S; Burnex; C-Bact; C-Bactum; C-Fort; C-Lactum; C-Tab-SB; C-Tum; Cadcef-S; Cadizone-S; Cafage-S; Cafazone-S; Cameo-S; Cearium; Cebac; Cebactum; Cebanex; Cebect; Cef-S; Cefac; Cefactam; Cefaday-S; Cefalin-S; Cefantral-S; Cefasul; Cefbect; Cefcin-SB; Cefdinex-SB; Cefglobe-S; Cefina-SB; Cefjoy; Cefla; Cefmate; Cefmol-SF; Cefobac; Cefobel-S; Cefobeta; Cefoden-SB; Cefogard-S; Cefom-S; Cefonet-S; Cefonex; Ceforex; Cefos-S; Cefosal; Cefosul; Cefosun S; Cefozed-S; Cefpar SB; Cefrobactum; Cefrosan; Cefrose-S; Cefset-S; Cefsine-S; Ceftichek; Ceftocin; Ceftop; Ceftraset-S; Ceftril-S; Ceftrimax; Ceftrol-S; Cefum Cefup; Cefurax-D; Cefurin; Cefwon-S; Cefzon SB; Cefzone-S Cefzox-SF; Cepoxit-S; Ceprazo-S; Ceprozone-S; Cerazone-S Cesal; Cetriax-S; Cetzone-S; Cezon-S; Cezone Plus; Champione-S; Chuncif-S; Cinclox-S; Cis-SL; Cizon-SB; Corcef-SB Cotyx-S; CSI-S; CT Ceff SM; CT Spar SM; CTrisana-SB; Cucef S; Cucef-S; Curemax; Cuxone-SL; Dalcefa-SB; Decef; Deczone S; Dewcef-S; Duotax; Duozone; Effimax Plus; Eftanu-S; Ekcef S; Emtri-S; Estxone-SB; Evacef-S; Extacef-XL; Finetriax-S Pofone-S; Formic; Forone-SB; Fro-Cef; Frone-SL; Fuzosul Fytobact; Geminate Plus; Glen-SB; Glicef-S; Gloriax-SB; Gramocef-S; Hocef-S; Hosizone; Ifytrox-SB; Imex; Inbac Kit; Incef SB; Indobact; Indocef-SB; Indoxone-S; Infoxon-S; Iszu; Ivimax Kafi-S; Kaircef-S; Kefbactam; Kelchek; Kefsurge; Keftragard Kephazon-S; Kexone Plus; Krasule; Kxone-SL; L-Cef; Labicef-S Labxone-SB; Lactagard; Lezone-S; Lifecare-SB; Lisel-S; Lycef Plus; Magnatax; Magnazone; Magnex; Magtam; Mahacef-SB Mat-CS; Maxitax; Mecef-S; Medinex; Mepef-S; Mintrax-S Mocef-S; Monoact; Monobact; Montero; Mutax Plus; Nebect Nefsul; Neftum-SB; Nexef-SB; Nizotrax-S; NKCef+S; Nosobac Novaceft-S; Novacip-S; Nubact; Nuperazone Plus; Nutaxin-S Nutracip-SB; Ocefa-SB; Oduspi-S; Ofirex; Oframax Forte Onbact; Opticef-S; Oramax; Oritaximax; Orozone-SB; Osocil lin-S; Osotax-S; Osul-S; Over-SB; Oxy-S; Pancef-S; Parabact Sulbacef; Sulbacin; Sultax; Zosul; *Indon.*: Bactazon; Ferotam Fosular; Soperam; Stabactam; Sulbacef; Sulperazon; Zotam *Israel*: Unasyn; *Ital.*: Bethacil; Loricin; Unasyn; *Jpn*: Unasyn-S *Malaysia*: Easyn; Shinasyn; Sulbacin; Sulbamp; Sulperazon Unasyn; *Mex.*: Megamox; Trifamox IBL; Unasyna; *Philipp.* Ambactam; Ampimax; Ampisul; Dinocin; Silgram; Subacillin Sulbacin; Sulperazone; Sultacillin; Ultramox; Unasan; Unasyn *Pol.*: Sulperazon; Unasyn; *Rus.*: Bacperazone (Бакперазон) Cebanex (Цебанекс); Cephpar (Цефпар); Libakcil (Либакцил) Sulbacin (Сульбацин); Sulcef (Сульцеф); Sulcefazor (Сульцефазон); Sulmover (Сульмовер); Sulperace (Сульперацеф); Sulperason (Сульперазон); Sultasin (Сультасин) Sulzoncef (Сульзонцеф); Trifamox IBL (Трифамокс ИБЛ); Unasyn (Уназин)†; *Singapore*: Unasyn; *Thai.*: Bacticep; Cebactam Cefpar; Cefper; Prazone-S; Sulam; Sulbaccin; Sulbacilline; Sulcef; Sulperazon; Sulpermed; Unasyn; Zonbactam; *Turk.*: Alfasid; Combicid; Devasid; Duobak; Duobaktam; Duocid; Nobecid Primasef†; Probicid; Sefbaktam; Sulbaksit; Sulcid; Sulperazon Sultasid; Sultibac; *Ukr.*: Ampisid (Амписид); Ampisulbin (Амписульбин); Cebanex (Цебанекс); Cefoperazone Plus (Цефоперазон плюс); Cefosulbin (Цефосульбин); Cesulpin (Цесульпин); Gepacef Combi (Гепацеф Комби); Prazone-S (Празон-С); Sulperasone (Сульперазон); Taxtam (Тактам) Unasyn (Уназин)†; *USA*: Unasyn; *Venez.*: Ampibactan; Fipex iam; Sinif; Sulperazon; Unasyn.

Pharmacopoeial Preparations
USP 36: Ampicillin and Sulbactam for Injection.

Sulbenicillin Sodium *(rINNM)*

Natrii Sulbenicillinum; Sulbenicilina sódica; Sulbénicilline Sodique; α-Sulfobenzylpenicillin Sodium; Sulfocillin Sodium; Натрий Сульбенициллин.

The disodium salt of (6*R*)-6-(2-phenyl-2-sulphoacetamido) penicillanic acid.

$C_{16}H_{16}N_2Na_2O_7S_2$=458.4

CAS — 34779-28-7 (sulbenicillin); 41744-40-5 (sulbenicillin), 36417-90-0 (sulbenicillin sodium).

ATC — J01CA16.

ATC Vet — QJ01CA16.

UNII — 29SO9LJM1Q.

Pharmacopoeias. In *Chin.* and *Jpn*.

Profile

Sulbenicillin sodium has actions and uses similar to those o carbenicillin sodium (p. 232.1). It is given by intramuscula or intravenous injection or infusion.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Indon.*: Kedacillin; *Mex.*: Kedacil lin†; *Philipp.*: Kedacillin.

Sulfabenzamide *(BAN, USAN, rINN)*

Sulfabensamid; Sulfabentsamidi; Sulfabenzamida; Sulfabenzamidum; Sulfabenzide; Сульфабензамид.

N-Sulphanilylbenzamide.

$C_{13}H_{12}N_2O_3S$=276.3

CAS — 127-71-9.

UNII — G58F8OPL4I.

Pharmacopoeias. In *US*.

USP 36: (Sulfabenzamide). A fine, white, practicall odourless powder. Insoluble in water and in ether; solubl

in alcohol, in acetone, and in sodium hydroxide 4% solution. Protect from light.

Profile

Sulfabenzamide is a sulfonamide with properties similar to those of sulfamethoxazole (p. 367.2). It is reported to exert an optimal bacteriostatic action at pH 4.6. It has been used with sulfacetamide and sulfathiazole in pessaries or a vaginal cream for the treatment of bacterial vaginosis, although its value has been questioned. The vaginal cream has also been used for the prevention of bacterial infection after cervical and vaginal surgery.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Braz.*: Vagi-Sulfa; *Gr.*: Kronoderm; Sultrin; *Philipp.*: Sultrin†; *S.Afr.*: Sultrin†; *USA*: Sultrin†.

Pharmacopoeial Preparations
USP 36: Triple Sulfa Vaginal Cream; Triple Sulfa Vaginal Tablets.

Sulfacarbamide *(BAN, rINN)*

Sulfacarbamida; Sulfacarbamidum; Sulfakarbamid; Sulfanilcarbamide; Sulfaurea; Sulphacarbamide; Sulphanilylurea; Sulphaurea; Urosulphanum; Сульфакарбамид.
Sulphanilylurea monohydrate.
$C_7H_9N_3O_3S,H_2O$=233.2
CAS — 547-44-4 (anhydrous sulfacarbamide); 6101-35-5 (sulfacarbamide monohydrate).
UNII — W6CD25Z4QR.

Pharmacopoeias. In *Pol.*

Profile

Sulfacarbamide is a sulfonamide with properties similar to those of sulfamethoxazole (p. 367.2). It has been used in the treatment of urinary-tract infections, sometimes with other drugs.

Sulfacetamide *(BAN, rINN)*

Acetosulfaminum; Sulfacetamid; Sulfacetamida; Sulfacétamide; Sulfacetamidum; Sulfatsetamidi; Sulphacetamide; Сульфацетамид.
N-Sulphaniloylacetamide.
$C_8H_{10}N_2O_3S$=214.2
CAS — 144-80-9.
ATC — S01AB04.
ATC Vet — QJ01EQ21; QS01AB04.
UNII — 4965G3J0F5.

Pharmacopoeias. In *Int.* and *US.*

USP 36: (Sulfacetamide). A white, odourless, crystalline powder. Slightly soluble in water and in ether; soluble in alcohol; very slightly soluble in chloroform; freely soluble in dilute mineral acids and in solutions of potassium and sodium hydroxides; practically insoluble in benzene. Solutions in water are acid to litmus and sensitive to light; they are unstable when acidic or strongly alkaline. Protect from light.

Sulfacetamide Sodium *(BANM, rINNM)*

Natrii Sulfacetamidum; Soluble Sulphacetamide; Sulfacetamid-Natrium; Sulfacetamid sodná sůl monohydrát; Sulfacetamid sodowy; Sulfacetamida sódica; Sulfacétamide Sodique; Sulfacetamidnatrium; Sulfacetamido natrio druska; Sulfacetamidum natricum; Sulfacetamidum Natricum Monohydricum; Sulfacylum; Sulfasetamid Sodyum; Sulfasetamidinatrium; Sulphacetamide Sodium; Sulphacetamidum Sodium; Szulfacetamid-nátrium; Натрий Сульфацетамид.
$C_8H_9N_2NaO_3S,H_2O$=254.2
CAS — 127-56-0 (anhydrous sulfacetamide sodium); 6209-17-2 (sulfacetamide sodium monohydrate).
ATC — S01AB04.
ATC Vet — QJ01EQ21; QS01AB04.
UNII — 4NRT660KJQ.

NOTE. SULF is a code approved by the BP 2014 for use on single unit doses of eye drops containing sulfacetamide sodium where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 8: (Sulfacetamide Sodium). A white or yellowish-white, crystalline powder. Freely soluble in water; slightly soluble in dehydrated alcohol. A 5% solution in water has a pH of 8.0 to 9.5. Protect from light.

USP 36: (Sulfacetamide Sodium). A white odourless crystalline powder. Soluble 1 in 2.5 of water; sparingly soluble in alcohol; practically insoluble in chloroform and in ether. A 5% solution in water has a pH of 8.0 to 9.5. Store in airtight containers. Protect from light.

Stability. When solutions of sulfacetamide sodium are heated, hydrolysis occurs forming sulfanilamide which may be deposited as crystals, especially from concentrated solutions and under cold storage conditions.

Uses and Administration

Sulfacetamide is a short-acting sulfonamide antibacterial that is used with sulfabenzamide and sulfathiazole in preparations for vaginal use, and is applied, as the sodium salt, in infections or injuries of the eyes, although it is rarely of much value. Eye drops containing sulfacetamide sodium 10 to 30% and eye ointments containing 10% have been used. The sodium salt is also applied topically in the treatment of skin infections, and with sulfur in the management of rosacea.

Adverse Effects, Treatment, and Precautions

As for Sulfamethoxazole, p. 367.3.

Local application of sulfacetamide sodium to the eye may cause burning or stinging but this is rarely severe enough to require stopping treatment.

Antimicrobial Action

As for Sulfamethoxazole, p. 368.3.

Pharmacokinetics

When sulfacetamide sodium is applied to the eye it penetrates into ocular tissues and fluids and may be absorbed into the blood when the conjunctiva is inflamed.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Dermaseb; *Austral.*: Acetopt†; Bleph-10; *Austria*: Cetazin; *Belg.*: Anginamide; Antebor; Sulfa 10; *Braz.*: Queimalive; *Canad.*: Ak-Sulf; Bleph-10†; Cetamide†; Diosulf; Sodium Sulamyd; *Fr.*: Antebor†; *Hong Kong*: Sulfex; *India*: Albucid; Alektra; Andremide; Bleph; Locula; Ocu-Sulf; Optacd; *Indon.*: Albucid; Isotic Cetridet†; *Irl.*: Bleph-10†; *Israel*: Klaron†; Optisol†; Sulfacid; *Mex.*: Blef-10; Cetapred; Examida; Isoftalmol†; Sodamida; Sul 10; *NZ*: Acetopt; Bleph-10; *Philipp.*: Acetopt; Facetam; Sensocet; Vistasulf; *S.Afr.*: Spersamide†; *Singapore*: Sulfex; *Thai.*: Bleph-10; Optal; *Turk.*: Optamid; Sivex; *Ukr.*: Sulfacyl (Сульфацил); *USA*: Ak-Sulf; Bleph-10; Carmol Scalp Treatment†; Isopto Cetamide†; Klaron; Mexar; Ocusulf†; Ovace; Seb-Prev Wash; Sodium Sulamyd†; Sulf-10; Sulfac; Sulster; Vanocin; *Venez.*: Sulfacet.

Multi-ingredient Preparations. *Arg.*: Blefamide; *Braz.*: Isopto Cetapred; Paraqueimol; Sulnil; Vagi-Sulfa; *Canad.*: Ak-Cide; Blephamide; Dioptimyd; Sulfacet-R; *Chile*: Blefamide†; Blefamide; Deltamid; *Ger.*: Blephamide; *Gr.*: Blephamide; Eyecort; Geypirina; Isopto Cetapred; Kronoderm; Otenor; Sulfachlor; Sulfachloramphenicol; Sulfanicole; Sultrin; *India*: Cortola-M; Nebasulf; Neotop; Zinco Sulpha†; *Israel*: Blephamide; *Ital.*: Antisettico Astringente Sedativo; Aureomix; Brumeton Colloidale S; Cosmiciclina; Visublefarite; *Mex.*: Axel; Blefamide-F; Blefamide; Deltamid; Isopto Cetapred; Premid; Sulfa Cloran; Sulfa Hidro†; Sulvi; *NZ*: Blephamide†; *Philipp.*: Cetapred†; Isopto Cetapred†; Lonace; Sterilid-V; Sultrin†; *Port.*: Meocil; *S. Afr.*: Covancaine; Covosan†; Sultrin†; *Singapore*: Blephamide†; *Spain*: Celestone S†; Denticelso; *Switz.*: Blephamide; *Turk.*: Blephamide; Brumeton; Suprenil; *USA*: Avar; Blephamide; BP Cleansing Wash; Cerisa; Claris; Cleniat†; FML-S†; Garimide; Metimyd†; Nicosyn; Plexion; Rosac†; Rosaderm; Rosanil; Rosula NS†; Rosula†; SE SS; SSS; Sulfacet-R; SulfaCleanse; Sulfamide; Sultrin†; SulZee†; Sumadan; Sumaxin; Suphera; Vasocidin; Vasocine; Vasosulf†; Virti-Sulf; Zencia; Zetacet†; *Venez.*: Sulfacort.

Pharmacopoeial Preparations
USP 36: Neomycin Sulfate, Sulfacetamide Sodium, and Prednisolone Acetate Ophthalmic Ointment; Sulfacetamide Sodium and Prednisolone Acetate Ophthalmic Ointment; Sulfacetamide Sodium and Prednisolone Acetate Ophthalmic Suspension; Sulfacetamide Sodium Ophthalmic Ointment; Sulfacetamide Sodium Ophthalmic Solution; Sulfacetamide Sodium Topical Suspension; Triple Sulfa Vaginal Cream; Triple Sulfa Vaginal Tablets.

Sulfachlorpyridazine *(BAN, rINN)*

Sulfachlorpyridazin; Sulfachlorpyridazinum; Sulfaclorpiridazina; Sulphachlorpyridazine; Сульфахлорпиридазин.
N^1-(6-Chloropyridazin-3-yl)sulphanilamide.
$C_{10}H_9ClN_4O_2S$=284.7
CAS — 80-32-0.
ATC Vet — QJ01EQ12.
UNII — P78D9P90C0.

Pharmacopoeias. In *US* for veterinary use only.

USP 36: (Sulfachlorpyridazine). Protect from light.

Profile

Sulfachlorpyridazine is a sulfonamide antibacterial used in veterinary medicine.

Sulfachrysoidine *(rINN)*

Carboxysulfamidochrysoidine; Sulfachrysoidine; Sulfachrysoidinum; Sulfacrisoidina; Сульфахризоидин.
3,5-Diamino-2-(*p*-sulfamoylphenylazo) benzoic acid.
$C_{13}H_{13}N_5O_4S$=335.3
CAS — 485-41-6.
UNII — 39O1389K38.

Profile

Sulfachrysoidine is a sulfonamide antibacterial that has been used topically as the sodium salt for infections of the oral mucosa.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Collubiazol.

Sulfaclozine *(rINN)*

Sulfaclozin; Sulfaclozina; Sulfaclozinum; Sulfaklotsiini; Sulfaklozin; Сульфаклозин.
N^1-(6-Chloropyrazinyl)sulfanilamide.
$C_{10}H_9ClN_4O_2S$=284.7
CAS — 102-65-8; 27890-59-1.
ATC Vet — QP51AG04.
UNII — 69YP7Z48CW.

Profile

Sulfaclozine is a sulfonamide antibacterial that has been used in veterinary medicine.

Sulfadiazine *(BAN, rINN)*

Solfadiazina; Solfapirimidina; Sulfadiatsiini; Sulfadiazin; Sulfadiazin; Sulfadiazina; Sulfadiazinas; Sulfadiazinum; Sulphadiazine; Szulfadiazin; Сульфадиазин.
N^1-(Pyrimidin-2-yl)sulphanilamide.
$C_{10}H_{10}N_4O_2S$=250.3
CAS — 68-35-9.
ATC — J01EC02.
ATC Vet — QJ01EQ10.
UNII — 0N7609K889.

NOTE. Compounded preparations of sulfadiazine may be represented by the following names:
- Co-tetroxazine (*BAN*)—sulfadiazine 5 parts and tetroxoprim 2 parts (see p. 277.3)
- Co-trimazine (*BAN*)—sulfadiazine 5 parts and trimethoprim 1 part.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *US*, and *Viet.*

Ph. Eur. 8: (Sulfadiazine). White, yellowish-white, or pinkish-white, crystalline powder or crystals. Practically insoluble in water; very slightly soluble in alcohol; slightly soluble in acetone. It dissolves in solutions of alkali hydroxides and in dilute mineral acids. Protect from light.

USP 36: (Sulfadiazine). White or slightly yellow, odourless or nearly odourless, powder, slowly darkening on exposure to light. Soluble 1 in 13 000 of water; sparingly soluble in alcohol and in acetone; freely soluble in dilute mineral acids and in solutions of potassium and sodium hydroxides, and ammonia. Protect from light.

Sulfadiazine Sodium *(BANM, rINN)*

Sodium Sulfadiazine; Soluble Sulphadiazine; Sulfadiazina de sodio; Sulfadiazina sódica; Sulfadiazine sodique; Sulfadiazinum Natricum; Sulphadiazine Sodium; Сульфадиазин Натрий.
$C_{10}H_9N_4NaO_2S$=272.3
CAS — 547-32-0.
ATC — J01EC02.
UNII — 84CS1P306F.

Pharmacopoeias. In *Chin.* and *US.*

USP 36: (Sulfadiazine Sodium). A white powder. Soluble 1 in 2 of water; slightly soluble in alcohol. On prolonged exposure to humid air it absorbs carbon dioxide with the liberation of sulfadiazine and becomes incompletely soluble in water. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Incompatibility. Solutions of sulfadiazine sodium are alkaline, and incompatibility may reasonably be expected with acidic drugs or with preparations unstable at high pH. In the UK, licensed product information has stated that sulfadiazine sodium injection is incompatible with fructose, iron salts, and salts of heavy metals.

Uses and Administration

Sulfadiazine is a short-acting sulfonamide that has been used similarly to sulfamethoxazole (p. 367.2) in the treatment of infections due to susceptible organisms. It has been used in the treatment of nocardiosis and lymphogranuloma venereum, and has been given for the prophylaxis of rheumatic fever in penicillin-allergic patients. For details of these infections and their treatment, see Choice of Antibacterial, p. 172.2. Sulfadiazine is also given with pyrimethamine for the treatment and prevention of relapse of toxoplasmosis (p. 926.1) and has been tried in disseminated *Acanthamoeba* infection (p. 921.3).

In the treatment of susceptible infections, sulfadiazine may be given orally in usual doses of 2 to 4 g daily in divided doses.

Immunocompromised patients who have toxoplasmosis should be given a dose of 4 to 6 g daily in 4 divided doses for at least 6 weeks, followed by a suppressive dose of 2 to 4 g daily, which should continue indefinitely. Pyrimethamine should always be given as well.

For the prophylaxis of rheumatic fever, patients weighing less than about 30 kg are given 500 mg once daily, while those over 30 kg may receive 1 g once daily.

For details of doses in children, see p. 364.1.

Where oral use is not possible, treatment has also been begun intravenously using the sodium salt. Sulfadiazine sodium 1.09 g is equivalent to about 1 g of sulfadiazine. Intravenous doses of sulfadiazine sodium are given by infusion or by slow intravenous injection of a solution containing up to 5% sulfadiazine. It may be diluted with sodium chloride 0.9%. The usual dose is the equivalent of sulfadiazine 2 to 3 g initially, then 1 g four times daily for 2 days; subsequent treatment is given orally.

Sulfadiazine sodium has been given by deep intramuscular injection, but great care must be taken to prevent damage to subcutaneous tissues; the intravenous route is preferred.

Sulfadiazine has been used with trimethoprim as cotrimazine. Sulfadiazine has also been used with other sulfonamides, particularly sulfamerazine and sulfadimidine, to reduce the problems of low solubility in urine.

Administration in children. Sulfadiazine may be used in children for the management of infections caused by susceptible organisms, including toxoplasmosis, for which it may also be used in neonates. It is also used for prophylaxis of rheumatic fever. Although parenteral preparations may be available in some countries, the oral route is preferred.

In the UK, licensed product information recommends that children beyond the neonatal period may receive an initial oral dose of 75 mg/kg followed by a maintenance dose of 150 mg/kg daily in divided doses. Alternatively, in the USA, the American Academy of Pediatrics (AAP)[1] recommends 120 to 150 mg/kg daily in 4 to 6 divided doses. The maximum total daily dose should not exceed 6 g.

For treatment of **congenital toxoplasmosis**, the *BNFC* recommends that neonates may receive sulfadiazine 50 mg/kg twice daily for 12 months, *plus* pyrimethamine 1 mg/kg twice daily for 2 days, once daily for 6 months, then 3 times a week for 6 months.

For the treatment of **acquired toxoplasmosis** in HIV-infected children, US guidelines[2] suggest the following regimen for at least 6 weeks, followed by chronic suppressive therapy:

- sulfadiazine 25 to 50 mg/kg (to a maximum of 1.5 g) 4 times daily *plus*
- pyrimethamine 2 mg/kg (to a maximum of 50 mg) once daily for 3 days, then 1 mg/kg (to a maximum of 25 mg), once daily

For **chronic suppression of toxoplasmosis** in HIV-infected children, US guidelines[2] suggest sulfadiazine 85 to 120 mg/kg (to a maximum of 4 g) daily in 2 to 4 divided doses *plus* pyrimethamine 1 mg/kg (to a maximum of 25 mg) once daily.

In the prevention of recurrent **rheumatic fever**, sulfadiazine is dosed in children according to weight, similarly to adults (see Uses and Administration, above).

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.
2. Panel on Opportunistic Infections in HIV-Exposed and HIV-Infected Children. Guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and HIV-infected children: recommendations from the National Institutes of Health, CDC, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics (issued 6th November, 2013). Available at: http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/oi_guidelines_pediatrics.pdf (accessed 13/12/13)

Adverse Effects, Treatment, and Precautions

As for Sulfamethoxazole, p. 367.3.

Because of the low solubilities of sulfadiazine and its acetyl derivative in urine, crystalluria is more likely after use of sulfadiazine than after sulfamethoxazole.

Sulfadiazine sodium solution is strongly alkaline and it should therefore be given intravenously in a strength not exceeding 5%, over at least 10 minutes. For the same reason, intramuscular injections are painful and sulfadiazine sodium should not be given by intrathecal or subcutaneous injection.

Carnitine deficiency. Hyperammonaemia and carnitine deficiency developed in an immunocompromised patient given sulfadiazine and pyrimethamine for the treatment of toxoplasmosis.[1]

1. Sekas G, Harbhajan SP. Hyperammonemia and carnitine deficiency in a patient receiving sulfadiazine and pyrimethamine. *Am J Med* 1993; **95**: 112–13.

Effects on the eyes. Numerous white stone-like concretions of sulfadiazine occurred in the conjunctiva of a woman who had used sulfadiazine eye drops for about 1 year.[1]

1. Boettner EA, *et al.* Conjunctival concretions of sulfadiazine. *Arch Ophthalmol* 1974; **92**: 446–8.

Effects on the kidneys. There have been reports of crystalluria and renal failure associated with the use of sulfadiazine in immunocompromised patients,[1-8] including the suggestion that AIDS patients may be particularly prone to sulfadiazine-induced renal toxicity.[3] Renal failure and leucopenia in a patient treated with sulfadiazine silver for pyoderma gangrenosum were thought to be due to systemic absorption of the silver component.[9]

1. Goadsby PJ, *et al.* Acquired immunodeficiency syndrome (AIDS) and sulfadiazine-associated acute renal failure. *Ann Intern Med* 1987; **107**: 783–4.
2. Ventura MG, *et al.* Sulfadiazine revisited. *J Infect Dis* 1989; **160**: 556–7.
3. Simon DI, *et al.* Sulfadiazine crystalluria revisited: the treatment of Toxoplasma encephalitis in patients with acquired immunodeficiency syndrome. *Arch Intern Med* 1990; **150**: 2379–84.
4. Díaz P, *et al.* Sulfadiazine-induced multiple urolithiasis and acute renal failure in a patient with AIDS and Toxoplasma encephalitis. *Ann Pharmacother* 1996; **30**: 41–2.
5. Guitard J, *et al.* Sulfadiazine-related obstructive urinary tract lithiasis: an unusual cause of acute renal failure after kidney transplantation. *Clin Nephrol* 2005; **63**: 405–7.
6. Solano Remírez M, *et al.* Insuficiencia renal por sulfadiazina en paciente VIH con toxoplasmosis cerebral. *An Med Interna* 2005; **22**: 395–6.
7. Hyvernat H, *et al.* Insuffisance rénale aiguë obstructive lors d'un traitement par sulfadiazine. *Presse Med* 2006; **35**: 423–4.
8. de la Prada Alvarez FJ, *et al.* Insuficiencia renal aguda por depósito de cristales de sulfadiacina. *An Med Interna* 2007; **24**: 235–8.
9. Chaby G, *et al.* Insuffisance rénale aiguë après application topique de sulfadiazine argentique. *Ann Dermatol Venereol* 2005; **132**: 891–3.

Effects on the liver. A case of severe hepatotoxicity and probable hepatorenal syndrome occurred in a patient about 14 days after taking sulfadiazine as part of a treatment regimen for toxoplasmosis retinitis. The patient stopped all medicines after 3 weeks. She made a complete recovery with supportive management which included haemodialysis, and treatment with acetylcysteine.[1]

1. Khalili H, *et al.* Severe hepatotoxicity and probable hepatorenal syndrome associated with sulfadiazine. *Am J Health-Syst Pharm* 2011; **68**: 888–92.

Effects on the salivary glands. Enlargement of the salivary glands (sialadenitis) has been reported[1] in a patient who received a preparation containing sulfadiazine; complete recovery followed within 3 days of stopping therapy. Rechallenge confirmed that sulfadiazine was the causative agent.

1. Añibarro B, Fontela JL. Sulfadiazine-induced sialadenitis. *Ann Pharmacother* 1997; **31**: 59–60.

Interactions

As for Sulfamethoxazole, p. 368.2.

Antimicrobial Action

As for Sulfamethoxazole, p. 368.3.

Pharmacokinetics

Sulfadiazine is readily absorbed from the gastrointestinal tract and peak blood concentrations occur 3 to 6 hours after a single dose; 20 to 55% has been reported to be bound to plasma proteins. It penetrates into the CSF within 4 hours of an oral dose to produce therapeutic concentrations, which may be more than half those in the blood. Up to 40% of sulfadiazine in the blood is present as the acetyl derivative. The half-life of sulfadiazine is about 10 hours; it is prolonged in renal impairment.

About 50% of a single dose of sulfadiazine given orally is excreted in the urine in 24 hours; 15 to 40% is excreted as the acetyl derivative.

The urinary excretion of sulfadiazine and the acetyl derivative is dependent on pH. About 30% is excreted unchanged in both fast and slow acetylators when the urine is acidic whereas about 75% is excreted unchanged by slow acetylators when the urine is alkaline. The half-life of sulfadiazine ranges from 7 to 12 hours and that of its metabolite from 8 to 12 hours.[1]

1. Vree TB, *et al.* Determination of the acetylator phenotype and pharmacokinetics of some sulphonamides in man. *Clin Pharmacokinet* 1980; **5**: 274–94.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Suladrin†; *Fr.*: Adiazine *Gr.*: Adiazine†; *Mex.*: Bioarginol-C; Hebermin; Sularyn†; *Port.* Labdiazina; *Thal.*: Odiazine; Rediazine; Sul BCO; Sulfazine-M.

Multi-ingredient Preparations. *Arg.*: Afonisan; Anginotrat; Pastillas Lorbi†; *Austria*: Rhinon; *Braz.*: Triglobe; *China*: Zengxiac Lianhuangpian (增效联磺); *Fin.*: Ditrim; Trimetin Duplo† *India*: Aubril; Zad-G; *Indon.*: Trisulfa; *Malaysia*: Balin; Beaglobe; Trizine; *Mex.*: Agin; Estrefen; *Philipp.*: Triglobe†; Trizine *Port.*: Broncodiazina†; *Singapore*: Balin; Trizine; *Thai.*: Sulfatril†; Triple Sulphas; Trisulfa Co-P; Trisulfapyrimidines; *Turk.* Sulfatrim†.

Pharmacopoeial Preparations

BP 2014: Sulfadiazine Injection;
USP 36: Sulfadiazine Sodium Injection; Sulfadiazine Tablets; Trisulfapyrimidines Oral Suspension; Trisulfapyrimidines Tablets.

Sulfadiazine Silver *(BANM, rINNM)*

Argenti Sulfadiazinum; Gümüş Sülfadiazin; Hopeasulfadiatsiini; Silbersulfadiazin; Silver Sulfadiazine (USAN); Silver Sulfadiazine; Silver Sulphadiazine; Silversulfadiazin; Sulfadiazina argéntica; Sulfadiazina de plata; Sulfadiazine Argentique; Sulfadiazinum Argenticum; Sulfadiazinum Argentum; Sulphadiazine Silver; Zilversulfadiazine; Сульфадиазин Серебра.

$C_{10}H_9AgN_4O_2S$=357.1

CAS — 22199-08-2.

ATC — D06BA01.

ATC Vet — QD06BA01.

UNII — W46JY43EJR.

Pharmacopoeias. In *Chin.*, *Int.*, *Jpn*, and *US*.

USP 36: (Silver Sulfadiazine). A white to creamy-white, odourless or almost odourless crystalline powder. It becomes yellow on exposure to light. Practically insoluble in alcohol, in chloroform, and in ether; slightly soluble in acetone; freely soluble in 30% ammonia solution. It decomposes in moderately strong mineral acids. Protect from light.

Uses and Administration

Sulfadiazine silver is a sulfonamide that is used as a 1% cream for the prevention and treatment of infection in severe burns (p. 1683.1).

Sulfadiazine silver has also been used in other skin conditions, such as leg ulcers (p. 1690.1), where infection may prevent healing and for the prophylaxis of infection in skin grafting. It has also been applied to the eyes in the treatment of superficial *Aspergillus* infections.

Catheters impregnated with sulfadiazine silver have been used to reduce catheter colonisation and related bloodstream infection (p. 1733.1).

Adverse Effects, Treatment, and Precautions

Sulfadiazine silver may be absorbed after topical application and produce systemic effects similar to those of other sulfonamides (see Sulfamethoxazole, p. 367.3).

Local pain or irritation are uncommon; the separation of the eschar may be delayed and fungal invasion of the wound may occur.

Transient leucopenia does not usually require withdrawal of sulfadiazine silver, but blood counts should be monitored to ensure they return to normal within a few days. Systemic absorption of silver, resulting in argyria, can occur when sulfadiazine silver is applied to large area wounds or over prolonged periods.

References.

1. Fuller FW. The side effects of silver sulfadiazine. *J Burn Care Res* 2009; **30**: 464–70.

Argyria. Argyria, with discoloration of the skin and sensorimotor neuropathy, has been reported after excessive application of sulfadiazine silver 1% cream to extensive leg ulcers.[1] Systemic argyria associated with loss of proprioception and impaired coordination has also been

reported with long-term use of the 1% cream under occlusive dressing in a patient with severe generalised dystrophic epidermolysis bullosa.[2]

1. Payne CMER, *et al.* Argyria from excessive use of topical silver sulphadiazine. *Lancet* 1992; 340: 126.
2. Flohr C, *et al.* Topical silver sulfadiazine-induced systemic argyria in a patient with severe generalized dystrophic epidermolysis bullosa. *Br J Dermatol* 2008; 159: 740–1.

Effects on the kidneys. For mention of renal failure and leucopenia associated with the use of sulfadiazine silver see under Sulfadiazine, p. 362.2.

Interactions

As for Sulfamethoxazole, p. 368.2.

Sulfadiazine silver is not antagonised by *p*-aminobenzoic acid or related compounds. The silver content of sulfadiazine silver may inactivate enzymatic debriding agents.

Antimicrobial Action

Sulfadiazine silver has broad antimicrobial activity against Gram-positive and Gram-negative bacteria including *Pseudomonas aeruginosa*, and some yeasts and fungi. Sulfadiazine silver has a bactericidal action; in contrast to sulfadiazine, the silver salt acts mainly on the cell membrane and cell wall and its action is not antagonised by *p*-aminobenzoic acid. Resistance to sulfadiazine silver has been reported and may develop during therapy.

Pharmacokinetics

Sulfadiazine silver slowly releases sulfadiazine when in contact with wound exudates. Up to about 10% of the sulfadiazine may be absorbed; concentrations in blood of 10 to 20 micrograms/mL have been reported, although higher concentrations may occur when extensive areas of the body are treated. Some silver may also be absorbed.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Sulfatral; *Austral.*: Allevyn Ag; Flamazine; *Austria*: Flammazine; *Belg.*: Flammazine; Sedoflame; Sulfasil; *Braz.*: Dermazine; Gino Dermazine†; Silglos; Sulfaderm†; *Canad.*: Dermazin; Flamazine; *Cz.*: Dermazin†; *Denm.*: Flamazine; Flammazine; *Fin.*: Flamazine; *Fr.*: Flammazine; Sicazine†; *Ger.*: Brandiazin†; Flammazine; InfectoFlam; *Gr.*: Brandiazin; Flammazine; Sedoflame; Sylfio; *Hong Kong*: Dermazin; Flamazine†; Silvederma; Silvex; *Hung.*: Dermazin; *India*: Burn Aid; Ceptidar; SSZ; *Indon.*: Burnazin; *Irl.*: Flamazine; *Israel*: Silverol; *Ital.*: Bacternil; Sofargen; *Mex.*: Argemol; Argentafil; Argental; Silvadene†; Zitep†; *Neth.*: Flammazine; *Norw.*: Flamazine; *NZ*: Flamazine; *Philipp.*: Burnsil; Flammazine; Innoxiderm; Silvex; Sterizol; Sulfadin; Synvodex; *Pol.*: Dermazin†; *Port.*: Flammazine; Sicazine; Silvederma; Silvespray†; *Rus.*: Dermazin (Дермазин); Silvederma (Сильведерм); Sulphargin (Сульфаргин); *S.Afr.*: Argent-Eze†; Bactrazine; Flamazine; Silbecor; *Spain*: Flammazine; Silvederma; *Switz.*: Flammazine; Silvertone†; *Thai.*: Dermazin; Flamazine; Silverderm; Silverol; Silvex; *Turk.*: Silder; Silvaden; Silvadiazin; Silvamed; Silverdin; *UAE*: Silvadiazin; *UK*: Flamazine; *Ukr.*: Argedin (Аргедин); Dermazin (Дермазин); Sulfargin (Сульфаргин); *USA*: Silvadene; SSD; Thermazene; *Venez.*: Menaderm; Protosulfil; Silvederma.

Multi-ingredient Preparations. *Arg.*: Fisioderm; Iuronico Biotic; Platsul A; Sulfadiazina de Plata; Sulfaplat; *Austral.*: Silvazine†; *Belg.*: Flammacerium; *Braz.*: Dermacerium; *Chile*: FCE; Platsul A; *Cz.*: Ialugen Plus; *Fr.*: Altreet Ag; Flammacerium; Ialuset Plus; Urgotul S.Ag; *Ger.*: Physiotulle-Ag; Urgotul S.Ag; *Gr.*: Flammacerium; *Hong Kong*: Flammacerium; *Hung.*: Ialugen Plus; *India*: AG-X; Aloederm-B; Alorex; Argisept; Burnheal; Burnil; Burnkul; Burnoff; Burnosym; Burnowin; Dermogard; Dibact; Drez-S; Glosilex; Heal; Silverex; *Ital.*: Altergen; Connettivina Plus; *Neth.*: Flammacerium; *NZ*: Silvazine†; *Philipp.*: Flammacerium; *Pol.*: Flammacerium†; *Singapore*: Silvazine†; Silvin; *Spain*: Flammazine Cerio; *Switz.*: Ialugen Plus; *UK*: Flammacerium; Physiotulle-Ag; *Ukr.*: Ebermin (Эбермин).

Pharmacopoeial Preparations
USP 36: Silver Sulfadiazine Cream.

Sulfadicramide *(rINN)*

Sulfadicramid; Sulfadicramida; Sulfadicramidum; Sulfadikramid; Sulfadikramidi; Сульфадикрамид.

N-(3,3-Dimethylacroyl)sulphanilamide

$C_{11}H_{14}N_2O_3S$=254.3

CAS — 115-68-4.

ATC — S01AB03.

ATC Vet — QS01AB03.

UNII — 7WZ5EG263C.

Profile

Sulfadicramide is a sulfonamide with properties similar to those of sulfamethoxazole (p. 367.2). It has been applied as a 15% ointment for superficial infections of the eye.

Sulfadimethoxine *(BAN, rINN)*

Solfadimetossina; Sulfadimetossipirimidina; Sulfadimethoxin; Sulfadiméthoxine; Sulfadimethoxinum; Sulfadimetoksiini; Sulfadimetoxin; Sulfadimetoxina; Sulphadimethoxine; Сульфадиметоксин.

N^1-(2,6-Dimethoxypyrimidin-4-yl)sulphanilamide

$C_{12}H_{14}N_4O_4S$=310.3

CAS — 122-11-2.

ATC — J01ED01.

ATC Vet — QJ01EQ09; QP51AG02.

UNII — 30CPC5LDEX.

Pharmacopoeias. In *Fr.* and *It.* In *US* for veterinary use only.

USP 36: (Sulfadimethoxine). Practically white, crystalline powder. Practically insoluble in water; slightly soluble in alcohol, in chloroform, in ether, and in hexane; soluble in 2N sodium hydroxide; sparingly soluble in 2N hydrochloric acid. Store in airtight containers. Protect from light.

