

Martindale

The Complete Drug Reference

Thirty-seventh edition

Edited by

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The book should be interpreted in light of professional knowledge and supplemented as necessary by specialised publications and product literature. The reader should ensure that the information being used is consistent with normal, generally accepted healthcare practice.

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Preface

The aim of Martindale is to provide healthcare professionals with unbiased evaluated information on drugs and medicines used throughout the world. It therefore has to develop as the body of knowledge on existing drugs grows, new drugs emerge, new preparations are launched, and old preparations are abandoned, reformulated, or redefined. It also has to reflect the changing needs of those practising pharmacy and medicine. We try to ensure that each new edition continues to meet all these needs.

In order to provide more up-to-date information the interval between the publication of the printed versions of Martindale has been reduced over successive editions and the book is now produced about every 2 years. For those who require even more up-to-date information from Martindale there are various electronic versions, sections of which are updated more frequently.

Martindale has been continuously expanded since it was first published in 1883, and to present all the extra information this edition of Martindale maintains the recent return to a two-volume publication. The first volume contains this preface and the drug monographs, and the second holds the proprietary preparations and the indexes, as well as manufacturers' contact information.

As always the contents have been extensively revised, with all the text scanned and revalidated where necessary by a team of experienced pharmacists. Over 240 monographs have been added, and 171 removed from the book (abbreviated information on the latter remains available in the electronic versions). In our continuing attempts to improve the usefulness of the book, the chapters on Colouring Agents, Nonionic Surfactants, Organic Solvents, Paraffins and Similar Bases, Soaps and Other Anionic Surfactants, and Stabilising and Suspending Agents have been amalgamated and with additional material now form the new chapter Pharmaceutical Excipients.

The disease treatment reviews, 675 in all and generally located in the chapter introductions, have also been revised in order to reflect current trends and provide key references. Cross-references to these reviews appear in the monographs of the drugs cited; the reviews can also be accessed via the general index. It is hoped that these reviews will be of use to readers who want an overview of a particular disease and its drug treatment and will provide a useful starting point for those who want to pursue particular aspects further.

Martindale contains much nomenclature information intended to assist the reader in identifying a particular drug or compound, and for this edition we have again greatly expanded our coverage of synonyms, with increased coverage of Russian synonyms and 'street names' for substances of abuse. Coverage of ATC codes has been expanded to include codes assigned to herbal medicines. This edition also carries for the first time the unique ingredient identifiers (UNII) that are generated by the joint FDA/USP Substance Registration System.

This edition of Martindale also sees the number of graphical representations of the chemical structures increased.

The information on proprietary preparations, an important feature of Martindale, has been updated and the number of countries covered has again been increased. For this edition homeopathic proprietary preparations have also been listed at the end of the relevant monographs according to their ingredients.

Martindale is based on published information and more than 54 500 selected references are included. The amount of drug information now published electronically has increased significantly since the last printed edition of Martindale and this edition now includes over 3400 citations to material 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. All URLs in Martindale are rechecked shortly before publication to ensure that a document is present. The accession date given in the citation represents the last date on which the content of the document was referred to during revalidation.

Our objective is to evaluate the literature, covering important studies, guidelines, and useful reviews and placing them in context. 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 many of our chapters. 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 extensive use is made of the drug's licensed product information as published in various countries and

approved by the relevant regulatory health bodies. 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 Pharmacopoeia*.

Martindale is not a book of standards. 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. While considerable efforts have been made to check the material in Martindale, the publisher cannot accept any responsibility for errors and omissions. Also the reader is assumed to possess the necessary knowledge to interpret the information that Martindale provides.

Philosophy and methodology

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

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

In order to achieve the aims specified above, our working practices have to optimise internal knowledge management.

MARTINDALE STAFF. Martindale is currently produced by a team of 21 people, 18 of whom are pharmacists or pharmacy technicians with relevant expertise. The team is divided into 5 revising groups each of 2 or 3 staff editors, as well as 5 assistant editors, 1 editor-in-chief, a co-ordinator for the processing of information on proprietary medicines, and 3 clerical and support staff. A number of pharmacists work as external evaluators to maintain coverage of non-UK preparations.

Staff editors receive formal training in literature evaluation and searching techniques, as well as specific, 'on-the-job' training in internal procedures. Each revision team has responsibility for the re-evaluation and update of a particular group of chapters. Senior editorial staff edit and approve the output of the teams. Staff are responsible for ongoing data collection as well as the revision process.

DATA COLLECTION. In order to reduce the amount of formal data collection required at revision, a prospective data-collection roster is in operation. This involves all staff members in hand-searching selected major medical journals, as well as regular searches of the internet sites of regulatory authorities (EMA, FDA, Health Canada, and MHRA), and sources of high-quality systematic reviews and guidelines (such as Clinical Evidence, Cochrane, and NICE), for drug information. In addition, pharmacopoeial, governmental and WHO publications are hand-searched for information relating to drugs and drug therapy.

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

PROPRIETARY PREPARATIONS. The Martindale proprietary preparations team evaluate licensed product information for 41 countries and regions, in order 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, and any significant additional information is forwarded to the relevant revision team.

REVISION. In order to maintain the quality and currency of our content, it is constantly revised and updated. Our revision processes cover both scheduled, in-depth revision of the content of every chapter in the book on a chapter-by-chapter basis, and updates in reaction to new information as it arrives. The revision procedure involves the formalised re-evaluation of all standing information, the assessment of new collected references for quality and relevance, and the selective use of search techniques on bibliographic databases and the Internet to identify further candidate information.

CHECKING. Once the material for a given chapter has been re-evaluated and updated it undergoes a rigorous check, designed to ensure not only that all changes are valid and appropriate, but also that important points have not been missed.

EDITING. The chapter is then passed to a member of the senior editorial staff, who performs a second check and preliminary editing of the data. This process

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is designed to ensure consistency of approach and style, as well as offering an opportunity to pick up any errors missed at the first check. Changes and questions are fed back to the revision team in an iterative process that may involve more than one cycle. Once past its preliminary edit the chapter is sent to the Editor for a final check and approval, which again may require changes to be made and checked, before passing it to the next stage.

KEYING, PROOF-READING, AND DOSE-CHECKING. Once approved by the Editor, amendments can be incorporated into the database, which remains 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 chapter then undergoes an independent check of the dose information against its recorded sources. This check is performed by a member of staff outside the original revising and editing team, and is an additional safeguard against the inadvertent introduction of potentially dangerous dose errors. Once past these stages the data are cleared for release, and can be published in the next update of the Martindale electronic products, and, at appropriate points in the publishing cycle, in the book.

ADDITIONAL CHECKS FOR PUBLICATION. Some additional checks are made before publishing a print edition of Martindale. A second independent dose check of all chapters is made by an external expert, all cross-references are revalidated, and tests of the typesetting and page structure are made. In addition our extensive index is generated and carefully checked for accuracy, order, and consistency. All URLs are also rechecked at this stage to ensure that they still link to the material cited.

FEEDBACK. We are always grateful to get feedback from our users and, whenever possible, we try to incorporate information or suggestions that help us to improve Martindale. Anyone wishing to comment on the editorial content of Martindale can contact us at the following e-mail address: martindale@rpsgb.org

Arrangement

VOLUME A: • MONOGRAPHS ON DRUGS AND ANCILLARY SUBSTANCES (pages 1–2658). This section contains 5930 monographs arranged in 49 chapters. These chapters generally bring together monographs on drugs and groups of drugs that have similar uses or actions. The introductions of those chapters that describe drugs used in the management of disease may contain disease treatment reviews—descriptions of those diseases together with reviews of the choice of treatments. The last chapter in this section consists of a series of monographs arranged in the alphabetical order of their main titles. It includes monographs on drugs not easily classified, on herbals, and on 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: • PREPARATIONS (pages 2659–3554). This section contains over 161 700 proprietary preparations from a range of countries and regions. For this edition we have covered Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Czech Republic, Denmark, Finland, France, Germany, Greece, Hong Kong, Hungary, India, Indonesia, Ireland, Israel, Italy, 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. We have also included some proprietary preparations from Japan. 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** (pages 3555–3636). In Martindale the names of manufacturers and distributors are abbreviated. Their full names are given in this directory together with the full address and website if it is available. This directory contains about 15 300 entries.

- **MULTILINGUAL PHARMACEUTICAL TERMS** (pages 3637–3656). 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** (pages 3657–4112). To make fullest use of the contents of Martindale the general index should always be consulted. The exhaustive index, prepared from 172 000 entries, includes 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** (pages 4113–4147). Both nonproprietary and proprietary names in Russian may be found in Russian alphabetical order in this section.

Nomenclature

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 Community 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 now general policy to use 'f' for 'ph' in sulpha, 't' for 'th', and 'i' for 'y'; for this reason entries in alphabetical lists and indexes 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. A table of contracted names for ions and groups used in approved names and titles is given on page xi. INNs in the four other main official languages (French, Latin, Russian, and Spanish) have also been included in the list of synonyms where these differ from the English INN. 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-'.¹

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, and Latin synonyms; names used in other languages when these may not be readily identifiable; manufacturers' code numbers; and chemical names. 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.

Graphical representations of the chemical structures for over 4100 of the drugs are also included.

STREET NAMES. This edition of Martindale once again includes greatly expanded coverage of 'street names' for substances of abuse. 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 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 2007 by the Commission on Atomic Weights and Isotopic Abundance, International Union of Pure and Applied Chemistry (IUPAC) and based on the ¹²C scale (see page xiii). 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 (see below) 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 page viii, 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, 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° and 25°. 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:

solubility

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 which 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° and 15°. 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 in Volume B. The definitive guide used for identifying restricted drugs for this edition is the 2010 Prohibited List issued by the World Anti-Doping Agency (WADA—see www.wada-ama.org). However, 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 adverse effects, treatment of adverse effects, precautions (including contra-indications), interactions, pharmacokinetics, and uses and administration 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 over 16 400 such abstracts or reviews based on information in an ever widening range of publications.

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

The risks of giving 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 heading with as much detail as is necessary and available. Unless otherwise stated the doses represent the average range of quantities which 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.

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London October 2010

Abbreviations

For abbreviations of the names of manufacturers or their distributors, see Directory of Manufacturers, page 3555.

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 2010 edition.
BP(Vet)—British Pharmacopoeia (Veterinary) 2010.
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.
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.
FEV₁—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 Française, 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.
- INN^M**—International Nonproprietary Name Modified.
- Int. P.**—International Pharmacopoeia 4th ed., 2006, and Supplement 1, 2008.
- IPCS**—International Programme on Chemical Safety.
- IQ**—intelligence quotient.
- IrI.**—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).
- m²**—square metre(s).
- m³**—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).
- mm²**—square millimetre(s).
- mm³**—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.
- pCO₂**—plasma partial pressure (concentration) of carbon dioxide.
- p_aCO₂**—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, 6th ed., 2008 and Supplements 6.1 to 6.8.
- Pharm. Soc. Lab. Rep.**—Royal Pharmaceutical Society’s Laboratory Report.
- Philipp.**—Philippines.
- PHLS**—Public Health Laboratory Service (UK).
- pINN**—Proposed International Nonproprietary Name.
- pINN^M**—Proposed International Nonproprietary Name Modified.
- pK_a**—the negative logarithm of the dissociation constant.
- pl**—Polish.
- p.m.**—*post meridiem*, ‘afternoon’.
- pO₂**—plasma partial pressure (concentration) of oxygen.
- p_aO₂**—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.

rINN^M—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 28', 2010, and Supplement 1.

USP—The United States Pharmacopeia 33, 2010, and Supplement 1.

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.

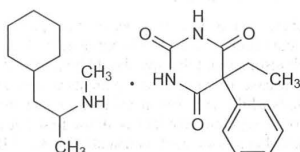
w/v—weight in volume.

w/w—weight in weight.

Barbexacone (rINN)

Barbeksaklon; Barbexacona; Barbexaconum. Compound of (–)-N,α-Dimethylcyclohexanecarboxamide with 5-ethyl-5-phenylbarbituric acid.

Барбексаклон
 $C_{12}H_{12}N_2O_3 \cdot C_{10}H_{11}N = 387.5$.
 CAS — 4388-82-3.
 ATC — N03AA04.
 ATC Vet — QN03AA04.
 UNII — 291GX1YB65.

**Profile**

Barbexacone is a compound of levopropylhexedrine (see under Propylhexedrine, p.2363) with phenobarbital (p.536). It is used in the treatment of various types of epilepsy (p.507). Usual adult doses are 200 to 400 mg daily given orally in divided doses.

Preparations

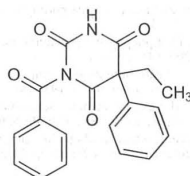
Proprietary Preparations (details are given in Volume B)

Austria: Malasin; Braz.: Malasin; Gr.: Malasin; Ital.: Malasin; Switz.: Malasin; Turk.: Malasin.

Benzobarbital (rINN)

Benzobarbitalum; Benzobarbitone; Benzonal; Benzonalum. 1-Benzoyl-5-ethyl-5-phenylbarbituric acid.

Бензобарбитал
 $C_{19}H_{16}N_2O_4 = 336.3$.
 CAS — 744-80-9.
 UNII — YNJ78BD0AH.



NOTE. The name benzonal has also been used as a proprietary name for benzonate (p.1691).

Pharmacopoeias. In *Int.*

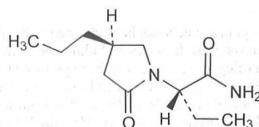
Profile

Benzobarbital is a barbiturate that has been used in the treatment of epilepsy.

Brivaracetam (USAN, rINN)

Brivaracetam; Brivaracetamum; UCB-34714. (2S)-2-[(4R)-2-Oxo-4-propylpyrrolidin-1-yl]butanamide.