Profile

Sulfadimethoxine is a long-acting sulfonamide with properties similar to those of sulfamethoxazole (p. 367.2). It is used in preparations for the treatment of skin infections and was formerly used for the treatment of urinary-tract infections. It is also used in veterinary medicine, sometimes with baquiloprim or ormetoprim.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Rus.*: Levosin (Левосин); *Thai.*: D-Med; Ximeprim.

Sulfadimidine *(BAN, rINN)*

Solfametazina; Sulfadimerazine; Sulfadimezinum; Sulfadimidiini; Sulfadimidin; Sulfadimidina; Sulfadimidinas; Sulfadimidinum; Sulfamethazine; Sulphadimethylpyrimidine; Sulphadimidine; Sulphamethazine; Szulfadimidin; Сульфадимидин.

N^1-(4,6-Dimethylpyrimidin-2-yl)sulphanilamide.

$C_{12}H_{14}N_4O_2S$=278.3

CAS — 57-68-1.

ATC — J01EB03.

ATC Vet — QJ01EQ03; QP51AG01.

UNII — 48U51W007F.

NOTE. Sulfadimethylpyrimidine has been used as a synonym for sulfisomidine (p. 371.1). Care should be taken to avoid confusion between the two compounds, which are isomeric.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *US*, and *Viet.* Also in *BP(Vet)*.

Ph. Eur. 8: (Sulfadimidine). White or almost white powder or crystals. Very slightly soluble in water; slightly soluble in alcohol; soluble in acetone. It dissolves in solutions of alkali hydroxides and in dilute mineral acids. Protect from light.

USP 36: (Sulfamethazine). White to yellowish-white, practically odourless, powder. It may darken on exposure to light. Very slightly soluble in water and in ether; slightly soluble in alcohol; soluble in acetone. Protect from light.

Sulfadimidine Sodium *(BANM, rINNM)*

Natrii Sulfadimidinum; Soluble Sulphadimidine; Sulfadimidina sódica; Sulfadimidine Sodique; Sulfamethazine Sodium; Sulphadimidine Sodium; Натрий Сульфадимидин.

$C_{12}H_{13}N_4NaO_2S$=300.3

CAS — 1981-58-4.

ATC — J01EB03.

UNII — 7Z13P9Q95C.

Pharmacopoeias. In *Int.*

Profile

Sulfadimidine is a short-acting sulfonamide with properties similar to those of sulfamethoxazole (p. 367.2).

It is well absorbed from the gastrointestinal tract and is about 80 to 90% bound to plasma proteins. Reported half-lives have ranged from 1.5 to 4 hours in fast and 5.5 to 8.8 hours in slow acetylators. Because of the relatively high solubility of the drug and its acetyl metabolite, crystalluria may be less likely than with sulfamethoxazole.

In the treatment of susceptible infections, sulfadimidine has been given orally in an initial dose of 2 g, followed by 0.5 to 1.0 g every 6 to 8 hours. It has also been given parenterally as the sodium salt.

Sulfadimidine has also been used with other sulfonamides, particularly sulfamerazine and sulfadiazine. It is also used in veterinary medicine, sometimes with baquiloprim or trimethoprim.

Because its pharmacokinetics differ in fast and slow acetylators, sulfadimidine has been used to determine acetylator status.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Hung.*: Septosyl; *Thai.*: Famidine.

Multi-ingredient Preparations. *Indon.*: Trisulfa; *Thai.*: Sulfatril†; Triple Sulphas; Trisulfa Co-P; Trisulfapyrimidines.

Pharmacopoeial Preparations
USP 36: Trisulfapyrimidines Oral Suspension; Trisulfapyrimidines Tablets.

Sulfadoxine *(BAN, USAN, rINN)*

Ro-4-4393; Sulfadoksiini; Sulfadoksinas; Sulfadossina; Sulfadoxin; Sulfadoxina; Sulfadoxinum; Sulformethoxine; Sulforthomidine; Sulphormethoxine; Sulphorthodimethoxine; Szulfadoxin; Сульфадоксин.

N^1-(5,6-Dimethoxypyrimidin-4-yl)sulphanilamide.

$C_{12}H_{14}N_4O_4S$=310.3

CAS — 2447-57-6.

ATC Vet — QJ01EQ13.

UNII — 88463U4SMS.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 8: (Sulfadoxine). White or yellowish-white crystalline powder or crystals. Very slightly soluble in water; slightly soluble in alcohol and in methyl alcohol. It dissolves in solutions of alkali hydroxides and in dilute mineral acids. Protect from light.

USP 36: (Sulfadoxine). Protect from light.

Uses and Administration

Sulfadoxine is an ultra-long-acting sulfonamide that has been used in the treatment of various infections but is now rarely used alone.

It is given as a fixed-dose combination of 20 parts sulfadoxine with 1 part pyrimethamine (*Fansidar, Roche*) in the treatment of falciparum malaria (p. 644.1), usually with artesunate. Although the combination has been used in the prophylaxis of malaria, the risk of toxicity is now generally considered to outweigh its value.

In the treatment of malaria, the usual oral dose is 1.5 g of sulfadoxine with 75 mg of pyrimethamine as a single dose.

For details of doses in children, see p. 365.3.

Sulfadoxine with pyrimethamine has also been given intramuscularly.

Sulfadoxine with pyrimethamine has also been tried in the treatment of actinomycetomas (see Mycetoma p. 193.1), and for prophylaxis of pneumocystis pneumonia in immunocompromised patients (see p. 567.2 for the more usual prophylactic regimens).

A mixture of 5 parts of sulfadoxine with 1 part trimethoprim is used in veterinary medicine.

Administration in children. Sulfadoxine may be used in children, with pyrimethamine, for the treatment of falciparum malaria. It may be given as a single oral dose to children 2 months of age and older according to bodyweight as follows:

- 5 to 10 kg: 250 mg, with 12.5 mg pyrimethamine
- 11 to 20 kg: 500 mg, with 25 mg pyrimethamine
- 21 to 30 kg: 750 mg, with 37.5 mg pyrimethamine
- 31 to 45 kg: 1 g, with 50 mg pyrimethamine
- over 45 kg: as for adults (see Uses and Administration, above)

Adverse Effects, Treatment, and Precautions

As for Sulfamethoxazole, p. 367.3. For reference to the adverse effects of a combination of sulfadoxine and pyrimethamine, see Pyrimethamine, p. 663.3.

If adverse effects occur, sulfadoxine has the disadvantage that several days are required for elimination from the body.

References.

1. Peters PJ, *et al.* Safety and toxicity of sulfadoxine/pyrimethamine: implications for malaria prevention in pregnancy using intermittent preventive treatment. *Drug Safety* 2007; 30: 481–501.

Interactions

As for Sulfamethoxazole, p. 368.2.

Antimicrobial Action

As for Sulfamethoxazole, p. 368.3. Synergy exists between sulfadoxine and pyrimethamine, which act against folate metabolism at different points of the metabolic cycle.

Resistance to the combination of sulfadoxine and pyrimethamine in plasmodia, first noted in Thailand in the late 1970s, has become widespread in many malarious areas of the world. For further details of resistance to antimalarial drugs, see p. 644.1.

Pharmacokinetics

Sulfadoxine is readily absorbed from the gastrointestinal tract and peak concentrations of about 60 micrograms/mL occur about 4 hours after a 500-mg dose. It has an elimination half-life of about 200 hours. About 90 to 95% is reported to be bound to plasma proteins.

Sulfadoxine is widely distributed to body tissues and fluids; it passes into the fetal circulation and has been detected in low concentrations in breast milk. Sulfadoxine is excreted in urine, mainly unchanged.

References.
1. Karunajeewa HA, *et al.* Pharmacokinetic properties of sulfadoxine-pyrimethamine in pregnant women. *Antimicrob Agents Chemother* 2009; 53: 4368–76.
2. Nyunt MM, *et al.* Pharmacokinetics of sulfadoxine and pyrimethamine in intermittent preventive treatment of malaria in pregnancy. *Clin Pharmacol Ther* 2010; 87: 226–34.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Malaysia*: Fansidar.

Multi-ingredient Preparations. *Austral.*: Fansidar†; *Braz.*: Fansidar; *Fr.*: Fansidar; *Gr.*: Fansidar; *India*: Amalar; Croydox-in-FM; Domine; Laridox; Larinate Kit; Malasulf; Malcidal; Malocide; Masunate; Metasulfin; Onli-2; Pyralfin; Rimodar; *Indon.*: Fansidar; Plasmodin; Suldox; *Irl.*: Fansidar†; *Israel*: Fansidar†; *Malaysia*: Madomine; Malafon; *Philipp.*: Fansidar; *Rus.*: Fansidar (Фансидар); *S.Afr.*: Fansidar; *Switz.*: Fansidar†; *Thai.*: Vinsilar; *UK*: Fansidar; *Ukr.*: Fansidar (Фансидар)†; *USA*: Fansidar†.

Pharmacopoeial Preparations
USP 36: Sulfadoxine and Pyrimethamine Tablets.

Sulfafurazole *(BAN, pINN)*

Sulfafuratsoli; Sulfafurazol; Sulfafurazolas; Sulfafurazolo; Sulfafurazolum; Sulfisossazolo; Sulfisoxazole; Sülfizoksazol; Sulphafuraz; Sulphafurazole; Szulfafurazol; Сульфафуразол.
N^1-(3,4-Dimethylisoxazol-5-yl)sulphanilamide.
$C_{11}H_{13}N_3O_3S$=267.3
CAS — 127-69-5.
ATC — J01EB05; S01AB02.
ATC Vet — QJ01EQ05; QS01AB02.
UNII — 740T4C525W.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Sulfafurazole). White or yellowish-white, crystalline powder or crystals. Practically insoluble in water; sparingly soluble in alcohol; slightly soluble in dichloromethane. It dissolves in solutions of alkali hydroxides and in dilute mineral acids. Protect from light.

USP 36: (Sulfisoxazole). A white to slightly yellowish, odourless crystalline powder. Soluble 1 in 7700 of water and 1 in 10 of boiling alcohol; soluble in 3N hydrochloric acid. Store in airtight containers. Protect from light.

Acetyl Sulfafurazole

Acetilsulfafurazol; Acetyl Sulphafurazole; Sulfisoxazole Acetyl; Ацетилсульфафуразол.
N^1-Acetyl Sulphafurazole; *N*-(3,4-Dimethylisoxazol-5-yl)-*N*-sulphanilylacetamide.
$C_{13}H_{15}N_3O_4S$=309.3
CAS — 80-74-0.
ATC — J01EB05; S01AB02.
ATC Vet — QJ01EB05; QS01AB02.
UNII — WBT5QH3KED.

NOTE. Acetyl sulfafurazole is to be distinguished from the N^4-acetyl derivative formed from sulfafurazole by conjugation in the body.

Compounded preparations of acetyl sulfafurazole may be represented by the following name:
- Co-erynsulfisox (*PEN*)—acetyl sulfafurazole and erythromycin ethyl succinate.

Pharmacopoeias. In *US*.

USP 36: (Sulfisoxazole Acetyl). A white or slightly yellow crystalline powder. Practically insoluble in water; soluble 1 in 176 of alcohol, 1 in 35 of chloroform, 1 in 1064 of ether, and 1 in 203 of methyl alcohol. Store in airtight containers. Protect from light.

Sulfafurazole Diolamine *(pINN)*

NU-445; Sulfafurazol diolamina; Sulfafurazol, Diolamine de; Sulfafurazoli Diolaminum; Sülfisoksazol Dietanolamin; Sulfisoxazole Diolamine (USAN); Sulphafurazole Diethanolamine; Sulphafurazole Diolamine; Сульфафуразола Диоламин.
The 2,2′-iminobisethanol salt of sulphafurazole.
$C_{11}H_{13}N_3O_3S,C_4H_{11}NO_2$=372.4
CAS — 4299-60-9.
ATC — J01EB05; S01AB02.
ATC Vet — QS01AB02.
UNII — 30S4B46J8B.

Uses and Administration

Sulfafurazole is a short-acting sulfonamide that has been used similarly to sulfamethoxazole (p. 367.2), notably in the treatment of urinary-tract infections, pneumonia due to *Chlamydophila pneumoniae* (*Chlamydia pneumoniae*), nocardiosis, and trachoma. It is also used, usually with erythromycin, in the treatment of otitis media. For details of these infections and their treatment see Choice of Antibacterial, p. 172.2.

Sulfafurazole is usually given orally. In the treatment of susceptible infections, it has been given in an initial dose of 2 to 4 g, followed by 4 to 8 g daily in divided doses every 4 to 6 hours. Dosage modification may be necessary in patients with renal impairment. For details of doses in children, see p. 366.2. Acetyl sulfafurazole is tasteless and is used in liquid oral preparations of the drug; doses are expressed in terms of sulfafurazole. 1.16 g of acetyl sulfafurazole is equivalent to about 1 g of sulfafurazole.

Sulfafurazole diolamine has been used, as an ophthalmic ointment or solution containing the equivalent of 4% of sulfafurazole, in the topical treatment of susceptible eye infections. Sulfafurazole diolamine 1.39 g is equivalent to about 1 g of sulfafurazole.

Sulfafurazole diolamine has also been given parenterally.

Administration in children. Sulfafurazole may be used in infants and children 2 months of age and older for the treatment of infections caused by susceptible organisms, and is usually given orally. It is usually given in an initial dose of 75 mg/kg, followed by a maintenance dose of 150 mg/kg daily (to a maximum of 6 g) in 4 to 6 divided doses.

Adverse Effects, Treatment, and Precautions

As for Sulfamethoxazole, p. 367.3.

Sulfafurazole and its acetyl derivative are relatively soluble in urine and the risk of crystalluria is generally slight, but nevertheless adequate fluid intake is recommended.

Breast feeding. A study[1] in 6 women given sulfafurazole concluded that the amount of drug appearing in breast milk posed no risk to the healthy infant beyond the immediate newborn period, but potential risk in breast-fed infants with jaundice or G6PD deficiency, or who are ill, stressed, or premature, was more difficult to evaluate. Based on this evidence, the last available guidance from the American Academy of Pediatrics[2] stated that sulfafurazole was usually compatible with breast feeding, but caution was required in the infants mentioned above.

1. Kauffman RE, *et al.* Sulfisoxazole secretion into human milk. *J Pediatr* 1980; 97: 839–41.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *Ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/05/04)

Interactions

As for Sulfamethoxazole, p. 368.2.

Sulfafurazole has been reported to increase the anaesthetic effect of thiopental.

Eye preparations of sulfafurazole diolamine should not be applied with preparations of silver salts.

Antimicrobial Action

As for Sulfamethoxazole, p. 368.3.

Pharmacokinetics

Sulfafurazole is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur 1 to 4 hours after an oral dose. Acetyl sulfafurazole (the N^1-acetyl derivative) is broken down to sulfafurazole in the gastrointestinal tract before absorption, resulting in delayed and somewhat lower peak concentrations. Sulfafurazole is about 85 to 90% is bound to plasma proteins. It readily diffuses into extracellular fluid, but very little diffuses into cells. Concentrations in the CSF are about one-third of those in the blood. Sulfafurazole crosses the placenta into the fetal circulation and is distributed into breast milk. About 30% of sulfafurazole in the blood and in the urine is in the form of the N^4-acetyl derivative.

Sulfafurazole is excreted rapidly in the urine, up to 97% of a single dose being eliminated in 48 hours. The half-life is reported to range from about 5 to 8 hours. Both sulfafurazole and its N^4-acetyl derivative are more soluble than many other sulfonamides in urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Turk.*: Gansol; *USA*: Gantrisin†; *Venez.*: Ganticol.

Multi-ingredient Preparations. *Canad.*: Pediazole; *Chile*: Bioquin; *Fr.*: Pediazole; *Gr.*: Pediazole; *Israel*: Pediazole†; *Mex.*: Pediazole; *Ucovec*†; *Thai.*: Pyrizole; *Turk.*: Azo Gantrisin; *USA*: Pediazole†.

Pharmacopoeial Preparations
USP 36: Erythromycin Estolate and Sulfisoxazole Acetyl Oral Suspension; Erythromycin Ethylsuccinate and Sulfisoxazole Acetyl for Oral Suspension; Sulfisoxazole Acetyl Oral Suspension; Sulfisoxazole Tablets.

Sulfaguanidine *(BAN, rINN)*

Solfaguanidina; Sulfaguanidini; Sulfaguanidin; Sulfaguanidina; Sulfaguanidinas; Sulfaguanidinum; Sulfaguanidyna; Sulfamidinum; Sulginum; Sulphaguanidine; Szulfaguanidin; Сульфагуанидин.
1-Sulphanilylguanidine; *N*′-Amidinosulphanilamide.
$C_7H_{10}N_4O_2S$=214.2
CAS — 57-67-0 (anhydrous sulfaguanidine); 6190-55-2 (sulfaguanidine monohydrate).
ATC — A07AB03.
ATC Vet — QA07AB03.
UNII — 15XQ8043FN.

Pharmacopoeias. In *Eur.* (see p. vii).

Viet. includes the monohydrate.

Ph. Eur. 8: (Sulfaguanidine). A white or almost white, fine crystalline powder. Very slightly soluble in water and in alcohol; slightly soluble in acetone; practically insoluble in dichloromethane. It dissolves in dilute solutions of mineral acids. Protect from light.

Profile

Sulfaguanidine is a sulfonamide with properties similar to those of sulfamethoxazole (p. 367.2). It is absorbed to a limited extent from the gastrointestinal tract and may therefore be more likely to cause systemic effects than less well absorbed drugs such as phthalylsulfathiazole and succinylsulfathiazole. It is used, usually with other drugs, in the treatment of gastrointestinal infections, and has also been applied locally to the skin and throat.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Enteropathyl†; *Rus.*: Sulgin (Сульгин); *Thai.*: Sulfayel.

Multi-ingredient Preparations. *Chile*: Carbon Sulfaguanidina; *India*: Enteroguanidine; *Mex.*: Neopecsul; *Thai.*: Biodan.

Sulfamerazine *(BAN, rINN)*

RP-2632; Solfamerazina; Sulfamerasinum; Sulfameratsiini; Sulfamerazin; Sulfamerazina; Sulfamerazinas; Sulfamérazine; Sulfamerazinum; Sulfamethyldiazine; Sulfamethylpyrimidine; Sulphamerazine; Szulfamerazin; Сульфамеразин.
N^1-(4-Methylpyrimidin-2-yl)sulphanilamide.
$C_{11}H_{12}N_4O_2S$=264.3
CAS — 127-79-7.
ATC — D06BA06; J01ED07.
ATC Vet — QD06BA06.
UNII — UR1SAB295F.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *BP(Vet)*.

Ph. Eur. 8: (Sulfamerazine). White, yellowish-white, or pinkish-white, crystalline powder or crystals. Very slightly soluble in water and in dichloromethane; slightly soluble in alcohol; sparingly soluble in acetone. It dissolves in solutions of alkali hydroxides and in dilute mineral acids. Protect from light.

Sulfamerazine Sodium *(BANM, rINN)*

Soluble Sulphamerazine; Sulfamerazina de sodio; Sulfamerazina sódica; Sulfamérazine sodique; Sulfamerazinum Natricum; Sulphamerazine Sodium; Сульфамеразин Натрий.

$C_{11}H_{11}N_4NaO_2S$=286.3
CAS — 127-58-2.
ATC — D06BA06; J01ED07.
ATC Vet — QD06BA06.
UNII — JOV4UJY07O.

Profile

Sulfamerazine is a short-acting sulfonamide with properties similar to those of sulfamethoxazole (p. 367.2). It has usually been given with other sulfonamides, or with trimethoprim.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Indon.*: Trisulfa; *Thai.*: Sulfatril†; Triple Sulphas; Trisulfa Co-P; Trisulfapyrimidines.

Pharmacopoeial Preparations
USP 36: Trisulfapyrimidines Oral Suspension; Trisulfapyrimidines Tablets.

Sulfamethizole *(BAN, rINN)*

Sulfaméthizol; Sulfaméthizol; Sulfamethizolum; Sulfametitsoli; Sulfamétizol; Sulfametizolas; Sulfametizolo; Sulphamethizole; Szulfametizol; Сульфаметизол.
N^1-(5-Methyl-1,3,4-thiadiazol-2-yl)sulphanilamide.
$C_9H_{10}N_4O_2S_2$=270.3
CAS — 144-82-1.
ATC — B05CA04; D06BA04; J01EB02; S01AB01.
ATC Vet — QB05CA04; QD06BA04; QJ01EQ02; QS01AB01.
UNII — 25W8454H16.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Sulfamethizole). White or yellowish-white crystalline powder or crystals. Very slightly soluble in water; sparingly soluble in alcohol; soluble in acetone. It dissolves in dilute solutions of alkali hydroxides and in dilute mineral acids. Protect from light.

USP 36: (Sulfamethizole). Practically odourless, white crystals or powder. Soluble 1 in 2000 of water, 1 in 38 of alcohol, 1 in 13 of acetone, and 1 in 1900 of chloroform and of ether; freely soluble in solutions of ammonium, potassium, and sodium hydroxides; soluble in dilute mineral acids; practically insoluble in benzene. Protect from light.

Uses and Administration

Sulfamethizole is a short-acting sulfonamide that is given orally in the treatment of infections of the urinary tract, sometimes with other antibacterials; it is unsuitable for the treatment of systemic infection since only relatively low concentrations of drug occur in the blood and tissues.

It is given in usual adult doses of 1 g twice daily. For details of doses in children, see p. 367.1.

Sulfamethizole monoethanolamine has also been used.

Administration in children. Sulfamethizole has been used orally in infants and children 2 months of age and older for the treatment of urinary-tract infections due to susceptible organisms, in a typical dose of 50 mg/kg daily in 2 to 4 divided doses.

Adverse Effects, Treatment, and Precautions

As for Sulfamethoxazole, p. 367.3.

Sulfamethizole and its acetyl derivative are relatively soluble in urine, and the risk of crystalluria is quite low, but an adequate fluid intake should generally be maintained.

Interactions

As for Sulfamethoxazole, p. 368.2.

Antimicrobial Action

As for Sulfamethoxazole, p. 368.3.

Pharmacokinetics

Sulfamethizole is readily absorbed from the gastrointestinal tract; about 90% has been reported to be bound to plasma proteins. Its half-life has been reported to range from about 1.5 to 3 hours. It is only slightly acetylated in the body and is rapidly excreted, about 60% of a dose being eliminated in the urine in 5 hours and around 90% within 10 hours. Sulfamethizole and its acetyl derivative are readily soluble in urine over a wide pH range. Concentrations in blood and tissues are low because of its rapid excretion.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Denm.*: Lucosil; *Fr.*: Rufol.

Multi-ingredient Preparations. *Spain*: Micturol Sedante; *USA*: Urobiotic-250; *Venez.*: Bacteval.

Pharmacopoeial Preparations
USP 36: Sulfamethizole Oral Suspension; Sulfamethizole Tablets.

Sulfamethoxazole *(BAN, USAN, rINN)*

Ro-4-2130; SMX; SMZ; Sulfamethoxazol; Sulfaméthoxazole; Sulfamethoxazolum; Sulfametoksatsoli; Sulfametoksazol; Sulfametoksazolas; Sulfametoxazol; Sulfametoxazolo; Sulfisomezole; Sulphamethoxazole; Szulfametoxazol; Сульфаметоксазол.
N^1-(5-Methylisoxazol-3-yl)sulphanilamide.
$C_{10}H_{11}N_3O_3S$=253.3
CAS — 723-46-6.
ATC — J01EC01.
ATC Vet — QJ01EQ11.
UNII — JE42381TNV.

NOTE. Compounded preparations of sulfamethoxazole may be represented by the following names:
- Co-trimoxazole (*BAN*)—sulfamethoxazole 5 parts and trimethoprim 1 part (see p. 277.3)
- Co-trimoxazole (*PEN*)—sulfamethoxazole and trimethoprim.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Sulfamethoxazole). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in acetone. It dissolves in dilute solutions of sodium hydroxide and in dilute acids. Protect from light.

USP 36: (Sulfamethoxazole). A white to off-white, practically odourless, crystalline powder. Soluble 1 in 3400 of water, 1 in 50 of alcohol, and 1 in 1000 of chloroform and of ether; slowly and usually incompletely soluble 1 in 2 of carbon disulfide; freely soluble in acetone and in dilute solutions of sodium hydroxide. Protect from light.

Uses and Administration

The use of sulfamethoxazole and other sulfonamides has been limited by the increasing incidence of resistant organisms. Their main use has been in the treatment of acute, uncomplicated urinary-tract infections, particularly those caused by *Escherichia coli*. They have also been used in nocardiosis, and in some other bacterial infections such as otitis media, *Chlamydia* and *Chlamydophila* infections, and prophylaxis of meningococcal meningitis, but have largely been replaced by other drugs: even where pathogens retain some sensitivity to sulfonamides, a combination such as co-trimoxazole (sulfamethoxazole with trimethoprim) has often been preferred. The usual treatment of these infections is discussed under Choice of Antibacterial, p. 172.2.

Sulfonamides are also used, often with pyrimethamine or trimethoprim, in the treatment of protozoal infections, particularly malaria (p. 644.1) and toxoplasmosis (p. 926.1). They are also used similarly in pneumocystis pneumonia (p. 567.2).

Sulfamethoxazole is a medium-acting sulfonamide that has been given orally in a usual dose of 2 g initially, followed by 1 g twice daily. In severe infections 1 g three times daily has been given.

For details of doses in children, see p. 367.2.

Reduction of dosage may be required in patients with renal impairment.

For the uses and dosage of sulfamethoxazole with trimethoprim, see Co-trimoxazole, p. 277.3.

Sulfamethoxazole lysine has also been used.

Administration. US licensed product information for a former product of sulfamethoxazole recommended that blood concentrations be measured in patients receiving sulfonamides for serious infections. The following concentrations of free sulfonamide in the blood were considered to be therapeutically effective:
- for most infections, 50 to 150 micrograms/mL
- for serious infections, 120 to 150 micrograms/mL

Concentrations of 200 micrograms/mL should not be exceeded since the incidence of adverse reactions might be increased.

Administration in children. Sulfamethoxazole may be used orally in children for the treatment of infections caused by susceptible organisms. It has been given in an initial dose of 50 to 60 mg/kg, followed by a maintenance dose of 25 to 30 mg/kg twice daily (to a maximum daily dose of 75 mg/kg).

Adverse Effects and Treatment

Nausea, vomiting, anorexia, and diarrhoea are relatively common after use of sulfamethoxazole and other sulfonamides.

Hypersensitivity reactions to sulfonamides have proved a problem. Fever is relatively common, and reactions involving the skin may include rashes, pruritus, photosensitivity reactions, exfoliative dermatitis, and erythema nodosum. Severe, potentially fatal, skin reactions including toxic epidermal necrolysis and the Stevens-Johnson syndrome have occurred in patients treated with sulfonamides. Dermatitis may also occur from contact of sulfonamides with the skin. SLE, particularly exacerbation of pre-existing disease, has also been reported.

Nephrotoxic reactions including interstitial nephritis and tubular necrosis, which may result in renal failure, have been attributed to hypersensitivity to sulfamethoxazole. Lumbar pain, haematuria, oliguria, and anuria may also occur due to crystallisation in the urine of sulfamethoxazole or its less soluble acetylated metabolite. The risk of crystalluria can be reduced by giving fluids to maintain a high urine output. If necessary, alkalinisation of the urine with sodium bicarbonate may increase solubility and aid the elimination of sulfonamides.

Blood disorders have occasionally occurred during treatment with the sulfonamides including sulfamethoxazole, and include agranulocytosis, aplastic anaemia, thrombocytopenia, leucopenia, hypoprothrombinaemia, and eosinophilia. Many of these effects on the blood may result from hypersensitivity reactions. Sulfonamides may rarely cause cyanosis due to methaemoglobinaemia. Acute haemolytic anaemia is a rare complication which may be associated with G6PD deficiency.

Other adverse effects that may be manifestations of a generalised hypersensitivity reaction to sulfonamides include a syndrome resembling serum sickness, hepatic necrosis, hepatomegaly and jaundice, myocarditis, pulmonary eosinophilia and fibrosing alveolitis, and vasculitis including polyarteritis nodosa. Anaphylaxis has been reported only very rarely.

Other adverse reactions reported after sulfamethoxazole or other sulfonamides include hypoglycaemia, hypothyroidism, neurological reactions including aseptic meningitis, ataxia, benign intracranial hypertension, convulsions, dizziness, drowsiness, fatigue, headache, insomnia, mental depression, peripheral or optic neuropathies, psychoses, tinnitus, vertigo, and pancreatitis.

Sulfonamides may displace serum-bound bilirubin, resulting in kernicterus in premature neonates.

As with other antimicrobials, sulfamethoxazole may cause alterations of the bacterial flora in the gastrointestinal tract. There is, therefore, the possibility, although it appears to be small, that pseudomembranous colitis may occur.

Slow acetylators of sulfamethoxazole may be at greater risk of adverse reactions than fast acetylators.

For further information on the adverse effects of sulfamethoxazole when used with trimethoprim, see Co-trimoxazole, p. 278.3.

Hypersensitivity. Adverse effects to sulfonamide antibacterials are a relatively common problem, occurring in about 3% of courses; about 3% of these are true hypersensitivity reactions some of which can be severe or life-threatening.[1]

The sulfa moiety ($-SO_2NH_2$) which is contained in the chemical structure of sulfonamide antibacterials is also part of many other drugs, including the carbonic anhydrase inhibitors (such as acetazolamide), the thiazide diuretics (such as hydrochlorothiazide and indapamide), loop diuretics (such as furosemide), sulfonylurea antidiabetics (such as tolbutamide and glyburide), selective cyclo-oxygenase-2 inhibitors (such as celecoxib), serotonin agonists (such as sumatriptan), HIV-protease inhibitors (amprenavir and fosamprenavir), dapsone, and probenecid.[1-3] However, chemical differences between the sulfonamide antibacterials and these others mean that the latter are less likely to cause severe hypersensitivity reactions.[1,4,5] The immunological determinant of type I immunologic reaction to sulfonamide antibacterials is the N1 heterocyclic ring, and nonantibacterial sulfonamides do not have this structural feature. Many non-type I hypersensitivity responses to sulfonamide antibacterials are due to reactive metabolites; metabolite formation is stereospecific to the N4 amino nitrogen of the sulfonamide antibacterials and this structure is also not found on any nonantibacterial sulfonamides.[4,5] Although severe cases of presumed cross-hypersensitivity have been reported rarely,[1] the chemical differences and the stereospecificity of these reactions makes true cross-reactivity between antibacterial and nonantibacterial sulfonamides extremely unlikely.[1-5]

Even though the risk of cross-reactivity is low, concerns about it continue to complicate treatment as patients who have had a reaction after taking a sulfonamide are thought to be at increased risk for another reaction or a cross-

hypersensitivity reaction and prescribers are often warned that all sulfonamides should be contra-indicated in those with a history of sulfa allergy, even though data supporting this advice are mainly limited to a few case reports. A retrospective cohort study in the UK[2] found that while allergy to a sulfonamide antibacterial was a risk factor for a subsequent allergic reaction to nonantibacterial sulfonamide-containing drugs, a history of penicillin allergy was also at least as strong a risk factor. This finding was thought to be due to a general tendency to allergic reactions among certain patients rather than a specific cross-reactivity with drugs containing the sulfa moiety. The authors therefore considered that patients with a history of any type of allergic reaction after taking sulfonamides or penicillins should be regarded as at increased general risk of reactions to other drugs, rather than specifically contra-indicating sulfonamides.

A review of case reports and observational studies of cross-reactivity between antibacterial and nonantibacterial sulfonamides published in the literature between 1966 and March 2004[3] also found that the concerns about cross-reactivity between the two groups were not supported by the published data. The authors suggested that except for patients with serious allergic reactions and/or multiple drug allergies, all other patients with a sulfa allergy might be given sulfonamide-containing drugs provided there is no alternative drug available and they were appropriately monitored while on treatment. Others have suggested giving a test dose, preferably orally and in a monitored environment.[1]

1. Ponka D. Approach to managing patients with sulfa allergy: use of antibiotic and nonantibiotic sulfonamides. *Can Fam Physician* 2006; **52**: 1434–8.
2. Strom BL, *et al.* Absence of cross-reactivity between sulfonamide antibiotics and sulfonamide nonantibiotics. *N Engl J Med* 2003; **349**: 1628–35.
3. Johnson KK, *et al.* Sulfonamide cross-reactivity: fact or fiction? *Ann Pharmacother* 2005; **39**: 290–301.
4. Brackett CC, *et al.* Likelihood and mechanisms of cross-allergenicity between sulfonamide antibiotics and other drugs containing a sulfonamide functional group. *Pharmacotherapy* 2004; **24**: 856–70.
5. Brackett CC. Sulfonamide allergy and cross-reactivity. *Curr Allergy Asthma Rep* 2007; **7**: 41–8.

Precautions

In patients given sulfamethoxazole, adequate fluid intake is necessary to reduce the risk of crystalluria; the daily urine output should be 1200 mL or more. Compounds that render the urine acidic may increase the risk of crystalluria; the risk may be reduced with alkaline urine.

Treatment with sulfonamides should be stopped immediately a rash appears because of the danger of severe allergic reactions such as the Stevens-Johnson syndrome.

Sulfamethoxazole should be given with care to patients with renal or hepatic impairment and is contra-indicated in patients with severe impairment or with blood disorders. Dosage reduction may be necessary in renal impairment. Complete blood counts and urinalyses with microscopic examination should be carried out, particularly during prolonged therapy. Sulfamethoxazole should not be given to patients with a history of hypersensitivity to sulfonamides as cross-sensitivity may occur between drugs of this group. Care is generally advisable in patients with a history of allergy or asthma. Caution is also needed in the elderly, who may be more likely to have other risk factors for reactions. Some consider sulfamethoxazole to be contra-indicated in lupus erythematosus as it may exacerbate the condition. Patients with glucose 6-phosphate dehydrogenase deficiency may be at risk of haemolytic reactions.

Sulfamethoxazole and other sulfonamides are not usually given to infants within 1 to 2 months of birth because of the risk of producing kernicterus; for the same reason, they are generally contra-indicated in pregnant women before delivery (see p. 368.2).

Patients with AIDS may be particularly prone to adverse reactions, especially when sulfamethoxazole is given with trimethoprim as co-trimoxazole.

Sulfonamides have been reported to interfere with some diagnostic tests, including those for urea, creatinine, and urinary glucose and urobilinogen.

Breast feeding. Sulfonamides are distributed into breast milk in low concentrations and, although they are generally contra-indicated in the USA in breast-feeding women because of the risk of kernicterus, they are usually thought to pose a negligible risk to healthy neonates. However, sulfonamides should be used with caution in breast-feeding mothers of ill, stressed, or premature infants and of infants with jaundice, hyperbilirubinaemia or G6PD deficiency.

The last available guidance from the American Academy of Pediatrics considered sulfamethoxazole, when given with trimethoprim, to be compatible with breast feeding.[1]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/05/04)

Immunocompromised patients. Sulfamethoxazole is mainly conjugated in the liver to the N^4-acetyl derivative, but is also oxidised, to a limited extent, to the hydroxylamine metabolite.[1-3] Although this metabolite was originally implicated[4] in the development of adverse reactions to sulfonamides, recent work[7] has cast some doubt on this hypothesis. The metabolite appears to be produced through cytochrome P450 oxidative metabolism, and it has been suggested that slow acetylators of sulfamethoxazole show increased oxidation compared with other metabolic routes.[1] AIDS patients also have increased oxidation, since they may be depleted of substrates such as acetylcoenzyme A or glutathione necessary for acetylation or detoxification, and this may explain their susceptibility to sulfamethoxazole toxicity.[2,3]

There have been attempts to inhibit the formation of the hydroxylamine metabolite by competitive inhibition of cytochrome P450 enzymes, notably with fluconazole and ketoconazole.[4,5] Encouraging results have been obtained with fluconazole in healthy subjects, but the potential for clinical benefit in AIDS patients requires further study.[5]

However, one successful method of overcoming adverse effects in AIDS patients has been **desensitisation**. Desensitisation by use of initial doses of 4 mg of sulfamethoxazole or 5 mg of sulfadiazine every 6 hours, doubled at 24-hour intervals until the desired dose was reached, was uneventful in 9 of 13 patients with AIDS requiring sulfonamide treatment for opportunistic infections.[8] The remaining 4 had cutaneous reactions with fever, but in 2 of these the reactions were successfully managed with an antihistamine. Although there is a risk of anaphylaxis, patients with AIDS can be successfully treated with sulfonamides after desensitisation.

See also Immunocompromised Patients under Precautions of Co-trimoxazole, p. 279.2.

1. Cribb AE, Spielberg SP. Sulfamethoxazole is metabolized to the hydroxylamine in humans. *Clin Pharmacol Ther* 1992; **51**: 522–6.
2. Lee BL, *et al.* The hydroxylamine of sulfamethoxazole and adverse reactions in patients with acquired immunodeficiency syndrome. *Clin Pharmacol Ther* 1994; **56**: 184–9.
3. van der Ven AJA, *et al.* Urinary recovery and kinetics of sulphamethoxazole and its metabolites in HIV-seropositive patients and healthy volunteers after a single oral dose of sulphamethoxazole. *Br J Clin Pharmacol* 1995; **39**: 621–5.
4. Mitra AK, *et al.* Inhibition of sulfamethoxazole hydroxylamine formation by fluconazole in human liver microsomes and healthy volunteers. *Clin Pharmacol Ther* 1996; **59**: 332–40.
5. Gill HJ, *et al.* The effect of fluconazole and ketoconazole on the metabolism of sulphamethoxazole. *Br J Clin Pharmacol* 1996; **42**: 347–53.
6. van der Ven AJAM, *et al.* Adverse reactions to co-trimoxazole in HIV infection. *Lancet* 1991; **338**: 431–3.
7. ter Hofstede HJM, *et al.* Drug reactions to cotrimoxazole in HIV infection: possibly not due to the hydroxylamine metabolites of sulphamethoxazole. *Br J Clin Pharmacol* 1999; **47**: 571–3.
8. Torgovnick J, Arsura E. Desensitization to sulfonamides in patients with HIV infection. *Am J Med* 1990; **88**: 548–9.

Pregnancy. Some sulfonamides have been shown to cause fetal abnormalities including cleft palate in *animals*, but fears of **teratogenic effects** in humans do not appear to be substantiated. Sulfonamides are probably safe in the first trimester of pregnancy, although throughout pregnancy they should be used only in the absence of a suitable alternative drug.[1]

Sulfonamides may displace serum-bound bilirubin and they should be avoided close to delivery because of the risk of kernicterus in the neonate. The risk of drug-induced **bilirubin displacement** has been reviewed.[2] The initial evidence suggesting a kernicterus-promoting effect of drugs in neonates was reported for sulfafurazole, and this drug now serves as a standard displacing agent against which other drugs are evaluated. Although all sulfonamides are highly protein bound, each has a different capacity to displace bilirubin. Sulfadiazine and sulfanilamide have been found to be the least displacing of the sulfonamides and the effects of sulfadiazine on bilirubin may not be clinically significant; an increased incidence of hyperbilirubinaemia and kernicterus has not been shown after use for prophylaxis of rheumatic fever during pregnancy. Sulfasalazine should theoretically cause significant bilirubin displacement, but studies suggest that the drug may be given to patients with Crohn's disease who are pregnant or breast feeding. Metabolites of sulfonamides have also been evaluated for kernicterus-promoting effects; glucuronide metabolites are expected to compete for binding sites less effectively than the parent compound, whereas acetylated metabolites of some sulfonamides appear to be more potent bilirubin displacers.

1. Wise R. Prescribing in pregnancy: antibiotics. *BMJ* 1987; **294**: 42–4.
2. Walker PC. Neonatal bilirubin toxicity: a review of kernicterus and the implications of drug-induced bilirubin displacement. *Clin Pharmacokinet* 1987; **13**: 26–50.

Interactions

The action of sulfonamides may be antagonised by *p*-aminobenzoic acid and its derivatives, particularly potassium aminobenzoate and the procaine group of local anaesthetics.

Sulfamethoxazole and other sulfonamides may potentiate the effects of some drugs, such as oral anticoagulants (p. 1531.1), methotrexate (p. 827.3), and phenytoin (p. 542.3); this may be due to displacement of the drug from plasma protein binding sites or to inhibition of metabolism. However, the clinical significance of these interactions appears to depend on the particular sulfonamide involved. The possibility of interactions with other highly protein-bound drugs, such as NSAIDs, should be considered.

High doses of sulfonamides have been reported to have a hypoglycaemic effect; the antidiabetic effect of the sulfonylurea compounds may be enhanced by sulfonamides (p. 505.3). Some sulfonamides have been associated with a decrease in plasma-ciclosporin concentrations when used together (p. 1956.2). Isolated reports have described possible failures of hormonal contraceptives resulting in pregnancy in patients given sulfonamides (p. 2243.1).

The use of compounds that render the urine acidic may increase the risk of crystalluria.

Antimicrobial Action

Sulfamethoxazole and other sulfonamides have a similar structure to *p*-aminobenzoic acid and interfere with the synthesis of nucleic acids in sensitive micro-organisms by blocking the conversion of *p*-aminobenzoic acid to the coenzyme dihydrofolic acid, a reduced form of folic acid; in man, dihydrofolic acid is obtained from dietary folic acid so sulfonamides do not affect human cells. Their action is mainly bacteriostatic, although they may be bactericidal where concentrations of thymine are low in the surrounding medium. The sulfonamides have a broad spectrum of action, but the development of widespread resistance (see below) has greatly reduced their usefulness, and susceptibility often varies widely even among nominally sensitive pathogens.

- Gram-positive cocci, such as *Staphylococcus aureus, S. saprophyticus, Streptococcus pyogenes, Str. pneumoniae*, and the viridans streptococci are susceptible to sulfonamides, but enterococci are resistant.
  Gram-positive bacilli reported to be susceptible include *Bacillus anthracis, Clostridium perfringens, C. tetani*, and most strains of *B. cereus*.
  Actinomycetes spp. and *Nocardia* spp. are generally susceptible, while *Listeria monocytogenes* shows variable susceptibility.
- Among the Gram-negative organisms, most of the Enterobacteriaceae including *Enterobacter, Escherichia coli, Klebsiella, Proteus, Salmonella, Shigella*, and *Yersinia* species are susceptible to sulfonamides (but see Resistance below); *Providencia* are, however, often resistant.
  Although pathogenic *Neisseria* spp. were formerly extremely susceptible to sulfonamides, many strains are now resistant.
  Haemophilus influenza type b is susceptible but susceptibility rates for *H. ducreyi* vary.
  Sulfonamides may be effective against most strains of *Burkholderia pseudomallei* (*Pseudomonas pseudomallei*) and some strains of *Pseudomonas aeruginosa*.
  Other Gram-negative organisms that have been reported to be susceptible include *Acinetobacter* spp., *Legionella pneumophila*, and most *Bacteroides fragilis* strains.
- Some serotypes of *Chlamydia trachomatis* are susceptible to sulfonamides but *C. psittaci* and *C. pneumonia* are resistant. *Mycoplasma, Ureaplasma urealyticum, Treponema, Leptospira, Rickettsia*, and *Coxiella burnetii* are resistant to sulfonamides.
- Atypical mycobacteria show variable susceptibility to sulfonamides while the long-acting sulfonamides are bacteriostatic against *Mycobacterium leprae*.
- Although sulfonamides have some *in vitro* activity against the protozoa *Plasmodium falciparum* and *P. vivax*, malaria parasites may become resistant to sulfonamides. Some sulfonamides may be active against *Toxoplasma gondii* and *Pneumocystis jirovecii*.
- The fungi *Paracoccidioides brasiliensis* is usually susceptible to sulfonamides, although resistant strains occur naturally and resistance may also develop during treatment. Sulfonamides (alone or with trimethoprim) have been effective in the treatment of histoplasmosis.

Sulfamethoxazole and other sulfonamides show synergy with the dihydrofolate reductase inhibitors pyrimethamine and trimethoprim which inhibit a later stage in folic acid synthesis. For reports of the antimicrobial activity of sulfamethoxazole with trimethoprim, see Co-trimoxazole, p. 280.1.

The *in-vitro* antimicrobial activity of sulfamethoxazole is very dependent on both the culture medium and size of inoculum used.

Resistance. Acquired resistance to sulfonamides is common and widespread among formerly susceptible organisms, particularly *Neisseria* spp., *Pseudomonas* spp.,

Enterobacteriaceae (such as *Shigella, Escherichia coli,* and *Salmonella*), staphylococci, and streptococci.

There appear to be several mechanisms of resistance including alteration of dihydropteroate synthetase, the enzyme inhibited by sulfonamides, to a less sensitive form, or an alteration in folate biosynthesis to an alternative pathway; increased production of *p*-aminobenzoic acid; or decreased uptake or enhanced metabolism of sulfonamides.

Resistance may result from chromosomal alteration, or may be plasmid-mediated and transferable, as in many resistant strains of enterobacteria. High-level resistance is usually permanent and irreversible. There is complete cross-resistance between the different sulfonamides.

Pharmacokinetics

Sulfamethoxazole is readily absorbed from the gastrointestinal tract and peak plasma concentrations occur after about 2 hours. Blood concentrations of up to 100 micrograms/mL occur after a single 2-g oral dose. About 70% is bound to plasma proteins. The plasma half-life is about 6 to 12 hours; it is prolonged in patients with severe renal impairment.

Sulfamethoxazole, like most sulfonamides, diffuses freely throughout the body tissues and may be detected in the urine, saliva, sweat, and bile, in the cerebrospinal, peritoneal, ocular, and synovial fluids, and in pleural and other effusions. It crosses the placenta into the fetal circulation and low concentrations have been detected in breast milk.

Sulfamethoxazole undergoes conjugation mainly in the liver, chiefly to the inactive N^4-acetyl derivative; this metabolite represents about 15% of the total amount of sulfamethoxazole in the blood. Metabolism is increased in patients with renal impairment and decreased in those with hepatic impairment. Elimination in the urine is dependent on pH. About 80 to 100% of a dose is excreted in the urine, of which about 60% is in the form of the acetyl derivative, with the remainder as unchanged drug and glucuronide.

Sulfamethoxazole is also oxidised to the hydroxylamine, a metabolite that has been implicated in adverse reactions to sulfonamides (see also Immunocompromised Patients, under Precautions, p. 366.2), although some doubt has been cast upon this hypothesis.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Adrenol; Bacti-Uril; Bacticel; Bactrim Balsamico; Bactrim; Cotrizol-G; Danferane; Dosulfin Bronquial; Dosulfin Fuerte; Enterobacticel; Netocur Balsamico; Netocur; Neumobacticel; Novidrine; Sulfagrand; Tritenk; Urisept NF; *Austral.*: Bactrim; Resprim; Septrin; Trimoxazole†; *Austria*: Bactrim; Cotribene; Eusaprim; Oecotrim†; *Belg.*: Bactrim; Cotrim†; Eusaprim; *Braz.*: Assepium Balsamico; Assepium; Bac-Sulfitrin; Bacfar; Bacprotin†; Bacteracin; Bactrim; Bactrisan; Bactrizol†; Bactropin; Batrox; Belfactrim F; Benectrin Balsamico; Benectrin; Diazol; Dientrin; Disseptrin†; Ectrin Balsamico; Ectrin; Gamactrin†; Imuneprim†; Infectrin; Metoprin Balsamico†; Metoprin; Neotrin; Pulkrin†; Qiftrim; Roytrin; Selectrin Balsamico; Selectrin†; Teutrin; Tricban; Trimexazol; Uroctrim; Uropol†; *Canad.*: Apo-Sulfatrim; Novo-Trimel; Nu-Cotrimox; Protrin; Septra; Trisulfa; *Chile*: Bacterol; Bactrimel; Entero Micinovo; Septrin; Trelibec; Uro-Micinovo; *China*: Fu Fang Xin Nuo Ming Pian (复方新诺明片); Kui Jian (蝉建); Morbifurb (诺德菲); Nuo Da Ming (诺达明); Ou Lin (欧林); Xiaoke (消刻); Yu An Li Qing (玉安立清); Zengxiao Lianhuangpian (增效联磺); *Cz.*: Biseptol; Bismoral†; Primotren†; Sumetrolim; *Fin.*: Cotrim; *Fr.*: Bactrim; *Ger.*: Bericocid†; Cotrim-Diolan; Cotrim; CotrimHefa†; Cotrimhexal†; Cotrimox-Wolff†; Cotrimstada†; Drylin†; Eusaprim; Kepinol; TMS†; *Gr.*: Bactrimel; Bioprim; Blaxezan; Blexon; Epahol; Oradin; Santafurin; Septrin; Solfoton; Stremycil-T; Sunicol; Trilogan; Ylestrom; *Hong Kong*: Chemoprim; Cotrim; Dhatrin; Letus; Resprim†; Septol†; Septrin†; Suprim†; Synco-SMZT†; Trimetrin†; Trisul†; Uni-Sulfaprim†; *Hung.*: Cotripharm; Sumetrolim; *India*: Alcorim-F; Antrima; Bactrim; Chemotrin; Ciplin; Colizole; Cotribid Kid; Cotrimox; Cotrizole; Kombina; L-Trim; Larprim; Malarwin; Methoxaprim; Moly Kid; Mountrim; Neoprim; Okatrim DS; Oriprim; Otrim; Pyramet; Sepmax; Septran; Tabrol; Trisulfose; *Indon.*: Bactoprim Combi; Bactricid; Bactrim; Bactrizol; Cotrim†; Cotrimol†; Dotrim; Dumotrim†; Erphatrim; Ikaprim; Infatrim; Kaftrim; Lapikot; Licoprima; Meditrim†; Meprotrin; Moxalas; Nufaprim; Ottoprim; Pehatrim; Primadex; Primazole; Primsulfon; Sanprima; Septrin; Spectrem; Sulprim†; Sultrimmix†; Trimezol; Triminex†; Trimoxsul; Trixzol†; Trizole; Ulfaprim†; Wiatrim; Xepaprim; Zoltrim; Zultrop; *Irl.*: Septrin; *Israel*: Diseptyl; Resprim; Septrin; *Ital.*: Bactrim; Chemitrim; Eusaprim†; *Jpn*: Bactramin; Baktar; *Malaysia*: Bacin; Bactrim; Chemix; Cotrim; Resprim†; Trimexazole; Trizole; *Mex.*: Andoprim†; Anitrim; Apo-Trinelax; Bacpiryl; Bactelan; Bacteric†; Bactide†; Bactilen; Bactiver; Bactrim Compositum; Bactrim; Bactropin; Bateral; Batrizol; Bioprim; Bisultrim; Brogamax; Dertrin; Dibaprim; Ectaprim; Esteprim; Eutrim; Fartropin; Fectri; Guayaprin; Kaltrim; Maxtrim; Metoxiprim; Mixange; Neofatrim; Octex; Octiban; Odisulfan; Pisatrina†; Polibatrin; Pribac; Protaxol†; Protrim; Sadocin; Septrin; Servitrim; Soltrim; Sulfawal; Sulfoid Trimetho; Sulfort; Sulprim; Sultral; Thriazol; Tribakin; Trimetoger; Trimetox; Trimexazol; Trimexole Compositum; Trimexole; Trimzol; TS-Bac; Vanadyl; *Neth.*: Bactrimel; *Norw.*: Bactrim; *NZ*: Apo-Sulfatrim†; Deprim; Trisul; *Philipp.*: Bacidal; Bactille; Bactrim; Bactrinol; Bacxal; Baczole†; Bantizol; Chromo-Z; Combi-Methoxan; Comsid; Costazole†; Cozole†; CTR; Doctrimox; Drilozole; Embatrim; Fedimed; Forteprim; Frocimole; Globaxol; Ivatrim†; Kassemox; Kathrex; Lictora†; Macromed; Moxadden; Moxzole; Neotrim; Onetrim; Oprizole†; Pediatrim; Prizogen; Procor; Renatrim; Rimezone; Rotrace; Scribcin; Septrin; Suprex; Syltrifil; Syndal; Synermed; Timizol; Tricomed; Triforam; Trim-S; Trimephar; Trimetazole; Trimitrix; Trimocom; Trimoxis; Triphimox; Trizole; Xanazole; Zamboprim†; Zolmed; *Pol.*: Bactrim; Biseptol; Septrin†; Two-Septol; *Port.*: Bactrim; Microcetim†; Septrin; *Rus.*: Bactrim (Бактрим); Biseptol (Бисептол); Brifeseptol (Брифесептол); Cotrimol (Котримол); Cotripharm (Котрифарм); Groseptol (Гроссептол); Oriprim (Ориприм); Rancotrim (Ранкотрим)†; Sumetrolim (Суметролим); *S.Afr.*: Acuco†; Adco-Bencole; Bactrim; Casicot; Co Trim; Cocydal†; Cozole; Doctrim; Durobac; Dynazole; Ilvitrim; Lagatrim; Meditrim; Nucotrim; Purbac; Septran; Spectrim; Trimethox; Trimzol†; Trixazole; Ultrasept; Xerazole; *Singapore*: Apo-Sulfatrim; Bacin; BS; Chemix; Co-Trimexazole; Dhatrin; Mortin; Primzole; Suprim; Synco-SMZT; Trimaxazole; *Spain*: Bactopumon; Balsoprim; Bronco Aseptilex Fuerte†; Broncovir; Bronquicisteina†; Bronquidiazina CR; Bronquimar†; Cotrazol†; Eduprim Mucolitico†; Momentol†; Septrin; Soltrim; *Swed.*: Bactrim; Eusaprim; *Switz.*: Bactrim; Cotrim; Escoprim; Lagatrim; Nopil; *Thai.*: Actin; Actrim; Addtrim; Agsulfa; Babytrim; Bacin; Bactin; Bactoprim; Bactrim; Baczole; Co-Fatrim; Co-Star; Co-Tasian; Co-Tri; Co-Trimed; Co-tromoxazole†; Comox; Comoxole; Conprim†; Coprim; Cotamox; Cotrim; GPO-Trim; Herocetine-D; KB Famate; Ko-Cap†; Ko-Kure†; Ladar†; Lastrim; Letus†; M-Moxa; M-Trim; Mano-Trim; Maxitrin; Maxtrim; Medcotrim; Mega-Prim; Metrim; Metxaprim; Mezine; Mycosamthong; Pantrim; Patartim; Po-Trim; Spectrim; Sulbacta†; Sulfometh; Sulprim; Suntrim; Sutrim; Tactrim; Tampo; Toprim; Trifatrim; Trimexazole; Triprim†; Trixzol†; Zoleprim; *Turk.*: Bactrim; Bakton; Co-Tripirim; Cotriver; Kemoprim; Metoprim; Mikrosid; Septrin; Sulfaprim; Trifen; Trimoks; *UAE*: Trimol; *UK*: Fectrim; Septrin; *Ukr.*: Bactrim (Бактрим); Biseptol (Бисептол); Groseptol (Гроссептол); Soluseptol (Солосептол); Sumetrolim (Суметролим); *USA*: Bactrim; Cotrim†; Septra; SMZ-TMP; Sulfatrim; *Venez.*: Bactrimel; Co-Sultrin; Forcrim; Trimecor; Tripur.

Pharmacopoeial Preparations

BP 2014: Co-trimoxazole Infusion; Co-trimoxazole Oral Suspension; Co-trimoxazole Tablets; Dispersible Co-trimoxazole Tablets; Paediatric Co-trimoxazole Oral Suspension; Paediatric Co-trimoxazole Tablets;

USP 36: Sulfamethoxazole and Trimethoprim Injection; Sulfamethoxazole and Trimethoprim Oral Suspension; Sulfamethoxazole and Trimethoprim Tablets; Sulfamethoxazole Oral Suspension; Sulfamethoxazole Tablets.

Sulfamethoxypyridazine *(BAN, rINN)*

Solfametossipiridazina; Sulfaméthoxypyridazine; Sulfamethoxypyridazin; Sulfamethoxypyridazinum; Sulfamethoxypyridazinum ad usum veterinarium; Sulfametoksipyridatsiini; Sulfametoxipiridazina; Sulfametoxipyridazin; Sulphamethoxypyridazine; Szulfametoxipiridazin; Сульфаметоксипиридазин.

N^1-(6-Methoxypyridazin-3-yl)sulphanilamide.

$C_{11}H_{12}N_4O_3S$=280.3

CAS — 80-35-3.

ATC — J01ED05.

ATC Vet — QJ01EQ15.

UNII — T034E4NS2Z.

Pharmacopoeias. In *Int.* and *Viet.* In *Eur.* (see p. vii) for veterinary use only.

Ph. Eur. 8: (Sulfamethoxypyridazine for Veterinary Use; Sulfametoxypyridazine BP(Vet) 2014). A white or slightly yellowish crystalline powder which colours slowly on exposure to light. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in acetone; very slightly soluble in dichloromethane; dissolves in dilute mineral acids and solutions of alkali hydroxides. Protect from light.

Profile

Sulfamethoxypyridazine is a long-acting sulfonamide with properties similar to those of sulfamethoxazole (p. 365.2) and has been used for the treatment of susceptible infections. It is rapidly absorbed from the gastrointestinal tract and excreted slowly in urine, partly as the N^4-acetyl metabolite; it remains detectable for up to 7 days after a dose. It has also been used with trimethoprim similarly to co-trimoxazole.

Acetyl sulfamethoxypyridazine, which is hydrolysed in the gastrointestinal tract forming sulfamethoxypyridazine, and sulfamethoxypyridazine sodium have also been used.

Skin disorders. Sulfamethoxypyridazine has been used in the treatment of pemphigoid,[1,2] and also in the management of dermatitis herpetiformis.[3]

1. Thornhill M, *et al.* An open clinical trial of sulphamethoxypyridazine in the treatment of mucous membrane pemphigoid. *Br J Dermatol* 2000; 143: 117–26.
2. Gach JE, *et al.* Sulfamethoxypyridazine-responsive pemphigoid nodularis: a report of two cases. *J Am Acad Dermatol* 2005; 53 (2 suppl 1): S101–S104.
3. Fry L. Dermatitis herpetiformis. *Baillieres Clin Gastroenterol* 1995; 9: 371–93.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Braz.*: Uropac.

Sulfamethylthiazole

Methylsulfathiazole; Sulfametiltiazol; Sulphamethylthiazole; Сульфаметилтиазол.

4-Amino-*N*-(4-methyl-2-thiazolyl)benzenesulfonamide.

$C_{10}H_{11}N_3O_2S_2$=269.3

CAS — 515-59-3.

Profile

Sulfamethylthiazole is a sulfonamide with properties similar to those of sulfamethoxazole (p. 365.2). It is applied topically with tetracycline in the treatment of eye infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Ital.*: Pensulvit.

Sulfametopyrazine *(BAN)*

AS-18908; NSC-110433; Solfametopirazina; Solfametossipirazina; Sulfaleeni; Sulfalen; Sulfalene (pINN); Sulfalene (USAN); Sulfalène; Sulfaleno; Sulfalenum; Sulfamethoxypyrazine; Sulfapirazinmetossina; Sulfapyrazin Methoxyne; Sulphalene; Сульфален.

N^1-(3-Methoxypyrazin-2-yl)sulphanilamide.

$C_{11}H_{12}N_4O_3S$=280.3

CAS — 152-47-6.

ATC — J01ED02.

ATC Vet — QJ01EQ19.

UNII — T68L4ZC15G.

Pharmacopoeias. In *It.*

Uses and Administration

Sulfametopyrazine is a long-acting sulfonamide that has been used orally in the treatment of respiratory- and urinary-tract infections due to sensitive organisms.

Sulfametopyrazine is given with pyrimethamine (p. 662.3) in the treatment of malaria.

It has also been given in the ratio 4 parts of sulfametopyrazine to 5 parts of trimethoprim as a combination with uses similar to those of co-trimoxazole (p. 277.3).

Adverse Effects, Treatment, and Precautions

As for Sulfamethoxazole, p. 365.3.

If adverse effects occur, sulfametopyrazine has the disadvantage that several days are required for its elimination from the body.

Interactions

As for Sulfamethoxazole, p. 366.2.

Antimicrobial Action

As for Sulfamethoxazole, p. 366.3.

Pharmacokinetics

Sulfametopyrazine is readily absorbed from the gastrointestinal tract; 60 to 80% is bound to plasma proteins. Only about 5% of a dose is metabolised to the acetyl derivative. It is slowly excreted in the urine. The biological half-life has been reported to be about 60 to 65 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Irl.*: Kelfizine W; *Thai.*: Eadazine.

Multi-ingredient Preparations. *Belg.*: Co-Arinate; Dafrafin†; *India*: Metakelfin; *Ital.*: Metakelfin.

Sulfametrole *(BAN, rINN)*

Sulfametrol; Sulfametrole; Sulfametrolo; Sulfametrolum; Сульфаметрол.
N^1-(4-Methoxy-1,2,5-thiadiazol-3-yl)sulphanilamide.
$C_9H_{10}N_4O_3S_2$=286.3
CAS — 32909-92-5.
UNII — F5AK41IPQG.

Profile

Sulfametrole is a sulfonamide with properties similar to those of sulfamethoxazole (p. 365.2). It is given in the ratio of 5 parts of sulfametrole to 1 part of trimethoprim as a combination with uses similar to those of co-trimoxazole (p. 277.3). Usual oral doses are 960 mg (800 mg of sulfametrole and 160 mg of trimethoprim) twice daily; for severe infections, the dose may be doubled. It has also been given as the sodium salt by intravenous infusion.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Lidaprim; *Gr.*: Lidaprim; *Hong Kong*: Lidaprim; *Neth.*: Lidatrim†; Rokiprim; *Rus.*: Lidaprim (Лидаприм)†.

Sulfamonomethoxine *(BAN, USAN, rINN)*

DJ-1550; DS-36; ICI-32525; Ro-4-3476; Sulfamonomethoxin; Sulfamonomethoxine; Sulfamonomethoxinum; Sulfamonometoxina; Сульфамонометоксин.
N^1-(6-Methoxypyrimidin-4-yl)sulphanilamide monohydrate.
$C_{11}H_{12}N_4O_3S.H_2O$=298.3
CAS — 1220-83-3 (anhydrous sulfamonomethoxine).
ATC Vet — QJ01EQ18.
UNII — U700P169W2.

Pharmacopoeias. In *Jpn*.

Profile

Sulfamonomethoxine is a sulfonamide antibacterial with properties similar to those of sulfamethoxazole (p. 365.2). It is used in veterinary medicine.

Sulfamoxole *(BAN, USAN, rINN)*

Sulfamoksoli; Sulfamoxol; Sulfamoxolo; Sulfamoxolum; Sulphadimethyloxazole; Sulphamoxole; Сульфамоксол.
N^1-(4,5-Dimethyloxazol-2-yl)sulphanilamide.
$C_{11}H_{13}N_3O_3S$=267.3
CAS — 729-99-7.
ATC — J01EC03.
UNII — HGG82XE020.

NOTE. Compounded preparations of sulfamoxole may be represented by the following name:

- Co-trifamole *(BAN)*—sulfamoxole 5 parts and trimethoprim 1 part (see p. 277.3).

Pharmacopoeias. In *Fr*.

Profile

Sulfamoxole is a sulfonamide antibacterial with properties similar to those of sulfamethoxazole (p. 365.2). It has been used with trimethoprim as co-trifamole (p. 277.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *India*: Cortina; Supristol.

Sulfanilamide *(rINN)*

Solfammide; Streptocidum; Sulfaminum; Sulfaniilamidi; Sulfanilamid; Sulfanilamida; Sulfanilamidas; Sulfanilamidum; Sulphanilamide; Szulfanilamid; Сульфаниламид.
4-Aminobenzenesulphonamide; *p*-Sulphamidoaniline.
$C_6H_8N_2O_2S$=172.2
CAS — 63-74-1.
ATC — D06BA05; J01EB06.
ATC Vet — QD06BA05; QJ01EQ06.
UNII — 21240MF57M.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *BP(Vet)*.

Ph. Eur. 8: (Sulfanilamide). White or yellowish-white crystals or fine powder. Slightly soluble in water; sparingly soluble in alcohol; freely soluble in acetone; practically insoluble in dichloromethane; dissolves in solutions of alkali hydroxides and in dilute mineral acids. Protect from light.

Profile

Sulfanilamide is a short-acting sulfonamide with properties similar to those of sulfamethoxazole (p. 365.2). Its antibacterial activity is less than that of sulfamethoxazole. It has been used topically, including vaginally, for the treatment of susceptible infections, often with other drugs. The sodium, sodium mesilate, and camsilate salts have also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Rus.*: Streptocide (Стрептоцид); *Spain*: Azol.

Multi-ingredient Preparations. *Arg.*: Clinal; *Belg.*: Polyseptol; Sulfa-Sedemol; *Rus.*: Inhalipt (Ингалипт); Novoinhalipt (Новоингалипт); Osarcid (Осарцид); *S.Afr.*: Achromide; Daromide†; Ung Vernleigh; *Spain*: Buco Regis; Cilinafosal Dihidroestreptomicina†; Cilinafosal Hidrocortisona†; Cilinafosal†; Kanafosal Predni†; Kanafosal†; Nasopomada†; Vitavox†; *Ukr.*: Nitacid (Нитацид); Streptonitol (Стрептонитол); *USA*: Alasulf; Deltavac; DIT1-2.

Sulfapyridine *(BAN, rINN)*

Sulfapiridina; Sulfapyridiini; Sulfapyridin; Sulfapyridinum; Sulphapyridine; Сульфапиридин.
N^1-(2-Pyridyl)sulphanilamide.
$C_{11}H_{11}N_3O_2S$=249.3
CAS — 144-83-2.
ATC — J01EB04.
ATC Vet — QJ01EQ04.
UNII — Y5V2N1KE8U.

Pharmacopoeias. In *Fr*. and *US*.

USP 36: (Sulfapyridine). White or faintly yellowish-white, odourless or practically odourless, crystals, granules, or powder. It slowly darkens on exposure to light. Soluble 1 in 3500 of water, 1 in 440 of alcohol, 1 in 65 of acetone; freely soluble in dilute mineral acids and in solutions of potassium and sodium hydroxides. Protect from light.

Profile

Sulfapyridine is a short- or intermediate-acting sulfonamide, with properties similar to those of sulfamethoxazole (p. 365.2). It is slowly and incompletely absorbed from the gastrointestinal tract and excreted in urine; sulfapyridine and its acetyl metabolite are poorly soluble in urine and the risk of crystalluria is relatively high. Adverse effects are common, and gastrointestinal disturbances may preclude continued therapy. Because of its toxicity, sulfapyridine is now seldom used except occasionally for dermatitis herpetiformis and related skin disorders when alternative treatment is unsuitable; oral doses of up to 1 g four times daily have been given initially, reduced to the minimum effective maintenance dose once improvement occurs.

Breast feeding. The last available guidance from the American Academy of Pediatrics[1] stated that, although sulfapyridine was usually compatible with breast feeding, caution was required in breast-fed infants with jaundice or G6PD deficiency, or who were ill, stressed, or premature.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/05/04)

Pemphigoid. Benefit has been seen with sulfapyridine in ocular cicatricial pemphigoid.[1]

1. Elder MJ, *et al.* Sulphapyridine—a new agent for the treatment of ocular cicatricial pemphigoid. *Br J Ophthalmol* 1996; 80: 549–52.

Preparations

Pharmacopoeial Preparations
USP 36: Sulfapyridine Tablets.

Sulfaquinoxaline *(BAN, rINN)*

Sulfabenspyrazin; Sulfabentspyratsiini; Sulfabenzpyrazine; Sulfabenzpyrazinium; Sulfabenzpyrazinum; Sulfachinossalina; Sulfaquinoxalin; Sulfaquinoxalina; Sulfaquinoxalinum; Sulphaquinoxalina; Sulphaquinoxaline; Сульфахиноксалин.
N^1-(Quinoxalin-2-yl)sulphanilamide.
$C_{14}H_{12}N_4O_2S$=300.3
CAS — 59-40-5 (sulfaquinoxaline); 967-80-6 (sulfaquinoxaline sodium).
ATC Vet — QJ01EQ16; QP51AG03.
UNII — WNW8115TM9.

Pharmacopoeias. In *Fr*. Also in *BP(Vet)* and in *US* for veterinary use only.

Fr. also includes Sulfaquinoxaline Sodium, $C_{14}H_{11}N_4NaO_2S$ = 322.3.

BP(Vet) 2014: (Sulfaquinoxaline). A yellow powder. Practically insoluble in water and in ether; very slightly soluble in alcohol. It dissolves in aqueous solutions of alkalis. Protect from light.

USP 36: (Sulfaquinoxaline). Protect from light.

Profile

Sulfaquinoxaline is a sulfonamide antibacterial used in veterinary medicine, sometimes with trimethoprim.

Sulfathiazole *(BAN, rINN)*

M&B-760; Norsulfazole; RP-2090; Solfatiazolo; Sulfanilamidothiazolum; Sulfathiazol; Sulfathiazolum; Sulfatiatsoli; Sulfatiazol; Sulfatiazolas; Sulfatiazolo; Sulfonazolum; Sulphathiazole; Szulfatiazol; Сульфатиазол.
N^1-(1,3-Thiazol-2-yl)sulphanilamide.
$C_9H_9N_3O_2S_2$=255.3
CAS — 72-14-0.
ATC — D06BA02; J01EB07.
ATC Vet — QD06BA02; QJ01EQ07.
UNII — Y7FKS2XWQH.

Pharmacopoeias. In *Eur.* (see p. vii), *US*, and *Viet*.

Ph. Eur. 8: (Sulfathiazole). A white or slightly yellowish, crystalline powder. Practically insoluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane. It dissolves in dilute solutions of alkali hydroxides and in dilute mineral acids. Protect from light.

USP 36: (Sulfathiazole). A white or faintly yellowish-white, practically odourless, fine powder. Very slightly soluble in water; slightly soluble in alcohol; soluble in acetone, in dilute mineral acids, in solutions of alkali hydroxides, and in 6N ammonium hydroxide. Protect from light.

Sulfathiazole Sodium *(BANM, rINNM)*

Natrii Sulfathiazolum; Soluble Sulphathiazole; Sulfathiazol Sodique; Sulfathiazolum Natricum; Sulfatiazol sódico; Sulphathiazole Sodium; Натрий Сульфатиазол.
$C_9H_8N_3NaO_2S_2.5H_2O$=367.4
CAS — 144-74-1 (anhydrous sulfathiazole sodium); 6791-71-5 (sulfathiazole sodium pentahydrate).
ATC — D06BA02; J01EB07.
ATC Vet — QD06BA02.
UNII — PV16N742VM.

Pharmacopoeias. In *BP(Vet)* ($1\frac{1}{2}H_2O$ or $5H_2O$).

BP(Vet) 2014: (Sulfathiazole Sodium). A white or yellowish-white crystalline powder or granules. Freely soluble in water; soluble in alcohol. A solution in water containing the equivalent of 1% of the anhydrous substance has a pH of 9.0 to 10.0. Protect from light.

Profile

Sulfathiazole is a short-acting sulfonamide with properties similar to those of sulfamethoxazole (p. 365.2). It is now rarely used systemically due to its toxicity.

Sulfathiazole is used with other sulfonamides, usually sulfabenzamide and sulfacetamide, in preparations for the topical treatment of vaginal infections and is also used with other drugs in the treatment of skin infections.

Sulfathiazole sodium has been applied topically with other drugs in the treatment of eye infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Blefarosan†; Welt-Sulfazol; *Rus.*: Norsulfazol (Норсульфазол).

Multi-ingredient Preparations. *Arg.*: Otocuril; *Braz.*: Vagi-Sulfa; *Chile*: Indocalm; Tru; *Gr.*: Kronoderm; Sultrin; *Ital.*: Streptosil con Neomicina; *Mex.*: Unguento Cruz; Unguento Sulfatiazol Rojtier; *Philipp.*: Sultrin†; *Pol.*: Sulfarinol; *Rus.*: Inhalipt (Ингалипт); Novoinhalipt (Новоингалипт); *S.Afr.*: Sultrin†; *Spain*: Cremsol†; Salitanol Estreptomicina†; *USA*: Sultrin†.

Pharmacopoeial Preparations
USP 36: Triple Sulfa Vaginal Cream; Triple Sulfa Vaginal Tablets.

Sulfathiazole Silver *(BANM, rINNM)*

Argenti Sulfathiazolum; Sulfathiazol Argentique; Sulfatiazol argéntica; Серебра Сульфатиазол.

4-Amino-*N*-2-thiazolylbenzenesulfonamide monosilver(1+).
$C_9H_9N_3O_2S_2Ag$=363.2
CAS — 24342-30-1.
UNII — TG8Z82ZC56.

Profile

Sulfathiazole silver is a sulfonamide antibacterial used topically for burns, ulcers, and other infections of the skin.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Hung.***: Argosulfan; ***Pol.***: Argosulfan; ***Rus.***: Argosulfan (Аргосульфан); ***Ukr.***: Argosulphan (Аргосульфан).

Sulfatroxazole *(BAN, rINN)*

Sulfatroxazol; Sulfatroxazolum; Сульфатроксазол.
N^1-(4,5-Dimethyl-1,2-oxazol-3-yl)sulfanilamide.
$C_{11}H_{13}N_3O_3S$=267.3
CAS — 23256-23-7.
ATC Vet — QJ01EQ14.
UNII — ZXC0PT8FFS.

Profile

Sulfatroxazole is a sulfonamide antibacterial used with trimethoprim in veterinary medicine.

Sulfisomidine *(BAN, rINN)*

Sulfa-isodimérazine; Sulfaisodimidlini; Sulfaisodimidin; Sulfaisodimidine; Sulfaisodimidinum; Sulfasomidine; Sulfisomidlini; Sulfisomidin; Sulfisomidina; Sulfisomidinum; Sulfizomidinas; Sulphasomidine; Szulfizomidin; Сульфизомидин.
N^1-(2,6-Dimethylpyrimidin-4-yl)sulphanilamide.
$C_{12}H_{14}N_4O_2S$=278.3
CAS — 515-64-0.
ATC — J01EB01.
UNII — W03L3ODK6E.

NOTE. Sulfadimethylpyrimidine has been used as a synonym for sulfisomidine, and sulphadimethylpyrimidine is sometimes used as a synonym for sulfadimidine (p. 363.2). Care should be taken to avoid confusion between the two compounds, which are isomeric.

Profile

Sulfisomidine is a short-acting sulfonamide with properties similar to those of sulfamethoxazole (p. 365.2). It has been used topically for skin or vaginal infections and has also been given orally. The sodium salt has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Thai.***: Aristamid.

Sultamicillin *(BAN, USAN, rINN)*

CP-49952; Sultamicilin; Sultamicilina; Sultamicilline; Sultamicillinum; Sultamisilin; Sultamisillilini; Sultamycylina; VD-1827; Сультамициллин.
Penicillanoyloxymethyl (6*R*)-6-(D-2-phenylglycylamino)penicillanate 3′,3′-dioxide.
$C_{25}H_{30}N_4O_9S_2$=594.7
CAS — 76497-13-7.
ATC — J01CR04.
ATC Vet — QJ01CR04.
UNII — 65DT0ML581.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Sultamicillin). A semisynthetic product derived from a fermentation product. A white or almost white, slightly hygroscopic, crystalline powder. Practically insoluble in water and in alcohol; very slightly soluble in methyl alcohol. Store in airtight containers.

Sultamicillin Tosilate *(BANM, rINNM)*

Sultamicilina, tosilato de; Sultamicilin-tosylat; Sultamicillin Tosylate; Sultamicilline, tosilate de; Sultamicillini Tosilas; Sultamicillintosilat; Sultamisillinitosilaatti; Sultamycyliny tozylan; Tosilato de sultamicilina; Сультамициллина тозилат.
Sultamicillin toluene-4-sulphonate.
$C_{25}H_{30}N_4O_9S_2.C_7H_8O_3S$=766.9
CAS — 83105-70-8.
UNII — 46940LU8EO (anhydrous sultamicillin tosilate); 2M66QX49ZZ (sultamicillin tosilate dihydrate).

Pharmacopoeias. In *Chin.*

Eur. (see p. vii) and *Jpn* include the dihydrate.

Ph. Eur. 8: (Sultamicillin Tosilate Dihydrate; Sultamicillini Tosilas Dihydricus). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol. Store in airtight containers.

Profile

Sultamicillin is a prodrug of ampicillin (p. 218.2) and of the beta-lactamase inhibitor sulbactam (p. 360.1); it consists of the two compounds linked as a double ester. During absorption from the gastrointestinal tract it is hydrolysed, releasing equimolar quantities of ampicillin and sulbactam.

Sultamicillin is given orally as tablets containing sultamicillin tosilate or as oral suspension containing sultamicillin. It is used in the treatment of infections where beta-lactamase-producing organisms might occur, including uncomplicated gonorrhoea, otitis media, and respiratory-tract and urinary-tract infections. The usual dose is 375 to 750 mg of sultamicillin (equivalent to 147 to 294 mg of sulbactam and 220 to 440 mg of ampicillin) twice daily. A single dose of sultamicillin 2.25 g with probenecid 1 g may be used for uncomplicated gonorrhoea.

When parenteral therapy is necessary a combined preparation of ampicillin with sulbactam is given.

References.

1. Friedel HA, *et al.* Sultamicillin: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1989; 37: 491–522.
2. Lode H. Role of sultamicillin and ampicillin/sulbactam in the treatment of upper and lower bacterial respiratory tract infections. *Int J Antimicrob Agents* 2001; 18: 199–209.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Ampigen SB; Unasyna; ***Austria***: Unasyn; ***Braz.***: Unasyn; ***Chile***: Unasyna; ***China***: Bei Zong (倍宗); BeiLong (贝隆); Bo De (博德); Caderyn (凯德林); Kailanxin (凯兰欣); Shilijing (施利静); Shu An (舒氨); Shutaxian (舒他仙); Si Hai Neng (思海能); Su Ke (苏克); Yin Shu (垠舒); ***Ger.***: Unacid PD; ***Gr.***: Begalin; ***Hong Kong***: Unasyn; ***Hung.***: Unasyn; ***India***: Sulbacin; ***Indon.***: Bactesyn; Cinam; Picyn; Unasyn; Vicillin-SX; ***Ital.***: Unasyn; Unasyn; ***Malaysia***: Sulbacin; Unasyn; ***Mex.***: Pentrexyl-S12-H; Unasyna; ***Philipp.***: Sulbacillin; Sulmicil; Unasyn; Unicilin; Zunamyn; ***Pol.***: Unasyn; ***Singapore***: Unasyn; ***Thai.***: Ambacitam; Ampitam†; Amsubac; Sulam; Unasyn; ***Turk.***: Alfasid; Ampisid; Combicid; Devasid; Duobak; Duobaktam; Duocid; Nobecid; Sulcid; Sultamat; Sultasid; Sultibac; ***Venez.***: Pipexiam; Sinif; Sulamp; Sultamilan; Unasyn.

Multi-ingredient Preparations. *Cz.*: Unasyn.

Taurolidine *(BAN, rINN)*

Taurolidina; Taurolidinum; Тауролидин.
4,4′-Methylenebis(perhydro-1,2,4-thiadiazine 1,1-dioxide).
$C_7H_{16}N_4O_4S_2$=284.3
CAS — 19388-87-5.
ATC — B05CA05.
ATC Vet — QB05CA05.
UNII — 8OBZ1M4V3V.

Profile

Taurolidine is a broad-spectrum antibacterial. It is hydrolysed in aqueous solution to its monomeric form taurultam and other metabolites, with the release of what was originally thought to be formaldehyde but are now considered to be activated methylene glycol or methylol groups, from which it is believed to derive its activity. Its antibacterial activity *in vitro* is modest but is reported to be enhanced in the presence of serum or urine; it is active against pathogens including *Staphylococcus aureus, Escherichia coli,* and *Pseudomonas aeruginosa*. Taurolidine is also reported to inactivate bacterial endotoxin.

Taurolidine is used in peritonitis; a solution containing 0.5% is used for irrigation and a 2% solution is available for instillation. The drug has been given experimentally as an intravenous infusion in the treatment of severe sepsis or endotoxic shock and in pancreatitis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Taurolin; ***Ger.***: Taurolin; ***Irl.***: Taurolin; ***Neth.***: Taurolin; ***Switz.***: Taurolin; ***Turk.***: Taurolin.

Tazobactam Sodium *(BANM, USAN, rINNM)*

CL-298741 (tazobactam); CL-307579; Natril Tazobactamum; Tazobactam sódico; Tazobactam Sodique; Tazobactamum natricum; Tazobaktam Sodyum; YTR-830; YTR-830H (tazobactam); Натрий Тазобактам.
Sodium (2*S*,3*S*,5*R*)-3-methyl-7-oxo-3-(1*H*-1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0]-heptane-2-carboxylate 4,4-dioxide.
$C_{10}H_{11}N_4NaO_5S$=322.3
CAS — 89786-04-9 (tazobactam); 89785-84-2 (tazobactam sodium).
ATC — J01CG02.
ATC Vet — QJ01CG02.
UNII — UXA545ABTT.