Бриварацетам
 $C_{11}H_{20}N_2O_3 = 212.3$.
 CAS — 357336-20-0.
 UNII — U863JGG2IA.

**Profile**

Brivaracetam is under investigation for the treatment of various types of epilepsy including progressive myoclonic epilepsy and refractory partial seizures.

References.

1. Sargentini-Maier ML, *et al.* The pharmacokinetics, CNS pharmacodynamics and adverse event profile of brivaracetam after single increasing oral doses in healthy males. *Br J Clin Pharmacol* 2007; **63**: 680–8.

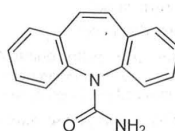
All cross-references refer to entries in Volume A

2. Rolan P, *et al.* The pharmacokinetics, CNS pharmacodynamics and adverse event profile of brivaracetam after multiple increasing oral doses in healthy men. *Br J Clin Pharmacol* 2008; **66**: 71–5.
3. Malawska B, Kulig K. Brivaracetam: a new drug in development for epilepsy and neuropathic pain. *Expert Opin Invest Drugs* 2008; **17**: 361–9.

Carbamazepine (BAN, USAN, rINN)

Carbamazepina; Carbamazépine; Carbamazepinum; G-32883; Karbamatsepiini; Karbamazepin; Karbamazepinas; Karbamazepinum. 5H-Dibenz[b,f]azepine-5-carboxamide.

Карбамазепин
 $C_{15}H_{12}N_2O = 236.3$.
 CAS — 298-46-4.
 ATC — N03AF01.
 ATC Vet — QN03AF01.
 UNII — 33CM2913M.



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

Ph. Eur. 6.8 (Carbamazepine). A white or almost white crystalline powder. It exhibits polymorphism. Very slightly soluble in water; sparingly soluble in alcohol and in acetone; freely soluble in dichloromethane. Store in airtight containers.

USP 33 (Carbamazepine). A white or off-white powder. Practically insoluble in water; soluble in alcohol and in acetone. Store in airtight containers.

Incompatibility. Carbamazepine suspension should be mixed with an equal volume of diluent before nasogastric use as undiluted suspension is adsorbed onto PVC nasogastric tubes.¹

The FDA has received a report of a patient who passed an orange rubbery mass in his faeces the day after taking a carbamazepine suspension (Tegretol; Novartis, USA) followed immediately by chlorpromazine solution (Thorazine; GSK, USA). Subsequent testing showed that mixing the same carbamazepine suspension with a thioridazine hydrochloride solution (Mellaril; Novartis, USA) also resulted in the precipitation of a rubbery orange mass.

1. Clark-Schmidt AL, *et al.* Loss of carbamazepine suspension through nasogastric feeding tubes. *Am J Hosp Pharm* 1990; **47**: 2034–7.

Stability. FDA studies indicate that carbamazepine tablets could lose up to one-third of their efficacy if stored in humid conditions.¹ This appears to be due to formation of a dihydrate form which leads to hardening of the tablet and poor dissolution and absorption.^{2,3} As the dihydrate has also been detected after storage under ambient conditions some suggest that storage with silica gel sachets may be necessary to avoid physical deterioration of carbamazepine tablets.²

1. Anonymous. Moisture hardens carbamazepine tablets, FDA finds. *Am J Hosp Pharm* 1990; **47**: 958.
2. Lowes MMJ. More information on hardening of carbamazepine tablets. *Am J Hosp Pharm* 1991; **48**: 2130–1.
3. Wang JT, *et al.* Effects of humidity and temperature on in vitro dissolution of carbamazepine tablets. *J Pharm Sci* 1993; **82**: 1002–5.

Adverse Effects

Fairly common adverse effects of carbamazepine, particularly in the initial stages of therapy, include dizziness, drowsiness, and ataxia. Gastrointestinal disturbances, such as nausea and vomiting, and mild skin reactions are also common. These effects may be minimised by starting therapy with a low dose. Drowsiness and disturbances of cerebellar and ocular-motor function (with ataxia, nystagmus, and diplopia) are also symptoms of excessive plasma concentrations of carbamazepine, and may disappear spontaneously with continued treatment or at reduced or divided dosage.

Although rare, generalised erythematous rashes can be severe and treatment may have to be withdrawn. Photosensitivity reactions, urticaria, alopecia, exfoliative dermatitis, toxic epidermal necrolysis, erythema multiforme and Stevens-Johnson syndrome, and SLE (but see below) have also been reported.

Transient leucopenia is common and usually resolves with continued therapy; however, rarer blood disorders reported include agranulocytosis, aplastic anaemia, eosinophilia, persistent leucopenia, leucocytosis, thrombocytopenia, and purpura. Lymphadenopathy,

splenomegaly, pneumonitis, abnormalities of liver and kidney function, hepatitis, and cholestatic jaundice have occurred. Some or all of these symptoms as well as fever and rashes may represent a generalised hypersensitivity reaction to carbamazepine.

Gastrointestinal symptoms reported to be less common include dry mouth, abdominal pain, anorexia, and diarrhoea or constipation. Hyponatraemia, and sometimes oedema, have occurred. Other adverse effects reported include paraesthesia, headache, arrhythmias and heart block, heart failure, impotence, male infertility, gynaecomastia, galactorrhoea, and dystonias and dyskinesias with asterixis. Rectal use has resulted in local irritation.

Overdosage may be manifested by many of the adverse effects listed above, especially those on the CNS, and may result in stupor, coma, convulsions, respiratory depression, and death.

In rare cases, carbamazepine has been reported to exacerbate seizures in patients suffering from mixed-type epilepsy—see Precautions, below.

Congenital malformations have been reported in infants born to women given carbamazepine during pregnancy.

Effects on the blood. Occasional reports of fatal haematological reactions associated with carbamazepine led the manufacturers to recommend extensive blood monitoring during therapy. However, because of the rarity of such reactions these recommendations were questioned and the manufacturers subsequently modified their guidelines (see Precautions, below).

Case reports and studies of carbamazepine's haematological effects have been reviewed.¹ The incidence of haematological reactions to carbamazepine has been estimated to range between 1:10 800 and 1:38 000 per year while one group reported the rate of bone marrow suppression to be between 1:10 000 and 1:50 000 cases. The incidence of aplastic anaemia has been calculated to be 1:200 000 per year. Another investigator indicated that 2.2 deaths per million exposures were associated with aplastic anaemia and agranulocytosis. However, of 27 reports of aplastic anaemia (16 fatal) associated with carbamazepine many were found to have had co-incident disease or were receiving multiple-drug therapy. Benign or clinically insignificant leucopenia has occurred, usually during the first 3 months of treatment, in about 12% of children and 7% of adults but in most patients this resolved despite continuation of therapy. Mild transient thrombocytopenia has occurred in about 2% of patients; transient eosinophilia has also occurred.

The reviewers¹ suggested that all patients should have blood and platelet counts before treatment. Patients with low white cell and neutrophil counts were at risk of developing leucopenia and should be monitored every 2 weeks for the first 1 to 3 months. If counts fell further the dose should be reduced or treatment stopped. It should be noted that the *BNF* 59 doubts the practical value of routine monitoring: in particular, aplastic anaemia, agranulocytosis, and thrombocytopenia have a rapid onset and are best monitored by instructing the patient to report warning symptoms (see Precautions, below).

For a discussion of the effects of antiepileptics, including carbamazepine, on serum folate, see Folic Acid Deficiency, under Phenytoin, p.540.

1. Sobotka JL, *et al.* A review of carbamazepine's hematologic reactions and monitoring recommendations. *DICP Ann Pharmacother* 1990; **24**: 1214–19.

Effects on bone. For the effects of antiepileptics including carbamazepine on bone and on calcium and vitamin D metabolism, see under Phenytoin, p.540.

Effects on electrolytes. There have been reports of hyponatraemia or water intoxication in patients receiving carbamazepine.^{1–7} One review⁸ states that although hyponatraemia occurs in 10 to 15% of patients taking carbamazepine, it is seldom symptomatic or severe enough to cause fluid retention. However, care should be taken to distinguish the confusion, dizziness, nausea and headache of water intoxication from the central and gastrointestinal effects of the drug.² The mechanism is uncertain; although some studies suggest an increase in secretion of antidiuretic hormone in subjects given carbamazepine,^{3,4,6} others indicate the reverse,^{5,9} and the fact that the hyponatraemic effects of carbamazepine can be partly reversed by demeclocycline⁵ is cited as evidence for an effect on the kidney, either directly upon the distal tubule or by increasing sensitivity to the effects of antidiuretic hormone. Risk factors for developing carbamazepine-induced hyponatraemia include age of over 40 years, use of sodium-depleting drugs, and low pre-treatment plasma-sodium concentrations; it is unclear whether this adverse effect is dose-related.⁷

1. Henry DA, *et al.* Hyponatraemia during carbamazepine treatment. *BMJ* 1977; **1**: 83–4.
2. Stephens WP, *et al.* Water intoxication due to carbamazepine. *BMJ* 1977; **1**: 754–5.

3. Ashton MG, *et al.* Water intoxication associated with carbamazepine treatment. *BMJ* 1977; 1: 1134-5.
4. Smith NJ, *et al.* Raised plasma arginine vasopressin concentration in carbamazepine-induced water intoxication. *BMJ* 1977; 2: 804.
5. Ballard FW, Mucklow JC. Partial reversal of carbamazepine-induced water intolerance by demeclocycline. *Br J Clin Pharmacol* 1984; 17: 763-5.
6. Sørensen PS, Hammer M. Effects of long-term carbamazepine treatment on water metabolism and plasma vasopressin concentration. *Eur J Clin Pharmacol* 1984; 26: 719-22.
7. Kuz GM, Manssourian A. Carbamazepine-induced hyponatremia: assessment of risk factors. *Ann Pharmacother* 2005; 39: 1943-6.
8. Mucklow J. Selected side-effects 2: carbamazepine and hyponatremia. *Prescribers' J* 1991; 31: 61-4.
9. Stephens WP, *et al.* Plasma arginine vasopressin concentrations and antidiuretic action of carbamazepine. *BMJ* 1978; 1: 1445-7.

Effects on the endocrine system. Carbamazepine may reduce serum concentrations of thyroid hormones through enzyme induction—see under Interactions of Levthyroxine, p.2373. For mention of the effects of antiepileptics on sexual function in male epileptic patients, see under Phenytoin, p.540.

Effects on the eyes. On rare occasions lenticular opacities have been associated with carbamazepine.¹ Retinotoxicity associated with long-term carbamazepine use has been reported² in 2 patients. After stopping the drug visual function and retinal morphological changes improved. A review³ of the effect of antiepileptics on the eyes noted that despite reports of colour vision disturbances and impaired contrast sensitivity associated with carbamazepine therapy, studies in healthy subjects had shown conflicting results.

1. Anonymous. Adverse ocular effects of systemic drugs. *Med Lett Drugs Ther* 1976; 18: 63-4.
2. Nielsen NV, Syversen K. Possible retinotoxic effect of carbamazepine. *Acta Ophthalmol (Copenh)* 1986; 64: 287-90.
3. Hilton EJ, *et al.* The effect of antiepileptic drugs on visual performance. *Seizure* 2004; 13: 113-28.

Effects on the heart. A review¹ of reports of cardiac effects associated with carbamazepine revealed that patients could be divided into 2 distinct groups based on their symptoms. One group consisted mainly of young patients with non life-threatening sinus tachycardia after carbamazepine overdosage while the other group was composed of older female patients with potentially life-threatening bradycardia or AV block associated with therapeutic or modestly raised blood concentrations of carbamazepine. However, there has been a report of fatal syncope, probably due to ventricular asystole, in a 20-year-old patient.² Carbamazepine should be avoided in patients who develop conduction abnormalities, or who have conditions such as myotonic dystrophy in which conduction abnormalities are likely.¹

Elevation of ventricular and atrial stimulation thresholds was reported in a 59-year-old man with a permanent dual-chamber pacemaker, 5 days after starting carbamazepine for mania.³ For a report of carbamazepine producing fatal eosinophilic myocarditis, see under Hypersensitivity, below.

1. Kasarkis EI, *et al.* Carbamazepine-induced cardiac dysfunction: characterization of two distinct clinical syndromes. *Arch Intern Med* 1992; 152: 186-91.
2. Stone S, Lange LS. Syncope and sudden unexpected death attributed to carbamazepine in a 20-year-old epileptic. *J Neurol Neurosurg Psychiatry* 1986; 49: 1460-1.
3. Ambrosi P, *et al.* Carbamazepine and pacing threshold. *Lancet* 1993; 342: 365.

Effects on the immune system. There have been reports of hypogammaglobulinaemia associated with carbamazepine.^{1,4} The authors of one report² stated that this was a recognised but rare adverse effect of carbamazepine and noted that the UK CSM had 9 reports on file of hypogammaglobulinaemia or gammaglobulin abnormalities related to the use of carbamazepine.

1. Moschione Castro APB, *et al.* Secondary hypogammaglobulinemia after use of carbamazepine: case report and review. *Rev Hosp Clin Fac Med Sao Paulo* 2001; 56: 189-92.
2. Hayman G, Bansal A. Antibody deficiency associated with carbamazepine. *BMJ* 2002; 325: 1213.
3. Rice CM, *et al.* Recurrent herpes simplex virus encephalitis secondary to carbamazepine induced hypogammaglobulinaemia. *J Neurol Neurosurg Psychiatry* 2007; 78: 1011-12.
4. Tamada T, *et al.* Secondary bronchiolitis obliterans organising pneumonia in a patient with carbamazepine-induced hypogammaglobulinemia. *Thorax* 2007; 62: 100.

Effects on the liver. A report in 1990 commented that of 499 reports of unwanted effects of carbamazepine on the liver about half comprised only abnormal results from liver function tests;¹ however, deaths have occurred from liver failure^{1,2} or hepatic necrosis.³ Reversible vanishing bile duct syndrome has been associated with long-term use of carbamazepine.⁴ Hepatotoxicity may form part of the antiepileptic hypersensitivity syndrome reported with carbamazepine (see below).

1. Hadžić N, *et al.* Acute liver failure induced by carbamazepine. *Arch Dis Child* 1990; 65: 315-17.
2. Zucker P, *et al.* Fatal carbamazepine hepatitis. *J Pediatr* 1977; 91: 667-8.
3. Smith DW, *et al.* Fatal hepatic necrosis associated with multiple anticonvulsant therapy. *Aust N Z J Med* 1988; 18: 575-81.
4. Ramos AMO, *et al.* Reversible vanishing bile duct syndrome induced by carbamazepine. *Eur J Gastroenterol Hepatol* 2002; 14: 1019-22.

Effects on mental function. Carbamazepine therapy has been associated in a few patients with the development of acute psychotic and paranoid symptoms^{1,3} and with phobias² and mood

disturbances, including mania⁴ and melancholia.⁵ One case of acute paranoid psychosis was associated with the addition of carbamazepine to long-term sodium valproate therapy in a patient subsequently diagnosed as having a schizotypal personality.³ For nonconvulsive status epilepticus associated with carbamazepine presenting as psychiatric disorders, see under Effects on the Nervous System, below. The problems of antiepileptic therapy adversely affecting cognition and the risk of mood disorders, including suicidal ideation, are discussed on p.510.

1. Berger H. An unusual manifestation of Tegretol® (carbamazepine) toxicity. *Ann Intern Med* 1971; 74: 449-50.
2. Mathew G. Psychiatric symptoms associated with carbamazepine. *BMJ* 1988; 296: 1071.
3. McKee RJW, *et al.* Acute psychosis with carbamazepine and sodium valproate. *Lancet* 1989; i: 167.
4. Reiss AL, O'Donnell DJ. Carbamazepine-induced mania in two children: case report. *J Clin Psychiatry* 1984; 45: 272-4.
5. Gardner DL, Cowdry RW. Development of melancholia during carbamazepine treatment in borderline personality disorder. *J Clin Psychopharmacol* 1986; 6: 236-9.

Effects on the nervous system. ASEPTIC MENINGITIS. Aseptic meningitis has developed in a patient with Sjögren's syndrome given carbamazepine. It abated when the drug was withdrawn and symptoms recurred on rechallenge.¹ Aseptic meningitis has also been associated with carbamazepine in patients without Sjögren's syndrome.^{2,4}

1. Hilton E, Stroh EM. Aseptic meningitis associated with administration of carbamazepine. *J Infect Dis* 1989; 159: 363-4.
2. Simon LT, *et al.* Carbamazepine-induced aseptic meningitis. *Ann Intern Med* 1990; 112: 627-8.
3. Hemet C, *et al.* Aseptic meningitis secondary to carbamazepine treatment of manic-depressive illness. *Am J Psychiatry* 1994; 151: 1393.
4. Dang CT, Riley DK. Aseptic meningitis secondary to carbamazepine therapy. *Clin Infect Dis* 1996; 22: 729-30.

ENCEPHALOPATHY. Carbamazepine-induced encephalopathy with symptoms resembling Creutzfeldt-Jakob disease was reported in a 71-year-old man; the cognitive decline, bradykinesia, tremor, and abnormal EEG improved on stopping carbamazepine.¹ In another report,² carbamazepine use was associated with the development of hyperammonaemia and associated behavioural changes on 2 occasions.

1. Horvath J, *et al.* Carbamazepine encephalopathy masquerading as Creutzfeldt-Jakob disease. *Neurology* 2005; 65: 650-1.
2. Adams EN, *et al.* Carbamazepine-induced hyperammonemia. *Am J Health-Syst Pharm* 2009; 66: 1468-70.

EXTRAPYRAMIDAL EFFECTS. Although carbamazepine has been associated with extrapyramidal adverse effects,^{1,4} it has also been tried in the treatment of movement disorders—see under Uses and Administration, below.

1. Schwartzman MJ, Leppik IE. Carbamazepine-induced dyskinesia and ophthalmoplegia. *Cleve Clin J Med* 1990; 57: 367-72.
2. Soman P, *et al.* Dystonia—a rare manifestation of carbamazepine toxicity. *Postgrad Med J* 1994; 70: 54-5.
3. Lee JW. Persistent dystonia associated with carbamazepine therapy: a case report. *N Z Med J* 1994; 107: 360-1.
4. Stryer R, *et al.* Segmental dystonia as the sole manifestation of carbamazepine toxicity. *Gen Hosp Psychiatry* 2002; 24: 114-15.

STATUS EPILEPTICUS. Nonconvulsive status epilepticus, misdiagnosed as behavioural and psychiatric disorders, was reported¹ to have been precipitated by carbamazepine in 2 patients; seizure control and behaviour improved when carbamazepine was stopped and replaced with valproate.

1. Marini C, *et al.* Nonconvulsive status epilepticus precipitated by carbamazepine presenting as dissociative and affective disorders in adolescents. *J Child Neurol* 2005; 20: 693-6.

Effects on the skin. Rashes occurring with carbamazepine may form part of an antiepileptic hypersensitivity syndrome (see below). In a report,¹ erythema multiforme occurred when a generic formulation was given instead of a proprietary brand of carbamazepine. Skin lesions resolved when the patient stopped taking the generic formulation and did not recur when the proprietary brand was restarted. In another report, a 6-year-old boy developed Stevens-Johnson syndrome 5 weeks after carbamazepine was added to valproic acid, which he had been taking as sole antiepileptic therapy for several weeks.² Carbamazepine was stopped and the patient eventually made a full recovery; valproic acid was continued because it was not thought to be the causative agent (but see under Valproate, p.554). Fatal toxic epidermal necrolysis has been seen when carbamazepine was given to a patient who had previously had Stevens-Johnson syndrome during carbamazepine treatment.³ Pseudo mycosis fungoides with lymphoid cell infiltration of the dermis and raised liver enzymes has been reported⁴ in a 54-year-old man who was taking carbamazepine for seizures; symptoms resolved within about 2 weeks of stopping therapy.

For a warning that severe skin reactions may be more likely in patients of certain genotypes, see Skin Reactions, under Precautions, below. For the relative incidence of skin reactions to different antiepileptics, see under Phenytoin, p.540.

1. Busch RL. Generic carbamazepine and erythema multiforme: generic-drug non-equivalency. *N Engl J Med* 1989; 321: 692-3.
2. Keating A, Blahunka P. Carbamazepine-induced Stevens-Johnson syndrome in a child. *Ann Pharmacother* 1995; 29: 538-9.
3. Huang L-Y, *et al.* Fatal toxic epidermal necrolysis induced by carbamazepine treatment in a patient who previously had carbamazepine-induced Stevens-Johnson syndrome. *J Formos Med Assoc* 2007; 106: 1032-7.
4. Gül Ü, *et al.* Carbamazepine-induced pseudo mycosis fungoides. *Ann Pharmacother* 2003; 37: 1441-3.

Hypersensitivity. An antiepileptic hypersensitivity syndrome, comprising fever, rash, and lymphadenopathy and less commonly hepatosplenomegaly and eosinophilia, has been associated with some antiepileptic drugs including carbamazepine.^{1,3} Although a literature search¹ was only able to find 20 published cases to 1986, 22 cases had been reported to the Australian Adverse Drug Reactions Advisory Committee between 1975 and 1990. Some have estimated the incidence at 1 in 1000 to 1 in 10 000 new exposures to aromatic anticonvulsants,^{2,3} but the true incidence is uncertain due to variations in presentation and reporting. Most reactions occurred within 30 days of the start of carbamazepine treatment,¹ although symptoms may occur anywhere between 1 and 8 weeks after exposure.² In previously sensitised individuals the reactions may occur within 1 day of rechallenge. The potential for cross-reactivity between carbamazepine, phenobarbital, and phenytoin is about 75%, and patients who develop the syndrome, and their close relatives, should be warned of the risk associated with use of these antiepileptics.² Suspected cross-sensitivity between carbamazepine and lamotrigine has also been reported in a patient.⁴

Carbamazepine antibodies were detected in an 8-year-old child who developed symptoms of serum sickness including fever, skin rash, oedema, and lymphadenopathy during treatment with carbamazepine.⁵ Hypersensitivity to carbamazepine with multi-system effects clinically resembling a mononucleosis syndrome was reported in a 15-year-old boy 2 weeks after starting monotherapy with carbamazepine;⁶ all symptoms resolved on stopping carbamazepine and giving prednisone. There have been other cases⁷⁻⁹ of an infectious mononucleosis syndrome associated with hypersensitivity to carbamazepine, leading the authors to suggest that reactivation of human herpesvirus 6 or 7 infection is a cofactor and an early manifestation of carbamazepine hypersensitivity syndrome; however, further studies are warranted.

A hypersensitivity reaction producing fatal eosinophilic myocarditis has been reported in a 13-year-old patient; initial symptoms mimicked scarlet fever.¹⁰ A 21-year-old woman developed fatal fulminant hepatic failure after taking carbamazepine for about 2 months; she had presented with initial symptoms of fever, breathlessness, bloody diarrhoea, and a spreading rash.¹¹

Generalised erythroderma with renal, hepatic, and bone-marrow failure (characterised by hypercellularity and dyserythropoiesis) has been reported¹² in an 81-year-old man 50 days after starting carbamazepine therapy. Symptoms recurred following an inadvertent rechallenge. The presence of underlying lymphoproliferative disease may have potentiated the severe drug-induced reaction.

If the antiepileptic hypersensitivity syndrome develops, immediate withdrawal of carbamazepine is recommended. In most cases this is all that is required and does not seem to precipitate an increase in seizures, compared with gradual withdrawal.¹³

Successful desensitisation to carbamazepine was reported¹⁴ in a 12-year-old boy who was sensitive to carbamazepine, sodium valproate, and phenytoin. Starting with a low dose of carbamazepine 100 micrograms daily the dose was doubled, generally every 2 days, up to 100 mg daily. The dose was then gradually increased over 4 weeks to a maintenance dose of 200 mg twice daily. The same technique was used to desensitise 7 patients, all of whom developed dramatic skin rashes when first exposed to carbamazepine.¹⁵ Carbamazepine therapy in full doses was achieved without problem in about 6 weeks. Some¹⁶ consider that desensitisation is not to be recommended in patients with full-blown antiepileptic hypersensitivity syndrome.

1. Anonymous. Anticonvulsants and lymphadenopathy. *WHO Drug Inf* 1991; 5: 11.
2. Knowles SR, *et al.* Anticonvulsant hypersensitivity syndrome: incidence, prevention and management. *Drug Safety* 1999; 21: 489-501.
3. Bessmerly O, *et al.* Antiepileptic hypersensitivity syndrome in children. *Ann Pharmacother* 2001; 35: 533-8.
4. Aoum K, *et al.* Hypersensitivity syndrome induced by anticonvulsants: possible cross-reactivity between carbamazepine and lamotrigine. *J Clin Pharmacol* 2009; 49: 1488-91.
5. Hosoda N, *et al.* Anticarbamazepine antibody induced by carbamazepine in a patient with severe serum sickness. *Arch Dis Child* 1991; 66: 722-3.
6. Merino N, *et al.* Multisystem hypersensitivity reaction to carbamazepine. *Ann Pharmacother* 1994; 28: 402-3.
7. Zeller A, *et al.* Drug hypersensitivity syndrome to carbamazepine and human herpes virus 6 infection: case report and literature review. *Infection* 2003; 31: 254-6.
8. Aihara Y, *et al.* Carbamazepine-induced hypersensitivity syndrome associated with transient hypogammaglobulinaemia and reactivation of human herpesvirus 6 infection demonstrated by real-time quantitative polymerase chain reaction. *Br J Dermatol* 2003; 149: 165-9.
9. Oskay T, *et al.* Association of anticonvulsant hypersensitivity syndrome with Herpesvirus 6. *T. Epilepsy Res* 2006; 70: 27-40.
10. Salzman MB, *et al.* Carbamazepine and fatal eosinophilic myocarditis. *N Engl J Med* 1997; 336: 878-9.
11. Syn WK, *et al.* Carbamazepine-induced acute liver failure as part of the DRESS syndrome. *Int J Clin Pract* 2005; 59: 988-91. Correction, *ibid*; 1371.
12. Lombardi SM, *et al.* Severe multisystemic hypersensitivity reaction to carbamazepine including dyserythropoietic anemia. *Ann Pharmacother* 1999; 33: 571-5.
13. Pirmohamed M, *et al.* Hypersensitivity to carbamazepine and lamotrigine: clinical considerations. *Br J Clin Pharmacol* 2000; 49: 519P-520P.
14. Smith H, Newton R. Adverse reactions to carbamazepine managed by desensitisation. *Lancet* 1985; i: 753.
15. Eames P. Adverse reactions to carbamazepine managed by desensitisation. *Lancet* 1989; i: 509-10.

Sudden unexplained death in epilepsy. Sudden unexpected death in epilepsy (SUDEP), a common cause of seizure-related mortality in patients with chronic epilepsy, has been reviewed.^{1,2} Risk factors may include early onset of epilepsy, frequent generalised tonic-clonic seizures, intractability, frequent medication changes, and polytherapy. Carbamazepine use has also been implicated but the evidence was considered to be tenuous although frequent dose change resulting in plasma-carbamazepine levels outside the therapeutic range was found to be an independent risk factor. Although the FDA in the USA had required data about the specific risk of SUDEP to be included in the prescribing information for the newer antiepileptic drugs gabapentin, lamotrigine, tiagabine, topiramate, and zonisamide, some commentators³ consider that none of these antiepileptics have shown an associated change in the risk of SUDEP. It has been suggested^{2,3} that the incidence of SUDEP is related to the disease rather than a specific drug effect.