Profile

Tazobactam is a penicillanic acid sulfone derivative with beta-lactamase inhibitory properties similar to those of sulbactam (p. 360.2) although it is regarded as more potent. It has the potential to enhance the activity of beta-lactam antibacterials against beta-lactamase-producing bacteria.

Tazobactam sodium is given intravenously with piperacillin sodium (p. 340.1) for the treatment of bacterial infections. The pharmacokinetics of tazobactam and piperacillin are similar.

References.

1. Bush K, *et al.* Kinetic interactions of tazobactam with β-lactamases from all major structural classes. *Antimicrob Agents Chemother* 1993; 37: 851–8.
2. Payne DJ, *et al.* Comparative activities of clavulanic acid, sulbactam, and tazobactam against clinically important β-lactamases. *Antimicrob Agents Chemother* 1994; 38: 767–72.
3. Lee NLS, *et al.* β-Lactam antibiotic and β-lactamase inhibitor combinations. *JAMA* 2001; 285: 386–8.
4. Lee N, *et al.* Clinical role of β-lactam/β-lactamase inhibitor combinations. *Drugs* 2003; 63: 1511–24.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Petezam; ***Gr.***: Zobactam; Zoracilin.

Multi-ingredient Preparations. ***Arg.***: Pipetexina; Tazonam; Vredian; ***Austral.***: PiperTaz; Tazocin; Tazopip; ***Austria***: Pipitaz; Tazonam; ***Belg.***: Tazocin; ***Braz.***: Tazocilina; Tazocin; ***Canad.***: Tazocin; ***Chile***: Aurotaz-P; Tazonam; ***China***: An Di Tai (安迪泰); Bang Da (邦达); Caryn (凯伦); Fengtailing (锋泰灵); Haitaxin (海他欣); Kai Si (凯斯); Kang De Li (康得力); Tazocin (特冶星); Xian Bi Ta (仙必他); ***Cz.***: Tazabax; Tazip; Tazocin; Tazopet; Tazoratio; Tebranic; ***Denm.***: Tazocin; ***Fin.***: Tazocin; ***Fr.***: Tazocilline; ***Ger.***: Tazobac; ***Gr.***: Bactalin; Gramenox; Oliten; Tavoctame; Tazepen; Tazidron; Tazobion; Tazocin; Tazorex; ***Hong Kong***: Tazocin; ***Hung.***: Tazocin; ***India***: Adzopip; Almacef-T; Ampip-T; Arixon-TZB; Augtaz; Avcef-TZ; Axocare-T; Baclin; Boxter; Broadcef-T; C-Plme-T; Cadipip; Cadizone-XP; Cefa-T Kit; Cefaday-TZ; Cefcin-TJ; Ceflrone T; Cefmol-TZ; Cefritz-TZ; Cefs-T; Cefset-TX; Cefsine-TZ; Cefzox-TZ; Cesafe-TZ; Cetzone-TZ; Cidal; Cinpip-TZ; Combitaz; Combiwin; Crucef; CT Ceff-TZ; CTMor-TZ; CTX-TZ; Cureact; Deczone-T; Deczone-TP; Dibact; Durataz; Elzox; Europep-T; Everpip-TZ; Extacef-Tazo; Finecef-T; Fobidime-TZ; Forpep; Glen-TZB; Glicef-T; Gotaz; Gramotaz; Hicef-T; Hocef-T; Boslin; Ifytrox-TB; Incef-TZ; Infocer; Inforcer; Infoxon-T; Ip-Taz; Jope; Kafi-TBZ; Kombat; KPT; Lazocin Forte; Lazopip; Lezone-XP; Lifecare-A; Lifecare-C; Lifecare-T; Lintaz; Lisel-TBZ; Lupitaz; Magnova; Matlin; Medipip; Megacillin; Mezobact-P; Microtaz; Mocef-TZ; Monal; Montaz; Nexef-TBZ; Olin; Oritiz; Pactum; Tazact; Tazofast; Tazopen; Zosyn; ***Indon.***: Tazocin; ***Irl.***: Pipercin; Piperin; Tazocin; ***Israel***: Tazocillin; Tazocin; Tazopip; Tazorex; ***Ital.***: Ibitazina; Limerick; Tazobac; Tazocin; Tazopenil; ***Jpn***: Zosyn; ***Malaysia***: Tazocin; ***Mex.***: Tasovak; Tazocin; Tazpen; ***Neth.***: Tazocin; ***Norw.***: Piptazira; Tazocin; ***NZ***: Tazocin; ***Philipp.***: Bactaz; Peprasan-T; Piptaz; Pizobac; Pletzolyn; Tanzo; Tapimycin; Tazobak; Tazocin; Tazolin†; Tazopen; Tazotaz; Tebranic; Vigocid; ***Pol.***: Tazacylin; Tazocin; Tazoratio; ***Port.***: Tazobac; ***Rus.***: Tacillin-J (Тациллин ДК); Tazocin (Тазоцин); ***S.Afr.***: Curitaz; Tazobax; Tazocin; ***Singapore***: Tazocin; Tazpen; ***Spain***: Tazocel; ***Swed.***: Tazocin†; ***Switz.***: Tazobac; ***Thai.***: Astaz-P; Pipertaz; Tazocin; Tazrobida; Tebranic; ***Turk.***: Tazocin; Tazoper; ***UK***: Tazocin; ***Ukr.***: Tazar (Тазар); Zopercin (Зопеpцин); ***USA***: Zosyn; ***Venez.***: Tazopril; Tazpen.

Pharmacopoeial Preparations
USP 36: Piperacillin and Tazobactam for Injection.

Teicoplanin *(BAN, USAN, rINN)*

A-8327; DL-507-II; L-12507; MDL-507; Teichomycin A_2; Teicoplanina; Teicoplanine; Teicoplaninum; Teikoplaniini; Teikoplanin; Тейкопланин.
CAS — 61036-62-2 (teichomycin); 61036-64-4 (teichomycin A_2).
ATC — J01XA02.
ATC Vet — QJ01XA02.
UNII — 4U3D3YY81M.

Description. A glycopeptide antibacterial obtained from cultures of *Actinoplanes teichomyceticus* or the same substance obtained by any other means.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.*

Ph. Eur. 8: (Teicoplanin). A fermentation product that is a mixture of glycopeptides produced by certain strains of *Actinoplanes teichomyceticus*. The 6 principal components of the mixture are teicoplanin A_{2-1} to A_{2-5} and teicoplanin A_{3-1}. The anhydrous and sodium chloride-free substance has a minimum potency of 900 units/mg.

A yellowish, amorphous powder. Freely soluble in water; practically insoluble in alcohol; sparingly soluble in dimethylformamide. A 5% solution in water has a pH of 6.5 to 7.5. Store at a temperature of 2 degrees to 8 degrees. Protect from light.

Uses and Administration

Teicoplanin is a lipoglycopeptide antibacterial that may be used as an alternative to vancomycin (p. 386.3) in the treatment or prophylaxis of serious staphylococcal or other Gram-positive infections where other drugs cannot be used. Teicoplanin, given orally, has been suggested as a possible alternative to vancomycin or metronidazole in antibiotic-associated colitis. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Teicoplanin is given intravenously, as a bolus dose or by infusion over 30 minutes, or by intramuscular injection. The usual mean dose is 6 mg/kg intravenously or intramuscularly initially, followed by 3 mg/kg intravenously or intramuscularly on each subsequent day of treatment (in practice this equates to a usual dose of 400 mg initially followed by 200 mg daily, except in patients weighing more than 85 kg in whom it is adapted accordingly). In more severe infections, 6 mg/kg may be given every 12 hours for the first 3 doses, followed by 6 mg/kg daily. Higher doses have been given (see Administration, p. 372.1). The duration of therapy should not exceed 4 months.

In the treatment of antibiotic-associated colitis caused by *Clostridium difficile* teicoplanin may be given orally at a dose of 200 mg twice daily for 10 days.

For the prophylaxis of Gram-positive infection in high-risk patients undergoing surgical procedures who are unable to receive penicillin, teicoplanin may be given in a single intravenous dose of 400 mg at induction of anaesthesia; a dose of 800 mg has been recommended by the *BNF* for those undergoing skeletal stabilisation and definitive soft-tissue closure.

Although no relationship between plasma concentrations and toxicity has been established, the *BNF* suggests that the former may sometimes be used as a guide to optimise treatment: trough concentrations should be above 10 micrograms/mL (above 20 micrograms/mL in patients with endocarditis or with deep-seated infections such as those of the bones and joints) but less than 60 micrograms/mL.

For CAPD-associated peritonitis, teicoplanin may be added to the dialysis solution at a concentration of 20 mg/litre; this dose should be given in each bag of solution in the first week, in alternate bags in the second week, and in the overnight dwell bag only during the third week. Patients may be given an initial loading dose of 400 mg intravenously if they are febrile.

Dosage should be adjusted in patients with impaired renal function (see Administration in Renal Impairment, p. 372.2). For doses in children and neonates see Administration in Children, p. 372.2.

The use of teicoplanin has been reviewed.[1-6] Two systematic reviews[5,6] comparing teicoplanin and vancomycin found that teicoplanin was at least as effective as the other drug, and was associated with a lower incidence of adverse effects, particularly nephrotoxicity. It was suggested that teicoplanin might be preferred in patients at higher risk of acute kidney injury.[6]

1. Murphy S, Pinney RJ. Teicoplanin or vancomycin in the treatment of Gram-positive infections? *J Clin Pharm Ther* 1995; 20: 5–11.
2. de Lalla F, Tramarin A. A risk-benefit assessment of teicoplanin in the treatment of infections. *Drug Safety* 1995; 13: 317–28.
3. Periti P, *et al.* Antimicrobial prophylaxis in orthopaedic surgery: the role of teicoplanin. *J Antimicrob Chemother* 1998; 41: 329–40.
4. Schaison G, *et al.* Teicoplanin in the treatment of serious infection. *J Chemother* 2000; 12 (suppl 5): 26–33.
5. Svetitsky S, *et al.* Comparative efficacy and safety of vancomycin versus teicoplanin: systematic review and meta-analysis. *Antimicrob Agents Chemother* 2009; 53: 4069–79.
6. Cavalcanti AB, *et al.* Teicoplanin versus vancomycin for proven or suspected infection. Available in The Cochrane Database of Systematic Reviews; Issue 6. Chichester: John Wiley; 2010 (accessed 09/12/10).

Administration. It has been suggested that increased loading doses or maintenance doses of teicoplanin may be needed in severe or deep-seated infections. In patients with bone and joint infection standard daily maintenance doses of 400 mg intravenously have been reported to result in trough concentrations above the recommended 20 micrograms/mL in only about 40% of cases, whereas of those given 600 mg intravenously once daily, over 70% achieved the desired trough concentration.[1] Others have found that an intravenous dose of 6 mg/kg (400 mg) twice daily achieved trough concentrations of 20 micrograms/mL only after 4 days of treatment;[2] it was pointed out that some have advocated loading doses of 12 mg/kg or even 15 mg/kg every 12 hours for at least 3 doses in patients with bone and joint infections. A conventional regimen with a loading dose of 6 mg/kg twice daily for 48 hours followed by 6 mg/kg daily was thought appropriate for most infections with sensitive organisms other than infective endocarditis, septic arthritis, or osteomyelitis.

UK licensed product information notes that in some clinical situations, such as in infected, severely burnt patients or those with *Staphylococcus aureus* endocarditis, unit maintenance doses of up to 12 mg/kg have been given intravenously.

1. Matthews PC, *et al.* Teicoplanin levels in bone and joint infections: are standard doses subtherapeutic? *J Infect* 2007; 55: 408–13.
2. Brink AJ, *et al.* Gauteng Understanding Teicoplanin Serum levels (GUTS) study group. Recommendations to achieve rapid therapeutic teicoplanin plasma concentrations in adult hospitalised patients treated for sepsis. *Int J Antimicrob Agents* 2008; 32: 455–8.

Administration in children. In the UK, teicoplanin is licensed for use in *children* from the age of 2 months to treat Gram-positive infections, but the *BNFC* considers that the same doses may be given from one month of age. It is given preferably by intravenous injection or infusion over 30 minutes, but the intramuscular route may be used if necessary after the first 3 doses. For moderate infections a loading dose of 10 mg/kg (maximum 400 mg) every 12 hours for three doses is followed by a daily dose of 6 mg/kg (maximum 400 mg). For severe infections or neutropenic patients the daily dose is maintained at 10 mg/kg.

The recommended dosage regimen for *neonates* is a loading dose of 16 mg/kg followed by a maintenance dose of 8 mg/kg once daily. The *BNFC* specifies that it should be given by intravenous infusion in this age group.

Administration in renal impairment. Doses of teicoplanin should be adjusted in patients with renal impairment, though reduction is not required until the fourth day of treatment. Teicoplanin should be given in usual intravenous or intramuscular doses (see Uses and Administration, above) for the first 3 days of therapy, thereafter the dose is adjusted according to creatinine clearance (CC):

- CC 40 to 60 mL/minute: half initial dose given daily or initial dose given every 2 days
- CC less than 40 mL/minute and for haemodialysed patients: one-third initial dose given daily or initial dose given every 3 days

Critically ill patients undergoing continuous venovenous haemofiltration (CVVH) may require higher than standard doses of teicoplanin, as considerable amounts of the drug are removed by CVVH. After a 1.2-g intravenous loading dose, daily maintenance doses of 0.6 to 1.8 g were required to produce adequate trough concentrations (defined by the authors as 15 to 25 micrograms/mL) in a pharmacokinetic study;[1] the authors considered that serum-drug concentration monitoring was essential for patients on CVVH, as teicoplanin elimination can be variable depending on patient condition and individual filtration protocols.

1. Bellmann R, *et al.* Teicoplanin pharmacokinetics in critically ill patients on continuous veno-venous hemofiltration. *Int J Clin Pharmacol Ther* 2010; 48: 243–9.

Adverse Effects and Precautions

Fever, rash and pruritus, and occasional bronchospasm and anaphylaxis have been reported with teicoplanin, but, in comparison with vancomycin (p. 388.1), it appears to be better tolerated when given by rapid intravenous injection and, although erythema and flushing of the upper body have occurred, the 'red-man syndrome' has been reported less often. In addition, unlike vancomycin, teicoplanin does not appear to cause tissue necrosis and can be given by intramuscular injection. Other hypersensitivity reactions have included rigors, angioedema, and, rarely, severe skin reactions including exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

Other reported reactions include gastrointestinal disturbances, dizziness, headache, thrombocytopenia (especially at high doses), leucopenia, neutropenia, eosinophilia, disturbances in liver enzyme values, and pain, erythema, and thrombophlebitis or abscess at the injection site. Rare cases of agranulocytosis have occurred. Renal impairment and ototoxicity have been reported but both appear to be less frequent than with vancomycin.

Renal and auditory function should be monitored during prolonged therapy in patients with pre-existing renal impairment, and in those receiving other ototoxic or nephrotoxic drugs, although opinions conflict as to whether increased risk of nephrotoxicity exists with combined therapy with drugs such as the aminoglycosides. In general, periodic blood counts and liver- and renal-function tests are advised during treatment.

No relationship has yet been established between plasma concentration and toxicity, and plasma-concentration monitoring is not generally considered necessary, although it may be used to optimise therapy (see Uses and Administration, above). Dosage adjustment is required in renal impairment.

Hypersensitivity. Although there have been occasional reports of cross-sensitivity to teicoplanin in patients hypersensitive to vancomycin,[1-5] the majority of reports suggest that cross-sensitivity is very rare and teicoplanin can usually be used in patients intolerant of vancomycin.[4-9]

1. McElrath MJ, *et al.* Allergic cross-reactivity of teicoplanin and vancomycin. *Lancet* 1986; i: 47.
2. Grek V, *et al.* Allergic cross-reaction of teicoplanin and vancomycin. *J Antimicrob Chemother* 1991; 28: 476–7.
3. Marshall C, *et al.* Glycopeptide-induced vasculitis—cross-reactivity between vancomycin and teicoplanin. *J Infect* 1998; 37: 82–3.
4. Kwon HS, *et al.* A case of hypersensitivity syndrome to both vancomycin and teicoplanin. *J Korean Med Sci* 2006; 21: 1108–10.
5. Hsiao SH, *et al.* Teicoplanin-induced hypersensitivity syndrome with a preceding vancomycin-induced neutropenia: a case report and literature review. *J Clin Pharm Ther* 2010; 35: 729–32.
6. Schlemmer B, *et al.* Teicoplanin for patients allergic to vancomycin. *N Engl J Med* 1988; 318: 1127–8.
7. Smith SR, *et al.* Teicoplanin administration in patients experiencing reactions to vancomycin. *J Antimicrob Chemother* 1989; 23: 810–12.
8. Wood G, Whitby M. Teicoplanin in patients who are allergic to vancomycin. *Med J Aust* 1989; 150: 668.
9. Hung YP, *et al.* Tolerability of teicoplanin in 117 hospitalized adults with previous vancomycin-induced fever, rash, or neutropenia: a retrospective chart review. *Clin Ther* 2009; 31: 1977–86.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies teicoplanin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 09/08/11)

Red-man syndrome. Although teicoplanin is believed[1,2] to be less likely than vancomycin to induce the red-man syndrome, symptoms consistent with the syndrome have nevertheless been reported after intravenous use.[3]

1. Sahai J, *et al.* Comparison of vancomycin- and teicoplanin-induced histamine release and "red man syndrome". *Antimicrob Agents Chemother* 1990; 34: 763–9.
2. Rybak MJ, *et al.* Absence of "red man syndrome" in patients being treated with vancomycin or high-dose teicoplanin. *Antimicrob Agents Chemother* 1992; 36: 1204–7.
3. Dubettier S, *et al.* Red man syndrome with teicoplanin. *Rev Infect Dis* 1991; 13: 770.

Antimicrobial Action

As for Vancomycin Hydrochloride, p. 389.1, although in general teicoplanin is more active against susceptible strains. In particular, it may be more active *in vitro* against enterococci and some anaerobic organisms, including strains of *Clostridium*. However, some coagulase-negative staphylococci are less sensitive to teicoplanin than to vancomycin.

Acquired resistance to teicoplanin has developed in staphylococci during treatment with teicoplanin. Cross-resistance with vancomycin has occurred in staphylococci and enterococci. See also under Antimicrobial Action of Vancomycin, p. 389.1.

Pharmacokinetics

Teicoplanin is poorly absorbed from the gastrointestinal tract. After a 400-mg intravenous dose, peak plasma concentrations 1 hour later are reported to be in the range 20 to 50 micrograms/mL. It is well absorbed on intramuscular injection with a bioavailability of about 90%; after a dose of 3 mg/kg intramuscularly, peak plasma concentrations of 5 to 7 micrograms/mL have been reported after 2 to 4 hours.

The pharmacokinetics of teicoplanin are triphasic, with a biphasic distribution and a prolonged elimination. Penetration into the CSF is poor. It is taken up into white blood cells, and about 90 to 95% of teicoplanin in plasma is protein bound. It is excreted almost entirely by glomerular filtration in the urine, as unchanged drug. The terminal half-life is prolonged, but reported half-lives have ranged from about 30 to 190 hours or longer, depending on the sampling time; an effective clinical half-life of about 60 hours has been suggested for use in calculating dosage regimens. Half-life is increased progressively with increasing degrees of renal impairment. Teicoplanin is not removed by haemodialysis.

Teicoplanin is a mixture of several components, the pharmacokinetics of which have been shown to vary slightly, depending on their lipophilicity.

Reviews.

1. Wilson APR. Clinical pharmacokinetics of teicoplanin. *Clin Pharmacokinet* 2000; 39: 167–83.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Targocid; Teicox; Telklonal; Terbiox; *Austral.*: Targocid; *Austria*: Targocid; *Belg.*: Targocid; *Braz.*: Bactomax; Kirom; Targocid; Teicon†; Teicoston; Teicozid†; Teiplan; Toplanina; *Chile*: Targocid; *China*: Jialixin (加立信); Tapocin (大贝辛); Targocid (他格适); *Cz.*: Targocid; *Denm.*: Targocid; *Fin.*: Targocid; *Fr.*: Targocid; *Ger.*: Targocid; *Gr.*: Talinac; Targocid; Targoplanin; *Hong Kong*: Targocid; *Hung.*: Targocid; *India*: Icop; Targocid; Ticocin; *Indon.*: Targocid; *Irl.*: Targocid; *Israel*: Targocid; *Ital.*: Targosid; Teicomid; *Jpn*: Targocid; *Malaysia*: Targocid; *Mex.*: Tarbiglem; Targocid; Teripol; *Neth.*: Targocid; *Norw.*: Targocid; *NZ*: Targocid; *Pol.*: Targocid; *Port.*: Targosid; *S.Afr.*: Targocid; *Singapore*: Targocid; *Spain*: Targocid; *Swed.*: Targocid; *Switz.*: Targocid; *Thai.*: Targocid; *Turk.*: Targocid; Tekosit; *UK*: Targocid; *Ukr.*: Norteic (Нортейк); Targocid (Таргоцид); Teico (Тейко); *Venez.*: Targocid.

Multi-ingredient Preparations. *Ger.*: Targobone†.

Telavancin *(rINN)*

Telavancina; Télavancine; Telavancinum; Телаванцин.

(3*S*,6*R*,7*R*,22*R*,23*S*,26*S*,36*R*,38a*R*)-3-(2-Amino-2-oxoethyl)-10,19-dichloro-44-[(3-{[2-(decanylamino)ethyl]amino}-2,3,6-trideoxy-3-C-methyl-α-L-*lyxo*-hexopyranosyl-(1→2)-β-D-glucopyranosyl)oxy]-7,22,28,30,32-pentahydroxy-6-[(2*R*)-4-methyl-2-(methylamino)pentanamido]-2,5,24,38,39-pentaoxo-29-{[[(phosphonomethyl)amino]methyl}-2,3,4,5,6,7,23,24,25,26,36,37,38,38a-tetradecahydro-1*H*,22*H*-23,36-(epiminomethano)-8,11:18,21-dietheno-13,16:31,35-bis(metheno)[1,6,9]oxadiazacyclohexadecino[4,5-*m*][10,2,16]benzoxadiazacyclotetracosine-26-carboxylic acid.

$C_{80}H_{106}Cl_2N_{11}O_{27}P$=1755.7

CAS — 372151-71-8.

ATC — J01XA03.

ATC Vet — QJ01XA03.

UNII — XK134822Z0.

Telavancin Hydrochloride *(USAN, rINNM)*

Hidrocloruro de telavancina; TD-6424; Télavancine, Chlorhydrate de; Telavancini Hydrochloridum; Телаванцина Гидрохлорид.

$C_{80}H_{106}Cl_2N_{11}O_{27}P,HCl$=1792.1

CAS — 560130-42-9.

UNII — 0701472ZG0.

NOTE. Telavancin hydrochloride used commercially has been stated to be a mixture of the mono-, di-, and trihydrochlorides.

Uses and Administration

Telavancin is a lipoglycopeptide antibacterial with properties similar to those of vancomycin (p. 386.3). It is used for the treatment of complicated skin and skin structure infections caused by susceptible Gram-positive bacteria and of nosocomial pneumonia (including ventilator associated pneumonia) known or suspected to be caused by MRSA.

Telavancin is given as a mixture of the mono-, di-, and tri hydrochloride salts but doses are expressed in terms of the base. It is given by intermittent intravenous infusion over 60 minutes to reduce the risk of infusion-related reactions such as the red-man syndrome. For infusion, a concentrated solution containing the equivalent of telavancin 15 mg/mL in sterile water, glucose 5%, or sodium chloride 0.9% is prepared and then further diluted in an appropriate infusion solution (such as glucose 5%, sodium chloride 0.9%, or lactated Ringer's solution) to a final concentration of 0.6 to 8 mg/mL.

The usual recommended dose in patients 18 years of age and older is the equivalent of telavancin 10 mg/kg once every 24 hours. Dose adjustment may be required in patients with renal impairment (see p. 373.2).

Reviews.[1-4] A review[3] of dalbavancin, oritavancin, and telavancin noted that the lipophilic side-chain of such lipoglycopeptides prolonged their half-life and helped to anchor the drug to the cell membrane and increase its activity against Gram-positive cocci. In addition to their common activity against cell-wall synthesis, oritavancin and telavancin can alter cell-membrane permeability; oritavancin may also inhibit RNA synthesis and has some activity against vanA resistant enterococci. Phase III studies have suggested that all 3 are effective in complicated skin and skin-structure infections. The half-life of dalbavancin is between 147 and 258 hours, which would allow for once-weekly dosing, while that of oritavancin (393 hours) might allow for a single dose per treatment course. However, the authors noted that only telavancin had gained regulatory approval, and the status of the other lipoglycopeptide antibacterials was unclear.

1. Charneski L, *et al.* Telavancin: a novel lipoglycopeptide antibiotic. *Ann Pharmacother* 2009; 43: 928–38.
2. Saravolatz LD, *et al.* Telavancin: a novel lipoglycopeptide. *Clin Infect Dis* 2009; 49: 1908–14.
3. Lyseng-Williamson KA, Blick SKA. Telavancin. *Drugs* 2009; 69: 2607–20.
4. Zhanel GG, *et al.* New lipoglycopeptides: a comparative review of dalbavancin, oritavancin and telavancin. *Drugs* 2010; 70: 859–86.

Administration in renal impairment. The dose of telavancin intravenous infusion should be adjusted in renal impairment according to creatinine clearance (CC):

- greater than 50 mL/minute: 10 mg/kg every 24 hours
- 30 to 50 mL/minute: 7.5 mg/kg every 24 hours
- 10 to less than 30 mL/minute: 10 mg/kg every 48 hours

No recommendations have been made for those with end-stage renal disease or undergoing haemodialysis, due to insufficient data.

Adverse Effects and Precautions

The most common adverse effects of telavancin are transient taste disturbance, mild nausea and vomiting, and foamy urine. As with vancomycin (see p. 388.1), infusion-related reactions (so-called 'red-neck' or 'red-man' syndrome) may occur but often can be alleviated by stopping or slowing the rate of the infusion.

Nephrotoxicity may occur more frequently with telavancin than with vancomycin. Adverse renal effects are more likely to occur in patients with comorbidities predisposing them to renal dysfunction such as pre-existing renal disease, diabetes mellitus, congestive heart failure, or hypertension, and are also more frequent in the elderly. Serum-creatinine concentration and creatinine clearance should be measured before starting telavancin, periodically throughout treatment, and when the treatment course is complete. Decreased clinical efficacy of telavancin has been noted in patients with moderate or severe baseline renal impairment (creatinine clearance ≤50 mL/minute).

Telavancin may prolong the QT-interval and should be avoided in patients with pre-existing risk factors such as congenital long QT syndrome, known prolongation of the QT-interval, uncompensated heart failure, or severe left ventricular hypertrophy.

Although telavancin does not interfere with coagulation, it may interfere with certain monitoring tests such as prothrombin time, international normalised ratio, activated partial thromboplastin time, activated clotting time, and coagulation based factor Xa tests. Blood samples for such tests should ideally be collected at trough serum-telavancin concentrations, as shortly as possible before the next dose of telavancin.

Interactions

Risk of renal toxicity with telavancin is increased in patients using other drugs known to affect kidney function (including NSAIDs, ACE inhibitors, and loop diuretics).

Because telavancin may prolong the QT interval, it should be used with caution in patients taking other drugs known to have this effect.

Antimicrobial Action

Telavancin, a lipoglycopeptide, is a semisynthetic derivative of vancomycin with concentration-dependent bactericidal activity against Gram-positive aerobic and anaerobic bacteria; it has no activity against Gram-negative organisms.

Mechanism of action. While telavancin shares the mechanism of action of vancomycin (see p. 389.1) it differs in that it also potently inhibits cross-linking of peptidoglycan in a similar manner to the penicillins. The rapid bactericidal activity of telavancin is thought to be a result of its novel ability to bind and depolarise the bacterial cell membrane, altering cell permeability.

Spectrum of activity. Like vancomycin (see p. 389.1), telavancin has good *in-vitro* activity against most *Staphylococcus* and *Streptococcus* spp., including meticillin-resistant *Staph. aureus*. Enterococci are also susceptible, although vancomycin-resistant strains have reduced susceptibility to telavancin. Telavancin is also active against anaerobic Gram-positive bacteria including *Corynebacterium* and *Clostridium* spp. *In-vitro* studies indicate that telavancin has a post-antibiotic effect ranging from 1 to 6 hours against clinically relevant Gram-positive pathogens.

Pharmacokinetics

Telavancin is not absorbed to any significant extent after oral doses. The pharmacokinetics of telavancin in adults are generally linear for intravenous doses ranging from 7.5 to 15 mg/kg once daily for up to 7 days. Steady-state concentrations occur by the third day. Telavancin is about 90% bound to plasma proteins, mainly albumin. Protein binding is concentration-independent and unaffected by renal or hepatic impairment.

In-vitro studies indicate that telavancin is not metabolised by the cytochrome P450 isoenzyme system. Although hydroxylated metabolites have been detected in the urine and plasma of patients given telavancin, the metabolic pathway that produces them has not been identified.

Telavancin is excreted mainly by the kidneys, with about 76% of a dose recovered from the urine; the elimination half-life is about 8 hours after a dose of 10 mg/kg once daily. Telavancin exposure is significantly increased in renal impairment, and dose adjustment is required for patients with creatinine clearance ≤50 mL/minute (see Administration in Renal Impairment, above).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Irl.*: Vibativ†; *USA*: Vibativ.

Telithromycin *(BAN, USAN, rINN)*

HMR-3647; RU-66647; Télithromycine; Telithromycinum; Telitromicina; Telitromisin; Телитромицин.

(3a*S*,4*R*,7*R*,9*R*,10*R*,11*R*,13*R*,15*R*,15a*R*)-4-Ethyloctahydro-11-methoxy-3a,7,9,11,13,15-hexamethyl-1-[4-[4-(3-pyridyl)imidazol-1-yl]butyl]-10-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-2*H*-oxacyclotetradecino[4,3-*d*][1,3]oxazole-2,6,8,14(1*H*,7*H*,9*H*)-tetrone.

$C_{43}H_{65}N_5O_{10}$=812.0

CAS — 173838-31-8; 191114-48-4.

ATC — J01FA15.

ATC Vet — QJ01FA15.

UNII — KI8H7H19WL.

Uses and Administration

Telithromycin is a ketolide antibacterial used for the treatment of susceptible respiratory-tract infections in adults including mild to moderate community-acquired pneumonia. In some countries it is also licensed for use in the treatment of acute sinusitis and acute bacterial exacerbations of chronic bronchitis when resistance to beta-lactam and/or macrolide antibacterials is known or suspected; and as an alternative to beta-lactam antibacterials for tonsillitis or pharyngitis caused by Group A *beta streptococci* in patients over 12 years of age. It is given orally in a usual dose of 800 mg once daily.

Doses may need to be reduced in patients with renal impairment (see p. 373.3).

References.

1. Zhanel GG, *et al.* The ketolides: a critical review. *Drugs* 2002; 62: 1771–1804.
2. Zhanel GG, Hoban DJ. Ketolides in the treatment of respiratory infections. *Expert Opin Pharmacother* 2002; 3: 277–97.
3. Ackermann G, Rodloff AC. Drugs of the 21st century: telithromycin (HMR 3647)—the first ketolide. *J Antimicrob Chemother* 2003; 51: 497–511.
4. Reinert RR. Clinical efficacy of ketolides in the treatment of respiratory tract infections. *J Antimicrob Chemother* 2004; 53: 918–27.
5. Zuckerman JM. Macrolides and ketolides: azithromycin, clarithromycin, telithromycin. *Infect Dis Clin North Am* 2004; 18: 621–49.
6. Wellington K, Noble S. Telithromycin. *Drugs* 2004; 64: 1683–94.
7. Kasbekar N, Acharya PS. Telithromycin: the first ketolide for the treatment of respiratory infections. *Am J Health-Syst Pharm* 2005; 62: 905–16.
8. Lonks JR, Goldmann DA. Telithromycin: a ketolide antibiotic for treatment of respiratory tract infections. *Clin Infect Dis* 2005; 40: 1657–64.
9. Nguyen M, Chung EP. Telithromycin: the first ketolide antimicrobial. *Clin Ther* 2005; 27: 1144–63.
10. Brown SD. Benefit-risk assessment of telithromycin in the treatment of community-acquired pneumonia. *Drug Safety* 2008; 31: 561–75.

Administration in renal impairment. Doses of telithromycin should be reduced in severe renal impairment (creatinine clearance of less than 30 mL/minute):

- UK licensed product information states that alternating daily oral doses of 800 mg and 400 mg, starting with 800 mg may be given whether or not hepatic function is also impaired
- US licensed product information recommends a dose of 600 mg once daily if there is no hepatic impairment but a dose of 400 mg once daily if there is co-existing impairment

Doses should be given after dialysis sessions to patients on haemodialysis.

Respiratory disorders. As well as their established antibacterial effect, it has been suggested that macrolides also have immunomodulatory effects that could be useful in the management of respiratory diseases (see also Respiratory Disorders, under Uses of Erythromycin, p. 292.3). Ketolides also appear to have such effects: a 10-day course of oral telithromycin 800 mg daily, started with standard treatment for acute asthma (p. 1195.2) in adults, was reported to improve asthma symptoms regardless of infection with *Chlamydophila pneumoniae* (*Chlamydia pneumoniae*) or *Mycoplasma pneumoniae*.[1] The mechanism of this effect is unclear, however, and further studies are needed.

1. Johnston SL, *et al.* The TELICAST Investigators. The effect of telithromycin in acute exacerbations of asthma. *N Engl J Med* 2006; 354: 1589–1600.

Adverse Effects

Diarrhoea and other gastrointestinal disturbances such as nausea, vomiting, abdominal pain, and flatulence are among the most common adverse reactions after use of telithromycin. Severe, but usually reversible, hepatic dysfunction, including elevation of liver enzymes and hepatitis, with or without jaundice has been reported; however, there have been cases of fatal hepatotoxicity including fulminant hepatitis, hepatic necrosis, and hepatic failure. Effects on the CNS may include dizziness, headache, vertigo, and, occasionally, insomnia or drowsiness. Taste, and very rarely smell, disturbances may occur. Other less commonly reported adverse effects include paraesthesia, eosinophilia, rashes, and cardiovascular effects such as arrhythmias, hypotension, and bradycardia. Visual disturbances, particularly affecting accommodation, have occurred. Syncope, usually associated with the vagal syndrome, has been noted. Very rarely reported adverse effects include angioedema and anaphylaxis. There have been isolated cases of erythema multiforme, pseudomembranous colitis, and muscle cramps. Life-threatening acute respiratory failure has been reported in patients with myasthenia gravis (see also Precautions, p. 374.2).

Effects on the eyes. Visual disturbances, namely blurred vision, difficulty with focusing, and diplopia have been associated with telithromycin. These have been reported to be more common in females under the age of 40 years and to occur in 1.1% of patients compared with 0.28% in those receiving a comparable antibacterial.[1] Licensed product information reports that symptoms are fully reversible, mostly mild to moderate in severity, and typically occur within a few hours of the first or second dose, lasting for several hours and recurring upon subsequent dosing. They have not been associated with any ocular abnormality.

1. Lonks JR, Goldmann DA. Telithromycin: a ketolide antibiotic for treatment of respiratory tract infections. *Clin Infect Dis* 2005; **40**: 1657–64.

Effects on the kidneys. Acute interstitial nephritis has been reported[1] in an 18-year-old man who received telithromycin for 5 days. Complete recovery of renal function occurred 2 weeks after starting symptomatic treatment with methylprednisolone.

1. Tintillier M, *et al.* Telithromycin-induced acute interstitial nephritis: a first case report. *Am J Kidney Dis* 2004; **44**: e25–e27.

Effects on the liver. Hepatotoxicity, including raised liver enzymes,[1] is an established adverse effect of telithromycin and may be severe or fatal.[2] A spontaneous-report case-control study[3] of hepatotoxicity in patients who had taken telithromycin estimated an 82% increased risk of hepatotoxicity compared with users of other drugs; the risk was greater in men than in women. However, this study also estimated an 85% increased risk among users of macrolide antibacterials in general. The association between the reporting of hepatotoxicity and the use of telithromycin was further confirmed by using 4 data mining algorithms.[4]

A subsequent expert review[5] of 42 cases of telithromycin-associated hepatotoxicity reported to the FDA noted that 5 had a severe outcome (4 deaths and 1 liver transplant). Typical clinical features were considered to be short latency (a median of 10 days but as short as 2 days in some cases), and abrupt onset of fever, abdominal pain, and jaundice; ascites occurred in some, even if liver injury was only moderately severe. Because of the short latency, monitoring of liver enzyme values was thought to be unhelpful in preventing severe toxicity.

1. Bolesta S, Rostund BP. Elevated hepatic transaminases associated with telithromycin therapy: a case report and literature review. *Am J Health-Syst Pharm* 2008; **65**: 37–41.
2. Clay KD, *et al.* Brief communication: severe hepatotoxicity of telithromycin: three case reports and literature review. *Ann Intern Med* 2006; **144**: 415–20.
3. Dore DD, *et al.* Telithromycin use and spontaneous reports of hepatotoxicity. *Drug Safety* 2007; **30**: 697–703.
4. Chen Y, *et al.* Risk of hepatotoxicity associated with the use of telithromycin: a signal detection using data mining algorithms. *Ann Pharmacother* 2008; **42**: 1791–6.
5. Brinker AD, *et al.* Telithromycin-associated hepatotoxicity: Clinical spectrum and causality assessment of 42 cases. *Hepatology* 2009; **49**: 250–7.

Effects on the skin. A 26-year-old woman with a history of rash to penicillin and sulfonamides developed toxic epidermal necrolysis after 13 doses of oral telithromycin for treatment of sinusitis; she was discharged 4 weeks after admission to hospital but had scars on her face and body and had lost her eyelashes.[1]

1. Health Canada. Telithromycin (Ketek): suspected association with toxic epidermal necrolysis. *Can Adverse React News* 2007; **17** (2): 2. Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v17n2-eng.pdf (accessed 18/06/08)

Precautions

Telithromycin should not be given to patients with known hypersensitivity to it or to the macrolides; similarly, a history of hepatitis and/or jaundice associated with telithromycin or macrolides is a contra-indication.

Telithromycin is contra-indicated in patients with myasthenia gravis because it may exacerbate symptoms of the disease; exacerbations usually occur within 1 to 3 hours of the first dose. Fatalities have been reported.

Patients with a congenital or family history of QT interval prolongation should not receive telithromycin; it should be used with care in those with coronary heart disease, cardiac arrhythmias, and in those with hypokalaemia or hypomagnesaemia, due to its potential to prolong the QT interval. Certain medications may also increase the risk of cardiac arrhythmias and prolong the QT interval (see Interactions, p. 374.2).

Patients or their carers should be informed about signs and symptoms of hepatitis. Should any of these develop during treatment with telithromycin, they should stop taking the drug and consult their doctor. It should be used with caution in patients with hepatic impairment; however, this is based on limited data in such patients. Reduced doses may be necessary in those with severe renal impairment (see p. 371.3).

Since telithromycin can produce visual disturbances or loss of consciousness caution is advised when driving, operating machinery, or undertaking similar hazardous activities.

Breast feeding. Telithromycin has been shown in *animal* studies to be excreted in breast milk at concentrations about 5 times greater than those in maternal plasma, although corresponding data for humans are not available.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies telithromycin as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Pregnancy. Reproductive toxicity, but not teratogenicity, has been seen in *animals*; the potential risk for humans is unknown.

Interactions

Telithromycin is an inhibitor of the cytochrome P450 isoenzymes CYP3A4 and CYP2D6. Although there have been few clinical reports, drug interactions with telithromycin may be expected to be similar to those seen with erythromycin (see p. 294.2). In particular, caution is required when telithromycin is given with drugs that may prolong the QT interval. Use of telithromycin with cisapride, ergot alkaloid derivatives, pimozide, astemizole, or terfenadine is usually contra-indicated. Caution is usually necessary with benzodiazepines such as alprazolam, midazolam, and triazolam, and with metoprolol. Telithromycin should not be given with drugs that induce the cytochrome P450 isoenzyme CYP3A4, such as rifampicin, phenytoin, carbamazepine, or St John's wort. Telithromycin increases plasma concentrations of some statins and hence the risk of myopathy; it should not be given with atorvastatin, lovastatin, or simvastatin.