1. Walczak T. Do antiepileptic drugs play a role in sudden unexpected death in epilepsy? *Drug Safety* 2003; 26: 673–83.
2. Nashef L, et al. Risk factors in sudden death in epilepsy (SUDEP): the quest for mechanisms. *Epilepsia* 2007; 48: 859–71.
3. Lathers CM, Schraeder PL. Clinical pharmacology: drugs as a benefit and/or risk in sudden unexpected death in epilepsy? *J Clin Pharmacol* 2002; 42: 123–36.

Systemic lupus erythematosus. A review¹ of 80 cases of SLE-like syndromes associated with carbamazepine that had been reported to the manufacturer suggested that the frequency of reports (less than 0.001%) was below that for idiopathic lupus. There have been subsequent reports^{2–4} of late-onset SLE occurring after up to 8 years of carbamazepine therapy without previous adverse effects. The symptoms due to carbamazepine usually resolved on stopping treatment.

1. Jain KK. Systemic lupus erythematosus (SLE)-like syndromes associated with carbamazepine therapy. *Drug Safety* 1991; 6: 350–60.
2. Toepfer M, et al. Drug-induced systemic lupus erythematosus after 8 years of treatment with carbamazepine. *Eur J Clin Pharmacol* 1998; 54: 193–4.
3. Pelizza L, et al. Drug-induced systemic lupus erythematosus after 7 years of treatment with carbamazepine. *Acta Biomed* 2006; 77: 17–19.
4. Amerio P, et al. Drug-induced cutaneous lupus erythematosus after 5 years of treatment with carbamazepine. *Eur J Dermatol* 2006; 16: 281–3.

Treatment of Adverse Effects

In the treatment of carbamazepine overdose repeated doses of activated charcoal may be given orally to adults and children who have ingested more than 20 mg/kg; the aim is not only to prevent absorption but also to aid elimination. Gastric lavage may be considered if undertaken within 1 hour of ingestion. Supportive and symptomatic therapy alone may then suffice, with particular attention to correcting hypoxia and hypotension; haemoperfusion has been suggested for severe poisoning. If there is doubt about the diagnosis, or if multiple-dose oral activated charcoal is being considered, then monitoring plasma-carbamazepine concentration can be useful; it may also help determine when carbamazepine therapy should be restarted. See also Overdose, below.

Hypersensitivity reactions. For reference to successful desensitisation in patients sensitive to carbamazepine, see Hypersensitivity under Adverse Effects, above.

Overdose. Carbamazepine poisoning and its management has been reviewed.¹ Management is mainly supportive, with prompt attention to airway management and seizure control. Activated charcoal should be given; although multiple-dose activated charcoal has been recommended for carbamazepine overdose, care must be taken to protect the airway since carbamazepine inhibits intestinal motility and there is a significant risk of aspiration. In patients with seizures unresponsive to benzodiazepines phenobarbital should be used; phenytoin is not a drug of choice in this situation. Hypertension is rare, and should be managed with fluid and vasopressor support; hypotension with refractory seizures should be treated aggressively as it has led to permanent neurological disability and death.

Haemodialysis or haemoperfusion may be warranted in patients with unstable cardiac status or status epilepticus complicated by bowel hypomotility and unresponsive to more conventional therapy. However, a report² of the use of plasmapheresis in the treatment of an acute overdose of carbamazepine concluded that plasmapheresis removed a very small percentage of the total body load of carbamazepine and could not be recommended. As carbamazepine is highly protein-bound, albumin-enhanced continuous venovenous haemodialysis was tried and found to be effective in the treatment of a 10-year-old child after ingestion of 1.4 g of carbamazepine.³

1. Spiller HA. Management of carbamazepine overdose. *Pediatr Emerg Care* 2001; 17: 452–6.

All cross-references refer to entries in Volume A

2. Kale PB, et al. Evaluation of plasmapheresis in the treatment of an acute overdose of carbamazepine. *Ann Pharmacother* 1993; 27: 866–70.
3. Askenazi DJ, et al. Management of a severe carbamazepine overdose using albumin-enhanced continuous venovenous hemodialysis. *Pediatrics* 2004; 113: 406–9.

Precautions

Carbamazepine should be avoided in patients with AV conduction abnormalities. It should not be given to patients with a history of bone marrow depression. Carbamazepine should be given with caution to patients with a history of blood disorders or haematological reactions to other drugs, or of cardiac, hepatic, or renal disease. Patients or their carers should be told how to recognise signs of blood, liver, and skin toxicity and they should be advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, bruising, or bleeding develop. Carbamazepine should be withdrawn, if necessary under cover of a suitable alternative antiepileptic, if severe, progressive, or symptomatic leucopenia develops, or if symptoms suggestive of Stevens-Johnson syndrome or toxic epidermal necrolysis occur. Licensed product information recommends blood counts and hepatic and renal-function tests before starting carbamazepine therapy and periodically during treatment, but the BNF 59 considers the evidence of practical value unsatisfactory. Clinical monitoring is of primary importance throughout treatment. Some patients of Asian ancestry may be at increased risk of severe skin reactions; for recommendations that such patients' genotype should be tested before beginning carbamazepine, see Skin Reactions, below.

Care is required in identifying patients with mixed seizure disorders that include generalised absence or atypical absence seizures, who may be at risk of an increase in generalised seizures if given carbamazepine. Carbamazepine may also exacerbate absence and myoclonic seizures.

Care is required when withdrawing carbamazepine therapy—see also Uses and Administration, below.

Since carbamazepine has mild antimuscarinic properties caution should be observed in patients with glaucoma or raised intra-ocular pressure; scattered punctate lens opacities occur rarely with carbamazepine and it has been suggested that patients should be examined periodically for eye changes.

Abuse. Overdose requiring hospital admission has been reported after abuse of carbamazepine.¹

1. Crawford PJ, Fisher BM. Recreational overdose of carbamazepine in Paisley drug abusers. *Scott Med J* 1997; 42: 44–5.

Breast feeding. The American Academy of Pediatrics considers¹ that carbamazepine is usually compatible with breast feeding, although there have been reports² of transient cholestatic hepatitis in breast-fed infants.

For further comment on antiepileptic therapy and breast feeding, see p.509.

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 09/06/08)
2. Frey B, et al. Neonatal cholestatic hepatitis from carbamazepine exposure during pregnancy and breast feeding. *Ann Pharmacother* 2002; 36: 644–7.

Driving. For comment on antiepileptic drugs and driving, see p.510.

Multiple sclerosis. Exacerbation of symptoms of multiple sclerosis has been reported¹ in 5 patients on starting carbamazepine therapy for paroxysmal neurological symptoms and pain. There was a close temporal association between starting carbamazepine and worsening of symptoms, followed by resolution when it was stopped. A 3-year follow-up observational study² found that out of 36 multiple sclerosis patients who received carbamazepine therapy, 12 developed neurological adverse effects that mimicked a relapse. The authors concluded that carbamazepine was associated with higher rates of adverse effects and stopping therapy than gabapentin or lamotrigine.

1. Ramsarsingh G, et al. Worsening of symptoms of multiple sclerosis associated with carbamazepine. *BMJ* 2000; 320: 1113.
2. Solaro C, et al. Antiepileptic medications in multiple sclerosis: adverse effects in a three-year follow-up study. *Neurol Sci* 2005; 25: 307–10.

Porphyria. Carbamazepine has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Pregnancy. For comments on the management of epilepsy during pregnancy, see p.510.

There is an increased risk of neural tube defects in infants exposed *in utero* to antiepileptics including carbamazepine; syndromes such as craniofacial and digital abnormalities and, less commonly, cleft lip and palate have also been described. Exposure to carbamazepine has been calculated to carry a 1% risk of spina bifida.¹ A 'carbamazepine syndrome' characterised by facial dysmorphic features and mild mental retardation has been described;² such syndromes are now often seen as aspects of a single 'fetal antiepileptic syndrome'. There is also a risk of neonatal bleeding.

1. Rosa FW. Spina bifida in infants of women treated with carbamazepine during pregnancy. *N Engl J Med* 1991; 324: 674–7.
2. Ornoy A, Cohen E. Outcome of children born to epileptic mothers treated with carbamazepine during pregnancy. *Arch Dis Child* 1996; 75: 517–20.

Skin reactions. The FDA has issued a warning¹ that severe and potentially fatal skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis are significantly more common in patients with the HLA allele HLA-B*1502, which occurs almost exclusively in persons of Asian ancestry. They recommend that patients with such ancestry should be screened for the presence of this allele before beginning therapy with carbamazepine, and if present the risks and benefits of therapy should be considered with particular care; those who have already taken carbamazepine for more than a few months without developing skin reactions are, however, at low risk of them ever developing, regardless of genotype. Similar recommendations have since been issued in the UK by the MHRA.² See also under Phenytoin, p.541.

1. FDA. Information for healthcare professionals: dangerous or even fatal skin reactions—carbamazepine (marketed as Carbatrol, Equetrol, Tegretol, and generics) (issued 12th December, 2007). Available at: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124718.htm> (accessed 25/08/10)
2. MHRA/CHM. Carbamazepine: genetic testing recommended in some Asian populations. *Drug Safety Update* 2008; 1 (9): 5. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&DocName=CON014506&RevisionSelectionMethod=Latest (accessed 09/06/08)

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy.

The metabolism of carbamazepine is reported to be less susceptible to inhibition by other drugs than that of phenytoin but a few drugs are reported to inhibit its metabolism by the cytochrome P450 isoenzyme CYP3A4, resulting in raised plasma concentrations and associated toxicity. Conversely, drugs that induce CYP3A4 may increase the metabolism of carbamazepine, leading to reduced plasma concentrations and potentially a decrease in therapeutic effect. Licensed product information advises that, in such situations, the dose of carbamazepine should be adjusted accordingly and/or the plasma concentrations monitored.

Carbamazepine is itself a hepatic enzyme inducer, and induces its own metabolism as well as that of several other drugs including some antibacterials (notably, doxycycline), anticoagulants, and sex hormones (notably oral contraceptives). Carbamazepine and phenytoin may mutually enhance one another's metabolism. The metabolism of carbamazepine is similarly enhanced by enzyme inducers such as phenobarbital.

◇ General references.

1. Spina E, et al. Clinically significant pharmacokinetic drug interactions with carbamazepine: an update. *Clin Pharmacokinet* 1996; 31: 198–214.

Alcohol. Alcohol may exacerbate the CNS adverse effects of carbamazepine and vice versa.

Analgesics. Dextropropoxyphene has been reported to cause substantial elevation of serum-carbamazepine concentrations¹ and carbamazepine toxicity,^{1,2} probably due to inhibition of carbamazepine metabolism.¹

Use of enzyme-inducing antiepileptics such as carbamazepine affects the threshold for use of antidote in the treatment of paracetamol poisoning, see p.115.

For the effect of carbamazepine on methadone, see p.87, and on tramadol, see p.136.

1. Dam M, Christiansen J. Interaction of propoxyphene with carbamazepine. *Lancet* 1977; ii: 509.
2. Yu YL, et al. Interaction between carbamazepine and dextropropoxyphene. *Postgrad Med J* 1986; 62: 231–3.

Anthelmintics. For the effect of carbamazepine on *mebendazole* and *praziquantel*, see p.156 and p.162, respectively.

Antibacterials. The antimycobacterial *isoniazid*^{1,2} and *macrolides*³ such as *clarithromycin*, *erythromycin*, and *troleanomycin* have been reported to cause substantial elevations of serum concentrations of carbamazepine and symptoms of carbamazepine toxicity. Clarithromycin has also been reported to have caused hyponatraemia when added to carbamazepine therapy in a 30-year-old epileptic woman.⁴ *Rifampicin* and *isoniazid* decreased the serum concentrations of carbamazepine in a 44-year-old woman being treated for bipolar disorder and suspected tuberculosis, resulting in hypomania.⁵

Use of carbamazepine with *isoniazid* may increase the risk of *isoniazid*-induced hepatotoxicity.

1. Valsalan VC, Cooper GL. Carbamazepine intoxication caused by interaction with *isoniazid*. *BMJ* 1982; **285**: 261–2.
2. Wright JM, et al. Isoniazid-induced carbamazepine toxicity and vice versa. *N Engl J Med* 1982; **307**: 1325–7.
3. Pauwels O. Factors contributing to carbamazepine-macrolide interactions. *Pharmacol Res* 2002; **45**: 291–8.
4. Kanbay M, et al. Hyponatremia due to an additive effect of carbamazepine and clarithromycin. *South Med J* 2007; **100**: 222.
5. Zolezzi M. Antituberculous agents and carbamazepine. *Am J Psychiatry* 2002; **159**: 874.

Anticoagulants. For the effect of carbamazepine on *warfarin*, see p.1567.

Antidepressants. As with all antiepileptics, antidepressants may antagonise the antiepileptic activity of carbamazepine by lowering the convulsive threshold.

Antidepressants such as *desipramine*,¹ *fluoxetine*,² *fluvoxamine*,³ *nefazodone*⁴ (and perhaps *trazodone*⁵), and *viloxazine*⁶ increase plasma concentrations of carbamazepine and may induce carbamazepine toxicity. A toxic serotonin syndrome (see p.447) has been reported in a patient who received fluoxetine with carbamazepine.⁷ Severe neurotoxicity reported during therapy with *lithium* and carbamazepine^{8,9} may be due to a synergistic effect as reports indicate that either drug was tolerated when not given with the other and measured plasma concentrations did not indicate overdose.⁹ However, toxic serum concentrations of *lithium* have also been reported, due to carbamazepine-induced acute renal failure (see p.435).

Because of the structural similarity to tricyclic antidepressants licensed product information suggests that carbamazepine should not be given to patients taking an *MAOI* or within 14 days of stopping such treatment.

St John's wort has been shown to induce several drug metabolising enzymes (see p.454) and consequently it has been suggested that it might reduce the blood concentrations of carbamazepine leading to an increased risk of seizure.¹⁰ However, a multiple-dose study¹¹ in healthy subjects reported that *St John's wort* had no significant effect on the pharmacokinetics of carbamazepine or its active epoxide metabolite.

For the effect of carbamazepine on antidepressants, see *Bupropion* (p.415), *Fluoxetine* (p.427), *Mianserin* (p.440), *Nefazodone* (p.444), and *Amitriptyline* (p.410).

1. Lesser I. Carbamazepine and desipramine: a toxic reaction. *J Clin Psychiatry* 1984; **45**: 360.
2. Pearson HJ. Interaction of fluoxetine with carbamazepine. *J Clin Psychiatry* 1990; **51**: 126.
3. Fritze J, et al. Interaction between carbamazepine and fluvoxamine. *Acta Psychiatr Scand* 1991; **84**: 583–4.
4. Ashton AK, Wolin RE. Nefazodone-induced carbamazepine toxicity. *Am J Psychiatry* 1996; **153**: 733.
5. Sánchez Romero A, et al. Interaction between trazodone and carbamazepine. *Ann Pharmacother* 1999; **33**: 1370.
6. Scarpello JHB, Cottrell N. Overuse of monitoring of blood concentrations of antiepileptic drugs. *BMJ* 1987; **294**: 1355.
7. Dursun SM, et al. Toxic serotonin syndrome after fluoxetine plus carbamazepine. *Lancet* 1993; **342**: 442–3.
8. Andrus PF. Lithium and carbamazepine. *J Clin Psychiatry* 1984; **45**: 525.
9. Chaudhry RP, Waters BGH. Lithium and carbamazepine interaction: possible neurotoxicity. *J Clin Psychiatry* 1983; **44**: 30–1.
10. CSM/MCA. Reminder: *St John's wort* (Hypericum perforatum) interactions. *Current Problems* 2000; **26**: 6–7.
11. Burstein AH, et al. Lack of effect of *St John's Wort* on carbamazepine pharmacokinetics in healthy volunteers. *Clin Pharmacol Ther* 2000; **68**: 605–12.

Antiepileptics. Interactions of varying degrees of clinical significance have been reported between carbamazepine and other antiepileptics.

Serum concentrations of carbamazepine are reported to be reduced by *phenobarbital*, but without loss of seizure control;^{1,2} this reduction is probably due to induction of carbamazepine metabolism.

The interaction with *phenytoin* is somewhat more complex and the consequences vary. There is evidence of a lowering of serum carbamazepine concentrations, presumably due to induction of metabolism by *phenytoin*;^{1,3} in return carbamazepine has been reported both to lower and increase serum *phenytoin*—see p.542. Again, these reports do not indicate a loss of seizure control or toxicity resulting from the interaction, although the possibility presumably exists. Gradually withdrawing *phenytoin* from 2 patients who had been receiving carbamazepine and *phenytoin* resulted in a dramatic increase in plasma-carbamazepine concentrations;⁴ one patient exhibited neurotoxic symptoms. The authors recommended that plasma-carbamazepine monitoring

should be carried out whenever *phenytoin* is withdrawn in patients taking these two drugs together.

Valproic acid produces an increase in serum concentrations of the active epoxide metabolite of carbamazepine. This is usually attributed to inhibition of its hydrolysis by epoxide hydrolase, although an additional proposed mechanism⁵ is inhibition of the glucuronidation of carbamazepine-10,11-trans-diol, the compound to which the epoxide is converted under normal circumstances. Adverse effects may be a problem if unusually high epoxide concentrations arise but, in general, this interaction is of limited clinical significance. However, *valpromide*, the amide derivative, is a much more powerful inhibitor of epoxide hydrolase than *valproic acid*,^{6,8} and therefore produces greater increases in epoxide plasma concentrations with clinical signs of toxicity.⁷ Switching from sodium valproate to *valpromide* has resulted in toxicity in patients also receiving carbamazepine.⁷ Neither *valproic acid* nor *valpromide* have any significant effect on plasma concentrations of the parent drug, carbamazepine. *Valnoctamide*, an isomer of *valpromide*, appears to be at least as potent as *valpromide* in inhibiting the elimination of the epoxide metabolite of carbamazepine.⁹ *Valnoctamide* has been used as an anxiolytic, although it does appear to possess some antiepileptic activity. For a report of acute psychosis associated with the combination of carbamazepine and sodium valproate, see Effects on Mental Function under Adverse Effects, above. For the effects of carbamazepine on valproate, see p.556.

Of the other antiepileptics *stiripentol*^{10,11} has been reported to inhibit carbamazepine metabolism, while *felbamate* causes a significant fall in plasma-carbamazepine concentrations which may require an increase in the dose of carbamazepine.¹² However, another study¹³ has shown a significant increase in plasma concentrations of the active epoxide metabolite, which may counteract the effect of the decrease in plasma concentrations of the parent compound. Neurotoxicity has been seen after use of carbamazepine with *lamotrigine*.¹⁴ The suggestion that this was due to raised concentrations of carbamazepine epoxide was not confirmed in a controlled study in which the 2 drugs were used together safely and effectively.¹⁵ Toxic epidermal necrolysis occurred¹⁶ when *lamotrigine* was added to carbamazepine therapy in a patient who had been taking carbamazepine for 3 years; symptoms resolved progressively when both drugs were stopped. Symptoms of carbamazepine toxicity have been reported¹⁷ when *levetiracetam* was added to carbamazepine therapy; this interaction may be due to a pharmacodynamic mechanism as blood levels of carbamazepine and its epoxide metabolite were not altered. There have also been reports¹⁸ of carbamazepine toxicity when *topiramate* was added to carbamazepine therapy; symptoms resolved when the dose of carbamazepine was reduced. Fulminant liver failure has been reported¹⁹ after an increase in adjunctive *topiramate* dose in a patient maintained on carbamazepine for 2 years without any signs of hepatotoxicity. The GABA agonist *progabide* has increased plasma concentrations of the epoxide metabolite, probably due to inhibition of microsomal epoxide hydrolase.²⁰ *Vigabatrin* is reported²¹ to increase the clearance of carbamazepine by about 35%.

For the effects of carbamazepine on *ethosuximide*, see p.523, on *lamotrigine*, see p.530, on *oxcarbazepine*, see p.535, on *primidone*, see p.548, on *tiagabine*, see p.550, and on *topiramate*, see p.551. For interactions with benzodiazepines, see below.

1. Cereghino JJ, et al. The efficacy of carbamazepine combinations in epilepsy. *Clin Pharmacol Ther* 1975; **18**: 733–41.
2. Rane A, et al. Kinetics of carbamazepine and its 10,11-epoxide metabolite in children. *Clin Pharmacol Ther* 1976; **19**: 276–83.
3. Christiansen J, Dam M. Influence of phenobarbital and diphenylhydantoin on plasma carbamazepine levels in patients with epilepsy. *Acta Neurol Scand* 1973; **49**: 543–6.
4. Chapron DJ, et al. Unmasking the significant enzyme-inducing effects of phenytoin on serum carbamazepine concentrations during phenytoin withdrawal. *Ann Pharmacother* 1993; **27**: 708–11.
5. Bernus I, et al. The mechanism of the carbamazepine-valproate interaction in humans. *Br J Clin Pharmacol* 1997; **44**: 21–7.
6. Levy RH, et al. Inhibition of carbamazepine epoxide elimination by valpromide and valproic acid. *Epilepsia* 1986; **27**: 592.
7. Meijer JWA, et al. Possible hazard of valpromide-carbamazepine combination therapy in epilepsy. *Lancet* 1984; **i**: 802.
8. Pisani F, et al. Effect of valpromide on the pharmacokinetics of carbamazepine-10,11-epoxide. *Br J Clin Pharmacol* 1988; **25**: 611–13.
9. Pisani F, et al. Impairment of carbamazepine-10,11-epoxide elimination by valnoctamide, a valpromide isomer, in healthy subjects. *Br J Clin Pharmacol* 1992; **34**: 85–7.
10. Levy RH, et al. Stiripentol level-dose relationship and interaction with carbamazepine in epileptic patients. *Epilepsia* 1985; **26**: 544–5.
11. Cazali N, et al. Inhibitory effect of stiripentol on carbamazepine and saquinavir metabolism in human. *Br J Clin Pharmacol* 2003; **56**: 526–36.
12. Albani F, et al. Effect of felbamate on plasma levels of carbamazepine and its metabolites. *Epilepsia* 1991; **32**: 130–2.
13. Wagner ML, et al. Effect of felbamate on carbamazepine and its major metabolites. *Clin Pharmacol Ther* 1993; **53**: 536–43.
14. Warner T, et al. Lamotrigine-induced carbamazepine toxicity: an interaction with carbamazepine-10,11-epoxide. *Epilepsia* Res 1992; **11**: 147–50.
15. Stolarek I, et al. Vigabatrin and lamotrigine in refractory epilepsy. *J Neurol Neurosurg Psychiatry* 1994; **57**: 921–4.
16. Mansouri P, et al. Toxic epidermal necrolysis associated with concomitant use of lamotrigine and carbamazepine: a case report. *Arch Dermatol* 2005; **141**: 788–9.
17. Sisodiya SM, et al. Carbamazepine toxicity during combination therapy with levetiracetam: a pharmacodynamic interaction. *Epilepsia* Res 2002; **48**: 217–19.

18. Mack CJ, et al. Interaction of topiramate with carbamazepine: two case reports and a review of clinical experience. *Seizure* 2002; **11**: 464–7.
19. Bjoro K, et al. Topiramate and fulminant liver failure. *Lancet* 1998; **352**: 1119.
20. Kroetz DL, et al. In vivo and in vitro correlation of microsomal epoxide hydrolase inhibition by progabide. *Clin Pharmacol Ther* 1993; **54**: 485–97.
21. Sánchez-Alcaraz A, et al. Effect of vigabatrin on the pharmacokinetics of carbamazepine. *J Clin Pharm Ther* 2002; **27**: 427–30.

Antifungals. Malaise, myoclonus, and trembling were reported¹ to have developed in a patient receiving carbamazepine after the addition of *miconazole* to therapy. *Ketoconazole* was associated with a significant increase in plasma-carbamazepine concentrations in 8 epileptic patients stabilised on carbamazepine;² plasma concentrations of the epoxide metabolite were unchanged. A threefold increase in serum-carbamazepine concentrations, reported³ in a patient after addition of *fluconazole* to carbamazepine therapy, did not result in toxicity; however, the latter has been reported^{4,5} in 2 patients stabilised on carbamazepine who were given *fluconazole*. *Terbinafine* has also been reported⁶ to cause possible carbamazepine toxicity.

For the effect of carbamazepine on *itraconazole*, see p.583.

1. Loupi E, et al. Interactions médicamenteuses et miconazole. *Thérapie* 1982; **37**: 437–41.
2. Spina E, et al. Elevation of plasma carbamazepine concentrations by ketoconazole in patients with epilepsy. *Ther Drug Monit* 1997; **19**: 535–8.
3. Finch CK, et al. Fluconazole-carbamazepine interaction. *South Med J* 2002; **95**: 1099–1100.
4. Nair DR, Morris HH. Potential fluconazole-induced carbamazepine toxicity. *Ann Pharmacother* 1999; **33**: 790–2.
5. Ulivelli M, et al. Clinical evidence of fluconazole-induced carbamazepine toxicity. *J Neurol* 2004; **251**: 622–3.
6. Baath NS, et al. Possible carbamazepine toxicity with terbinafine. *Can J Clin Pharmacol* 2006; **13**: e228–e231.

Antihistamines. *Terfenadine* and carbamazepine are both highly protein bound and therefore may compete for protein binding sites. An 18-year-old woman receiving carbamazepine as an antiepileptic had symptoms of neurotoxicity shortly after starting treatment with *terfenadine* for rhinitis.¹ The concentration of free carbamazepine in the plasma was higher than normal and returned to normal on stopping *terfenadine*.

1. Hirschfeld S, Jarosinski P. Drug interaction of terfenadine and carbamazepine. *Ann Intern Med* 1993; **118**: 907–8.

Antimalarials. *Chloroquine* and *mefloquine* may antagonise the antiepileptic activity of carbamazepine by lowering the convulsive threshold.

Antiprotazoals. A patient receiving carbamazepine for bipolar disorder developed dizziness, diplopia, and nausea 4 days after the addition of *metronidazole* for diverticulitis.¹

1. Patterson BD. Possible interaction between metronidazole and carbamazepine. *Ann Pharmacother* 1994; **28**: 1303–4.

Antipsychotics. As with all antiepileptics, antipsychotics may antagonise the antiepileptic activity of carbamazepine by lowering the convulsive threshold.

Increased plasma concentrations of carbamazepine epoxide have been reported to occur during therapy with carbamazepine and *loxapine*¹ or *quetiapine*,² possibly due to induction of carbamazepine metabolism or inhibition of metabolism of the epoxide. Raised serum concentrations of carbamazepine have also been reported in patients receiving *haloperidol*.³

For the effect of carbamazepine on antipsychotics, see under *Chlorpromazine*, p.1077.