Antimicrobial Action

Telithromycin is a ketolide antibacterial with a bactericidal action and is highly active against certain Gram-positive bacteria, including multidrug-resistant strains of *Streptococcus pneumoniae*. Some strains of *Streptococcus pyogenes* and of *Staphylococcus aureus* are also sensitive.

Telithromycin also shows good activity against the Gram-negative organisms *Haemophilus influenzae* and *Moraxella catarrhalis* (*Branhamella catarrhalis*). Activity against *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* (*Chlamydia pneumoniae*) is comparable with macrolides, and it shows greater activity than erythromycin and roxithromycin against *Legionella* spp. *Mycobacterium* spp. are reported to be moderately susceptible.

Enterobacteriaceae, *Pseudomonas* spp., and *Acinetobacter* spp. are not susceptible.

References.

1. Hammerschlag MR, *et al.* Activity of telithromycin, a new ketolide antibacterial, against atypical and intracellular respiratory tract pathogens. *J Antimicrob Chemother* 2001; **48** (suppl T1): 25–31.
2. Felmingham D, *et al.* Activity of the ketolide antibacterial telithromycin against typical community-acquired respiratory pathogens. *J Antimicrob Chemother* 2001; **48** (suppl T1): 33–42.
3. Felmingham D, *et al.* Antibacterial resistance among children with community-acquired respiratory tract infections (PROTEKT 1999-2000). *J Infect* 2004; **48**: 39–55.
4. Drago L, *et al.* Selection of resistance of telithromycin against Haemophilus influenzae, Moraxella catarrhalis and streptococci in comparison with macrolides. *J Antimicrob Chemother* 2004; **54**: 542–5.
5. Farrell DJ, Felmingham D. Activities of telithromycin against 13,876 Streptococcus pneumoniae isolates collected between 1999 and 200 . *Antimicrob Agents Chemother* 2004; **48**: 1882–4.

Pharmacokinetics

Telithromycin is rapidly absorbed after an oral dose, with bioavailability of 57%. Peak plasma concentrations of about 2 micrograms/mL occur about 1 to 3 hours after an 800-mg dose. Food does not affect the absorption of telithromycin.

Telithromycin is widely distributed in body fluids and tissues, including those of the respiratory tract, and plasma protein binding is 60 to 70%. Concentrations in target tissues are reported to be higher than plasma concentrations, suggesting the drug may remain effective when the plasma concentration has fallen below the MIC.

About two-thirds of a dose is metabolised in the liver to inactive metabolites and the remaining third is eliminated unchanged in the urine and faeces. Metabolism is mediated both by cytochrome P450 isoenzymes (mainly CYP3A4) and non-cytochrome P450 enzymes. The pharmacokinetics of telithromycin are triphasic with a biphasic elimination phase; the elimination half-life is 2 to 3 hours and the terminal half-life about 10 hours.

Distribution into milk has been found in *animal* studies.

References.

1. Muller-Serieys C, *et al.* Tissue kinetics of telithromycin, the first ketolide antibacterial. *J Antimicrob Chemother* 2004; **53**: 149–57.
2. Shi J, *et al.* Clinical pharmacokinetics of telithromycin, the first ketolide antibacterial. *Clin Pharmacokinet* 2005; **44**: 915–34.
3. Ong CT, *et al.* Intrapulmonary concentrations of telithromycin: clinical implications for respiratory tract infections due to Streptococcus pneumoniae. *Chemotherapy* 2005; **51**: 339–46.
4. Zeitlinger M, *et al.* Ketolides—the modern relatives of macrolides: the pharmacokinetic perspective. *Clin Pharmacokinet* 2009; **48**: 23–38.
5. Traunmüller F, *et al.* Multiple-dose pharmacokinetics of telithromycin in peripheral soft tissues. *Int J Antimicrob Agents* 2009; **34**: 72–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Ketek†; *Belg.*: Ketek; *Braz.*: Ketek; *Canad.*: Ketek†; *Cz.*: Ketek; *Fin.*: Ketek; *Fr.*: Ketek; *Ger.*: Ketek; *Gr.*: Ketek; *Irl.*: Ketek; *Ital.*: Ketek; *Jpn*: Ketek†; *Mex.*: Ketek; *Neth.*: Ketek; *Pol.*: Ketek; *Port.*: Ketek; *S. Afr.*: Ketek; *Spain*: Ketek; *Swed.*: Ketek; *Thai.*: Ketek†; *Turk.*: Ketek; *UK*: Ketek; *USA*: Ketek; *Venez.*: Ketek.

Temocillin *(BAN, USAN, rINN)*

Temocilina; Témocilline; Temocillinum; Темоциллин.
(6*S*)-6-[2-carboxy-2-(3-thienyl)acetamido]-6-methoxypenicillanic acid.
$C_{16}H_{18}N_2O_7S_2$=414.4
CAS — 66148-78-5.
ATC — J01CA17.
ATC Vet — QJ01CA17.
UNII — 03QB156W6I.

Temocillin Sodium *(BANM, rINNM)*

BRL-17421; Natrii Temocillinum; Temocilina sódica; Temocillin Disodium; Témocilline Sodique; Натрий Темоциллин.
The disodium salt of (6*S*)-6-[2-carboxy-2-(3-thienyl)acetamido]-6-methoxypenicillanic acid.
$C_{16}H_{16}N_2Na_2O_7S_2$=458.4
CAS — 61545-06-0.
ATC — J01CA17.
ATC Vet — QJ01CA17.
UNII — 96IIP39ODH.

Profile

Temocillin is a semisynthetic penicillin that is highly resistant to many beta-lactamases and is used for the treatment of infections caused by beta-lactamase-producing strains of Gram-negative aerobic bacteria, including those resistant to third-generation cephalosporins.

It is given as the sodium salt and doses are expressed in terms of the base; 1.11 g of temocillin sodium is equivalent to about 1 g of temocillin. It is given by intramuscular injection, slow intravenous injection over 3 to 4 minutes, or by intravenous infusion over 30 to 40 minutes.

The usual dose is 1 g every 12 hours; this dose may be doubled in severe infections but should be given intravenously.

For doses used in children, and in renal impairment, see p. 375.1.

A brief review[1] suggesting that for Gram-negative infections where co-infection with Gram-positive organisms, anaerobes, or *Pseudomonas* spp. is unlikely, temocillin

may have a useful niche role in sparing the use of more broadly effective drugs such as the carbapenems.

1. Livermore DM, Tulkens PM. Temocillin revived. *J Antimicrob Chemother* 2009; 63: 243–5.

Administration in children. Temocillin may be used in children for the treatment of infections caused by susceptible organisms, and may be given by intramuscular injection, slow intravenous injection over 3 to 4 minutes, or by intravenous infusion over 30 to 40 minutes.

The recommended dose for children is 25 mg/kg daily in 2 divided doses; in severe infections, 50 mg/kg daily in 2 divided doses may be given intravenously.

Administration in renal impairment. Parenteral doses of temocillin should be modified in patients with moderate to severe renal impairment. In adults, the following parenteral doses are recommended based on creatinine clearance (CC):

- CC 30 to 60 mL/min: 1 g every 12 hours
- CC 10 to 30 mL/min: 1 g every 24 hours
- CC less than 10 mL/min: 1 g every 48 hours or 500 mg every 24 hours
- haemodialysis patients: 1 g every 48 hours; the dose should normally be given at the end of the dialysis run. In patients who are dialysed daily, 500 mg should be given after each dialysis session

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Negaban; *UK*: Negaban.

Terizidone *(rINN)*

B-2360; Terizidona; Térizidone; Terizidonum; Теризидон.

4,4′-[*p*-Phenylenebis(methyleneamino)]bis(isoxazolidin-3-one).

$C_{14}H_{14}N_4O_4$=302.3

CAS — 25683-71-0.

ATC — J04AK03.

ATC Vet — QJ04AK03.

UNII — 1199LEX5N8.

Profile

Terizidone has been used in the treatment of infections of the urinary tract and of pulmonary and extrapulmonary tuberculosis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Terizidex; *Rus.*: Rezonisate (Резонизат); Rezonisate Plus (Резонизат Плюс); *S.Afr.*: Terivalidin.

Tetracycline *(BAN, rINN)*

Tetraciclina; Tetraciklin; Tetraciklinas; Tetracyclin; Tétracycline; Tetracyclinum; Tetracyklin; Tetracyklina; Tetrasiklin; Tetrasykliini; Тетрациклин.

A variably hydrated form of (4*S*,4a*S*,5a*S*,6*S*,12a*S*)-4-Dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxonaphthacene-2-carboxamide.

$C_{22}H_{24}N_2O_8$=444.4

CAS — 60-54-8 (anhydrous tetracycline); 6416-04-2 (tetracycline trihydrate).

ATC — A01AB13; D06AA04; J01AA07; S01AA09; S02AA08; S03AA02.

ATC Vet — QA01AB13; QD06AA04; QG01AA90; QG51AA02; QJ01AA07; QJ51AA07; QS01AA09; QS02AA08; QS03AA02.

UNII — F8VB5M810T.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Tetracycline). A yellow crystalline powder. Very slightly soluble in water; soluble in alcohol and in methyl alcohol; sparingly soluble in acetone. It dissolves in dilute acid and alkaline solutions. A 1% suspension in water has a pH of 3.5 to 6.0. Protect from light.

USP 36: (Tetracycline). A yellow, odourless, crystalline powder. It darkens in strong sunlight. Soluble 1 in 2500 of water and 1 in 50 of alcohol; practically insoluble in chloroform and in ether; soluble in methyl alcohol; freely soluble in dilute acids and in alkali hydroxide solutions. It loses not more than 13% of its weight on drying. A 1% suspension in water has a pH of 3.0 to 7.0. The potency of tetracycline is reduced in solutions having a pH below 2 and it is rapidly destroyed in solutions of alkali hydroxides. Store in airtight containers. Protect from light.

Tetracycline Hydrochloride *(BANM, rINNM)*

Hidrocloruro de tetraciclina; Tetraciclina, hidrocloruro de; Tetraciklinhidroklorid; Tetraciklino hidrochloridas; Tétracycline, Chlorhydrate de; Tetracyclinhydrochlorid; Tetracyclini hydrochloridum; Tetracyklin hydrochlorid; Tetracyklinhydroklorid; Tetracykliny chlorowodorek; Tetrasiklin Hidroklorür; Tetrasykliinihydrokloridi; Тетрациклина гидрохлорид.

$C_{22}H_{24}N_2O_8$.HCl=480.9

CAS — 64-75-5.

ATC — A01AB13; D06AA04; J01AA07; S01AA09; S02AA08; S03AA02.

ATC Vet — QA01AB13; QD06AA04; QJ01AA07; QS01AA09; QS02AA08; QS03AA02.

UNII — P6R62377KV.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

US also includes Epitetracycline Hydrochloride.

Ph. Eur. 8: (Tetracycline Hydrochloride). A yellow crystalline powder. Soluble in water; slightly soluble in alcohol; practically insoluble in acetone. It dissolves in solutions of alkali hydroxides and carbonates. Solutions in water become turbid on standing, owing to the precipitation of tetracycline. A 1% solution in water has a pH of 1.8 to 2.8. Protect from light.

USP 36: (Tetracycline Hydrochloride). A yellow, odourless, hygroscopic, crystalline, powder. Tetracycline hydrochloride darkens in moist air when exposed to strong sunlight. Soluble 1 in 10 of water and 1 in 100 of alcohol; practically insoluble in chloroform and in ether; soluble in solutions of alkali hydroxides and carbonates, although it is rapidly destroyed by alkali hydroxide solutions. A 1% solution in water has a pH of 1.8 to 2.8. The potency of tetracycline hydrochloride is reduced in solutions having a pH below 2. Store in airtight containers. Protect from light.

Tetracycline Phosphate Complex *(BAN)*

Tetraciclina, complejo con fosfato.

CAS — 1336-20-5.

ATC — A01AB13; D06AA04; J01AA07; S01AA09; S02AA08; S03AA02.

ATC Vet — QA01AB13; QD06AA04; QJ01AA07; QS01AA09; QS02AA08; QS03AA02.

UNII — 6B7BKSH338.

Description. A complex of sodium metaphosphate and tetracycline.

Incompatibility. Tetracycline injections have an acid pH and incompatibility may reasonably be expected with alkaline preparations, or with drugs unstable at low pH. Tetracyclines can chelate metal cations to produce insoluble complexes, and incompatibility has been reported with solutions containing metallic salts. Reports of incompatibility are not always consistent, and other factors, such as the strength and composition of the vehicles used, may play a role.

Stability. Tetracycline undergoes reversible epimerisation in *solution* to the less active 4-epitetracycline;[1,2] the degree of epimerisation is dependent on pH, and is greatest at a pH of about 3, with conversion of some 55% to the epimer at equilibrium.[1] The rate at which epimerisation occurs is affected by a variety of factors including temperature and the presence of phosphate or citrate ions.[1] Intravenous solutions of tetracycline hydrochloride with a pH between 3 and 5 have been reported to be stable for 6 hours, but to lose about 8 to 12% of their potency in 24 hours at room temperature.[3] Although epimerisation is the dominant degradation reaction at pH 2.5 to 5, outside this pH range other reactions become important, with the pH-dependent formation of anhydrotetracycline at very low pH, and oxidation to isotetracycline at alkaline pH.[4]

In contrast to the case in solution, *suspensions* of tetracycline hydrochloride with a pH between 4 and 7 are stable for at least 3 months.[2] This is because epimerisation, which continues until an equilibrium is achieved between tetracycline and its epimer, depends only on the portion in solution, and the solubility of tetracycline at this pH range is low.

The stability of *solid* dosage forms and powder at various temperatures and humidities has also been studied; tetracycline hydrochloride was fairly stable when stored at 37 degrees and 66% humidity for 2 months, with about a 10% loss of potency, but the phosphate was rather less stable, with potency losses of 25 to 40% and the formation of potentially toxic degradation products.[5] Comparison with other tetracyclines indicated that tetracycline was less stable than demeclocycline and more stable than rolitetracycline.[5] However, although this study, and an accelerated stability study carried out by WHO[6] indicate that there is a risk of deterioration of solid dose tetracycline, in practice a study of its stability during shipment to the tropics found that deterioration was not a problem.[7]

1. Remmers EG, *et al.* Some observations on the kinetics of the C4 epimerization of tetracycline. *J Pharm Sci* 1963; 52: 752–6.
2. Grobben-Verpoorten A, *et al.* Determination of the stability of tetracycline suspensions by high performance liquid chromatography. *Pharm Weekbl (Sci)* 1985; 7: 104–8.
3. Parker EA. Solution additive chemical incompatibility study. *Am J Hosp Pharm* 1967; 24: 434–9.
4. Vej-Hansen B, Bundgaard H. Kinetic study of factors affecting the stability of tetracycline in aqueous solution. *Arch Pharm Chemi (Sci)* 1978; 6: 201–14.
5. Walton VC, *et al.* Anhydrotetracycline and 4-epianhydrotetracycline in market tetracyclines and aged tetracycline products. *J Pharm Sci* 1970; 59: 1160–4.
6. WHO. WHO expert committee on specifications for pharmaceutical preparations: thirty-first report. *WHO Tech Rep Ser 790* 1990. Also available at: http://libdoc.who.int/trs/WHO_TRS_790.pdf (accessed 18/05/07)
7. Hogerzeil HV, *et al.* Stability of essential drugs during shipment to the tropics. *BMJ* 1992; 304: 210–14.

Uses and Administration

The tetracyclines are bacteriostatic antibacterials with a wide spectrum of activity. They have been used in the treatment of many infections but emergence of bacterial resistance and the development of other antibacterials have limited their value. They are the drugs of choice or effective alternatives in treatment of rickettsial and coxiella infections (including Q fever, spotted fevers, and typhus), some chlamydial infections (including psittacosis, trachoma, lymphogranuloma venereum, and non-gonococcal urethritis), *Chlamydophila pneumonia* and mycoplasmal infections (especially pneumonia caused by *Mycoplasma pneumoniae*), as well as some other bacterial infections (such as brucellosis, cat-scratch disease, ehrlichiosis, Lyme disease, melioidosis, plague, relapsing fever, and trench fever). They are used as part of regimens for pelvic inflammatory disease and for gastritis and peptic ulcer disease caused by *Helicobacter pylori*. Tetracyclines are used as an alternative to other drugs in the treatment of actinomycosis, infected animal bites, chronic bronchitis, gas gangrene, gastro-enteritis (due to *Campylobacter* or *Yersinia enterocolitica*), granuloma inguinale, leptospirosis, syphilis, tularaemia, Whipples disease, *Vibrio* and *Aeromonas* spp. infections (including water-associated cellulitis), and infections due to *Mycobacterium marinum*. A tetracycline is often used with fluid and electrolyte replacement in the treatment of cholera. They may be used for mouth infections, especially in destructive forms of periodontal disease. There are now relatively few areas where tetracycline-resistant gonococci are uncommon, which limits the value of tetracyclines in gonorrhoea, but they are often given with antigonorrhoeal therapy to treat concomitant chlamydial infections, and they retain some value in the prophylaxis of neonatal gonococcal conjunctivitis by topical application. Tetracyclines are also recommended for the treatment and prophylaxis of anthrax.

For details of all these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Tetracyclines are also used in the oral treatment of acne and rosacea (see Skin Disorders, p. 376.3).

Tetracyclines have antiprotozoal actions and tetracycline or doxycycline may be given with quinine in the management of falciparum malaria resistant to chloroquine (p. 376.1). Tetracyclines are the usual treatment for balantidiasis (p. 922.3).

Tetracycline has been used in the management of malabsorption syndromes such as tropical sprue.

Tetracycline has been instilled as a sclerosant solution for pleurodesis and in the management of malignant effusions (p. 700.1).

Administration and dosage. In the treatment of systemic infections the tetracyclines are usually given orally. They should be taken with plenty of fluid while sitting or standing, and well before going to bed, to avoid the risk of oesophageal ulceration. In severe acute infections they have been given by slow intravenous infusion or, rarely, by intramuscular injection; parenteral therapy should be substituted by oral dosage as soon as practicable.

Doses of tetracycline base and tetracycline hydrochloride are expressed in terms of the hydrochloride. Tetracycline (anhydrous) 231 mg is equivalent to about 250 mg of tetracycline hydrochloride. The usual adult oral dosage of tetracycline hydrochloride is 250 or 500 mg every 6 hours, preferably 1 hour before or 2 hours after meals. Higher doses, up to 4 g daily, have occasionally been given to adults with severe infection, but increase the risk of adverse effects. It is also sometimes given orally with other tetracycline derivatives.

Tetracycline hydrochloride has been given by slow intravenous infusion or by intramuscular injection in severe infections. Intravenous products of tetracycline itself are no longer marketed in many countries because of the risk of hepatotoxicity, although other intravenous tetracyclines may be available. As intramuscular injections were painful,

procaine hydrochloride was usually included in the solution.

For details of doses in children and adolescents, see p. 376.1.

Care is required if tetracyclines are given to the elderly. They should be avoided if possible in renal impairment (with the exception of doxycycline and minocycline) and doses reduced if they must be used. For dosage recommendations in patients with hepatic impairment, see p. 376.1.

Other routes. Although topical application carries the risk of sensitisation and may contribute to the development of resistance, tetracycline hydrochloride has been used as a 3% ointment; a 0.2% solution has been used in acne but systemic treatment appears to produce better results. A 1% eye ointment or eye drops have been used in the treatment of ocular infections due to susceptible organisms. For the treatment of pleural effusions, 500 mg of tetracycline hydrochloride has been dissolved in 30 to 50 mL of sodium chloride 0.9% and instilled into the pleural space. For periodontal disease, fibres that release tetracycline have been inserted into the periodontal pocket.

Reviews.

1. Chopra L *et al.* Tetracyclines, molecular and clinical aspects. *J Antimicrob Chemother* 1992; 29: 245–77.
2. Smilack JD. The tetracyclines. *Mayo Clin Proc* 1999; 74: 727–9.
3. Voils SA, *et al.* Use of macrolides and tetracyclines for chronic inflammatory diseases. *Ann Pharmacother* 2005; 39: 86–94.
4. Shlaes DM. An update on tetracyclines. *Curr Opin Investig Drugs* 2006; 7: 167–71.
5. Sapadin AN, Fleischmajer R. Tetracyclines: nonantibiotic properties and their clinical implications. *J Am Acad Dermatol* 2006; 54: 258–65.
6. Webster G, Del Rosso JQ. Anti-inflammatory activity of tetracyclines. *Dermatol Clin* 2007; 25: 133–5.
7. Orsucci D, *et al.* Neuroprotective effects of tetracyclines: molecular targets, animal models and human disease. *CNS Neurol Disord Drug Targets* 2009; 8: 222–31.
8. Griffin MO, *et al.* Tetracyclines: a pleitropic family of compounds with promising therapeutic properties: Review of the literature. *Am J Physiol Cell Physiol* 2010; 299: C539–C548.
9. Monk E, *et al.* Clinical applications of non-antimicrobial tetracyclines in dermatology. *Pharmacol Res* 2011; 63: 130–45.
10. Richards C, *et al.* Antimicrobial and non-antimicrobial tetracyclines in human cancer trials. *Pharmacol Res* 2011; 63: 151–6.

Administration in children. In children, the effects on teeth should be considered and tetracyclines only used when absolutely essential. In the UK, tetracycline is licensed for use in children aged 12 years and over; the usual adult dose (see Uses and Administration, p. 373.3), to a maximum of 2 g daily, may be given orally. However, in the USA, it may be given to those over 8 years old in usual oral doses of 25 to 50 mg/kg daily in 4 divided doses.

Administration in hepatic impairment. Some licensed product information has stated that the oral dosage of tetracycline should not exceed 1 g daily in patients with known liver disease.

Asthma. The observed anti-inflammatory effects of tetracyclines have led to interest in their use for treatment of asthma or other allergic disorders. In a preliminary, randomised, placebo-controlled study of 17 adult asthmatics, the addition of minocycline 150 mg orally twice daily for 8 weeks to usual asthma therapy had a significant corticosteroid-sparing effect, leading to a 30% reduction in mean daily prednisone dose. Minocycline treatment also led to significant improvement in asthma symptoms brought on by environmental triggers.

1. Daoud A, *et al.* Minocycline treatment results in reduced oral steroid requirements in adult asthma. *Allergy Asthma Proc* 2008; 29: 286–94.

Diabetic complications. The *BNF* notes that diabetic diarrhoea in patients with autonomic neuropathy can often be managed with 2 or 3 doses of oral tetracycline 250 mg.

Malaria. Tetracyclines (particularly doxycycline) may be given for the treatment and prophylaxis of falciparum malaria and the non-falciparum malarias (usually caused by *Plasmodium vivax* or, less commonly, by *P. ovale* or *P. malariae*) (p. 644.1). The action of tetracyclines is relatively slow and they should never be used alone to treat malaria. They are active against both blood and tissue forms of the parasite, and high cure rates have been obtained when given with other antimalarials.[1]

For the treatment of falciparum malaria a usual oral regimen is a 3- or 7-day course of quinine given with or followed by 7 days of a tetracycline. The dose of tetracycline itself usually recommended is 250 mg four times daily, although 500 mg twice daily may be more practical. The dose of doxycycline given orally with or after quinine is 100 mg twice daily for at least 7 days. If the patient is too ill for oral medication quinine should be given parenterally until oral therapy can be begun to complete the course; US guidelines also suggest that doxycycline (100 mg every 12 hours) may be given intravenously until the patient can take oral therapy. A 2-week course of primaquine should be added when treating a non-falciparum malaria to kill hypnozoites. Although tetracycline therapy is normally contra-indicated in pregnant women and children, it may have to be given if the risk of withholding the drug is judged to outweigh the risk to developing teeth and bones.

Chemoprophylaxis with doxycycline has been shown to be effective against *Plasmodium falciparum* and *P. vivax* and short-term prophylaxis with oral doxycycline 100 mg daily is an option in areas of high risk where other drugs are likely to be ineffective. Chemoprophylaxis should be started 1 to 2 days before exposure to malaria and should continue throughout exposure and for at least 4 weeks after leaving the malarious area. Although long-term prophylaxis with doxycycline has not been specifically studied, use for up to 2 years is thought to be safe.

1. Tan KR, *et al.* Doxycycline for malaria chemoprophylaxis and treatment: report from the CDC Expert Meeting on Malaria Chemoprophylaxis. *Am J Trop Med Hyg* 2011; 84: 517–31.

Mouth ulceration. Tetracyclines may be used as mouthwashes in recurrent aphthous stomatitis (p. 1814.2) and reportedly reduce ulcer pain and duration,[1,2] but their potential for adverse effects if swallowed must be borne in mind, and their acidity can damage tooth enamel if poorly formulated. The results from a small crossover study[3] showed that 0.2% minocycline oral rinses (used 4 times daily for up to 10 days or until lesions and symptoms resolved) significantly reduced the severity and duration of pain compared with 0.25% tetracycline rinses for management of recurrent aphthous stomatitis. Benefit has also been reported with the use of a dental paste containing 3% chlortetracycline.[2] Topical application of a tetracycline has been tried for oral ulceration associated with Behçet's syndrome (p. 1601.1).

1. Henricsson V, Axéll T. Treatment of recurrent aphthous ulcers with Aureomycin mouth rinse or Zendium dentifrice. *Acta Odontol Scand* 1985; 43: 47–52.
2. Altenburg A, Zouboulis CC. Current concepts in the treatment of recurrent aphthous stomatitis. *Skin Therapy Lett* 2008; 13: 1–4.
3. Gorsky M, *et al.* Topical minocycline and tetracycline rinses in treatment of recurrent aphthous stomatitis: a randomized cross-over study. *Dermatol Online J* 2007; 13: 1. Available at: http://dermatology.cdlib.org/132/original/tcn/gorsky.html (accessed 09/02/11)

Musculoskeletal and joint disorders. Tetracyclines, usually minocycline, are among the wide range of drugs tried in rheumatoid arthritis (p. 13.2). Studies[1,2] indicate that minocycline can produce modest beneficial effects in patients with advanced disease, but the clinical significance of these improvements has been questioned.[3] Greater symptomatic improvements have been obtained with minocycline when it is used in patients with early rheumatoid arthritis;[4,5] continued treatment with minocycline may also reduce the need for disease-modifying antirheumatic drugs (DMARDs).[6] A systematic review,[7] which included these and some other studies, reported that the use of tetracyclines (doxycycline, minocycline, or tetracycline) for 3 months or longer was associated with a reduction in disease activity but not in joint damage when compared with placebo or a DMARD (hydroxychloroquine or methotrexate); the authors also noted that patients with early onset disease responded better to tetracyclines. There has been speculation over the role of infection as a cause of rheumatoid arthritis.[5,8] A later study[9] in patients with early seropositive disease found that initial therapy with methotrexate plus doxycycline was superior to methotrexate alone. It was also noted that therapeutic responses to doxycycline 100 mg twice daily and 20 mg twice daily were similar, suggesting that its anti-inflammatory effects were more important; however, further studies are needed.

Although there has been little convincing clinical evidence that any treatment can slow the progression of osteoarthritis (p. 12.3), a placebo-controlled study involving 431 women with unilateral osteoarthritis of the knee found that treatment with doxycycline 100 mg twice daily over 30 months was associated with a reduction in the rate of joint space narrowing.[10] It had no effect on the contralateral knee, and did not reduce pain scores, although these were low at baseline. A systematic review[11] did not support the use of doxycycline for the treatment of osteoarthritis of the knee or hip, and concluded that small benefits in terms of joint space narrowing were of questionable clinical relevance and outweighed by the adverse effects of doxycycline.

The role of antibacterials is also uncertain in reactive arthritis (see Bone and Joint Infections, p. 175.1), although long-term treatment with a tetracycline in addition to an NSAID has been reported to shorten the duration of reactive arthritis resulting from *Chlamydia trachomatis* infection.[12] However, another small study[13] found that treatment with a 4-month course of doxycycline 100 mg twice daily was not superior to a 10-day course.

1. Kloppenburg M, *et al.* Minocycline in active rheumatoid arthritis. *Arthritis Rheum* 1994; 37: 629–36.
2. Tilley BC, *et al.* Minocycline in rheumatoid arthritis: a 48-week, double-blind, placebo-controlled trial. *Ann Intern Med* 1995; 122: 81–9.
3. McKendry RJR. Is rheumatoid arthritis caused by an infection? *Lancet* 1995; 345: 1319–20.
4. O'Dell JR, *et al.* Treatment of early rheumatoid arthritis with minocycline or placebo: results of a randomized double-blind, placebo-controlled trial. *Arthritis Rheum* 1997; 40: 842–8.
5. O'Dell JR, *et al.* Treatment of early seropositive rheumatoid arthritis: a two-year, double-blind comparison of minocycline and hydroxychloroquine. *Arthritis Rheum* 2001; 44: 2235–41.
6. O'Dell JR, *et al.* Treatment of early seropositive rheumatoid arthritis with minocycline: four-year follow-up of a double-blind, placebo-controlled trial. *Arthritis Rheum* 1999; 42: 1691–5.
7. Stone M, *et al.* Should tetracycline treatment be used more extensively for rheumatoid arthritis? Metaanalysis demonstrates clinical benefit with reduction in disease activity. *J Rheumatol* 2003; 30: 2112–22.
8. O'Dell JR. Is there a role for antibiotics in the treatment of patients with rheumatoid arthritis? *Drugs* 1999; 57: 279–82.
9. O'Dell JR, *et al.* Treatment of early seropositive rheumatoid arthritis: doxycycline plus methotrexate versus methotrexate alone. *Arthritis Rheum* 2006; 54: 621–7.
10. Brandt KD, *et al.* Effects of doxycycline on progression of osteoarthritis: results of a randomized, placebo-controlled, double-blind trial. *Arthritis Rheum* 2005; 52: 2015–25.
11. Nüesch E, *et al.* Doxycycline for osteoarthritis of the knee or hip. Available in The Cochrane Database of Systematic Reviews; Issue 4 Chichester: John Wiley; 2009 (accessed 02/06/10).
12. Lauhio A. Reactive arthritis: consider combination treatment. *BMJ* 1994 308: 1302–3.
13. Putschky N, *et al.* Comparing 10-day and 4-month doxycycline course for treatment of Chlamydia trachomatis-reactive arthritis: a prospective double-blind trial. *Ann Rheum Dis* 2006; 65: 1521–4.

Peptic ulcer disease. Tetracycline has been used as part of triple therapy to eradicate *Helicobacter pylori* in patients with peptic ulcer disease (p. 1816.2). The usual dose of tetracycline in these regimens has been 500 mg four times daily for 2 weeks.

Periodontal disease. For the use of doxycycline in subantimicrobial doses as an adjunct in the treatment of periodontal disease, see Administration, Subantimicrobial Doses, p. 288.3.

Skin disorders. *ACNE.* Tetracyclines may be used topically or orally in the treatment of acne (p. 1682.2). In acne, antibacterials appear to act by suppressing the growth of *Propionibacterium acnes*, but also by suppressing inflammation. Topical tetracycline is used for mild inflammatory acne and as an adjunct to systemic treatment in more severe forms. Tetracyclines, given orally, are the drugs of choice for moderate acne and may be considered, in high doses, for severe acne. Licensed doses in the UK are:

- doxycycline 50 mg daily (the *BNF* advocates 100 mg daily)
- lymecycline equivalent to 300 mg of tetracycline daily
- minocycline 100 mg daily
- oxytetracycline 250 to 500 mg daily (the *BNF* advocates 500 mg twice daily)
- tetracycline 1 g daily

Treatment should be changed to another antibacterial if there has been no improvement in the first 3 months. Maximum improvement is said to occur after 4 to 6 months, but treatment may need to continue for 2 or more years.

Minocycline has been reported to have superior antibacterial activity against *P. acnes* and a reduced incidence of resistance compared with tetracycline;[1] it has also been reported to be more effective than erythromycin against oxytetracycline-resistant acne.[2] However, a later randomised study[3] found minocycline to be comparable in efficacy to oxytetracycline, topical erythromycin with benzoyl peroxide, and topical benzoyl peroxide alone in the treatment of mild to moderate acne; in another randomised study[4] lymecycline also showed comparable efficacy and safety. Doxycycline also appears to have similar efficacy to minocycline.[5] However, minocycline can cause skin pigmentation and may be associated rarely with immunologically-mediated reactions,[5,6] and some[5] therefore favour the use of doxycycline as the first-line systemic antibacterial in acne. An enteric-coated formulation may reduce adverse effects and improve compliance. For the use of doxycycline in subantimicrobial doses in patients with acne, see Administration, Subantimicrobial Doses, p. 288.3. Although the usual dose of minocycline is 100 mg daily in one or two divided doses some patients may need up to 200 mg daily.[7]

1. Eady EA, *et al.* Superior antibacterial action and reduced incidence of bacterial resistance in minocycline compared to tetracycline-treated acne patients. *Br J Dermatol* 1990; 122: 233–44.
2. Knaggs HE, *et al.* The role of oral minocycline and erythromycin in tetracycline therapy-resistant acne—a retrospective study and a review. *J Dermatol Treat* 1993; 4: 53–6.
3. Ozolins M, *et al.* Comparison of five antimicrobial regimens for treatment of mild to moderate inflammatory facial acne vulgaris in the community: randomised controlled trial. *Lancet* 2004; 364: 2188–95.
4. Bossuyt L, *et al.* Lymecycline in the treatment of acne: an efficacious, safe and cost-effective alternative to minocycline. *Eur J Dermatol* 2003; 13: 130–35.
5. Kircik LH. Doxycycline and minocycline for the management of acne: a review of efficacy and safety with emphasis on clinical implications. *J Drugs Dermatol* 2010; 9: 1407–11.
6. Ferner RE, Moss C. Minocycline for acne. *BMJ* 1996; 312: 138.
7. Goulden V, *et al.* Safety of long-term high-dose minocycline in the treatment of acne. *Br J Dermatol* 1996; 134: 693–5.

PEMPHIGUS AND PEMPHIGOID. Corticosteroids are generally given to control the blistering in pemphigus and pemphigoid (p. 1687.1), although there have been reports[1-8] suggesting that a tetracycline (often minocycline) may be of

value in controlling the lesions associated with various types of pemphigus and pemphigoid.

1. Sawai T, *et al.* Pemphigus vegetans with oesophageal involvement: successful treatment with minocycline and nicotinamide. *Br J Dermatol* 1995; 132: 668–70.
2. Poskitt L, Wojnarowska F. Minimizing cicatricial pemphigoid orodynia with minocycline. *Br J Dermatol* 1995; 132: 784–9.
3. Kolbach DN, *et al.* Bullous pemphigoid successfully controlled by tetracycline and nicotinamide. *Br J Dermatol* 1995; 133: 88–90.
4. Loo WJ, *et al.* Minocycline as a therapeutic option in bullous pemphigoid. *Clin Exp Dermatol* 2001; 26: 376–9.
5. Amato L, *et al.* Successful treatment with doxycycline and nicotinamide of two cases of persistent pemphigoid gestationis. *J Dermatol Treat* 2002; 13: 143–6.
6. Assmann T, *et al.* Therapieresistenter pemphigus vulgaris: Kombinationstherapie mit Methylprednisolon und Doxycyclin. *Hautarzt* 2003; 54: 979–81.
7. Kakurai M, *et al.* Localized pemphigoid (pretibial type) with IgG antibody to BP180 NC16a domain successfully treated with minocycline and topical corticosteroid. *Clin Exp Dermatol* 2007; 32: 759–61.
8. Carrozzo M, *et al.* Minocycline in combination with mycophenolate mofetil in oral mucous membrane pemphigoid. *Eur J Dermatol* 2008; 18: 198–200.

ROSACEA. Tetracyclines are commonly used[1] in the treatment of rosacea (p. 1688.3). Long-term treatment is usually necessary.

Tetracycline and doxycycline have also been shown to improve ocular manifestations of rosacea.[2] However, a review[3] of the literature concluded that the treatment effect and optimal dose and duration of these 2 drugs have yet to be established; oxytetracycline was found to be of moderate benefit.

For the use of doxycycline in subantimicrobial doses in patients with rosacea, see p. 288.3.

1. Alikhan A, *et al.* The role of tetracyclines in rosacea. *Am J Clin Dermatol* 2010; 11: 79–87.
2. Fruchi-Pery J, *et al.* Efficacy of doxycycline and tetracycline in ocular rosacea. *Am J Ophthalmol* 1993; 116: 88–92.
3. Stone DU, Chodosh J. Oral tetracyclines for ocular rosacea: an evidence-based review of the literature. *Cornea* 2004; 23: 106–9.

Adverse Effects

The adverse effects of tetracycline are common to all tetracyclines. Gastrointestinal effects including nausea, vomiting, and diarrhoea are common especially with high doses and most are attributed to irritation of the mucosa. Oesophageal ulceration has been reported with doxycycline, minocycline, and tetracycline, particularly after ingestion of capsules or tablets with insufficient water at bedtime. Other effects that have been reported include glossitis, stomatitis, and dysphagia.

Oral candidiasis, vulvovaginitis, and pruritus ani occur, mainly due to overgrowth with *Candida albicans*, and there may be overgrowth of resistant coliform organisms, such as *Pseudomonas* spp. and *Proteus* spp., causing diarrhoea. More seriously, enterocolitis due to superinfection with resistant staphylococci and pseudomembranous colitis due to *Clostridium difficile* have occasionally been reported. It has been suggested that disturbances in the intestinal flora are more common with tetracycline than with better absorbed derivatives such as doxycycline.

Renal dysfunction has been reported with tetracyclines, particularly exacerbation of dysfunction in those with pre-existing renal impairment. Usual therapeutic doses given to patients with renal impairment increase the severity of uraemia with increased excretion of nitrogen and loss of sodium, accompanied by acidosis and hyperphosphataemia, and may lead to excessive systemic accumulation of the tetracycline and possible liver toxicity. These effects are related to the dose and the severity of renal impairment and are probably due to the anti-anabolic effects of the tetracycline. Acute renal failure and interstitial nephritis have occurred rarely. Dialysis and renal transplantation have been required for tetracycline-induced renal failure.

Increases in liver enzyme values have been reported with tetracyclines. In some cases severe and sometimes fatal hepatotoxicity, associated with fatty changes in the liver and pancreatitis, has occurred in pregnant women and in patients with renal impairment or those given high doses (particularly intravenous) tetracycline. Intravenous products of tetracycline itself are no longer marketed in many countries because of the risk of hepatotoxicity, although other intravenous tetracyclines may be available. However, hepatotoxicity has also occurred in patients without these predisposing factors but is rarely reported in those given oral tetracycline in standard doses for up to 10 days, or in those given doxycycline.

Tetracyclines are deposited both in deciduous teeth (milk teeth; primary teeth) and in permanent teeth during their formation, causing permanent discoloration and enamel hypoplasia. The darkening effect of tetracyclines on permanent teeth appears to be related to the total dose given. Doxycycline binds less with calcium compared with other tetracyclines and these changes may occur less frequently. Tetracyclines are also deposited in calcifying areas in bone and the nails and interfere with bone growth when given in therapeutic doses to young infants or pregnant women.

Nail discoloration and onycholysis may occur. Abnormal pigmentation of the skin, conjunctiva, oral mucosa, tongue, and internal organs such as the thyroid has occurred rarely. Permanent discoloration of the cornea has been reported in infants born to mothers given tetracycline in high doses during pregnancy.

Intracranial hypertension with headache, dizziness, tinnitus, visual disturbances, and papilloedema has been reported. The use of tetracyclines in infants has been associated with a bulging fontanelle. If raised intracranial pressure occurs tetracycline treatment should be stopped. Transient myopia in patients taking tetracyclines may be due to changes in refractive power of the lens. Other adverse effects that have occasionally been reported with tetracyclines include increased muscle weakness in patients with myasthenia gravis and exacerbation of SLE.