1. Collins DM, et al. Potential interaction between carbamazepine and loxapine: case report and retrospective review. *Ann Pharmacother* 1993; **27**: 1180–3.
2. Fitzgerald BJ, Okos AJ. Elevation of carbamazepine-10,11-epoxide by quetiapine. *Pharmacotherapy* 2002; **22**: 1500–3.
3. Iwahashi K, et al. The drug-drug interaction effects of haloperidol on plasma carbamazepine levels. *Clin Neuropharmacol* 1995; **18**: 233–6.

Antivirals. *Ritonavir* inhibits several microsomal liver enzymes and therefore may potentially increase plasma concentrations of carbamazepine. Licensed product information for *ritonavir* advises that such combinations may require monitoring. Carbamazepine toxicity has been reported^{1,2} after interaction with *ritonavir*. In one report,² the patient was also taking *nelfinavir* and *lopinavir*, both of which are substrates and inhibitors of cytochrome P450 isoenzymes.

For the effect of carbamazepine on HIV-protease inhibitors, see p.975.

1. Mateu-de Antonio J, Grau S. Ritonavir-induced carbamazepine toxicity. *Ann Pharmacother* 2001; **35**: 125–6.
2. Bates DE, Herman RJ. Carbamazepine toxicity induced by lopinavir-ritonavir and nelfinavir. *Ann Pharmacother* 2006; **40**: 1190–5.

Anxiolytics. For a discussion of the potential interaction between carbamazepine and the anxiolytic *valnoctamide*, an isomer of the antiepileptic *valpromide*, see Antiepileptics, above. See also Benzodiazepines, below.

Benzodiazepines. The metabolism of benzodiazepines may be enhanced by induction of hepatic drug-metabolising enzymes in patients who have received long-term therapy with carbamazepine; benzodiazepine plasma concentrations are reduced, half-life is shorter, and clearance is increased^{1,2} (see also Antiepileptics, under Interactions of Diazepam, p.1094).

Some benzodiazepines may also affect carbamazepine. One group of workers reported that after addition of clobazam to carbamazepine therapy a dose reduction for the latter was required due to increased blood concentrations.³ In a later study⁴ it appeared that clobazam could produce a moderate increase in the metabolism of carbamazepine. The plasma ratio of metabolites of carbamazepine, including carbamazepine-10,11-epoxide, to parent compound was increased in patients taking clobazam and carbamazepine.

1. Dhillon S, Richens A. Pharmacokinetics of diazepam in epileptic patients and normal volunteers following intravenous administration. *Br J Clin Pharmacol* 1981; 12: 841-4.
2. Lai AA, et al. Time-course of interaction between carbamazepine and clobazepam in normal man. *Clin Pharmacol Ther* 1978; 24: 316-23.
3. Franceschi M, et al. Clobazam in drug-resistant and alcoholic withdrawal seizures. *Clin Trials J* 1983; 20: 119-25.
4. Muñoz JJ, et al. The effect of clobazam on steady state plasma concentrations of carbamazepine and its metabolites. *Br J Clin Pharmacol* 1990; 29: 763-5.

Calcium-channel blockers. Six patients with steady-state carbamazepine concentrations had symptoms of neurotoxicity consistent with carbamazepine intoxication within 36 to 96 hours of the first dose of verapamil.¹ In 5 patients, in whom plasma concentrations were measured, there was a mean increase of 46% in total carbamazepine and 33% in free carbamazepine; no effect on the plasma protein binding of carbamazepine was seen. The results suggested that verapamil inhibits the metabolism of carbamazepine to an extent likely to have important clinical repercussions. There has also been a report² of a patient in whom diltiazem, but not nifedipine, precipitated carbamazepine neurotoxicity.

For the effect of carbamazepine on dihydropyridine calcium-channel blockers, see under Nifedipine, p.1485.

1. Macphie GJA, et al. Verapamil potentiates carbamazepine neurotoxicity: a clinically important inhibitory interaction. *Lancet* 1986; i: 700-703.
2. Brodie MJ, Macphie GJA. Carbamazepine neurotoxicity precipitated by diltiazem. *BMJ* 1986; 292: 1170-1.

Ciclosporin. For the effect of carbamazepine on ciclosporin, see p.1985.

Corticosteroids. For the effect of carbamazepine on corticosteroids, see p.1632.

Danazol. Use of danazol with carbamazepine has been reported to increase the half-life and decrease clearance of carbamazepine,¹ resulting in increases in plasma-carbamazepine concentrations of up to 100%.^{1,2} and resultant toxicity in several patients.²

1. Krämer G, et al. Carbamazepine-danazol drug interaction: its mechanism examined by a stable isotope technique. *Ther Drug Monit* 1986; 8: 387-92.
2. Zielinski JJ, et al. Clinically significant danazol-carbamazepine interaction. *Ther Drug Monit* 1987; 9: 24-7.

Dermatological drugs. Addition of isotretinoin to regular carbamazepine therapy appeared to reduce plasma concentrations of the latter and its active epoxide metabolite.¹ However, no adverse events were noted during a 6-week period of treatment with isotretinoin. Nonetheless, licensed product information for carbamazepine recommends that the levels of carbamazepine are monitored if both are used together.

1. Marsden JR. Effect of isotretinoin on carbamazepine pharmacokinetics. *Br J Dermatol* 1988; 119: 403-4.

Diuretics. There has been a report of symptomatic hyponatraemia associated with use of carbamazepine and a diuretic (hydrochlorothiazide or furosemide—see under Interactions of Furosemide, p.1423). Carbamazepine serum concentrations are increased by acetazolamide.¹

1. McBride MC. Serum carbamazepine levels are increased by acetazolamide. *Ann Neurol* 1987; 16: 393.

Gastrointestinal drugs. Cimetidine is reported to produce a transient increase in plasma-carbamazepine concentrations, with a return to pre-cimetidine values within about a week;¹ some increase in adverse effects was seen. Ranitidine does not appear to affect plasma-carbamazepine concentrations.² Neurotoxicity has been seen in a patient receiving carbamazepine and metoclopramide.³

1. Dalton MJ, et al. Cimetidine and carbamazepine: a complex drug interaction. *Epilepsia* 1986; 27: 553-8.
2. Dalton MJ, et al. Ranitidine does not alter single-dose carbamazepine pharmacokinetics in healthy adults. *Drug Intell Clin Pharm* 1985; 19: 941-4.
3. Sandyk R. Carbamazepine and metoclopramide interaction: possible neurotoxicity. *BMJ* 1984; 288: 830.

Grapefruit juice. The bioavailability and plasma concentrations of carbamazepine have been reported¹ to be increased by grapefruit juice.

1. Garg SK, et al. Effect of grapefruit juice on carbamazepine bioavailability in patients with epilepsy. *Clin Pharmacol Ther* 1998; 64: 286-8.

Levothyroxine. For the effect of carbamazepine on levothyroxine, see p.2373.

Neuromuscular blockers. For the effect of carbamazepine on suxamethonium, see p.2075 and on competitive neuromuscular blockers, see under Atracurium, p.2068.

All cross-references refer to entries in Volume A

Sex hormones. For the effect of carbamazepine on oral contraceptives, see p.2272 and for the possible effect on tibolone, see p.2343.

See also Danazol, above

Theophylline. A decrease in serum-carbamazepine concentrations of about 50% was reported¹ in an epileptic patient given theophylline. The patient had seizures and the proposed mechanism was that theophylline had increased the metabolism of carbamazepine.

For the effect of carbamazepine on theophylline, see p.1259.

1. Mitchell EA, et al. Interaction between carbamazepine and theophylline. *N Z Med J* 1986; 99: 69-70.

Vitamins. The plasma concentration of carbamazepine was increased in 2 patients given nicotinamide.¹

For the effect of antiepileptics, including carbamazepine, on vitamin D concentrations, see Effects on Bone under the Adverse Effects of Phenytoin, p.540.

1. Bourgeois BFD, et al. Interactions between primidone, carbamazepine, and nicotinamide. *Neurology* 1982; 32: 1122-6.

Pharmacokinetics

Carbamazepine is slowly and irregularly absorbed from the gastrointestinal tract and has a bioavailability of 85 to 100%. It is extensively metabolised in the liver, notably by the cytochrome P450 isoenzymes CYP3A4 and CYP2C8. One of its primary metabolites, carbamazepine-10,11-epoxide, is also active. Carbamazepine is excreted in the urine almost entirely in the form of its metabolites; some are also excreted in faeces. Elimination of carbamazepine is reported to be more rapid in children and accumulation of the active metabolite may often be higher than in adults.

Carbamazepine is widely distributed throughout the body and is about 70 to 80% bound to plasma proteins. It induces its own metabolism so that the plasma half-life may be considerably reduced after repeated dosing. The mean plasma half-life of carbamazepine on repeated dosing is about 12 to 24 hours; it appears to be considerably shorter in children than in adults. Moreover, the metabolism of carbamazepine is readily induced by drugs that induce hepatic microsomal enzymes (see Interactions, above).

Monitoring of plasma concentrations may be performed when clinically indicated and the therapeutic range of total plasma-carbamazepine is usually quoted as being about 4 to 12 micrograms/mL (17 to 50 micromoles/litre), although this is subject to considerable variation. It has been suggested by some, but not all investigators, that measurement of free carbamazepine concentrations in plasma may prove more reliable, and concentrations in saliva or tears, which contain only free carbamazepine, have also been measured. Carbamazepine crosses the placental barrier and is distributed into breast milk.

The pharmacokinetics of carbamazepine are affected by use with other antiepileptics (see under Interactions, above).

References

1. Schmidt D, Haefel F. Therapeutic plasma levels of phenytoin, phenobarbital, and carbamazepine: individual variation in relation to seizure frequency and type. *Neurology* 1984; 34: 1252-5.
2. Bertilsson L, Tomson T. Clinical pharmacokinetics and pharmacological effects of carbamazepine and carbamazepine-10,11-epoxide: an update. *Clin Pharmacokinet* 1986; 11: 177-98.
3. Gilman JT. Carbamazepine dosing for pediatric seizure disorders: the highs and lows. *DJCP Ann Pharmacother* 1991; 25: 1109-12.
4. Kodama Y, et al. In vivo binding characteristics of carbamazepine and carbamazepine-10,11-epoxide to serum proteins in paediatric patients with epilepsy. *Eur J Clin Pharmacol* 1993; 44: 291-3.
5. Bernus I, et al. Early stage autoinduction of carbamazepine metabolism in humans. *Eur J Clin Pharmacol* 1994; 47: 355-60.
6. Caraco Y, et al. Carbamazepine pharmacokinetics in obese and lean subjects. *Ann Pharmacother* 1995; 29: 843-7.
7. Mahmood I, Chamberlin N. A limited sampling method for the estimation of AUC and C_{max} of carbamazepine and carbamazepine epoxide following a single and multiple dose of a sustained-release product. *Br J Clin Pharmacol* 1998; 45: 241-6.
8. Cohen H, et al. Feasibility and pharmacokinetics of carbamazepine oral loading doses. *Am J Health-Syst Pharm* 1998; 55: 1134-40.
9. Bondareva IB, et al. Population pharmacokinetic modelling of carbamazepine in epileptic elderly patients: implications for dosage. *J Clin Pharm Ther* 2006; 31: 211-21.
10. Vucicévić K, et al. Population pharmacokinetic model of carbamazepine derived from routine therapeutic drug monitoring data. *Ther Drug Monit* 2007; 29: 781-8.

11. Tothfalusi L, et al. Exposure-response analysis reveals that clinically important toxicity difference can exist between bioequivalent carbamazepine tablets. *Br J Clin Pharmacol* 2008; 65: 110-22.

12. Makmor-Bakry M, et al. Genetic variants in microsomal epoxide hydrolase influence carbamazepine dosing. *Clin Neuropharmacol* 2009; 32: 205-12.

Uses and Administration

Carbamazepine is a dibenzazepine derivative with antiepileptic and psychotropic properties. It is used to control secondarily generalised tonic-clonic seizures and partial seizures, and in some primary generalised seizures. Carbamazepine is also used in the treatment of trigeminal neuralgia and has been tried with variable success in glossopharyngeal neuralgia and other severe pain syndromes associated with neurological disorders such as tabes dorsalis and multiple sclerosis. Another use of carbamazepine is in the management of bipolar disorder unresponsive to lithium.

In the treatment of epilepsy (below), the dose of carbamazepine should be adjusted to the needs of the individual patient to achieve adequate control of seizures; this usually requires total plasma-carbamazepine concentrations of about 4 to 12 micrograms/mL (17 to 50 micromoles/litre). A low initial dose of carbamazepine is recommended to minimise adverse effects. The suggested initial oral dose is 100 to 200 mg once or twice daily gradually increased by increments of up to 200 mg daily every week to a usual maintenance dose of 0.8 to 1.2 g daily in divided doses; up to 2 g daily may occasionally be necessary.

For details of doses in children, see below.

Oral carbamazepine is usually given in divided doses 2 to 4 times daily. A twice-daily regimen may sometimes be suitable for monotherapy, and be associated with improved compliance but can produce widely fluctuating plasma-carbamazepine concentrations that lead to intermittent adverse effects. Modified-release formulations can minimise fluctuations in plasma concentration and may also allow effective twice-daily use. The time and manner of taking carbamazepine should be standardised for the patient since variations might affect absorption with consequent fluctuations in the plasma concentrations. Different preparations vary in bioavailability and it may be prudent to avoid changing the formulation.

Carbamazepine may be given by the rectal route in doses up to a maximum of 250 mg every 6 hours to patients for whom oral treatment is temporarily not possible. The dosage should be increased by about 25% when changing from an oral formulation to suppositories, and it is recommended that the rectal route should not be used for longer than 7 days.

As with other antiepileptics, withdrawal of carbamazepine therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p.507.

The treatment of trigeminal neuralgia (below) is typically begun with low oral doses, such as 100 mg of carbamazepine twice daily (although up to 200 mg twice daily has been suggested in the UK), and increased gradually as needed to maintain freedom from pain. This is usually at maintenance doses of 400 to 800 mg in divided doses; up to 1.2 g is the maximum daily dose recommended in the USA, while UK licensed product information considers that up to 1.6 g daily may be needed in some patients. When pain relief has been obtained attempts should be made to reduce, and if possible stop, therapy, until another attack occurs.

For the management of bipolar disorder (below), carbamazepine is given in an initial oral dose of 400 mg daily in divided doses, increased gradually as necessary up to a maximum of 1.6 g daily; the usual maintenance dose range is 400 to 600 mg daily.

Administration. A modified-release formulation of carbamazepine can reduce fluctuations in carbamazepine concentrations,¹ and tolerability and seizure control in patients with epilepsy may be improved.^{2,3} Such formulations should be considered in patients receiving high doses who suffer intermittent adverse effects, and might also permit a reduction to twice- or even, in some patients, once-daily dosage.^{2,4} However, bioavailability appears to be slightly less than conventional preparations and dosage adjustments may be required when changing between formulations.¹

1. McKee PJW, *et al.* Monotherapy with conventional and controlled-release carbamazepine: a double-blind, double-dummy comparison in epileptic patients. *Br J Clin Pharmacol* 1991; **32**: 99–104.
2. Anonymous. Carbamazepine update. *Lancet* 1989; **ii**: 595–7.
3. Ryan SW, *et al.* Slow release carbamazepine in treatment of poorly controlled seizures. *Arch Dis Child* 1990; **65**: 930–5.
4. McKee PJW, *et al.* Double dummy comparison between once and twice daily dosing with modified-release carbamazepine in epileptic patients. *Br J Clin Pharmacol* 1993; **36**: 257–61.

Administration in children. In the UK, the usual recommended oral dose of carbamazepine for generalised tonic-clonic and partial seizures in children is 10 to 20 mg/kg daily in divided doses. Alternatively the daily dose may be given according to age as follows:

- up to 1 year: 100 to 200 mg
- 1 to 5 years: 200 to 400 mg
- 5 to 10 years: 400 to 600 mg
- 10 to 15 years: 0.6 to 1 g

As with adults, children should be started on a low initial dose of carbamazepine to minimise adverse effects; the *BNFC 2010/11* suggests that those aged 1 month to 12 years may initially be given 5 mg/kg at night or 2.5 mg/kg twice daily, increasing by 2.5 to 5 mg/kg every 3 to 7 days as necessary to a usual maintenance dose of 5 mg/kg 2 or 3 times daily. Older children may be given the usual adult dose (see above) although a maximum of 1.8 g daily has been suggested.

The *BNFC 2010/11* also states that these doses may be used for the treatment of trigeminal neuralgia and prophylaxis of bipolar disorder.

Carbamazepine may be given rectally to children in whom oral treatment is temporarily not possible; the *BNFC 2010/11* suggests this route may be used from 1 month of age. Doses should be about 25% greater than the corresponding oral dose, to a maximum of 250 mg, and given up to 4 times daily.

Bipolar disorder. Carbamazepine may be given as an alternative to lithium or valproate in patients with bipolar disorder (p.402). Studies of its efficacy have been conflicting; although clearly effective in some patients, at least one early study suggested that short-term benefit was not sustained in the longer term.¹ More recent results^{2,3} have suggested that lithium or valproate are generally more effective, but that carbamazepine may conceivably have a role in patients with nonclassical features. Carbamazepine has also been used with lithium, particularly in patients unresponsive to either drug alone; although there are suggestions that the combination may be more effective than monotherapy, particularly in patients with a history of rapid cycling,⁴ it is associated with a potential risk of serious neurotoxicity—see Antidepressants, under Interactions, above. While some commentators have suggested that carbamazepine is falling out of favour with specialists prescribing for bipolar disorder,⁵ more recent reviews^{6,7} have concluded that it may still be a feasible treatment option.

1. Frankenburg FR, *et al.* Long-term response to carbamazepine: a retrospective study. *J Clin Psychopharmacol* 1988; **8**: 130–2.
2. Kleindienst N, Greil W. Differential efficacy of lithium and carbamazepine in the prophylaxis of bipolar disorder: results of the MAP study. *Neuropsychobiology* 2000; **42** (suppl 1): 2–10.
3. Vasudev K, *et al.* Carbamazepine and valproate monotherapy: feasibility, relative safety and efficacy, and therapeutic drug monitoring in manic disorder. *Psychopharmacology (Berl)* 2000; **150**: 15–23.
4. Denicoff KD, *et al.* Comparative prophylactic efficacy of lithium, carbamazepine, and the combination in bipolar disorder. *J Clin Psychiatry* 1997; **58**: 470–8.
5. Ferrier IN. Developments in mood stabilisers. *Br Med Bull* 2001; **57**: 179–92.
6. Stoner SC, *et al.* Historical review of carbamazepine for the treatment of bipolar disorder. *Pharmacotherapy* 2007; **27**: 68–88.
7. Ceron-Litove D, *et al.* Comparison of carbamazepine and lithium in treatment of bipolar disorder: a systematic review of randomised controlled trials. *Hum Psychopharmacol* 2009; **24**: 19–28.

Depression. Carbamazepine has been tried^{1–4} for the augmentation of antidepressant therapy in the treatment of resistant depression (p.403). However, such combined therapy may lead to interactions—see also Antidepressants, under Interactions, above.

1. De la Fuente JM, Mendlewicz J. Carbamazepine addition in tricyclic antidepressant-resistant unipolar depression. *Biol Psychiatry* 1992; **32**: 369–74.
2. Otani K, *et al.* Carbamazepine augmentation therapy in three patients with trazodone-resistant depression. *Int Clin Psychopharmacol* 1996; **11**: 55–7.

3. Cusani E, *et al.* Combination therapy with venlafaxine and carbamazepine in depressive patients not responding to venlafaxine: pharmacokinetic and clinical aspects. *J Psychopharmacol* 2004; **18**: 559–66.
4. Zhang Z-J, *et al.* The effectiveness of carbamazepine in unipolar depression: a double-blind, randomized, placebo-controlled study. *J Affect Disord* 2008; **109**: 91–7.

Diabetes insipidus. Cranial diabetes insipidus (p.2380) is usually treated by replacement therapy with antidiuretic hormone (ADH) in the form of desmopressin. Carbamazepine is one of a variety of other drugs that have been tried to promote ADH secretion, although some consider that it is usually ineffective and has unwanted effects.^{1,2} Oral doses of 200 to 600 mg daily have been given. See also Effects on Electrolytes, under Adverse Effects, above.

1. Seckl J, Dunger D. Postoperative diabetes insipidus. *BMJ* 1989; **298**: 2–3.
2. Singer I, *et al.* The management of diabetes insipidus in adults. *Arch Intern Med* 1997; **157**: 1293–1301.

Epilepsy. Carbamazepine is one of the drugs of choice for partial seizures with or without secondary generalisation (p.507). It has been used for generalised tonic-clonic seizures (although valproate is the drug of choice where these occur in primary generalised epilepsy), but it may exacerbate absence and myoclonic seizures.

Hemifacial spasm. Carbamazepine has been reported to have been of help in the treatment of hemifacial spasm (p.2055).

Hiccup. For the management of intractable hiccups see under Chlorpromazine, p.1079. Carbamazepine may be of value for the treatment of neurogenic hiccups such as those that occur in multiple sclerosis.¹ Carbamazepine has also been reported to have been of benefit in 3 patients with diaphragmatic flutter,² a rare disorder associated with involuntary contractions of the diaphragm.

1. McFarling DA, Susac JO. Hoquet diabolique: intractable hiccups as a manifestation of multiple sclerosis. *Neurology* 1979; **29**: 797–801.
2. Vantrappen G, *et al.* High-frequency diaphragmatic flutter: symptoms and treatment by carbamazepine. *Lancet* 1992; **339**: 265–7.

Hyperactivity. When drugs are indicated for attention deficit hyperactivity disorder (p.2347) initial treatment is usually with a central stimulant but meta-analysis of a small number of studies has provided evidence that carbamazepine may be effective.¹

1. Silva RR, *et al.* Carbamazepine use in children and adolescents with features of attention-deficit hyperactivity disorder: a meta-analysis. *J Am Acad Child Adolesc Psychiatry* 1996; **35**: 352–8.

Lesch-Nyhan syndrome. The severe self-mutilation that occurs in patients with Lesch-Nyhan syndrome (p.1079) has been reported to improve in those given antiepileptics such as carbamazepine.¹

1. Roach ES, *et al.* Carbamazepine trial for Lesch-Nyhan self-mutilation. *J Child Neurol* 1996; **11**: 476–8.

Movement disorders. Carbamazepine is one of many drugs that have been tried in the symptomatic treatment of chorea (p.1055); there have been anecdotal reports of benefit in both non-hereditary^{1,2} and hereditary choreas.³ Carbamazepine is also among the drugs that have been tried in the treatment of *dystonias* (p.894) that have not responded to levodopa or antimuscarinics. Although some patients may benefit from carbamazepine, it is not generally recommended because of a relatively low success rate and the possibility of adverse effects.⁴ Carbamazepine therapy has also been associated with movement disorders—see Effects on the Nervous System: Extrapyramidal Effects, under Adverse Effects, above.

Carbamazepine has also been used in resistant cases of *tardive dyskinesia* (see under Extrapyramidal Disorders, p.1074).

1. Roig M, *et al.* Carbamazepine: an alternative drug for the treatment of nonhereditary chorea. *Pediatrics* 1988; **82**: 492–5.
2. García González MM, *et al.* Corea de Sydenham: presentación de un caso tratado con carbamazepina con excelente respuesta clínica. *An Pediatr (Barc)* 2007; **66**: 80–3.
3. Roulet E, Deonna T. Successful treatment of hereditary dominant chorea with carbamazepine. *Pediatrics* 1989; **83**: 1077.
4. Anonymous. Dystonia: underdiagnosed and undertreated? *Drug Ther Bull* 1988; **26**: 33–6.

Neonatal seizures. Carbamazepine has been tried in the management of neonatal seizures (p.513).

Neuropathic pain. As well as being used to ease the pain of trigeminal neuralgia (see below) carbamazepine may be of use in other neuropathic pain including that associated with diabetic neuropathy (p.6). A systematic review¹ concluded that about two-fifths of patients who take carbamazepine for neuropathic pain will achieve moderate pain relief, but this was based on small studies. The authors found no evidence that carbamazepine was effective for acute pain.

Carbamazepine has also been tried in an attempt to prevent the painful sensory neuropathy associated with oxaliplatin treatment (see Effects on the Nervous System, p.833); results of small studies have been conflicting.^{2–4}

1. Wiffen PJ, *et al.* Carbamazepine for acute and chronic pain in adults. Available in the Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 09/06/08).
2. Eckel F, *et al.* Prophylaxe der Oxaliplatin-induzierten Neuropathie mit Carbamazepin: eine Pilotstudie. *Dtsch Med Wochenschr* 2002; **127**: 78–82.

3. Wilson RH, *et al.* Acute oxaliplatin-induced peripheral nerve hyperexcitability. *J Clin Oncol* 2002; **20**: 1767–74.
4. von Delius S, *et al.* Carbamazepine for prevention of oxaliplatin-related neurotoxicity in patients with advanced colorectal cancer: final results of a randomised, controlled, multicenter phase II study. *Invest New Drugs* 2007; **25**: 173–80.

Nocturnal enuresis. Carbamazepine has been reported to be of benefit in the treatment of primary nocturnal enuresis; a dose of 200 mg at night for 15 nights markedly decreased the frequency of bed-wetting episodes in 8 children.¹

For the conventional management of nocturnal enuresis see p.2381.

1. Al-Waili NS, *et al.* Effect of carbamazepine on urinary volume and osmolality, water clearance, and serum osmolality in patients with primary enuresis. *Eur Urol* 2006; **50**: 844–9.

Psychiatric disorders. Carbamazepine has psychotropic properties and has been tried in the management of several psychiatric disorders, particularly in patients with bipolar disorder (see above). Carbamazepine has also been used with mixed results in various disorders for the control of symptoms such as agitation, aggression, and rage^{1–4} (see Disturbed Behaviour, p.1056). It may produce modest benefit when used as an adjunct to antipsychotics in the management of refractory schizophrenia (p.1058) but any improvement appears to be related to its mood stabilising effect.⁵ However, a more recent systematic review,⁶ albeit based on small studies, found carbamazepine to have no significant benefit either as monotherapy or as an adjunct to antipsychotics; the authors considered that further randomised studies may be warranted. Carbamazepine also has the potential to reduce serum concentrations of antipsychotics, resulting in clinical deterioration (see under Interactions of Chlorpromazine, p.1077). Carbamazepine has also been tried⁷ in post-traumatic stress disorder (p.1055).

1. Mattes JA. Comparative effectiveness of carbamazepine and propranolol for rage outbursts. *J Neuropsychiatr Clin Neurosci* 1990; **2**: 159–64.
2. Gleason RP, Schneider LS. Carbamazepine treatment of agitation in Alzheimer's outpatients refractory to neuroleptics. *J Clin Psychiatry* 1990; **51**: 115–18.
3. Tariot PN, *et al.* Efficacy and tolerability of carbamazepine for agitation and aggression in dementia. *Am J Psychiatry* 1998; **155**: 54–61.
4. Cueva JE, *et al.* Carbamazepine in aggressive children with conduct disorder: a double-blind and placebo-controlled study. *J Am Acad Child Adolesc Psychiatry* 1996; **35**: 480–90.
5. Okuma T. Use of antiepileptic drugs in schizophrenia: a review of efficacy and tolerability. *CNS Drugs* 1994; **1**: 269–84.
6. Leucht S, *et al.* Carbamazepine for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 09/06/08).
7. Wolf ME, *et al.* Posttraumatic stress disorder in Vietnam veterans: clinical and EEG findings; possible therapeutic effects of carbamazepine. *Biol Psychiatry* 1988; **23**: 642–4.