Hypersensitivity to the tetracyclines is much less common than to the beta lactams, but hypersensitivity reactions, including rashes, fixed drug eruptions, exfoliative dermatitis, toxic epidermal necrolysis, drug fever, pericarditis, angioedema, urticaria, and asthma have been reported; anaphylaxis has occurred very rarely. Photosensitivity, which has been reported with most tetracyclines, occurs most frequently with demeclocycline and other long-acting derivatives, less with chlortetracycline, and very rarely with oxytetracycline and tetracycline; it appears to be phototoxic rather than photoallergic in nature. Paraesthesia may be an early sign of impending phototoxicity.

Local pain and irritation can occur when tetracyclines are given parenterally and thrombophlebitis may follow intravenous injections. A Jarisch-Herxheimer reaction occurs commonly in patients with relapsing fever treated with tetracyclines.

Although rare, agranulocytosis, aplastic anaemia, haemolytic anaemia, eosinophilia, neutropenia, and thrombocytopenia have been reported. Tetracyclines may produce hypoprothrombinaemia. They have also been associated with reductions in serum-vitamin B concentrations, including a case of folate deficiency and concomitant megaloblastic anaemia.

The use of tetracyclines that are out-of-date or which have deteriorated has been associated with the development of a reversible Fanconi-type syndrome characterised by polyuria and polydipsia with nausea, glycosuria, aminoaciduria, hyperphosphaturia, hypokalaemia, and hyperuricaemia with acidosis and proteinuria; these effects have been attributed to the presence of degradation products, in particular anhydroepitetracycline.

Effects on intracranial pressure. Raised intracranial pressure has been described in patients given tetracyclines.[1] Tetracycline is most commonly implicated, usually in patients being treated for acne; the syndrome has also been associated with doxycycline[2-4] and minocycline.[5,6] Presenting symptoms, such as headaches, tinnitus, visual loss, diplopia, nausea, and vomiting, usually develop from within 2 weeks to 1 year or more of starting a tetracycline. Most cases resolved when the drug was stopped although some required symptomatic treatment with diuretics (including acetazolamide), corticosteroids, and/or lumbar puncture. Nevertheless, permanently decreased visual acuity and irreversible visual-field defects have been reported.[2,7]

1. Digre KB. Not so benign intracranial hypertension. *BMJ* 2003; 326: 613–14.
2. Lochhead J, Elston JS. Doxycycline induced intracranial hypertension. *BMJ* 2003; 326: 641–2.
3. Friedman DI, *et al.* Doxycycline and intracranial hypertension. *Neurology* 2004; 62: 2297–9.
4. Roux X, *et al.* Hypertension intracrânienne bénigne secondaire à la prise de doxycycline. *Rev Med Interne* 2009; 30: 1058–60.
5. Weese-Mayer DE, *et al.* Minocycline and pseudotumor cerebri: the well-known but well-kept secret. *Pediatrics* 2001; 108: 519–20.
6. Adverse Drug Reactions Advisory Committee (ADRAC). Minocycline and not so benign intracranial hypertension. *Aust Adverse Drug React Bull* 2003; 22: 2–3. Also available at: http://www.tga.gov.au/adr/aadrb/aadrb0302.pdf (accessed 07/02/07)
7. Altinbas A, *et al.* Intracraniële hypertensie met ernstige en blijvende visusdaling en gezichtsvelduitval na gebruik van orale tetracycline. *Ned Tijdschr Geneeskd* 2005; 149: 1908–12.

Precautions

The tetracyclines are contra-indicated in patients hypersensitive to any of this group of antibacterials, since cross-sensitivity may occur.

Tetracyclines should not be used during pregnancy because of the risk of hepatotoxicity in the mother as well as the effects on the developing fetus. They should also be avoided during breast feeding and in children up to the age of 8, or according to the *BNF*, 12, years. Use in pregnancy, potentially during breast feeding, or in childhood, may result in impaired bone growth and permanent discoloration of the child's teeth.

In general the tetracyclines, with the exception of doxycycline, should be used with caution in those with renal impairment and, if they must be given, doses should be reduced. However, the *BNF* advises avoiding tetracyclines, except doxycycline and minocycline, even in mild impairment. Care should also be taken if tetracyclines are given to patients with hepatic impairment and high doses should be avoided.

Patients who may be exposed to direct sunlight should be warned of the risk of photosensitivity. Care is advisable in patients with myasthenia gravis, who may be at risk of neuromuscular blockade. Tetracyclines should be avoided in those with SLE.

Serum monitoring of tetracyclines may be helpful in patients with risk factors given prolonged therapy: it has been suggested that serum concentrations of tetracycline should not exceed 15 micrograms/mL. To avoid the risk of oesophageal ulceration oral tetracyclines (notably doxycycline, see p. 289.2) should be taken with plenty of fluid while sitting or standing, and well before going to bed.

Tetracycline may interfere with some diagnostic tests including determination of urinary catecholamines or glucose.

Breast feeding. The last available guidance from the American Academy of Pediatrics[1] stated that, after use of tetracycline by breast-feeding mothers, there was negligible absorption by the infant and that tetracycline was therefore usually compatible with breast feeding. However, licensed product information states that adverse effects including permanent tooth discoloration and enamel hypoplasia may occur in breast-fed infants and that breast feeding is contra-indicated during treatment with tetracyclines.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/05/04)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tetracycline as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 15/08/11)

Interactions

The absorption of the tetracyclines is reduced by divalent and trivalent cations such as aluminium, bismuth, calcium, iron, magnesium, and zinc, and therefore use of tetracyclines with antacids, iron preparations, some foods such as milk and dairy products, or other preparations containing such cations, whether as active ingredients or excipients, may result in subtherapeutic serum concentrations of the antibacterial. Sodium bicarbonate, colestipol, colestyramine, and kaolin-pectin are also reported to reduce tetracycline absorption, but potential reductions due to cimetidine or sucralfate are probably of little clinical significance. These interactions can be minimised by giving such products at least 1 to 3 hours apart from tetracyclines. Strontium ranelate should not be given with tetracyclines because of possible complex formation.

The nephrotoxic effects of tetracyclines may be exacerbated by diuretics, methoxyflurane, or other potentially nephrotoxic drugs. Potentially hepatotoxic drugs should be used with caution in patients receiving tetracyclines. An increased incidence of benign intracranial hypertension has been reported when retinoids and tetracyclines are given together; such use should be avoided. Tetracyclines have been reported to produce increased concentrations of lithium, digoxin, halofantrine, and theophylline (although these interactions are not strongly established); the effects of oral anticoagulants have also been increased in a few patients. There have been occasional reports of tetracyclines increasing the toxic effects of ergot alkaloids and methotrexate. Tetracyclines may decrease plasma-atovaquone concentrations. Ocular inflammation has occurred after the use of ocular preparations preserved with thiomersal in some patients receiving tetracyclines. Tetracyclines may decrease the efficacy of oral contraceptives.

Because of possible antagonism of the action of the penicillins by the mainly bacteriostatic tetracyclines it has been recommended that the two types of drug should not be used together, especially when a rapid bactericidal action is necessary.

Antimicrobial Action

The tetracyclines are mainly bacteriostatic, with a broad spectrum of antimicrobial activity including Chlamydiaceae, *Mycoplasma* spp., *Rickettsia* and *Coxiella* spp., *Mycobacteria* spp., spirochaetes, many aerobic and anaerobic Gram-positive and Gram-negative pathogenic bacteria, and some protozoa.

Mechanism of action. Tetracyclines are taken up into sensitive bacterial cells by an active transport process. Once within the cell they bind reversibly to the 30S subunit of the ribosome, preventing the binding of aminoacyl transfer RNA and inhibiting protein synthesis, and hence cell growth. Although tetracyclines also inhibit protein synthesis in mammalian cells they are not actively taken up, permitting selective activity against the infecting organism.

Spectrum of activity. The following pathogenic organisms are usually sensitive to tetracyclines:

- Gram-positive cocci including some strains of *Staphylococcus aureus* and coagulase-negative staphylococci, and streptococci including *Str. pneumoniae, Str. pyogenes* (group A), and some viridans streptococci
  Enterococci are essentially resistant
- Other Gram-positive bacteria including strains of *Actinomyces israelii, Bacillus anthracis, Erysipelothrix rhusiopathiae, Listeria monocytogenes,* and among the anaerobes some *Clostridium* spp.
  Nocardia spp. are generally much less susceptible although some are sensitive to minocycline
  Propionibacterium acnes is susceptible although the action of the tetracyclines in acne is complex and benefit may be seen even at subinhibitory concentrations
- Gram-negative cocci including *Neisseria meningitidis* (meningococci) and *N. gonorrhoeae* (gonococci), although some strains are resistant, and *Moraxella catarrhalis* (*Branhamella catarrhalis*)
  Acinetobacter spp. may be resistant to tetracycline, but most strains are susceptible to doxycycline and minocycline
- other sensitive Gram-negative aerobes including *Bartonella* spp., *Bordetella pertussis, Brucella* spp., *Klebsiella granulomatis, Campylobacter* spp., *Eikenella corrodens, Francisella tularensis, Helicobacter pylori, Haemophilus influenzae* and some strains of *H. ducreyi, Legionella* spp., *Pasteurella multocida, Streptobacillus moniliformis,* and various members of the Vibrionaceae including *Aeromonas hydrophila, Plesiomonas shigelloides, Vibrio cholerae, V. vulnificus, V. alginolyticus,* and *V. parahaemolyticus*
  although many of the Enterobacteriaceae, including *Salmonella, Shigella,* and *Yersinia* spp., are susceptible, resistant strains are common; however, doxycycline remains a treatment choice for *Y. pestis. Proteus* and *Providencia* spp. are not susceptible. *Pseudomonas aeruginosa* is not susceptible either, although some other species formerly classified as *Pseudomonas* respond, including *Burkholderia mallei, B. pseudomallei,* and *Stenotrophomonas maltophilia* (*Xanthomonas maltophilia*)
- Among the Gram-negative anaerobes *Bacteroides fragilis* may sometimes be susceptible, although wild strains are often resistant; *Fusobacterium* and *Prevotella* spp. may also be sensitive
- Other organisms usually sensitive to tetracyclines include Chlamydiaceae (such as *Chlamydia trachomatis* and *Chlamydophila pneumonia*), *Rickettsia* and *Coxiella* spp., many spirochaetes (including *Borrelia burgdorferi, Leptospira* spp., and *Treponema pallidum*), atypical mycobacteria (such as *Mycobacterium marinum, M. abscessus, M. chelonae,* and *M. fortuitum*), and mycoplasmas (including *Mycoplasma pneumoniae, M. hominis,* and *Ureaplasma urealyticum*)
- in addition the tetracyclines are active against some protozoa including *Plasmodium falciparum* and *Entamoeba histolytica*
- fungi, yeasts, and viruses are generally resistant

Resistance. Resistance to the tetracyclines is usually plasmid-mediated and transferable. It is often inducible, and appears to be associated with the ability to prevent accumulation of the antibacterial within the bacterial cell, both by decreasing active transport of the drug into the cell and by increasing tetracycline efflux.

Unsurprisingly, given the widespread use of the tetracyclines (including as components of animal feeds, although this is now banned in some countries), resistant strains of the majority of sensitive species have now been reported. Resistance has increased particularly among Enterobacteriaceae such as *Escherichia coli, Enterobacter, Salmonella,* and *Shigella* spp., especially in hospital isolates, and multiple resistance is common. Staphylococci are commonly resistant, although doxycycline or minocycline are occasionally effective against tetracycline-resistant strains. Resistance is now also common among group A streptococci, and even more so among group B streptococci; there is also resistance among pneumococci, which often show multiple drug resistance. Emergence of high-level tetracycline-resistant strains of *Neisseria gonorrhoeae* is common in some areas. Frequent resistance is also seen in clostridia, and in *Bacteroides fragilis* (among more than 60% of isolates in some countries), while increasing resistance amongst *Haemophilus ducreyi* has limited the value of tetracyclines in chancroid. Tetracycline resistance in *H. pylori* and *V. cholerae* has been reported. Rates of tetracycline resistance among *H. pylori* vary from less than 2% to about 56% depending on geographic area, while in other areas surveys of clinical isolates have reported no tetracycline-resistant strains. Resistance in *V. cholerae* fluctuates significantly under the selective pressure of antibacterial use.

Pharmacokinetics

Most tetracyclines (except minocycline and doxycycline) are incompletely absorbed from the gastrointestinal tract, about 60 to 80% of a dose of the drug usually being available. Doxycycline and minocycline are more lipophilic and are almost completely (90 to 100%) absorbed. The degree of absorption is reduced by the presence of divalent and trivalent metal ions and also certain drugs, with which tetracyclines form stable insoluble complexes, and to a variable degree by milk or food (see Interactions p. 375.3). However, the more lipophilic derivatives are little affected by food. Formulation with phosphate may enhance the absorption of tetracycline. Peak plasma concentrations of tetracycline occur about 1.5 to 4 hours after oral use. Higher concentrations occur after intravenous use; concentrations may be higher in women than in men.

Tetracyclines may be differentiated on the basis of their half-lives. Doxycycline and minocycline are long-acting; demeclocycline is intermediate-acting, while tetracycline and oxytetracycline are short-acting. The half-life of tetracyclines (except chlortetracycline) are generally determined by the rate of excretion by the kidneys. In the circulation, tetracyclines are bound to plasma proteins to varying degrees; protein binding tends to be higher for the intermediate- and long-acting drugs. Reported values range from about 20 to 40% for oxytetracycline, 20 to 65% for tetracycline, about 45% for chlortetracycline, 35 to 90% for demeclocycline, 75% for minocycline, and about 80 to 95% for methacycline and for doxycycline. Of the 'short-acting' analogues, chlortetracycline has a reported half-life of about 6 hours, oxytetracycline 9 hours, and tetracycline 8 hours, although reported values for the latter two range from about 6 to 12 hours. The 'intermediate-acting' tetracyclines, demeclocycline and methacycline, have reported half-lives of about 12 and 14 hours respectively, although various sources cite values of 7 to 17 hours, and the 'long-acting' minocycline and doxycycline have half-lives of about 16 and 18 hours, with reported values anywhere between 11 to 26 and 12 to 24 hours respectively.

The tetracyclines are widely distributed throughout the body tissues and fluids. Concentrations in CSF are relatively low, but may be raised if the meninges are inflamed, and small amounts appear in saliva and in the fluids of the eye; higher concentrations occur with more lipid-soluble derivatives such as minocycline and doxycycline. Tetracyclines appear in breast milk, but bioavailability to the infant is low because they form an insoluble complex with calcium. They diffuse across the placenta and reach concentrations in the amniotic fluid and umbilical cord plasma of 20% and 60% of the concentration in the maternal blood, respectively. Tetracyclines are retained at sites of new bone formation and recent calcification and in developing teeth.

The tetracyclines are excreted in the urine and in the faeces. Renal clearance is by glomerular filtration. Up to 60% of an intravenous dose of tetracycline, and up to 55% of an oral dose, is eliminated unchanged in the urine; tetracycline concentrations in the urine of up to 300 micrograms/mL may be reached 2 hours after a usual dose is taken and be maintained for up to 12 hours. Usually about 40 to 70% of a dose is excreted in the urine, but for chlortetracycline, doxycycline, and minocycline, rather less is eliminated by this route since chlortetracycline and minocycline undergo metabolism, and doxycycline is excreted mainly in the faeces. Urinary excretion is increased if urine is alkalinised.

The tetracyclines are excreted in the bile, where concentrations 5 to 25 times those in plasma can occur. Since there is some enterohepatic reabsorption complete elimination is slow. Considerable quantities occur in the faeces after oral doses.

Tetracyclines are slowly removed by haemodialysis, except for doxycycline which is not removed; they are not removed by peritoneal dialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Ciclotetryl; *Austral.*: Achromycin; Latycin†; Tetrex†; *Braz.*: Ambra-Sinto T; Aureciclina; Cinatrex; Inlex†; Parenzyme Tetraciclina; Prociclina†; Tetraben; Tetracaps†; Tetracilil; Tetracina; Tetraclin; Tetragel†; Tetraxil; Tetrex; *Canad.*: Apo-Tetra; Jaa Tetra; Nu-Tetra; *Fin.*: Apocyclin; Oricyclin; *Ger.*: Imex; Tefilin; *Gr.*: Cliten; Hostacyclin; Imex; Muvito; Tetrac; Tracyclin; *Hong Kong*: Akotid†; Medocycline; Tetraclin†; *India*: Achromycin; Hostacycline; Idilin; Ingacycline; Lupiterra; Resteclin; Subamycin; Tetrabact; *Indon.*: Cetacycline-P†; Conmycin; Corsatet; Dumocycline; Ikacycline; Indocycline; Licoklin; Sanlin; Spectrocycline†; Super Tetra; Tetra†; Tetrarco; Tetrin; *Irl.*: Topicycline†; *Israel*: Recycline; Tevacycline†; *Ital.*: Ambramicina; *Malaysia*: Beatacycline; Dhatracin; *Mex.*: Acromicina; Ambotetra; Bercidina; Biotricina; Dibaterr†; Educiclina; Miciclin; Neoprobal; Officlin†; Oxi-T†; Profalin CPS; Quimociclar; Senociclin; Solclin; Te-Br†; Tedizima; Terrakal†; Tetra-Zil; Tetra; Tetrapar; Tetrapres; Tetrex; Tetrim; *Philipp.*: Metrocycline; Moncycline; Traxetrine; *Rus.*: Polcortolon TC (Полькортолон ТС); *S.Afr.*: Tetrex†; *Singapore*: Apo-Tetra; Beatacycline; Biotine; Dhatracin; Tetracap; Xepacycline; *Spain*: Quimpe Antibiotico; *Thai.*: Achromycin; Bioman; Bomcin; Boramycin†; Forbiotin; Forcycline; Ganospec; Heromycin; Hydromycin; Lenocin; Pantocycline; Piccomycin; T-Buffer; TC-Mycin; TC-Ointment; Tetra Central; Tetra Prx; Tetra HCl; Tetrafilm; Tetralim; Tetraman; Tetrana; Tetrano†; Tetraphos; Tetrasin; TM Mycin; Utomycin; *Turk.*: Acnedur; Imex; Tetra; Tetralet; Tetramin; Vitasilin†; *UK*: Topicycline†; *USA*: Bristacycline; Sumycin†; Tetrex; *Venez.*: Alfaciclina.

Multi-ingredient Preparations. *Arg.*: Papasine; Solustres; *Austria*: Fluorex Plus; Mysteclin; *Braz.*: Anfoterin; Gino-Teracin; Monocetin†; Novasutin; Talsutin; Tericin AT; Tricangine; Tricociln B; Vagiklin†; *Fin.*: Helipak T; *Ger.*: Mysteclin; *Hong Kong*: Talsutin†; *Hung.*: Polcortolon TC†; *India*: Antibic-DF; Atrocin; Cortecyclin; Entakon-M; Meklin; *Indon.*: Enpicortyn; Talsutin†; *Irl.*: Pylera; *Ital.*: Alfaflor; Betafloroto; Colbiocin; Eubetal Antibiotico; Flumeciclina†; Mictasone†; Pensulvit; *Mex.*: Berciclina Enzimatica; Ditral; Pharbrix; Quimotrip†; Solfranicol; Treclorant†; Urovec†; *Philipp.*: Vagimycin†; *Pol.*: Polcortolon TC; *Rus.*: Colbiocin (Колбиоцин); Oletetrin (Олететрин); *S.Afr.*: Riostatin†; Tetrex-F†; Tritet†; Vagmycin†; *Spain*: Nasopomada†; *USA*: First Mary's Mouthwash; Helidac; Pylera.

Pharmacopoeial Preparations

BP 2014: Tetracycline Capsules; Tetracycline Tablets;
USP 36: Tetracycline Hydrochloride and Nystatin Capsules; Tetracycline Hydrochloride Capsules; Tetracycline Hydrochloride for Injection; Tetracycline Hydrochloride for Topical Solution; Tetracycline Hydrochloride Ointment; Tetracycline Hydrochloride Ophthalmic Ointment; Tetracycline Hydrochloride Ophthalmic Suspension; Tetracycline Hydrochloride Oral Suspension; Tetracycline Hydrochloride Tablets; Tetracycline Oral Suspension.

Tetroxoprim *(BAN, USAN, rINN)*

Tetroxoprima; Tétroxoprime; Tetroxoprimum; Тетроксоприм.

5-[3,5-Dimethoxy-4-(2-methoxyethoxy)benzyl]pyrimidine-2,4-diyldiamine.

$C_{16}H_{22}N_4O_4$=334.4

CAS — 53808-87-0.

UNII — 5R6712AY0K

NOTE. Compounded preparations of tetroxoprim may be represented by the following name:

- Co-tetroxazine (*BAN*)—tetroxoprim 2 parts and sulfadiazine 5 parts (see p. 277.3).

Profile

Tetroxoprim is a diaminopyrimidine antibacterial that acts as a dihydrofolate reductase inhibitor similar to, but less active than, trimethoprim (p. 383.2). It has been used, with sulfadiazine, as co-tetroxazine (p. 277.3).

Tetroxoprim embonate has been used similarly.

Thenoic Acid

Tenoic Acid; Tenoico, ácido; 2-Thiophenic Acid; Тиофенкарбоновая Кислота.

Thiophene-2-carboxylic acid.

$C_5H_4O_2S$=128.1

CAS — 527-72-0.

Profile

Thenoic acid has been given orally, rectally, or intranasally as the sodium salt, and orally as the lithium salt, in the treatment of respiratory-tract infections. The monoethanolamine salt has been used sublingually as a mucolytic.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Dolirhume; Gelutrophyl; Rhinotrophyl.

Multi-ingredient Preparations. *Fr.*: Glossithiase; Trophires Compose; Trophires†; Trophires.

Thiamphenicol *(BAN, USAN, rINN)*

CB-8053; Dextrosulphenidol; Thiamfenicol; Thiamfenikol; Thiamphénicol; Thiamphenicolum; Thiophenicol; Tiamfenicolo; Tiamfenikol; Tiamfenikoli; Tiamfenikolis; Tiamfenicol; Win-5063-2; Win-5063 (racephenicol); Тиамфеникол.

(αR,βR)-2,2-Dichloro-*N*-(β-hydroxy-α-hydroxymethyl-4-methylsulphonylphenethyl)acetamide.
$C_{12}H_{15}Cl_2NO_5S$=356.2
CAS — 15318-45-3 (thiamphenicol); 847-25-6 (racephenicol).
ATC — J01BA02.
ATC Vet — QJ01BA02; QJ51BA02.
UNII — FLQ7571NPM.

NOTE. Racephenicol, the racemic form of thiamphenicol, is *USAN*.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Ph. Eur. 8: (Thiamphenicol). A fine, white or yellowish-white, crystalline powder or crystals. Slightly soluble in water and in ethyl acetate; sparingly soluble in dehydrated alcohol and in acetone; freely soluble in acetonitrile and in dimethylformamide; very soluble in dimethylacetamide; soluble in methyl alcohol. Protect from light and moisture.

Thiamphenicol Glycinate Hydrochloride

Thiamphenicol Aminoacetate Hydrochloride; Tiamfenicolo Glicinato Cloridrato; Tianfenicol, hidrocloruro del glicinato de.
$C_{14}H_{18}Cl_2N_2O_6S,HCl$=449.7
CAS — 2393-92-2 (thiamphenicol glycinate); 2611-61-2 (thiamphenicol glycinate hydrochloride).
ATC — J01BA02.
ATC Vet — QJ01BA02.
UNII — 88VGC22BWE.

Pharmacopoeias. In *It.*

Uses and Administration

Thiamphenicol has been used similarly to chloramphenicol (p. 257.2) in the treatment of susceptible infections, including sexually transmitted diseases. The usual oral dose is 1.5 g daily in divided doses; up to 3 g daily has been given initially in severe infections. Equivalent doses, expressed in terms of thiamphenicol base, may be given by intramuscular or intravenous injection as the more water soluble glycinate hydrochloride; 1.26 g of thiamphenicol glycinate hydrochloride is equivalent to about 1 g of thiamphenicol. A maximum daily dose of 1 g has been suggested for elderly patients. Doses should also be reduced in patients with renal impairment (see p. 379.1).

For the treatment of gonorrhoea, oral doses of thiamphenicol have ranged from 2.5 g daily for 1 or 2 days through to 2.5 g on the first day followed by 2 g daily on each of 4 subsequent days. The single daily dose may be most appropriate for male patients with uncomplicated gonorrhoea.

Thiamphenicol glycinate hydrochloride may also be given by inhalation, or by endobronchial or intracavitary instillation.

Thiamphenicol has also been used as thiamphenicol glycinate acetylcysteinate and thiamphenicol sodium glycinate isophthalolate.

For details of doses in children, see p. 379.1.

Administration in children. In children, oral doses may range from 30 to 100 mg/kg daily according to age and severity of infection. Similar doses may also be given by intramuscular or intravenous injection.

Administration in renal impairment. Doses of thiamphenicol should be reduced in patients with renal impairment according to creatinine clearance (CC). For the oral preparation, suggested reduced doses are:
- CC 30 to 60 mL/minute: 500 mg twice daily
- CC 10 to 30 mL/minute: 500 mg once daily

Alternatively, for parenteral use the following doses have been suggested:
- CC 50 to 75 mL/minute: 500 mg every 12 hours
- CC 25 to 50 mL/minute: 500 mg every 18 hours
- CC 20 mL/minute: 500 mg every 24 hours
- CC 10 mL/minute: 500 mg every 48 hours

Adverse Effects and Precautions

As for Chloramphenicol, p. 258.1.

Thiamphenicol is probably more liable to cause dose-dependent reversible depression of the bone marrow than chloramphenicol, particularly in the elderly or in those with impaired renal function, but it is not usually associated with aplastic anaemia. Thiamphenicol also appears to be less likely to cause the 'grey syndrome' in neonates.

Doses of thiamphenicol should be reduced in patients with renal impairment. It is probably not necessary to reduce doses in patients with hepatic impairment.

Interactions

As for Chloramphenicol, p. 258.3.

Although thiamphenicol is not metabolised in the liver and might not be expected to be affected by drugs that induce hepatic enzymes, it is reported to inhibit hepatic microsomal enzymes and may affect the metabolism of other drugs.

Antimicrobial Action

Thiamphenicol has a broad spectrum of activity resembling that of chloramphenicol (p. 259.1). Although in general it is less active than chloramphenicol it is reported to be equally effective, and more actively bactericidal, against *Haemophilus* and *Neisseria* spp.

Cross-resistance occurs between thiamphenicol and chloramphenicol. However, some strains resistant to chloramphenicol may be susceptible to thiamphenicol.

Pharmacokinetics

Thiamphenicol is absorbed from the gastrointestinal tract after oral doses and peak serum concentrations of 3 to 6 micrograms/mL occur about 2 hours after a 500-mg dose.

Thiamphenicol diffuses into the CSF, across the placenta, into breast milk, and penetrates well into the lungs. About 10% is bound to plasma proteins. The half-life of thiamphenicol is around 2 to 3 hours; the half-life is increased in patients with renal impairment. It is excreted in the urine, about 70% of a dose being excreted in 24 hours as unchanged drug. Despite undergoing little or no conjugation with glucuronic acid in the liver, prolonged half-life and raised plasma concentrations may occur in patients with hepatitis or cirrhosis. A small amount is excreted in the bile and the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Fluimucil Antibiotic; Urfamycine; ***Braz.***: Glitisol; ***China***: Jiangke (将克); Pushijie (普施捷); Vicemycetin (赛美欣); ***Fr.***: Thiophenicol; ***Hong Kong***: Urfamycin; ***Indon.***: Biothicol; Canicol; Cetathiacol; Comthycol; Conucol; Corsafen; Daiticin; Dexycol; Fosicol; Genicol; Ipibiofen; Kalticol; Lacophen; Lanacol; Nikolam; Nilacol; Nufathiam; Opiphen; Phenobiotic†; Promixin; Renamoca†; Rindofen; Sendicol; Thiambiotic†; Thiamet; Thiamfilex; Thiamika; Thiamycin; Thislacol; Troviakol; Urfamycin; Urfekol†; Venacol; Zumatab; ***Ital.***: Fluimucil Antibiotico; Glitisol; ***Mex.***: Tiofenidin†; ***Rus.***: Fluimucil Antibiotic (Флуимуцил антибиотик); ***Thai.***: Doqua; Mycochlorin-T; Thiam-P; Thiamcin; Treomycin; Urfamycin; ***Turk.***: Thiophenicol†; Tiofen; Urfamycin†; Urfetem.

Multi-ingredient Preparations. ***Thai.***: Fluimucil Antibiotic†.

Thioacetazone *(BAN, rINN)*

Amithiozone; Amitiozon; TBI/698; Tebezonum; Thiacetazone; Thioacétazone; Thioacetazonum; Tiasetazon; Tioacetazona; Тиоацетазон.
4-Acetamidobenzaldehyde thiosemicarbazone.
$C_{10}H_{12}N_4OS$=236.3
CAS — 104-06-3.
UNII — MMG78X7SSR.

Pharmacopoeias. In *Int.*

Uses and Administration

Thioacetazone has been used with other antimycobacterials in the treatment of tuberculosis (p. 210.2). Thioacetazone-containing regimens are less effective than the short-course regimens recommended by WHO but are used in long-term regimens with isoniazid in some developing countries to reduce drug costs. Thioacetazone has been used as a second-line drug for multidrug-resistant tuberculosis but is no longer considered appropriate for routine use; in particular, it is not generally recommended for use in HIV-positive patients because of the risk of severe adverse reactions (but see Effects on the Skin, p. 379.3).

Thioacetazone has been used in the treatment of leprosy (p. 188.3), but WHO now considers that such use is no longer justified.

In the treatment of tuberculosis, thioacetazone has been given orally in doses of 150 mg daily. Daily use is recommended as the drug is less effective when given intermittently.

Adverse Effects

Gastrointestinal disturbances, hypersensitivity reactions including rashes, conjunctivitis, and vertigo are the adverse effects most frequently reported with thioacetazone although the incidence appears to vary between countries. Toxic epidermal necrolysis, exfoliative dermatitis (which has sometimes been fatal), and the Stevens-Johnson syndrome have been reported; the incidence of severe skin reactions is especially high in patients with HIV infection (see p. 379.3). Thioacetazone may cause bone-marrow depression with leucopenia, agranulocytosis, and thrombocytopenia. Acute haemolytic anaemia may occur and a large percentage of patients will have some minor degree of anaemia. Hepatotoxicity with jaundice may also develop and acute hepatic failure has been reported. Cerebral oedema has been reported. Dose-related ototoxicity may occur rarely.

Incidence of adverse effects. In a 10-year series of 1212 patients with tuberculosis who were treated with a regimen of streptomycin, isoniazid, and thioacetazone, 171 (14%) had adverse reactions associated with thioacetazone. The most common adverse effects were giddiness (10%), occurring mainly when used with streptomycin, and rashes (3%) including exfoliation and the Stevens-Johnson syndrome.[1]

1. Pearson CA. Thiacetazone toxicity in the treatment of tuberculosis patients in Nigeria. *J Trop Med Hyg* 1978; **81**: 238–42.

Effects on the nervous system. Acute peripheral neuropathy which occurred in a 50-year-old man on 2 separate occasions within 15 minutes of a dose of thioacetazone may have been due to an allergic reaction.[1]

1. Gupta PK, *et al.* Acute severe peripheral neuropathy due to thiacetazone. *Indian J Tuberc* 1984; **31**: 126–7.

Effects on the skin. A high incidence of severe and sometimes fatal cutaneous hypersensitivity reactions to thioacetazone has been reported in patients with HIV infection being treated for tuberculosis.[1,2] WHO advised that thioacetazone should be avoided in such patients.[3] Unfortunately, thioacetazone has been one of the mainstays of tuberculosis treatment in the developing world because of its relatively low cost.[4] Some have supported a change to rifampicin-based regimens in, for example, parts of Africa with a high incidence of HIV infection.[5] Others have found a lower frequency of fatalities from adverse cutaneous reactions to thioacetazone than reported previously and have suggested that improved management might allow retention of thioacetazone in tuberculosis programmes.[6] This was rejected by other workers who considered that better and more cost-effective regimens were available than those containing thioacetazone.[7] A pragmatic approach may be to adopt a strategy depending upon the prevailing incidence of HIV infection in the population.[8] Thus, where the incidence of HIV infection is high, ethambutol should be substituted for thioacetazone; where the incidence is moderate, routine HIV testing could be used to identify patients at risk; and where the incidence is low, education of patients on the risks of skin reaction would be adequate.

1. Nunn P, *et al.* Cutaneous hypersensitivity reactions due to thiacetazone in HIV-1 seropositive patients treated for tuberculosis. *Lancet* 1991; **337**: 627–30.
2. Chintu C, *et al.* Cutaneous hypersensitivity reactions due to thiacetazone in the treatment of tuberculosis in Zambian children infected with HIV-1. *Arch Dis Child* 1993; **68**: 665–8.
3. Raviglione MC, *et al.* HIV-associated tuberculosis in developing countries: clinical features, diagnosis, and treatment. *Bull WHO* 1992; **70**: 515–26.
4. Nunn P, *et al.* Thiacetazone—avoid like poison or use with care? *Trans R Soc Trop Med Hyg* 1993; **87**: 578–82.
5. Okwera A, *et al.* Randomised trial of thiacetazone and rifampicin-containing regimens for pulmonary tuberculosis in HIV-infected Ugandans. *Lancet* 1994; **344**: 1323–8.
6. Ipuge YAL, *et al.* Adverse cutaneous reactions to thiacetazone for tuberculosis treatment in Tanzania. *Lancet* 1995; **346**: 657–60.
7. Elliott AM, *et al.* Treatment of tuberculosis in developing countries. *Lancet* 1995; **346**: 1098–9.
8. van Gorkom J, Kibuga DK. Cost-effectiveness and total costs of three alternative strategies for the prevention and management of severe skin reactions attributable to thiacetazone in the treatment of human immunodeficiency virus positive patients with tuberculosis in Kenya. *Tubercle Lung Dis* 1996; **77**: 30–6.

Hypertrichosis. Hypertrichosis occurred in 2 children receiving thioacetazone.[1]

1. Nair LV, Sugathan P. Thiacetazone induced hypertrichosis. *Indian J Dermatol Venereol* 1982; **48**: 161–3.

Precautions

The efficacy and toxicity of a regimen of treatment which includes thioacetazone should be determined in a community before it is used widely since there appear to be geographical differences.

Thioacetazone should not be given to patients with hepatic impairment. It has also been suggested that, because thioacetazone has a low therapeutic index and is excreted mainly in the urine, it should not be given to patients with renal impairment. Treatment should be stopped if rash or other signs of hypersensitivity occur. It should probably be avoided in HIV-positive patients because they are at increased risk of severe adverse effects (see Effects on the Skin, above).

Interactions

Thioacetazone may enhance the ototoxicity of streptomycin.

Antimicrobial Action

Thioacetazone is bacteriostatic. It is effective against most strains of *Mycobacterium tuberculosis*, although sensitivity varies in different parts of the world.

Thioacetazone is also bacteriostatic against *M. leprae*. Resistance to thioacetazone develops when used alone. Cross-resistance can develop between thioacetazone and ethionamide or protionamide.

Pharmacokinetics

Thioacetazone is absorbed from the gastrointestinal tract and peak plasma concentrations of 1 to 2 micrograms/mL have been obtained about 4 to 5 hours after a 150-mg dose. About 20% of a dose is excreted unchanged in the urine. A half-life of about 12 hours has been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Turk.*: Citazon.

Multi-ingredient Preparations. *India*: Isokin-T Forte.

Thiostrepton

Thiostreptonum; Tiostreptón; Tiostrepton; Tiostreptoni; Тиострептон.

$C_{72}H_{85}N_{19}O_{18}S_5$=1664.9

CAS — 1393-48-2.

UNII — HR4S203Y18.

Pharmacopoeias. In *US* for veterinary use only.

USP 36: (Thiostrepton). An antibacterial substance produced by the growth of strains of *Streptomyces azureus*. It has a potency of not less than 900 units/mg, calculated on the dried basis. A white to off-white crystalline solid. Practically insoluble in water, in the lower alcohols, in nonpolar organic solvents, and in dilute aqueous acids or alkalis; soluble in glacial acetic acid, in chloroform, in dimethylformamide, in dimethyl sulfoxide, in dioxan, and in pyridine. Store in airtight containers.

Profile

Thiostrepton is an antibacterial produced by strains of *Streptomyces azureus*. It is included in topical antibacterial preparations for veterinary use.

Tiamulin *(BAN, rINN)*

SQ-14055; Tiamuliini; Tiamulina; Tiamuline; Tiamulinum; Тиамулин.

[[2-(Diethylamino)ethyl]thio]acetic acid 8-ester with octahydro-5,8-dihydroxy-4,6,9,10-tetramethyl-6-vinyl-3a,9-propano-3a*H*-cyclopentacycloocten-1(4*H*)-one.

$C_{28}H_{47}NO_4S$=493.7

CAS — 55297-95-5.

ATC Vet — QJ01XQ01; QP51AX15.

UNII — E38WZ4U54R.

Pharmacopoeias. In *Eur.* (see p. vii) and *US* for veterinary use only.

Ph. Eur. 8: (Tiamulin for Veterinary Use; Tiamulin BP(Vet) 2014). A sticky, translucent, slightly hygroscopic, yellowish mass. Practically insoluble in water; freely soluble in dehydrated alcohol; very soluble in dichloromethane. Protect from light.

USP 36: (Tiamulin). Protect from light.

Tiamulin Fumarate *(BANM, USAN, rINNM)*

Fumarato de tiamulina; 81723-hfu; SQ-22947; Tiamuliinivetyfumaraatti; Tiamulina, fumarato de; Tiamuline, Fumarate de; Tiamuline, hydrogénofumarate de; Tiamulin-fumarát; Tiamulini Fumaras; Tiamulini Hydrogenofumaras; Tiamulinvätefumarat; Тиамулина Фумарат.

$C_{28}H_{47}NO_4S.C_4H_4O_4$=609.8

CAS — 55297-96-6.

UNII — ION1Q02ZCX.

Pharmacopoeias. In *Eur.* (see p. vii) and *US* for veterinary use only.

Ph. Eur. 8: (Tiamulin Hydrogen Fumarate for Veterinary Use; Tiamulin Hydrogen Fumarate BP(Vet) 2014). A white or light yellow, crystalline powder. Soluble in water and in methyl alcohol; freely soluble in dehydrated alcohol. A 1% solution in water has a pH of 3.1 to 4.1. Protect from light.

USP 36: (Tiamulin Fumarate). A 1.0% solution in water has a pH of 3.1 to 4.1. Store in airtight containers. Protect from light.

Profile

Tiamulin fumarate is an antibacterial used in veterinary medicine.

Ticarcillin Monosodium *(BANM, rINNM)*

Ticarcilina monosódica; Ticarcilline Monosodique; Ticarcillinum Mononatricum; Мононатрий Тикарциллин.

Monosodium (6*R*)-6-[2-carboxy-2-(3-thienyl)acetamido] penicillanate monohydrate.

$C_{15}H_{15}N_2NaO_6S_2.H_2O$=424.4

CAS — 34787-01-4 (ticarcillin); 3973-04-4 (ticarcillin); 74682-62-5 (ticarcillin monosodium).

UNII — SM6JM116PM (anhydrous ticarcillin monosodium); 34GZ64SH49 (ticarcillin monosodium monohydrate).

Pharmacopoeias. In *US*.

USP 36: (Ticarcillin Monosodium). Store in airtight containers.

Ticarcillin Sodium *(BANM, rINNM)*

BRL-2288; Natrii Ticarcillinum; Ticarcilina sódica; Ticarcillin Disodium (USAN); Ticarcillin-Natrium; Ticarcilline sodique; Ticarcillinum Dinatricum; Ticarcillinum natricum; Tikarcilin disodná sůl; Tikarclin sodná sůl; Tikarcilino natrio druska; Tikarcillinnatrium; Tikarcillin-nátrium; Tikarsilliininatrium; Tykarcylina sodowa; Натрий Тикарциллин.

Disodium (6*R*)-6-[2-carboxy-2-(3-thienyl)acetamido]penicillanate.

$C_{15}H_{14}N_2Na_2O_6S_2$=428.4

CAS — 4697-14-7; 29457-07-6.

ATC — J01CA13.

ATC Vet — QJ01CA13.

UNII — G8TW6DSYG.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Ticarcillin Sodium). A white or slightly yellow, hygroscopic powder. Freely soluble in water; soluble in methyl alcohol. A 5% solution in water has a pH of 5.5 to 7.5. Store in airtight containers at a temperature of 2 degrees to 8 degrees.

USP 36: (Ticarcillin Disodium). A white to pale yellow powder or solid. 1 mg of monograph substance has a potency equivalent to not less than 800 micrograms of ticarcillin, calculated on the anhydrous basis. Freely soluble in water. A 1% solution in water has a pH of 6.0 to 8.0. Store in airtight containers.

Incompatibility. Ticarcillin sodium has been reported to be incompatible with aminoglycosides.

References.

1. Swenson E. *et al.* Compatibility of ticarcillin disodium clavulanate potassium with commonly used intravenous solutions. *Curr Ther Res* 1990; **48**: 385–94.

Stability. References.

1. Zhang Y, Trissel LA. Stability of piperacillin and ticarcillin in AutoDose Infusion System bags. *Ann Pharmacother* 2001; **35**: 1360–3.

Uses and Administration

Ticarcillin is a carboxypenicillin used in the treatment of severe Gram-negative infections, especially those due to *Pseudomonas aeruginosa*. Pseudomonal infections where ticarcillin is used include those in cystic fibrosis (respiratory-tract infections), immunocompromised patients (neutropenia), peritonitis, and septicaemia. Other infections that may be due to *Ps. aeruginosa* include bone and joint infections, meningitis, otitis media (chronic), skin infections (burns, ecthyma gangrenosum, ulceration), and urinary-tract infections. For details of these infections and their treatment, see under Choice of Antibacterial, p. 172.2.

Ticarcillin is given by injection as the sodium salt. Doses are expressed in terms of the equivalent amount of ticarcillin; 1.1 g of ticarcillin sodium is equivalent to about 1 g of ticarcillin. Doses may need to be reduced in renal impairment (see p. 380.3).

Ticarcillin is usually given in doses of 200 to 300 mg/kg daily by intravenous infusion in divided doses every 4 or 6 hours.

In adults the use of oral probenecid 500 mg four times daily may produce higher and more prolonged plasma concentrations of ticarcillin, but caution is advised in patients with renal impairment.

In the treatment of complicated urinary-tract infections, a dose of ticarcillin 150 to 200 mg/kg daily by intravenous infusion in divided doses every 4 or 6 hours may be used. For uncomplicated urinary-tract infections, the usual dose is ticarcillin 1 g every 6 hours intramuscularly or by slow intravenous injection.

In patients with cystic fibrosis, ticarcillin has been given by nebuliser in the management of respiratory-tract infections.

Ticarcillin is often used with an aminoglycoside but the injections must be given separately because of possible incompatibility.

Ticarcillin with clavulanic acid. Ticarcillin is often used with clavulanic acid (p. 268.3), a beta-lactamase inhibitor, to widen its antibacterial spectrum to organisms usually resistant because of the production of beta-lactamases. This combination is given by intravenous infusion in a ratio of 15 or 30 parts of ticarcillin (as the sodium salt) to 1 part of clavulanic acid (as the potassium salt). Doses have been variably described both in terms of the combined content of ticarcillin and clavulanic acid, and in terms of the ticarcillin content alone. In terms of the latter, usual adult doses range from 9 to 18 g daily in 3 to 6 divided doses.

For details of doses in children for both ticarcillin and ticarcillin plus clavulanic acid, see p. 380.3.

Administration in children. Ticarcillin, alone or more commonly with clavulanic acid, has been given to neonates and children for the treatment of infections caused by susceptible Gram-negative organisms. In the UK, the combination of ticarcillin plus clavulanic acid is licensed for use in neonates and children weighing more than 2 kg; in the USA licensed use is restricted to children 3 months of age and older.

In the UK, the *BNFC* recommends the following doses (expressed as the combined amount of ticarcillin and clavulanic acid) by intravenous infusion:

For infections due to *Pseudomonas* and *Proteus spp.*:

- preterm neonates weighing less than 2 kg: 80 mg/kg every 12 hours
- all other neonates: 80 mg/kg every 8 hours, increased to every 6 hours in more severe infections
- children from 1 month of age: 80 mg/kg (maximum 3.2 g) every 6 to 8 hours: may be increased to every 4 hours in those weighing over 40 kg with more severe infections

In the USA, doses are expressed as the ticarcillin component. An intravenous dose of 200 mg/kg daily in divided doses every 6 hours is suggested for mild to moderate infections. However, the American Academy of Pediatrics[1] considers that it should only be used for severe infections; they recommend a dose of 200 to 300 mg/kg daily in 4 to 6 divided doses (to a maximum of 12 to 18 g daily).

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*. 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics. 2012.

Administration in renal impairment. Doses of ticarcillin may need to be reduced in patients with renal impairment. After an initial intravenous loading dose of 3 g, the intravenous maintenance dosage should be adjusted according to the patient's creatinine clearance (CC):

- CC 30 to 60 mL/minute: 2 g every 4 hours
- CC 10 to 30 mL/minute: 2 g every 8 hours
- CC less than 10 mL/minute: 2 g every 12 hours (or 1 g intramuscularly every 6 hours)
- CC less than 10 mL/minute in presence of *hepatic impairment*: 2 g intravenously every 24 hours or 1 g intramuscularly every 12 hours
- peritoneal dialysis patients: 3 g every 12 hours
- haemodialysis patients: 2 g every 12 hours plus an additional dose of 3 g after each dialysis session

Adverse Effects and Precautions

As for Carbenicillin Sodium, p. 232.1.

Cholestatic jaundice and hepatitis have been reported when ticarcillin was used with clavulanic acid; the clavulanic acid component has been implicated.

Ticarcillin should be given with caution to patients with renal impairment.

Breast feeding. Although ticarcillin is distributed into breast milk in small amounts,[1] no adverse effects have been seen in breast-fed infants and the American Academy of Pediatrics considers that it is usually compatible with breast feeding.[2]

1. von Kobyletzki D, *et al.* Ticarcillin serum and tissue concentrations in gynecology and obstetrics. *Infection* 1983; **11**: 144–9.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/05/04)

Effects on the bladder. The Australian Adverse Drug Reactions Advisory Committee had received 15 reports of haemorrhagic cystitis associated with ticarcillin or ticarcillin-clavulanic acid between 1980 and June 2002, mainly in

paediatric cystic fibrosis patients.[1] Almost all patients recovered quickly after the withdrawal of ticarcillin.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Haemorrhagic cystitis with ticarcillin in cystic fibrosis patients. *Aust Adverse Drug React Bull* 2002; 21: 6–7. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0206.pdf (accessed 29/07/08)

Effects on the liver. Cholestatic jaundice and hepatitis have been associated with combined preparations of a penicillin and clavulanic acid (see Amoxicillin, p. 217.2) and as of February 1993, 2 cases had been reported to the UK CSM with ticarcillin and clavulanic acid.[1] It appeared that the clavulanic acid was probably responsible.

1. CSM/MCA. Cholestatic jaundice with co-amoxiclav. *Current Problems* 1993; 19: 2. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024454&RevisionSelectionMethod=LatestReleased (accessed 22/07/08)

Sodium content. Each g of ticarcillin sodium contains about 4.7 mmol of sodium.

Interactions

As for Benzylpenicillin, p. 230.1.

Immunosuppressants. For the effect of ticarcillin on *ciclosporin* disposition, see p. 1956.2.

Antimicrobial Action

Ticarcillin is bactericidal and has a mode of action and range of activity similar to that of carbenicillin (p. 232.1), but is reported to be 2 to 4 times more active against *Pseudomonas aeruginosa*.

Combinations of ticarcillin and aminoglycosides have been shown to be synergistic *in vitro* against *Ps. aeruginosa* and Enterobacteriaceae.

The activity of ticarcillin against organisms usually resistant because of the production of certain beta-lactamases is enhanced by clavulanic acid, a beta-lactamase inhibitor. Such organisms have included staphylococci, many Enterobacteriaceae, *Haemophilus influenzae*, and *Bacteroides* spp.; the activity of ticarcillin against *Ps. aeruginosa* is not enhanced by clavulanic acid. Resistance to ticarcillin with clavulanic acid has been reported.

There is cross-resistance between carbenicillin and ticarcillin.

References.

1. Pulverer G, *et al.* In-vitro activity of ticarcillin with and without clavulanic acid against clinical isolates of Gram-positive and Gram-negative bacteria. *J Antimicrob Chemother* 1986; 17 (suppl C): 1–5.
2. Masterton RG, *et al.* Timentin resistance. *Lancet* 1987; ii: 975–6.
3. Fass RJ, Prior RB. Comparative in vitro activities of piperacillin-tazobactam and ticarcillin-clavulanate. *Antimicrob Agents Chemother* 1989; 33: 1268–74.
4. Kempers J, MacLaren DM. Piperacillin/tazobactam and ticarcillin/clavulanic acid against resistant Enterobacteriaceae. *J Antimicrob Chemother* 1990; 26: 598–9.
5. Klepser ME, *et al.* Comparison of the bactericidal activities of piperacillin-tazobactam, ticarcillin-clavulanate, and ampicillin-sulbactam against clinical isolates of Bacteroides fragilis, Enterococcus faecalis, Escherichia coli, and Pseudomonas aeruginosa. *Antimicrob Agents Chemother* 1997; 41: 435–9.

Pharmacokinetics

Ticarcillin is not absorbed from the gastrointestinal tract. After intramuscular injection of 1 g peak plasma concentrations in the range of 22 to 35 micrograms/mL occur after 0.5 to 1 hour. About 50% of ticarcillin in the circulation is bound to plasma proteins. A plasma half-life of 70 minutes has been reported. A shorter half-life in patients with cystic fibrosis (about 50 minutes in one study) has been attributed to increased renal and non-renal elimination. The half-life is prolonged in neonates and also in patients with renal impairment, especially if hepatic function is also impaired. A half-life of about 15 hours has been reported in severe renal impairment.

Distribution of ticarcillin in the body is similar to that of carbenicillin. Relatively high concentrations have been reported in bile, but ticarcillin is excreted principally by glomerular filtration and tubular secretion. Concentrations of 2 to 4 mg/mL occur in the urine after the intramuscular injection of 1 or 2 g. Ticarcillin is metabolised to a limited extent. Up to 90% of a dose is excreted unchanged in the urine, mostly within 6 hours after a dose. Plasma concentrations are enhanced by probenecid.

Ticarcillin is removed by haemodialysis and, to some extent, by peritoneal dialysis.

Ticarcillin crosses the placenta and small amounts are distributed into breast milk.

Ticarcillin with clavulanic acid. The pharmacokinetics of ticarcillin and clavulanic acid are broadly similar and neither appears to affect the other to any great extent.

References.

1. Staniforth DH, *et al.* Pharmacokinetics of parenteral ticarcillin formulated with clavulanic acid: Timentin. *Int J Clin Pharmacol Ther Toxicol* 1986; 24: 123–9.
2. Brogard JM, *et al.* Biliary elimination of ticarcillin plus clavulanic acid (Claventin): experimental and clinical study. *Int J Clin Pharmacol Ther Toxicol* 1989; 27: 135–44.
3. de Groot R, *et al.* Pharmacokinetics of ticarcillin in patients with cystic fibrosis: a controlled prospective study. *Clin Pharmacol Ther* 1990; 47: 73–8.
4. Wang J-P, *et al.* Disposition of drugs in cystic fibrosis IV: mechanisms for enhanced renal clearance of ticarcillin. *Clin Pharmacol Ther* 1993; 54: 293–302.
5. Burstein AH, *et al.* Ticarcillin-clavulanic acid pharmacokinetics in preterm neonates with presumed sepsis. *Antimicrob Agents Chemother* 1994; 38: 2024–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Ticarpen; *USA*: Ticar†.

Multi-ingredient Preparations. *Austral.*: Timentin; *Belg.*: Timentin; *Braz.*: Timentin; *Canad.*: Timentin; *China*: A Le Xian (阿乐仙); Lieqi (列其); Timentin (特美汀); *Cz.*: Timentin†; *Fr.*: Claventin; *Gr.*: Timentin; *Hong Kong*: Timentin; *India*: Timentin†; *Israel*: Timentin; *Ital.*: Timentin; *Mex.*: Timentin; *NZ*: Timentin; *Philipp.*: Ticarcin; Timentin; *Pol.*: Timentin; *Rus.*: Timentin (Тиментин); *Turk.*: Timentin; *UK*: Timentin; *Ukr.*: Timentin (Тиментин); *USA*: Timentin.

Pharmacopoeial Preparations
BP 2014: Ticarcillin and Clavulanic Acid Infusion;
USP 36: Ticarcillin and Clavulanic Acid for Injection; Ticarcillin and Clavulanic Acid Injection; Ticarcillin for Injection.

Tigecycline *(BAN, USAN, rINN)*

GAR-936; TBG-MINO; Tigeciclina; Tigécycline; Tigecyclinum; WAY-GAR-936; Тигециклин.

(4*S*,4a*S*,5a*R*,12a*S*)-9-[2-(*tert*-Butylamino)acetamido]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide.

$C_{29}H_{39}N_5O_8$=585.7

CAS — 220620-09-7.

ATC — J01AA12.

ATC Vet — QJ01AA12.

UNII — 70JE2N95KR.

Stability and compatibility. In the UK, it is recommended that solutions of tigecycline be used immediately after reconstitution, however US licensed product information states that it may be stored at room temperature for up to 24 hours after reconstitution (up to 6 hours in the vial and the remaining time in the infusion bag), or up to 45 hours at 2 to 8 degrees after reconstitution and transfer to an infusion bag.

Tigecycline is compatible when given via a Y-site with amikacin, dobutamine, dopamine hydrochloride, gentamicin, haloperidol, lidocaine hydrochloride, morphine, noradrenaline, piperacillin with tazobactam (formulated with edetic acid), potassium chloride, propofol, ranitidine hydrochloride, theophylline, and tobramycin. It is incompatible with amphotericin B, diazepam, esomeprazole, omeprazole, or any intravenous solution that may result in a pH above 7.

Uses and Administration

Tigecycline is a glycylcycline antibacterial used in adults for the intravenous treatment of complicated skin and skin structure infections or complicated intra-abdominal infections caused by susceptible organisms. In the USA, tigecycline is also licensed for use in community-acquired pneumonia, including in cases with concurrent bacteraemia. Tigecycline is given by intravenous infusion over 30 to 60 minutes in an initial loading dose of 100 mg followed by 50 mg every 12 hours. For details of reduced dosage to be given in severe hepatic impairment, see p. 381.2.

Reviews.

1. Zhanel GG, *et al.* The glycylcyclines: a comparative review with the tetracyclines. *Drugs* 2004; 64: 63–88.
2. Rubinstein E, Vaughan D. Tigecycline: a novel glycylcycline. *Drugs* 2005; 65: 1317–36.
3. Frampton JE, Curran MP. Tigecycline. *Drugs* 2005; 65: 2623–35.
4. Kasbekar N. Tigecycline: a new glycylcycline antimicrobial agent. *Am J Health-Syst Pharm* 2006; 63: 1235–43.
5. Stein GE, Craig WA. Tigecycline: a critical analysis. *Clin Infect Dis* 2006; 43: 518–24.
6. Slover CM, *et al.* Tigecycline: a novel broad-spectrum antimicrobial. *Ann Pharmacother* 2007; 41: 965–72.
7. Grolman DC. Therapeutic applications of tigecycline in the management of complicated skin and skin structure infections. *Int J Infect Dis* 2007; 11 (suppl 1): S7–S15.
8. Karageorgopoulos DE, *et al.* Tigecycline for the treatment of multidrug-resistant (including carbapenem-resistant) Acinetobacter infections: a review of the scientific evidence. *J Antimicrob Chemother* 2008; 62: 45–55.
9. Curcio D. Tigecycline for treating bloodstream infections: a critical analysis of the available evidence. *Diagn Microbiol Infect Dis* 2008; 61: 358–9.
10. Mullangi PK, Pankey GA. Tigecycline in critical care. *Crit Care Clin* 2008; 24: 365–75.
11. McKeage K, Keating GM. Tigecycline: in community-acquired pneumonia. *Drugs* 2008; 68: 2633–44.
12. Nicolau DP. Management of complicated infections in the era of antimicrobial resistance: the role of tigecycline. *Expert Opin Pharmacother* 2009; 10: 1213–22. Correction. *ibid.*; 1527.

Administration in hepatic impairment. Dosage of tigecycline should be adjusted in patients with severe hepatic impairment (Child-Pugh category C); the initial intravenous loading dose should be 100 mg with reduced maintenance doses of 25 mg every 12 hours.

Adverse Effects

Tigecycline is a glycylcycline antibacterial with structural similarity to the tetracyclines and adverse effects similar to those of tetracyclines may potentially occur (see p. 375.1). The most common adverse effects associated with tigecycline have been nausea, vomiting, and diarrhoea. Other common adverse effects include abscess, abdominal pain, anorexia, dyspepsia, dizziness, headache, phlebitis, pruritus, and rash. Infection-related serious adverse events, including sepsis or septic shock have been reported; however, a causal relationship could not be established. Raised liver enzymes, bilirubinaemia, increased serum amylase, and increased blood urea nitrogen have also been reported. Occasionally, significant liver impairment, including fatal liver failure, has occurred. Local reactions have been reported at the infusion site and thrombocythaemia, anaemia, and leucocytosis may occur. Acute pancreatitis has been reported, usually after at least one week of treatment; symptoms generally resolve on stopping tigecycline. Potentially life-threatening anaphylaxis or anaphylactoid reactions have also been reported.

Precautions

Due to the potential for similar adverse effects, precautions applicable to the tetracyclines (see p. 375.2) should be taken with tigecycline. In particular, tigecycline should not be given in pregnancy as it has caused fetal harm in *animal* studies. Distribution into milk has also been found in *animal* studies. It should also not be given during tooth development (up to 8 years of age) as it may cause permanent tooth discoloration. Caution should be exercised when using tigecycline as monotherapy in patients with complicated intra-abdominal infections secondary to intestinal perforation. Patients taking anticoagulants should be closely monitored as tigecycline may prolong both the prothrombin time and the activated partial thromboplastin time. Dosage of tigecycline should be adjusted in patients with severe hepatic impairment (see above).

The FDA has issued a warning that tigecycline has been associated with an increased mortality risk when used to treat a variety of serious infections and has recommended that an alternative should be considered in patients with severe infections.[1]

1. FDA. Tygacil (tigecycline): label change - increased mortality risk (issued 1st September 2010). Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm224626.htm (accessed 02/09/10)

Interactions

Immunosuppressants. For mention of increased serum concentrations of *ciclosporin* associated with concomitant tigecycline treatment, see p. 1956.2.

Antimicrobial Action

Tigecycline is generally bacteriostatic and acts by binding to the 30S subunit of the ribosome and preventing the binding of aminoacyl transfer RNA, similarly to tetracyclines (see p. 375.3). It has activity against a broad range of Gram-positive and Gram-negative bacteria, including tetracycline-resistant organisms, and some anaerobic organisms. Tigecycline has shown activity both *in vitro* and in clinical infection with both meticillin-susceptible and meticillin-resistant *Staphylococcus aureus*, vancomycin-susceptible *Enterococcus faecalis*, and some streptococci. Gram-negative organisms that have proven susceptible include *Acinetobacter baumannii*, *Citrobacter freundii*, *Enterobacter cloacae*, *Escherichia coli*, and some *Klebsiella* spp. Tigecycline also has activity against some anaerobic bacteria including *Bacteroides fragilis* and some other *Bacteroides* spp., *Clostridium perfringens*, and *Peptostreptococcus micros*. Some activity has also been reported against plasmodia.

Pharmacokinetics

After intravenous doses tigecycline is widely distributed into the tissues. Binding to plasma proteins has been reported to be 71 to 89% *in vitro*. Tigecycline is not thought to be extensively metabolised, although some trace metabolites have been identified including a glucuronide, an *N*-acetyl metabolite, and a tigecycline epimer. Tigecycline is primarily eliminated (about 60%) via biliary excretion of unchanged drug and some metabolites with a reported half-life of about 42 hours after multiple doses. About 22% is excreted unchanged in the urine.

Reviews.

1. Meagher AK, *et al.* The pharmacokinetic and pharmacodynamic profile of tigecycline. *Clin Infect Dis* 2005; 41 (suppl 5): S333–S340.
2. Rello J. Pharmacokinetics, pharmacodynamics, safety and tolerability of tigecycline. *J Chemother* 2005; 17 (suppl 1): 12–22.

3. Agwuh KN, MacGowan A. Pharmacokinetics and pharmacodynamics of the tetracyclines including glycylcyclines. *J Antimicrob Chemother* 2006; **58**: 256–65.
4. MacGowan AP. Tigecycline pharmacokinetic/pharmacodynamic update. *J Antimicrob Chemother* 2008; **62** (suppl 1): i11–i16.
5. Barbour A, *et al.* Clinical pharmacokinetics and pharmacodynamics of tigecycline. *Clin Pharmacokinet* 2009; **48**: 575–84.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Tygacil; ***Austral.***: Tygacil; ***Austria***: Tygacil; ***Belg.***: Tygacil; ***Braz.***: Tygacil; ***Canad.***: Tygacil; ***Chile***: Tygacil; ***China***: Tygacil (泰阁); ***Cz.***: Tygacil; ***Denm.***: Tygacil; ***Fr.***: Tygacil; ***Ger.***: Tygacil; ***Gr.***: Tygacil; ***Hong Kong***: Tygacil; ***Hung.***: Tygacil; ***Indon.***: Tygacil; ***Irl.***: Tygacil; ***Israel***: Tygacil; ***Ital.***: Tygacil; ***Jpn***: Tygacil; ***Malaysia***: Tygacil; ***Mex.***: Tygacil; ***Neth.***: Tygacil; ***Norw.***: Tygacil; ***NZ***: Tygacil; ***Philipp.***: Tygacil; ***Pol.***: Tygacil; ***Port.***: Tygacil; ***Rus.***: Tigacil (Тигацил); ***Singapore***: Tygacil; ***Spain***: Tygacil; ***Swed.***: Tygacil; ***Switz.***: Tygacil; ***Thai.***: Tygacil; ***Turk.***: Tygacil; ***UK***: Tygacil; ***Ukr.***: Tygacil (Тигацил); ***USA***: Tygacil; ***Venez.***: Tygacil.

Tilmicosin *(BAN, USAN, rINN)*

EL-870; LY-177370; Tilmicosina; Tilmicosine; Tilmicosinum; Тильмикозин.

4^A-*O*-De(2,6-dideoxy-3-*C*-methyl-α-L-*ribo*-hexopyranosyl)-20-deoxo-20-(*cis*-3,5-dimethyl-piperidino)tylosin.

$C_{46}H_{80}N_2O_{13}$=869.1

CAS — 108050-54-0.

ATC Vet — QJ01FA91.

UNII — XL4103X2E3.

Pharmacopoeias. In *US* for veterinary use only.

USP 36: (Tilmicosin). White to off-white amorphous solid. Slightly soluble in water and in *n*-hexane. Store at a temperature not exceeding 40 degrees. Protect from light.

Tilmicosin Phosphate *(BANM, USAN, rINNM)*

Fosfato de tilmicosina; Tilmicosina, fosfato de; Tilmicosine, Phosphate de; Tilmicosini Phosphas; Тильмикозина Фосфат.

$C_{46}H_{80}N_2O_{13}H_3O_4P$=967.1

CAS — 137330-13-3.

UNII — SMH7U15683.

Profile

Tilmicosin is a macrolide antibacterial used as the base or the phosphate in veterinary medicine.

Adverse effects. Accidental self-injection of tilmicosin by a farm worker, resulted in asthenia and temporary pulmonary, gastrointestinal, and neuromuscular toxicity.[1] A review[2] of human exposures to tilmicosin injection reported between March 1992 and March 2005 suggested that the overall risk of serious adverse effects was about 2 cases per million doses. Serious cardiovascular adverse effects, including bradycardia, hypertension, hypotension, tachycardia, and tachypnoea, occurred in 156 of 3168 reported cases and, of these, fatalities occurred in 13.

1. Crown LA, Smith RB. Accidental veterinary antibiotic injection into a farm worker. *Tenn Med* 1999; **92**: 339–40.
2. Veenhuizen MF, *et al.* Analysis of reports of human exposure to Micotil 300 (tilmicosin injection). *J Am Vet Med Assoc* 2006; **229**: 1737–42.

Handling. Contact with tilmicosin should be avoided. It is irritating to the eyes and may cause allergic reactions.

Tobramycin *(BAN, USAN, rINN)*

47663; Nebramycin Factor 6; Tobramicin; Tobramicina; Tobramicinas; Tobramisin; Tobramycine; Tobramycinum; Tobramycyna; Tobramysilni; Тобрамицин.

6-*O*-(3-Amino-3-deoxy-α-D-glucopyranosyl)-2-deoxy-4-*O*-(2,6-diamino-2,3,6-trideoxy-α-D-*ribo*-hexopyranosyl)streptamine.

$C_{18}H_{37}N_5O_9$=467.5

CAS — 32986-56-4.

ATC — J01GB01; S01AA12.

ATC Vet — QJ01GB01; QS01AA12.

UNII — VZ8RRZ51VK.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Tobramycin). A substance produced by *Streptomyces tenebrarius* or obtained by any other means. A white or almost white powder. Freely soluble in water; very slightly soluble in alcohol. A 10% solution in water has a pH of 9.0 to 11.0.

USP 36: (Tobramycin). A white to off-white, hygroscopic powder. Freely soluble in water; very slightly soluble in alcohol; practically insoluble in chloroform and in ether. Contains not more than 8.0% w/w of water. A 10% solution in water has a pH of 9.0 to 11.0. Store in airtight containers.

Tobramycin Sulfate *(BANM, rINNM)*

Sulfato de tobramicina; Tobramicina, sulfato de; Tobramycin Sulphate; Tobramycine, Sulfate de; Tobramycini Sulfas; Tobramycyny siarczan; Тобрамицина Сульфат.

$(C_{18}H_{37}N_5O_9)_2.5H_2SO_4$=1425.4

CAS — 49842-07-1 ($C_{18}H_{37}N_5O_9.xH_2SO_4$); 79645-27-5 ($(C_{18}H_{37}N_5O_9)_2.5H_2SO_4$).

ATC — J01GB01; S01AA12.

ATC Vet — QJ01GB01; QS01AA12.

UNII — HJT0RXD7JK.

Pharmacopoeias. In *Pol.* and *US*.

USP 36: (Tobramycin Sulfate). It has a potency of not less than 634 micrograms and not more than 739 micrograms of tobramycin per mg. A 4% solution in water has a pH of 6.0 to 8.0. Store in airtight containers.

Incompatibility. For discussion of the incompatibility of aminoglycosides, including tobramycin, with beta lactams, see under Gentamicin Sulfate, p. 304.3. Tobramycin is also reported to be incompatible with various other drugs and, as injections have an acid pH, incompatibility with alkaline preparations or with drugs unstable at acid pH may reasonably be expected.

Uses and Administration

Tobramycin is an aminoglycoside antibacterial with actions and uses similar to those of gentamicin (p. 304.3). It is used, usually as the sulfate, particularly in the treatment of pseudomonal infections.

As with gentamicin, tobramycin may be used with penicillins or cephalosporins; the injections should be given separately.

Tobramycin sulfate is given by intramuscular injection, or by intravenous infusion over 20 to 60 minutes in 50 to 100 mL of sodium chloride 0.9% or glucose 5% injection; proportionately less fluid should be given to children. It has also been given slowly by direct intravenous injection. Doses are expressed in terms of tobramycin base; 1.5 g of tobramycin sulfate is equivalent to about 1 g of tobramycin.

Doses of tobramycin are similar to those of gentamicin, with the usual adult dose ranging from 3 to 5 mg/kg daily in 3 or 4 divided doses. For mild to moderate urinary-tract infections in adults, a single intramuscular dose of 2 to 3 mg/kg may be effective.

For details on dosage in children, including discussion of the use of tobramycin in the management of cystic fibrosis, see Administration in Children; p. 382.2.

Treatment should generally be limited to 7 to 10 days, and peak plasma concentrations greater than 12 micrograms/mL (the *BNF* suggests 10 micrograms/mL) or trough concentrations greater than 2 micrograms/mL should be avoided. In all patients, dosage should be adjusted according to plasma-tobramycin concentrations and particularly where factors such as age, renal impairment, or prolonged therapy may predispose to toxicity.

For discussion of the methods of calculating aminoglycoside dosage requirements, see Administration and Dosage under Uses and Administration of Gentamicin Sulfate, p. 305.2. As with some other aminoglycosides, once-daily and extended-interval dose regimens have been used successfully in selected patients for the treatment of other infections without increasing toxicity but local guidelines should be consulted for dosage and serum concentrations (see also Once-daily and Extended-interval Dose Regimens, under Gentamicin, p. 305.2).

Tobramycin may be used as a 0.3% eye ointment or eye drops in the treatment of eye infections.

Reviews.

1. Cheer SM, *et al.* Inhaled tobramycin (TOBI): a review of its use in the management of pseudomonas aeruginosa infections in patients with cystic fibrosis. *Drugs* 2003; **63**: 2501–20.

Administration in children. Tobramycin is licensed for use in children and may be given by intramuscular or intravenous injection, or by inhalation.

For *septicaemia, meningitis and other CNS infections, biliary-tract infection, acute pyelonephritis,* and *pneumonia* (in hospital patients) in infants and children the *BNFC* suggests:

- **a multiple daily dose regimen** of tobramycin by slow intravenous injection over at least 3 to 5 minutes
  - those 1 month to 12 years of age: 2 to 2.5 mg/kg every 8 hours
  - children 12 to 18 years of age: 1 mg/kg every 8 hours; in severe infections the dose may be increased up to 5 mg/kg daily in divided doses every 6 to 8 hours but should be reduced to 3 mg/kg daily as soon as clinically indicated, *or*
- **a once daily dose regimen** given by intravenous infusion of 7 mg/kg adjusted according to serum-tobramycin concentration in those from 1 month of age

For severe infections caused by susceptible bacteria in infants and children beyond the newborn period the American Academy of Pediatrics (AAP)[1] suggests an intravenous or intramuscular dose of tobramycin of 3 to 7.5 mg/kg daily, in 3 divided doses.

For the treatment of pseudomonal lung infection in *cystic fibrosis* the *BNFC* suggests:

- **a multiple daily dose regimen** of tobramycin by slow intravenous injection of 8 to 10 mg/kg daily in 3 divided doses in those from 1 month of age, *or*
- **a once daily dose regimen** by intravenous infusion over 30 minutes of 10 mg/kg (to a maximum of 660 mg adjusted according to serum-tobramycin concentration in children from 1 month of age
- **inhalation** of tobramycin, as either a powder or nebulised solution, may be given for chronic infections in children aged 6 years and older. The powder is given in a dose of 112 mg while the dose for the nebulised solution is 300 mg. Both formulations are given every 12 hours for 28 days, after which treatment is stopped for 28 days before being started for another 28-day course; this cycle may be repeated indefinitely

The AAP[1] recommends an intravenous or intramuscular dose of 8 to 10 mg/kg daily for pulmonary exacerbations in those with cystic fibrosis.

For *neonatal sepsis* the *BNFC* suggests:

- an **extended-interval dose regimen** by slow intravenous injection or intravenous infusion
  - those with a postmenstrual age of less than 32 weeks: 4 to 5 mg/kg every 36 hours
  - those with a postmenstrual age of 32 weeks and over: 4 to 5 mg/kg every 24 hours, *or*
- **a multiple daily dose regimen** by slow intravenous injection or intravenous infusion
  - those less than 7 days old: 2 mg/kg every 12 hours
  - those 7 to 28 days old: 2 to 2.5 mg/kg every 8 hours

An alternative regimen based on the age and body-weight of the neonate is suggested by the AAP;[1] doses should be given by intramuscular or intravenous injection:

- for neonates ≤7 days of age and weighing ≤2 kg: 5 mg/kg every 48 hours
- for neonates ≤7 days of age and weighing >2 kg: 4 mg/kg every 24 hours
- for neonates aged 8 to 28 days and weighing ≤2 kg: 4 to 5 mg/kg every 24 to 48 hours; the longer dosing interval may be needed in extremely low birth-weight neonates (weighing <1 kg) until 2 weeks of life
- for neonates aged 8 to 28 days and weighing >2 kg: 4 mg/kg every 12 to 24 hours

1. American Academy of Pediatrics. *2012 Red Book: Report of the Committee on Infectious Diseases*, 29th ed. Elk Grove Village, Illinois, USA: American Academy of Pediatrics, 2012.

Adverse Effects, Treatment, and Precautions

As for Gentamicin Sulfate, p. 306.2. Some studies suggest that tobramycin is slightly less nephrotoxic than gentamicin, but others have not found any significant difference in their effects on the kidneys.

Peak plasma-tobramycin concentrations above 12 micrograms/mL (the *BNF* suggests 10 micrograms/mL) and trough concentrations above 2 micrograms/mL should be avoided.

When tobramycin is given by inhalation with other inhaled drugs, they should be given first before the dose of tobramycin. After the first inhaled dose of tobramycin, patients should be monitored for bronchospasm and if it occurs, the test should be repeated using a bronchodilator. Peak flow should be measured before nebulisation and again after it. Caution should be exercised in the presence of severe haemoptysis. Renal function should be monitored before treatment and every six months during use.

Effects on the ear. Reversible vestibular toxicity (ataxia, dizziness, and oscillopsia) occurred in a patient on haemodialysis after about 3 weeks of treatment with inhaled tobramycin for bronchiectasis due to colonisation with *Pseudomonas aeruginosa*.[1]

1. Edson RS, *et al.* Vestibular toxicity due to inhaled tobramycin in a patient with renal insufficiency. *Mayo Clin Proc* 2004; **79**: 1185–91.

Effects on the kidneys. Irreversible acute renal failure requiring haemodialysis occurred in a high-risk patient with chronic renal failure after being treated for 4 weeks with inhaled tobramycin for *Pseudomonas aeruginosa* pneumonia.[1]

1. Cannella CA, Wilkinson ST. Acute renal failure associated with inhaled tobramycin. *Am J Health-Syst Pharm* 2006; **63**: 1858–61.

Effects on the liver. A case[1] of possible tobramycin-induced hepatotoxicity was reported in a 20-year-old patient receiving antibacterial treatment for *Pseudomonas aeruginosa* bacteraemia and osteomyelitis. Liver enzyme values started to increase when empirical treatment was changed to intravenous tobramycin and ceftazidime, and markedly increased when the regimen was changed, increasing the dose of tobramycin and replacing ceftazidime with piperacillin/tazobactam and then later

aztreonam. Enzyme values began to decrease after all treatment was stopped on day 12.

1. Nisly SA, *et al.* Tobramycin-induced hepatotoxicity. *Ann Pharmacother* 2007; 41: 2061–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tobramycin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)

Interactions

As for Gentamicin Sulfate, p. 307.2.

Antimicrobial Action

As for Gentamicin Sulfate, p. 307.2. Tobramycin is reported to be somewhat more active *in vitro* than gentamicin against *Pseudomonas aeruginosa* and less active against *Serratia*, staphylococci, and enterococci; however these differences do not necessarily translate into differences in clinical efficacy.

Cross-resistance between tobramycin and gentamicin is generally seen, but about 10% of strains resistant to gentamicin are susceptible to tobramycin.

Pharmacokinetics

As for Gentamicin Sulfate, p. 307.3.

After intramuscular use of tobramycin, peak plasma concentrations occur within 30 to 90 minutes and concentrations of about 4 micrograms/mL have been reported following doses of 1 mg/kg. Usual doses by slow intravenous injection may result in plasma concentrations which briefly exceed 12 micrograms/mL. A plasma half-life of 2 to 3 hours has been reported. Sufficient tobramycin may be absorbed after inhalation to produce systemic adverse effects (see Effects on the Ear, p. 380.3).

Inhalation. References.

1. Touw DJ, *et al.* Pharmacokinetics of aerosolized tobramycin in adult patients with cystic fibrosis. *Antimicrob Agents Chemother* 1997; 41: 184–7.
2. Beringer PM, *et al.* Pharmacokinetics of tobramycin in adults with cystic fibrosis: implications for once-daily administration. *Antimicrob Agents Chemother* 2000; 44: 809–13.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Alveoterol; Belbarmicina; Bideon Biotic; Bioptic; Fotex; Gotabiotic D; Gotabiotic; Klonamicin; Oftalbrax; Pulbronkal; Radina; Tobi; Tobrabiotic; Tobradosa; Tobragan; Tobral; Tobralep; Tobraler; Tobranet†; Tobrex; Tofib; Toflamixina†; Tuberbut; Xao T; Xibrax; ***Austral.***: Nebcin†; Tobi; Tobra-Day; Tobrex; ***Austria***: Bramitob; Cromycin; Tobi; Tobrasix; Tobrex; ***Belg.***: Obracin; Tobi; Tobravisc; Tobrex; ***Braz.***: Bramitob; Tobracin; Tobracular; Tobraftal; Tobragan; Tobralox; Tobramina; Tobranom†; Tobrex; ***Canad.***: Tobi; Tobrex; ***Chile***: Notrix; Tobragan; Tobrex; Tobrin; Trazil; Tuberbut; Xolof; Zoteon; ***China***: Eyebrex (艾若); Jia Nuo Tai (佳诺泰); Rui Nuo Sai (瑞诺赛); Tai Tuo (泰托); Tai Xing (泰星); Tobrex (托百士); *Tuo Xin* (妥欣); ***Cz.***: Bramitob; Brulamycin†; Tobi; Tobrex; ***Denm.***: Nebcina; Tobi; Tobrex; ***Fin.***: Tobi; Tobrex; Tomycin; ***Fr.***: Nebcine; Tobi; Tobrabact; Tobrex; ***Ger.***: Bramitob; Gemebcin; Tobi; Tobra-cell†; Tobramaxin; ***Gr.***: Bramitob; Brulamycin; Colther; Eyebrex; Eyetobrin; Ikobel; Monobracin; Monotobrin; Nebcin; Thilo-micine; Tirselon; Tobi; Tobrex; Zerodiar; ***Hong Kong***: Tobrex; Toracin†; ***Hung.***: Bramitob; Brulamycin; Tobi; Tobrex; ***India***: Bactob; Eltol; Eyebrex; Fytobra; Glytob; Ibrex; Intob; MDas; Mytob; Mytobra; Nutob; Obra; Ocutob; Tobacin; Tobazon†; Tobraneg; ***Indon.***: Bralifex; Dartobcin†; Isotic Tobryne; Tobrex; *Tobryne*†; ***Irl.***: Bramitob; Tobi; Tobravisc†; ***Israel***: Bramitob; Tobi; Tobrex; ***Ital.***: Bramicil; Bramitob; Nebicina; Tobi; Tobrabact; Tobral; Tobrastill; ***Jpn***: Tobi; ***Malaysia***: Tobrex; ***Mex.***: Eyebrex; Isenia; Micitrex†; Obry; Poentobral; Tobrex; Trazil; Verbram; ***Neth.***: Bramitob; Nebris; Obracin; Tobi; Tobrabact; Tobrex; ***Norw.***: Nebcina; Tobi; Tobrex; ***NZ***: Nebcin; Tobra-Day; Tobrex; ***Philipp.***: Consac; Ramitop; Tobra-V; Tobrex; ***Pol.***: Bramitob; Tobi; Tobrex; Tobrexan; Tobrosopt; ***Port.***: Bramitob; Tobi; Tobra-Gobens; Tobrex; Tobrexan; Tobridavi†; Tobrineb; ***Rus.***: Bramitob (Брамитоб); Brulamycin (Брулампцин); Nebcin (Небцин); Tobi (Тоби); Tobrex (Тоброкс); Tobropt (Тобропт); ***S.Afr.***: Nebcin; Tobi; Tobrex; ***Singapore***: Ocusyn; Tobrex; ***Spain***: Bramitob; Tobi; Tobra Gobens; Tobrabact; Tobrex; Tobrineb; ***Swed.***: Nebcina; Tobi; Tobrex; ***Switz.***: Bramitob; Obracin; Tobi; Tobrex; ***Thai.***: Tobrex; ***Turk.***: Nebcin; Promesin; Thilomaxine; Tobel; Tobi; Tobrased; Tobrex; Tobrinex; Tobsin; ***UK***: Bramitob; Tobi; Tobravisc; ***Ukr.***: Tobrex (Тоброкс); Tobrimed (Тобримед); ***USA***: AkTob; Bethkis; Tobi; Tobrasol; Tobrex; ***Venez.***: Poentobral; Tobranax; Tobrasol; Tobrex.

Multi-ingredient Preparations. *Arg.*: Antibioptal; Bicrinol; Bideon Biotic Plus; Biocort; Bioptic DX; Decadron con Tobramicina; Fotadex; Gotabiotic F; Ingebrax†; Klonamicin Compuesto; Larsen; *Lotemicin*; *Polioftal*; Purpumicina; Radina Dex; Tobrabiotic D; Tobracort†; Tobradex; Tobradicio†; Tobragan D; Tobralep DX; Tobraler DX; Tobratlas Dexa; Tobratlas; Toflam Plus; Toflam; Toflamixina Plus†; Vistadex; Xibradex; Zylet; ***Austria***: Tobradex; ***Belg.***: Ocubrax; Tobradex; ***Braz.***: Tobracin D; Tobracort; Tobradex; Zylet; ***Canad.***: Tobradex; ***Chile***: Poentobral Plus; Tobradex; Tobragan D; Tobrin-D; Todexona; Trazidex; Xolof D; ***China***: Dian Shu (典舒); Jia Ming (佳名); TobraDex (典必殊); ***Cz.***: Tobradex; ***Denm.***: Tobradex; ***Fin.***: Tobrasone; ***Fr.***: Tobradex; ***Ger.***: Tobradex; ***Gr.***: Dexamycin; Eyebrex-Dexa; Lofoto; O-Biotic Thilomicine Dex; Tobradex; Tobrafen; ***Hong Kong***: Tobradex; ***Hung.***: Tobradex; ***India***: FML-T; Glytob-D; LT-Cin; Mogitob-D; Nutob-F; Obra-D; Obra-F; Obrasone; Ocutob-D; Tobazon DM†; ***Indon.***: Bralifex Plus; Isotic Tobrizon; Tobradex; ***Israel***: Zylet; ***Ital.***: Tobradex; ***Malaysia***: Tobradex; ***Mex.***: Isenia-Dex; Obrydex; Obrypre; Poentobral D; Poentobral F; Tobracort; Tobradex; Trazidex; Trazinac; Zyleth; ***Neth.***: Tobradex; ***Norw.***: Tobrasone; ***NZ***: Tobradex; ***Philipp.***: Duocom; Mydexin; Mytodex; Ramtrex; Rapidex; Tobradex; ***Pol.***: Tobradex; ***Port.***: Tobradex; ***Rus.***: Tobradex (Тобрадекс); Tobrasone (Тобразон); ***S.Afr.***: Tobradex; ***Singapore***: Tobradex; Zylet; ***Spain***: Ocubrax; Tobradex; ***Swed.***: Tobrasone; ***Switz.***: Tobradex; Tobrafen; ***Thai.***: Tobradex; Zylet; ***Turk.***: Combidex; Ocubrax; Tobradex; ***UK***: Tobradex; ***Ukr.***: Ocubrax (Окуброкс)†; Tobradex (Тобрадекс); ***USA***: Tobradex; Zylet; ***Venez.***: Poentobral Plus; Tobracort; Tobradex; Tobragan D; Todenac; Todex; Trazidex; Trazinac.

Pharmacopoeial Preparations

BP 2014: Tobramycin Injection;

USP 36: Tobramycin and Dexamethasone Ophthalmic Ointment; Tobramycin and Dexamethasone Ophthalmic Suspension; Tobramycin and Fluorometholone Acetate Ophthalmic Suspension; Tobramycin for Injection; Tobramycin Inhalation Solution; Tobramycin Injection; Tobramycin Ophthalmic Ointment; Tobramycin Ophthalmic Solution.

Tosufloxacin *(USAN, rINN)*

A-61827; Abbott-61827; Tosufloxacine; Tosufloxacino; Tosufloxacinum; Тосуфлоксацин.

(±)-7-(3-Amino-1-pyrrolidinyl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid.

$C_{19}H_{15}F_3N_4O_3$=404.3

CAS — 100490-36-6 (anhydrous tosufloxacin); 108138-46-1 (anhydrous tosufloxacin); 107097-79-0 (tosufloxacin monohydrate).

UNII — GHJ553KQPS (tosufloxacin); 6239812J7L (tosufloxacin monohydrate).

Tosufloxacin Tosilate *(rINNM)*

A-64730; T-3262; Tosilato de tosufloxacino; Tosufloxacin Tosylate; Tosufloxacine, Tosilate de; Tosufloxacini Tosilas; Tosufloxacino, tosilato de; Тосуфлоксацина Тозилат.

Tosufloxacin toluene-4-sulphonate monohydrate.

$C_{19}H_{15}F_3N_4O_3C_7H_8O_3S.H_2O$=594.6

CAS — 115964-29-9; 144742-63-2.

UNII — NO6NM634EH.

Profile

Tosufloxacin is a fluoroquinolone antibacterial with properties similar to those of ciprofloxacin (p. 261.1). It is given orally as the tosilate in the treatment of susceptible infections in usual doses of 300 to 450 mg daily in 2 or 3 divided doses.

For blepharitis, conjunctivitis, corneal ulcers, and other eye infections caused by susceptible strains of bacteria, eye drops containing 0.3% of tosufloxacin tosilate are used.

References.

1. Niki Y. Pharmacokinetics and safety assessment of tosufloxacin tosilate. *J Infect Chemother* 2002; 8: 1–18.
2. Takahama H, Tazaki H. Tosufloxacin tosilate-induced thrombocytopenic purpura. *J Dermatol* 2007; 34: 465–7.
3. Kamiya K, *et al.* Corneal deposits after topical tosufloxacin in a patient with poor tear secretion. *Cornea* 2009; 28: 114–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***China***: Ang Te (昂特); Ci Er Tai (赐尔泰); Nuo Li Si (诺力思); ***Jpn***: Ozex.

Trimethoprim *(BAN, USAN, rINN)*

BW-56-72; NSC-106568; TMP; Triméthoprime; Trimethoprimum; Trimethoxyprim; Trimetoprimi; Trimetoprim; Trimetoprima; Trimetoprimas; Trimetoprym; Триметоприм.

5-(3,4,5-Trimethoxybenzyl)pyrimidine-2,4-diamine.

$C_{14}H_{18}N_4O_3$=290.3

CAS — 738-70-5.

ATC — J01EA01.

ATC Vet — QJ01EA01; QJ51EA01.

UNII — AN164J8Y0X.

NOTE. Compounded preparations of trimethoprim may be represented by the following names:

- Co-trifamole (*BAN*)—trimethoprim 1 part and sulfamoxole 5 parts (see p. 277.3)
- Co-trimazine (*BAN*)—trimethoprim 1 part and sulfadiazine 5 parts
- Co-trimoxazole (*BAN*)—trimethoprim 1 part and sulfamethoxazole 5 parts (see p. 277.3)
- Co-trimoxazole (*PEN*)—trimethoprim and sulfamethoxazole.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 8: (Trimethoprim). A white or yellowish-white powder. Very slightly soluble in water; slightly soluble in alcohol.

USP 36: (Trimethoprim). White to cream-coloured, odourless crystals or crystalline powder. Very slightly soluble in water; slightly soluble in alcohol and in acetone; soluble in benzyl alcohol; practically insoluble in carbon tetrachloride and in ether; sparingly soluble in chloroform and in methyl alcohol. Store in airtight containers. Protect from light.

Trimethoprim Sulfate *(BANM, USAN, rINNM)*

BW-72U; Sulfato de trimetoprima; Trimethoprim Sulphate; Triméthoprime, Sulfate de; Trimethoprimi Sulfas; Trimetoprim Sülfat; Trimetoprima, sulfato de; Триметоприма Сульфат.

$(C_{14}H_{18}N_4O_3)_2.H_2SO_4$=678.7

CAS — 56585-33-2.

UNII — E377MF8EQ8.

Pharmacopoeias. In *Viet.* and *US*.

USP 36: (Trimethoprim Sulfate). A white to off-white crystalline powder. Soluble in water, in alcohol, in dilute mineral acids, and in fixed alkalis. pH of a 0.05% solution in water is between 7.5 and 8.5. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Trimethoprim is a diaminopyrimidine antibacterial that is used for the treatment of infections due to sensitive organisms, including gastro-enteritis and respiratory-tract infections, and in particular for the treatment and prophylaxis of urinary-tract infections. For details of these infections and their treatment, see Choice of Antibacterial, p. 172.2.

Trimethoprim is also used with sulfonamides. The most common combination is co-trimoxazole (trimethoprim with sulfamethoxazole) (p. 277.3). Other combinations are co-trimazine (with sulfadiazine) and co-trifamole (with sulfamoxole) (see p. 277.3); trimethoprim has also been used with sulfamerazine, sulfametopyrazine, sulfametrole, and sulfamethoxypyridazine, and, in veterinary practice, with sulfadiazine, sulfadoxine, sulfamethoxazole, and sulfaquinoxaline.

Trimethoprim with sulfamethoxazole (co-trimoxazole) or with dapsone is used in the management of pneumocystis pneumonia (p. 567.2).

The usual oral dose of trimethoprim in acute infection is 100 or 200 mg twice daily; doses of 200 or 300 mg daily as a single dose are also used. For the dosage of trimethoprim when given with sulfamethoxazole, see under Co-trimoxazole, p. 277.3. Up to 20 mg/kg daily may be given with dapsone for the treatment of pneumocystis pneumonia. For long-term prophylaxis the usual dose is 100 mg at night.

Trimethoprim has been given intravenously by injection or infusion as the lactate although doses are in terms of the base. The usual dose has been 200 mg every 12 hours; initial doses may be higher or given more frequently in severely ill patients.

Care should be taken in patients with moderate to severe renal impairment and doses generally should be reduced.

For doses used in renal impairment, and for details of use in children, see p. 384.1.

Trimethoprim with polymyxin B has been used topically in the treatment and prophylaxis of eye infections. Trimethoprim sulfate and trimethoprim hydrochloride are also used.

Administration. *SINGLE-DOSE THERAPY.* Although there are obvious advantages to a single-dose regimen, one study[1] found that there was about a 1 in 4 risk of recurrence of urinary-tract infection within 10 days in 50 children given, according to age, a single oral dose of 75 to 450 mg of trimethoprim. The problems with a single-dose regimen were confirmed by others[2] in a study involving 344 evaluated cases of cystitis in 306 women. Only 122 of 173 cases treated with trimethoprim 320 mg as a single oral dose were evaluated as cured after 5 weeks, compared with 149 of 171 given 160 mg twice daily for 1 week (71 versus

87%). Again, these results suggest that about 1 patient in 4 would have to be re-treated.

1. Nolan T, *et al.* Single dose trimethoprim for urinary tract infection. *Arch Dis Child* 1989; 64: 581–6.
2. Österberg E, *et al.* Efficacy of single-dose versus seven-day trimethoprim treatment of cystitis in women: a randomized double-blind study. *J Infect Dis* 1990; 161: 942–7.

Administration in children. Trimethoprim may be used in children for the treatment of infections caused by susceptible organisms. Although in the UK, trimethoprim is only licensed for oral use in those 6 weeks of age and older, the *BNFC* provides the following dose recommendations:

For **treatment** of urinary- or respiratory-tract infections:

- neonates: initially 3 mg/kg as a single dose, followed by 1 to 2 mg/kg twice daily
- children from 1 month of age: 4 mg/kg (to a maximum of 200 mg) twice daily

  or

  children 6 weeks to 6 months of age: 25 mg twice daily
  children 6 months to 6 years of age: 50 mg twice daily
  children from 6 years of age: 100 mg twice daily

For the **prophylaxis** of urinary-tract infections:

- neonates and children: 2 mg/kg (to a maximum of 100 mg) at night

Administration in renal impairment. Oral doses of trimethoprim should generally be reduced in patients with moderate to severe renal impairment according to the estimated glomerular filtration rate (eGFR):

- eGFR 15 to 30 mL/minute per 1.73m^2: normal dose for 3 days reduced to one-half thereafter
- eGFR below 15 mL/minute per 1.73m^2: half the normal dose from the start of treatment

Plasma concentrations should be monitored in patients with severe renal impairment.

Adverse Effects and Treatment

Trimethoprim is reasonably well tolerated in general, and the most frequent adverse effects at usual doses are pruritus and rash (in about 3 to 7% of patients) and mild gastrointestinal disturbances including nausea, vomiting, and glossitis. Adverse effects, including hypersensitivity reactions, are more common in patients with AIDS, about 50 to 60% of whom will need to change their treatment due to adverse effects.

Rarely, more severe effects have been reported. Sulfonamide-like skin reactions including exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have occurred. Disturbances of liver enzyme values and cholestatic jaundice have been associated with trimethoprim. Rises in serum creatinine and blood-urea nitrogen have been reported although it is unclear whether this represents genuine renal dysfunction or inhibition of tubular secretion of creatinine. Photosensitivity has been reported. Fever is not uncommon but occasionally hypersensitivity reactions may be severe and anaphylaxis and angioedema have been reported. Cases of aseptic meningitis have also occurred.

Trimethoprim may cause a depression of haematopoiesis due to interference of the drug in the metabolism of folic acid, particularly when given over a prolonged period or in high doses. This may manifest as megaloblastic anaemia, or as thrombocytopenia and leucopenia; methaemoglobinaemia has also been seen. Folinic acid may be given to counter this effect; for details of the folinic acid dose regimen, see Uses and Administration of Folinic Acid, p. 2067.1. Trimethoprim is teratogenic in *animals*.

For further information on the adverse effects of trimethoprim when used with sulfamethoxazole, see Co-trimoxazole, p. 278.3.

Effects on the eyes. There have been isolated reports of bilateral anterior uveitis associated with trimethoprim.[1-4] The reaction has recurred on rechallenge with trimethoprim.[1,2] In one case a patient developed uveitis after co-trimoxazole, and subsequently uveitis with retinal haemorrhage after trimethoprim alone.[3] In one report,[2] uveitis was associated with arthritis and Stevens-Johnson syndrome.

1. Gilroy N, *et al.* Trimethoprim-induced aseptic meningitis and uveitis. *Lancet* 1997; 350: 112.
2. Arola O, *et al.* Arthritis, uveitis, and Stevens-Johnson syndrome induced by trimethoprim. *Lancet* 1998; 351: 1102.
3. Kristinsson JK, *et al.* Bilateral anterior uveitis and retinal haemorrhages after administration of trimethoprim. *Acta Ophthalmol Scand* 1997; 75: 314–15.
4. Pathak S, Power B. Bilateral acute anterior uveitis as a side effect of trimethoprim. *Eye* 2007; 21: 252–3.

Hyperkalaemia. Hyperkalaemia is a common complication of both high- and standard-dose trimethoprim therapy,[1] and in some cases may be serious or life-threatening. The drug is thought to have potassium-sparing properties similar to amiloride, with hyperkalaemia usually developing in the first 3 to 10 (usually 4 to 5) days of therapy. Although clinically important hyperkalaemia may develop in the absence of any predisposing factors, those at highest risk appear to be patients with renal impairment or other conditions affecting potassium homoeostasis (such as hypoaldosteronism), those taking other potassium-altering medications (including ACE inhibitors, NSAIDs, and potassium-sparing diuretics), or those taking high doses of trimethoprim.

1. Perazella MA. Trimethoprim-induced hyperkalaemia: clinical data, mechanism, prevention and management. *Drug Safety* 2000; 22: 227–36.

Precautions

Trimethoprim should not be given to patients with a history of hypersensitivity to the drug, and it should be stopped if a rash appears. Care is necessary in giving trimethoprim to patients with renal impairment to avoid accumulation and toxicity: it should not be given in severe renal impairment unless blood concentrations can be monitored. It should be used with caution in patients with severe hepatic damage as changes may occur in the absorption and metabolism of trimethoprim.

It is suggested that regular haematological examination should be made during prolonged courses of treatment although the *BNF* considers evidence of their practical value to be unsatisfactory; patients or their carers should be told how to recognise signs of blood toxicity and should be advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, purpura, bruising or bleeding develop. Trimethoprim should not usually be given to patients with serious haematological disorders and particularly not in megaloblastic anaemia secondary to folate depletion. Care should be taken in patients with actual, or possible, folate deficiency and use of folinic acid should be considered. Trimethoprim should be avoided during pregnancy. Elderly patients may be more susceptible to adverse effects and a lower dosage may be advisable.

Trimethoprim may interfere with some diagnostic tests, including serum-methotrexate assay where dihydrofolate reductase is used and the Jaffé reaction for creatinine.

For further information on precautions for trimethoprim given with sulfamethoxazole, see Co-trimoxazole, p. 279.1.

Breast feeding. Trimethoprim appears in breast milk and the US licensed product information has stated that care is required when it is used in breast-feeding mothers.

The last available guidelines from the American Academy of Pediatrics considered trimethoprim, when given with sulfamethoxazole, to be compatible with breast feeding.[1]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/05/04)

Fragile X syndrome. A warning that trimethoprim and other folate antagonists should be avoided in children with the fragile X chromosome, which is associated with mental retardation and is folate sensitive.[1]

1. Hecht F, Glover TW. Antibiotics containing trimethoprim and the fragile X chromosome. *N Engl J Med* 1983; 308: 285–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies trimethoprim as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 15/08/11)

Interactions

Trimethoprim may increase serum concentrations of some drugs, including phenytoin, digoxin, procainamide, rosiglitazone, and repaglinide, potentiating their effect. This may be due to competitive inhibition of renal excretion, decreased metabolism, or both. It has been suggested that trimethoprim may potentiate the effects of warfarin. Trimethoprim has been reported to reduce the renal excretion and increase blood concentrations of zidovudine, zalcitabine, and lamivudine. Trimethoprim and dapsone increase each other's serum concentrations, whereas rifampicin may decrease trimethoprim concentrations.

An increased risk of nephrotoxicity has been reported with the use of trimethoprim or co-trimoxazole and ciclosporin. Intravenous use of trimethoprim and sulfonamides may reduce ciclosporin concentrations in blood. Hyponatraemia has been reported in patients given trimethoprim with diuretics. An increased risk of thrombocytopenia has been seen in elderly patients given co-trimoxazole with diuretics, although it is unclear which component of the antibacterial is responsible.

Use of trimethoprim with other depressants of bone marrow function may increase the likelihood of myelosuppression, and there may be a particular risk of megaloblastic anaemia if it is given with other folate inhibitors, such as pyrimethamine or methotrexate.

Severe hyperkalaemia has been noted in patients given trimethoprim (or co-trimoxazole) with an ACE inhibitor.

Antimicrobial Action

Trimethoprim is a dihydrofolate reductase inhibitor. It inhibits the conversion of bacterial dihydrofolic acid to tetrahydrofolic acid which is necessary for the synthesis of certain amino acids, purines, thymidine, and ultimately DNA. It acts in the same metabolic pathway as the sulfonamides. It exerts its selective action because of a far greater affinity for the bacterial than the mammalian enzyme. Trimethoprim may be bacteriostatic or bactericidal depending on growth conditions; pus, for example, may inhibit the action of trimethoprim because of the presence of thymine and thymidine.

Spectrum of activity. Trimethoprim is active against many Gram-negative and Gram-positive aerobes, as well as some protozoa. The following species are usually susceptible (but see also Resistance, below).

- Many Gram-positive cocci are sensitive, including *Staphylococcus aureus*, streptococci including *Streptococcus pyogenes*, *Str. pneumoniae* (although resistance has been reported worldwide), and the viridans streptococci, and to a variable extent enterococci, although their sensitivity is reduced in the presence of folate. Trimethoprim is bactericidal against most strains of *Listeria monocytogenes* and some strains of *Nocardia* spp. are susceptible.
- Other sensitive Gram-positive organisms include strains of *Listeria*, *Corynebacterium diphtheriae*, and the Gram-positive bacilli.
- Among the Gram-negative organisms, most of the Enterobacteriaceae are susceptible, or moderately so, including *Citrobacter*, *Enterobacter*, *Escherichia*, *Hafnia*, *Klebsiella*, *Proteus*, *Providencia*, *Salmonella*, *Serratia*, *Shigella*, and *Yersinia* species. *Vibrio cholerae* are generally susceptible but resistant strains are well documented. *Haemophilus influenzae* and *H. ducreyi* are usually susceptible, however, *H. ducreyi* strains with increased resistance to trimethoprim have been reported. Pathogenic *Neisseria* spp. are moderately resistant, while strains of *Helicobacter pylori*, *Moraxella catarrhalis*, *Pseudomonas aeruginosa*, and *Bacteroides* spp. are generally resistant.
- Anaerobic species are usually resistant.
- *Chlamydiaceae*, *Mycoplasma*, and *Ureaplasma* species and *Treponema pallidum* are generally resistant.
- *Mycobacterium tuberculosis* and *M. haemophilum* are resistant although *M. marinum* may not be.
- Trimethoprim has some activity against *Pneumocystis jirovecii* and against some protozoa such as *Naegleria*, *Plasmodium*, and *Toxoplasma*.

Activity with other antimicrobials. Because their modes of action are complementary, affecting different stages in folate metabolism, a potent synergistic effect exists between trimethoprim and sulfonamides against many organisms *in vitro*.

Fixed-dose combinations of trimethoprim with various sulfonamides are available, of which co-trimoxazole (trimethoprim with sulfamethoxazole in a 1:5 mixture) is the most widely used. For further details on the antimicrobial action of co-trimoxazole, see p. 280.1.

Synergy has also been reported with rifampicin, and with the polymyxins.

Resistance. Resistance to trimethoprim may be due to several mechanisms. Clinical resistance is often due to plasmid-mediated dihydrofolate reductases that are resistant to trimethoprim: such genes may become incorporated into the chromosome via transposons. Resistance may also be due to overproduction of dihydrofolate reductase, changes in cell permeability, or bacterial mutants which are intrinsically resistant to trimethoprim because they depend on exogenous thymine and thymidine for growth. Despite fears of a rapid increase in resistance if trimethoprim was used alone there is little evidence that this has been any worse than in areas where it has been used with sulfonamides. Nonetheless, trimethoprim resistance has been reported in many species, and very high frequencies of resistance have been seen in some developing countries, particularly among the Enterobacteriaceae.

References.

1. Huovinen P, *et al.* Trimethoprim and sulfonamide resistance. *Antimicrob Agents Chemother* 1995; 39: 279–89.

Pharmacokinetics

Trimethoprim is rapidly and almost completely absorbed from the gastrointestinal tract and peak concentrations occur about 1 to 4 hours after an oral dose; peak plasma concentrations of about 1 microgram/mL have been reported after a single 100-mg dose. About 45% is bound

to plasma proteins. Trimethoprim is widely distributed to various tissues and fluids including kidneys, liver, lung and bronchial secretions, saliva, aqueous humour, prostatic tissue and fluid, and vaginal secretions; concentrations in many of these tissues are reported to be higher than serum concentrations but concentrations in the CSF are about one-quarter to one-half of those in serum. Trimethoprim readily crosses the placenta and it appears in breast milk. The half-life is about 8 to 10 hours in adults and somewhat less in children, but is prolonged in severe renal impairment and in neonates, whose renal function is immature.

Trimethoprim is excreted mainly by the kidneys through glomerular filtration and tubular secretion. About 10 to 20% of trimethoprim is metabolised in the liver and small amounts are excreted in the faeces via the bile, but most, about 40 to 60% of a dose, is excreted in urine, mainly as unchanged drug, within 24 hours. Trimethoprim is removed from the blood by haemodialysis to some extent.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Alprim; Triprim; ***Austria***: Infectotrimet; Motrim; Solotrim†; Triprim; ***Cz.***: Triprim; ***Denm.***: Trimopan; ***Fin.***: Trimetin; Trimex†; Trimopan; ***Ger.***: InfectoTrimet; ***Hong Kong***: Primsol; ***Irl.***: Monotrim; Trimoptin; ***Malaysia***: Alprim†; ***NZ***: TMP; ***Pol.***: Trimesan; Urotrim; ***S.Afr.***: Purium†; ***Singapore***: Alprim; ***Spain***: Tediprima; ***Swed.***: Idotrim; ***Thai.***: Trimethop; Utisept†; ***UAE***: Trimol-A; ***UK***: Monotrim; Trimopan; ***USA***: Primsol; Proloprim; Trimpex.

Multi-ingredient Preparations. ***Arg.***: Adrenol; Bacti-Uril; Bacticel; Bactrim Balsamico; Bactrim; Cotrizol-G; Danferane; Dosulfin Bronquial; Dosulfin Fuerte; Enterobacticel; Neoftalm Dexa; Neoftalm; Neolag; Netocur Balsamico; Netocur; Neumobacticel; Novidrine; Rifaprim; Sulfagrand; Trimepol D†; Trimepol†; Tritenk; Urisept NF; ***Austral.***: Bactrim; Resprim; Septrin; Trimoxazole†; ***Austria***: Bactrim; Cotribene; Eusaprim; Lidaprim; Oecotrim†; ***Belg.***: Bactrim; Cotrim†; Eusaprim; Polytrim; ***Braz.***: Assepium Balsamico; Assepium; Bac-Sulfitrin; Bacfar; Bacprotin†; Bacteracin; Bactrim; Bactrisan; Bactrizol†; Bactropin; Batrox; Belfactrim F; Benectrin Balsamico; Benectrin; Diazol; Dientrin; Dispeptrin†; Ectrin Balsamico; Ectrin; Gamacutrin†; Imuneprim†; Infectrin; Metoprin Balsamico†; Metoprin; Neotrin; Pulkrin†; Qiftrim; Roytrin; Selectrin Balsamico; Selectrin†; Teutrin; Triclan; Triglobe; Trimexazol; Uroctrim; Uropol†; ***Canad.***: Apo-Sulfatrim; Novo-Trimel; Nu-Cotrimox; PMS-Polytrimethoprim; Polytrim; Protrin; Septra; Trisulfa; ***Chile***: Bacterol; Bactrimel; Entero Micinovo; Septrin; Trelibec; Uro-Micinovo; ***China***: An Li Kang (安立康); Fu Fang Xin Nuo Ming Pian (复方新诺明片); Kui Jian (奎建); Morbifurb (诺德菲); Nuo Da Ming (诺达明); Ou Lin (欧林); Pixian (彼先); Xiaoke (消刻); Xindabao (新达宝); Yu An Li Qing (玉安立清); Zengxiao Lianhuangpian (增效联磺); ***Cz.***: Biseptol; Bismoral†; Primotren†; Sumetrolim; ***Fin.***: Cotrim; Ditrim; Trimetin Duplo†; ***Fr.***: Bactrim; ***Ger.***: Berlocid†; Cotrim-Diolan; Cotrim; CotrimHefa†; Cotrimhexal†; Cotrimox-Wolff†; Cotrimstada†; Drylin†; Eusaprim; Kepinol; TMS†; ***Gr.***: Bactrimel; Bioprim; Blaxezan; Biexon; Epahol; Lidaprim; Oradin; Santafurin; Septrin; Solfoton; Stremycil-T; Sunicol; Trilogan; Ylestrom; ***Hong Kong***: Chemoprim; Cotrim; Dhatrin; Letus; Lidaprim; Resprim†; Septol†; Septrin†; Suprim†; Synco-SMZT†; Trimetrin†; Trisul†; Uni-Sulfaprim†; ***Hung.***: Cotripharm; Sumetrolim; ***India***: Alcorim-F; Antrima; Aubril; Bactrim; Cadiprim; Chemotrin; Ciplin; Colizole; Cortina; Cotribid Kid; Cotrimox; Cotrizole; Kombina; L-Trim; Larprim; Methoxaprim; Moly Kid; Mountrim; Neoprim; Okatrim DS; Oriprim-P; Oriprim; Otrim; Sepmax; Septran; Supristol; Tabrol; Trisulfose; ***Indon.***: Bactoprim Combi; Bactricid; Bactrim; Bactrizol; Cotrim†; Cotrimol†; Dotrim; Dumotrim†; Erphatrim; Ikaprim; Infatrim; Kaftrim; Lapikot; Licoprima; Meditrim†; Meprotrin; Moxalas; Nufaprim; Ottoprim; Pehatrim; Primadex; Primazole; Primsulfon; Sanprima; Septrin; Spectrem; Sulprim†; Sultrimmix†; Trimezol; Triminex†; Trimoxsul; Trixzol†; Trizole; Ulfaprim†; Wiatrim; Xepaprim; Zoltrim; Zultrop; ***Irl.***: Septrin; ***Israel***: Diseptyl; Resprim; Septrin; ***Ital.***: Bactrim; Chemitrim; Eusaprim†; ***Jpn***: Bactramin; Baktar; ***Malaysia***: Bacin; Bactrim; Balin; Beaglobe; Chemix; Cotrim; Oftalmotrim; Resprim†; Trimexazole; Trizine; Trizole; ***Mex.***: Andoprim†; Anitrim; Apo-Trinelax; Bacpiryl; Bactelan; Bacteric†; Bactide†; Bactilen; Bactiver; Bactrim Compositum; Bactrim; Bactropin; Bateral; Batrizol; Bioprim; Bisultrim; Brogamax; Dertrin; Dibaprim; Ectaprim; Esteprim; Eutrim; Partropin; Fectri; Guayaprin; Kaltrim; Maxtrim; Metoxiprim; Mixange; Neofatrim; Octex; Octiban; Odisulfan; Pisatrina†; Polibatrin; Pribac; Protaxol†; Protrim; Rifaprim; Sadocin; Septrin; Servitrim; Soltrim; Sulfawal; Sulfoid Trimetho; Sulfort; Sulprim; Sultral; Thriazol; Tribakin; Trimetoger; Trimetox; Trimexazol; Trimexole Compositum; Trimexole; Trimzol; TS-Bac; Vanadyl; ***Neth.***: Bactrimel; Lidatrim†; Polytrim; Rokiprim; ***Norw.***: Bactrim; ***NZ***: Apo-Sulfatrim†; Deprim; Trisul; ***Philipp.***: Bacidal; Bactille; Bactrim; Bactrinol; Bacxal; Baczole†; Bantizol; Chromo-Z; Combi-Methoxan; Comsid; Costazole†; Cozole†; CTR; Doctrimox; Drilozole; Embatrim; Fedimed; Forteprim; Frocimole; Globaxol; Ivatrim†; Kassemox; Kathrex; Lictora†; Macromed; Moxadden; Moxzole; Neotrim; Onetrim; Oprizole†; Pediatrim; Prizogen; Procor; Renatrim; Rimezone; Rotrace; Scribcin; Septrin; Suprex; Syltrifil; Syndal; Synermed; Timizol; Tricomed; Triforam; Triglobe†; Trim-S; Trimephar; Trimetazole; Trimitrix; Trimocom; Trimoxis; Triphimox; Trizine; Trizole; Xanazole; Zamboprim†; Zolmed; ***Pol.***: Bactrim; Biseptol; Septrin†; ***Swed.***: Bactrim; Microcetim†; Oftalmotrim; Septrin; ***Rus.***: Bactrim (Бактрим); Biseptol (Бисептол); Brifeseptol (Брифесептол); Cotrimol (Котримол); Cotripharm (Котрифарм); Groseptol (Гросептол); Lidaprim (Лидаприм)†; Oriprim (Ориприм); Rancotrim (Ранкотрим)†; Sumetrolim (Суметролим); ***S.Afr.***: Acuco†; Adco-Bencole; Bactrim; Casicot; Co Trim; Cocydal†; Cozole; Doctrim; Durobac; Dynazole; Ilvitrim; Lagatrim; Meditrim; Nucotrim; Purbac; Septran; Spectrim; Trimethox; Trimzol†; Trixazole; Ultrasept; Xerazole; ***Singapore***: Apo-Sulfatrim; Bacin; Balin; BS; Chemix; Co-Trimexazole; Dhatrin; Mortin; Primzole; Suprim; Synco-SMZT; Trimaxazole; Trizine; ***Spain***: Bactopumon; Balsoprim; Bronco Aseptilex Fuerte†; Broncovir; Bronquicisteina†; Bronquidiazina CR; Bronquimar†; Cotrazol†; Eduprim Mucolitico†; Momentol†; Oftalmotrim; Otix; Septrin; Soltrim; ***Swed.***: Bactrim; Eusaprim; ***Switz.***: Bactrim; Cotrim; Escoprim; Lagatrim; Nopil; ***Thai.***: Actin; Actrim; Addtrim; Agsulfa; Babytrim; Bacin; Bactin; Bactoprim; Bactrim; Baczole; Co-Fatrim; Co-Star; Co-Tasian; Co-Tri; Co-Trimed; Co-tromoxazole†; Comox; Comoxole; Coprim†; Coprim; Cotamox; Cotrim; D-Med; GPO-Trim; Herocetine-D; KB Famate; Ko-Cap†; Ko-Kure†; Ladar†; Lastrim; Letus†; M-Moxa; M-Trim; Mano-Trim; Maxitrin; Maxtrim; Medcotrim; Mega-Prim; Metrim; Metxaprim; Mezine; Mycosamthong; Pantrim; Patartim; Po-Trim; Spectrim; Sulbacta†; Sulfometh; Sulprim; Suntrim; Sutrim; Tactrim; Tampo; Toprim; Trifatrim; Trimexazole; Triprim†; Trixzol†; Ximeprim; Zoleprim; ***Turk.***: Bactrim; Bakton; Co-Tripirim; Cotriver; Kemoprim; Metoprim; Mikrosid; Oftalmotrim†; Polycilline†; Polytrim; Septrin; Sulfaprim; Sulfatrim†; Trifen; Trimoks; ***UAE***: Trimol; ***UK***: Fectrim; Septrin; ***Ukr.***: Bactrim (Бактрим); Biseptol (Бисептол); Groseptol (Гросептол); Soluseptol (Солюсептол); Sumetrolim (Суметролим); ***USA***: Bactrim; Cotrim†; Polytrim; Septra; SMZ-TMP; Sulfatrim; ***Venez.***: Bactrimel; Co-Sultrin; Forcrim; Trimecor; Tripur.

Pharmacopoeial Preparations

BP 2014: Co-trimoxazole Infusion; Co-trimoxazole Oral Suspension; Co-trimoxazole Tablets; Dispersible Co-trimoxazole Tablets; Paediatric Co-trimoxazole Oral Suspension; Paediatric Co-trimoxazole Tablets; Trimethoprim Oral Suspension; Trimethoprim Tablets;

USP 36: Polymyxin B Sulfate and Trimethoprim Ophthalmic Solution; Sulfamethoxazole and Trimethoprim Injection; Sulfamethoxazole and Trimethoprim Oral Suspension; Sulfamethoxazole and Trimethoprim Tablets; Trimethoprim Tablets.

Troleandomycin *(BAN, USAN, rINN)*

NSC-108166; Triacetyloleandomycin; Troleandomicina; Troleandomisin; Troléandomycine; Troleandomycinum; Troleandomysiini; Тролеандомицин.

The triacetyl ester of oleandomycin .

$C_{41}H_{67}NO_{15}$=814.0

CAS — 2751-09-9.

ATC — J01FA08.

ATC Vet — QJ01FA08.

UNII — C4DZ64560D.

Pharmacopoeias. In *Fr.*

Profile

Troleandomycin is a prodrug of the macrolide antibacterial oleandomycin that has actions similar to those of erythromycin (p. 291.2). It has been given orally in the treatment of susceptible infections although more effective antibacterials are generally preferred.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Ital.***: Triocetin†; ***Turk.***: Tekmisin.

Tulathromycin *(USAN, rINN)*

CP-472295 (component A); CP-547272 (component B); Tulathromycine; Tulathromycinum; Tulatromicina; Тулатромицин.

$C_{41}H_{79}N_3O_{12}$=806.1

CAS — 217500-96-4 (component A); 280755-12-6 (component B).

ATC Vet — QJ01FA94.

UNII — Q839I13422 (tulathromycin); 897A3KN7AP (tulathromycin component A); T5PDD839DA (tulathromycin component B).

NOTE. The name Draxxin has been used as a trade mark for tulathromycin.

Profile

Tulathromycin is a macrolide antibacterial used in veterinary medicine for the treatment of susceptible infections in cattle and pigs.

Tylosin *(BAN, rINN)*

Tilosina; Tilozin; Tylosiini; Tylosine; Tylosinum; Tylozyna; Типозин.

$C_{46}H_{77}NO_{17}$=916.1

CAS — 1401-69-0.

ATC Vet — QJ01FA90; QJ51FA90.

UNII — YEF4JXN031.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*, both for veterinary use.

Ph. Eur. 8: (Tylosin for Veterinary Use; Tylosin BP 2014; Tylosin BP(Vet) 2014). A mixture of macrolide antibiotics produced by a strain of *Streptomyces fradiae* or by any other means. The main component of the mixture is tylosin A, but tylosin B (desmycosin), tylosin C (macrocin), and tylosin D (relomycin) may also be present. An almost white or slightly yellow powder. Slightly soluble in water; freely soluble in dehydrated alcohol and in dichloromethane. It dissolves in dilute solutions of mineral acids. A 2.5% suspension in water has a pH of 8.5 to 10.5. Protect from light.

USP 36: (Tylosin). A macrolide antibiotic substance or mixture of such substances produced by the growth of *Streptomyces fradiae* or by any other means. A white to buff-coloured powder. Slightly soluble in water; soluble in alcohol, in amyl acetate, in chloroform, and in dilute mineral acids; freely soluble in methyl alcohol. It loses not more than 5% of its weight on drying. Protect from light, moisture, and temperatures exceeding 40 degrees.

Tylosin Tartrate *(BANM, rINNM)*

Tartrato de tilosina; Tilosina, tartrato de; Tilozin-tartarát; Tylosiinitartraatti; Tylosin tartarát; Tylosine, Tartrate de; Tylosini tartras; Tylosintartrat; Tylozyny winian; Тилозина Тартрат.

$(C_{46}H_{77}NO_{17})_2.C_4H_6O_6$=1982.3

CAS — 1405-54-5.

UNII — 5P4625C51T.

Pharmacopoeias. In *Eur.* (see p. vii) and *US* for veterinary use.

Ph. Eur. 8: (Tylosin Tartrate for Veterinary Use; Tylosin Tartrate BP 2014; Tylosin Tartrate BP(Vet) 2014). An almost white or slightly yellow hygroscopic powder. Freely soluble in water and in dichloromethane; slightly soluble in dehydrated alcohol. It dissolves in dilute solutions of mineral acids. A 2.5% solution in water has a pH of 5.0 to 7.2. Store in airtight containers. Protect from light.

USP 36: (Tylosin Tartrate). A tartrate of a mixture of macrolide antibiotic substances, or the mixture of such substances, produced by the growth of *Streptomyces fradiae*, or by any other means. Its potency is not less than 800 micrograms of tylosin per mg, calculated on the dried basis.

An almost white or slightly yellow, hygroscopic powder. Freely soluble in water and in dichloromethane; slightly soluble in alcohol. It dissolves in dilute solutions of mineral acids. pH of a 2.5% solution in water is between 5.0 and 7.2. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Profile

Tylosin is a macrolide antibacterial with actions similar to those of erythromycin (p. 291.2). Tylosin and its phosphate and tartrate salts are used in veterinary medicine in the prophylaxis and treatment of infections caused by susceptible organisms.

Tylosin and tylosin phosphate have been added to animal feeding stuffs as growth promotors for pigs.

Tylvalosin Tartrate *(USAN, rINNM)*

Acetyl Isovaleryl Tylosin Tartrate; Acetylisovaleryltylosin Tartrate; Tartrato de tilvalosina; Tylvalosine, Tartrate de; Tylvalosini Tartras; Тильвальозина Тартрат.

(4*R*,5*S*,6*S*,7*R*,9*R*,11*E*,13*E*,15*S*,16*R*)-15-[[(6-Deoxy-2,3-di-*O*-methyl-β-*D*-allopyranosyl)oxy]methyl]-6-({3,6-dideoxy-4-*O*-[2,6-dideoxy-3-*C*-methyl-4-*O*-(3-methylbutanoyl)-α-L-*ribo*-hexopyranosyl]-3-(dimethylamino)-β-D-glucopyranosyl}oxy)-16-ethyl-5,9,13-trimethyl-2,10-dioxo-7-(2-oxoethyl)oxacyclohexadeca-11,13-dien-4-yl acetate (2*R*,3*R*)-2,3-dihydroxybutanedioate.

$C_{53}H_{83}NO_{19}.C_4H_6O_6$

CAS — 63409-12-1 (tylvalosin); 63428-13-7 (tylvalosin tartrate).

ATC Vet — QJ01FA92.

UNII — AL5667FY0W.

The symbol † denotes a preparation no longer actively marketed