Restless legs syndrome. The aetiology of restless legs syndrome (see Sleep-associated Movement Disorders, p.1060) is obscure and treatment has been largely empirical. In a double-blind study involving 174 patients carbamazepine appeared to be more effective than placebo.¹ Oxcarbazepine has been reported² to be of benefit in restless legs syndrome induced by paroxetine.

1. Telstad W, *et al.* Treatment of the restless legs syndrome with carbamazepine: a double blind study. *BMJ* 1984; **288**: 444–6.
2. Öztürk Ö, *et al.* Oxcarbazepine treatment for paroxetine-induced restless leg syndrome. *Gen Hosp Psychiatry* 2006; **28**: 264–5.

Tinnitus. Treatment of tinnitus (p.2027) is difficult, and many drugs have been tried. Although carbamazepine has been reported to be effective in some patients, it is rarely used because of its adverse effects.

Trigeminal neuralgia. Carbamazepine is the drug of choice in the treatment of the acute stages of trigeminal neuralgia (p.10). Satisfactory pain relief may be achieved in 70% or more of patients, although increasingly larger doses may be required and adverse effects can be troublesome.

Although not licensed in the UK for trigeminal neuralgia in children, the *BNFC 2010/11* suggests that carbamazepine may be tried in doses similar to those used for the treatment of epilepsy (see Administration in Children, above).

Withdrawal syndromes. Carbamazepine has been tried in the prophylaxis and treatment of various withdrawal syndromes. Reduction in cocaine use associated with carbamazepine treatment was found in one short-term controlled study,¹ although a systematic review² of data from later studies concluded that there was no evidence to support the use of antiepileptics, including carbamazepine, in the treatment of cocaine dependence (p.2021). It has been reported^{3–5} to be of benefit in some patients during benzodiazepine withdrawal but such adjunct therapy is not usually indicated (see p.1090). Carbamazepine has been shown^{5,6} to be effective in the treatment of symptoms of the *alcohol withdrawal syndrome* (p.1769) but as there are limited data on its efficacy in preventing associated delirium tremens and seizures it is usually recommended that it should only be used as an adjunct to benzodiazepine therapy. Carbamazepine has also been studied⁷ as an aid in the treatment of alcohol dependence.

1. Halikas JA, *et al.* Cocaine reduction in unmotivated crack users using carbamazepine versus placebo in a short-term, double-blind crossover design. *Clin Pharmacol Ther* 1991; **50**: 81–95.
2. Minozzi S, *et al.* Anticonvulsants for cocaine dependence. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 24/07/09).

Red Cherry

Cerasus; Cerise Rouge; Rojo cereza; Sour Cherry.

Вишня Кислая

UNII — 1L29G6428X (*Prunus cerasus* fruit); 4XTQ10247Y (*Prunus cerasus* fruit juice).

Pharmacopoeias. *USNF* includes cherry juice.

Fr. includes, under the title Griottier, cherry stalks from either the red (sour) cherry, *Prunus cerasus*, or from the sweet cherry, *P. avium*.

USNF 28 (Cherry Juice). The liquid expressed from the fresh ripe fruit of *Prunus cerasus* (Rosaceae). It contains not less than 1.0% of malic acid. pH 3.0 to 4.0. Store in airtight containers. Protect from light.

Profile

Red cherry is used as a colouring and flavouring agent.

Inflammation. A small placebo-controlled crossover study¹ indicated that some symptoms of muscle damage (pain and strength loss) induced by eccentric exercise could be reduced by drinking cherry juice. It was suggested that anthocyanins and flavonoids present in tart cherry juice might have anti-inflammatory properties.

1. Connolly DAJ, *et al.* Efficacy of a tart cherry juice blend in preventing the symptoms of muscle damage. *Br J Sports Med* 2006; 40: 679–83.

Preparations

USNF 28: Cherry Syrup.

Proprietary Preparations (details are given in Volume B)

Multi-ingredient: **Arg:** Vitamina C-Complex; **Fr:** Evacrine; Hydracur; **Switz:** Drosana Resiston avec vitamine C.

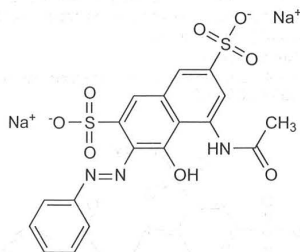
Red 2G

Acid Red 1; Azogermanina; Azogermanine; CI Food Red 10; Colour Index No. 18050; E128; Ext. D & C Red No. 11; Geranine 2G; Rojo 2G; Rouge 2G. Disodium 5-acetamido-4-hydroxy-3-phenylazonaphthalene-2,7-disulphonate.

Красный 2G

$C_{18}H_{13}N_3Na_2O_8S_2 = 509.4$.

CAS — 3734-67-6.

**Profile**

Red 2G may be used as a colouring agent in cosmetics. It has also been employed as a food colour but this use was suspended in the EU in 2007 on the basis that its main metabolite, aniline, has both genotoxic and carcinogenic effects in *rodents*.

Red-Poppy Petal

Aguonų biruliu žiedai; Coquelicot; Coquelicot, pétale de; Corn Poppy Petal; Klatschrose; Kornvallmo, kronblad; Květ máku vlčho; Papaveris rhoeas flos; Pétalos de amapola; Rhoead. Pet; Rhoeas Petalum; Unikonkukan terälehdet.

Мака Самосейки Лепестки

ATC Herb — HNO5CM5018 (*Papaver rhoeas*; flower); HRO5DB5009 (*Papaver rhoeas*; flower); HN02BG5011 (*Papaver rhoeas*; flower).

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

Ph. Eur. 6.8 (Red Poppy Petals). The dried, whole or fragmented petals of *Papaver rhoeas*.

Profile

Red-poppy petal has been used as a colouring agent. It is also included in several herbal preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient: **Canad:** Formula T13 Tea; **Fr:** Calmotsan; Nocvalene; **Ital:** Altus; **Gastroutus;** **Switz:** Baume; Pectosan Nf; Pomnade au Baume; Tisane pectorale et antitussive.

Red-Rose Petal

Fleur de Rose; Flos Rosae; Pétalos de rosa; Red Rose Petals; Ros. Pet; Rosae Gallicae Petala; Rosae Petalum; Rose Rouge; Rosenblüte.

Лепестки Розы

ATC Herb — HA01WX5002 (*Rosa gallica*; flower).

UNII — 9691QC5YJU (*rose petal extract*).

Pharmacopoeias. In *Fr.*

Profile

Red-rose petal, the petals of the red or Provins rose, *Rosa gallica* (Rosaceae), has been used as a colouring agent and for its mild astringent properties.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient: **Arg:** Expectosan Hierbas y Miel; **Fr:** Ophthalmine; **Spain:** Natusor Inferiof.

Homeopathic: **Fr:** Poconeol no 18.

Saccharin

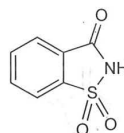
Benzoic Acid Sulphimide; Benzoic Sulfimide; Benzosulphimide; E954; Gluside; Sacarina; Sacarina; Saccharine; Saccharinum; Saccharin; Saccharinas; Sacharyna; Sackarin; Sackarini; o-Sulfolobenzimide; Szacharin; Zaharina. 1,2-Benzisothiazolin-3-one 1,1-dioxide.

Сахарин

$C_7H_5NO_3S = 183.2$.

CAS — 81-07-2.

UNII — FST467X57D.



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

Ph. Eur. 6.8 (Saccharin). A white or almost white, crystalline powder or colourless crystals. Slightly soluble in cold water; sparingly soluble in boiling water and in alcohol. It dissolves in dilute solutions of alkali hydroxides and carbonates. A saturated solution, prepared without heating, is acid to litmus.

USNF 28 (Saccharin). White crystals or white, crystalline powder. Is odourless or has a faint, aromatic odour. In dilute solutions, it is intensely sweet. Soluble 1 in 290 of water, 1 in 25 of boiling water, and 1 in 31 of alcohol; slightly soluble in chloroform and in ether; is readily dissolved by dilute solutions of ammonia, by solutions of alkali hydroxides, and by solutions of alkali carbonates with the evolution of carbon dioxide. Its solutions are acid to litmus.

Saccharin Calcium

Benzosulfimida cálcica; Calcium Benzosulphimide; Calcium Saccharin; E954; Sacarina cálcica; Saccharine calcique; Saccharinum calcium.

Кальция Сахарат

$C_{14}H_8CaN_2O_6S_2 \cdot 3\frac{1}{2}H_2O = 467.5$.

CAS — 6485-34-3 (*anhydrous saccharin calcium*); 6381-91-5 (*hydrated saccharin calcium*).

UNII — 51010P7P2I.

Pharmacopoeias. In *US*.

USP 33 (Saccharin Calcium). White crystals or white, crystalline powder. Is odourless, or has a faint, aromatic odour, and has an intensely sweet taste, even in dilute solutions. Its dilute solution is about 300 times as sweet as sucrose. Soluble 1 in 2.6 of water and 1 in 4.7 of alcohol.

Saccharin Potassium

E954; Potassium Benzosulphimide; Potassium Saccharate; Potassium Saccharin.

Калия Сахарат

$C_7H_5NO_3SK = 222.3$.

CAS — 10332-51-1.

NOTE. Although the name Potassium Saccharate has been applied to saccharin potassium do not confuse with Potassium Glucarate, the potassium salt of saccharic acid, which may also be named potassium saccharate.

Saccharin Sodium

Benzosulfimida sódica; E954; Sacarina sódica; Saccharin Sod.; Saccharine sodique; Saccharinnatrium; Saccharinum natricum; Saccharoidum Natricum; Saccharin sodná sůl; Saccharino natrio druska; Sacharyna sodowa; Saccharinnatrium; Sackarinnatrium; Sodium Benzosulphimide; Sodium Saccharin; Soluble Gluside; Soluble Saccharin; Szacharin-natrium.

Натрия Сахарат

$C_7H_5NNaO_3S = 205.2$.

CAS — 128-44-9 (*anhydrous saccharin sodium*); 6155-57-3 (*saccharin sodium dihydrate*).

UNII — 5B8ZUX40TY (*saccharin sodium*); I4807BK602 (*anhydrous saccharin sodium*).

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn.* and *US*. Some pharmacopoeias specify the dihydrate but it may contain a variable quantity of water as a result of efflorescence.

Ph. Eur. 6.8 (Saccharin Sodium). A white or almost white, crystalline powder or colourless crystals. It may contain a variable quantity of water. Efflorescent in dry air. Freely soluble in water; sparingly soluble in alcohol. Store in airtight containers.

USP 33 (Saccharin Sodium). White crystals or white, crystalline powder. Is odourless, or has a faint, aromatic odour, and has an intensely sweet taste, even in dilute solutions. Its dilute solution is about 300 times as sweet as sucrose. When in powdered form, it usually contains about one-third the theoretical amount of water of hydration as a result of efflorescence. Soluble 1 in 1.5 of water and 1 in 50 of alcohol.

Adverse Effects

There have been rare reports of hypersensitivity and photosensitivity reactions with saccharin.

Saccharin-associated bladder tumours in *rats* given high doses have been the cause of much concern and investigation. However, it is now generally accepted that these findings are not relevant to the use of saccharin as a sweetener in man.

Effects on the liver. Elevated liver enzyme values in an elderly woman followed use of two different medications sweetened with saccharin sodium.¹ Findings resolved on stopping all preparations containing saccharin, and recurred on rechallenge with a small amount of saccharin sodium.

1. Negro F, *et al.* Hepatotoxicity of saccharin. *N Engl J Med* 1994; 331: 134–5.

Pharmacokinetics

Saccharin is readily absorbed from the gastrointestinal tract. It is almost all excreted unchanged in the urine within 24 to 48 hours.

Uses and Administration

Saccharin and its salts are intense sweeteners, dilute solutions having about 300 times the sweetening power of sucrose. They are used in pharmaceuticals and in foods and beverages and are heat stable. They have no food value. The salts are more often used than saccharin itself as they are considered to be more palatable.

Preparations

USP 33: Saccharin Sodium Oral Solution; Saccharin Sodium Tablets.

Proprietary Preparations (details are given in Volume B)

Chile: Dul-Suc; Sukar-Sin; **Fr:** Sucreldulcor; **NZ:** Sactabs; **Turk:** Hermesetas; **Venez:** Hermesetas.

Multi-ingredient: **Arg:** Chuker; Rondo; Semble; Sucaryl; Suimet; **Austral:** Sucaryl; **Braz:** Finn Cristal; **Chile:** Sukar-Sin; **Fr:** Sucaryl; **Israel:** Sucrin; **Ital:** Diet Sucaryl; **NZ:** Sucaryl; **Port:** Dulcifer; **Rus:** Zuckli (Цюкли); **Thal:** Connap; **Turk:** Dolcep; Tadalın.

Saffron

Açafrão; Azafrán; CI Natural Yellow 6; Colour Index No. 75100; Croci stigma; Crocus; Estigmas de Azafrán; French Saffron; Keshar; Saffran; Saffraan; Saffran; Sahrami; Spanish Saffron.

Шафран

UNII — E849G4X5YJ.

NOTE. Do not confuse with the meadow saffron (*Colchicum autumnale*), the source of colchicum (p.607) and colchicine (p.604), or Indian saffron, which is a name sometimes used for Turmeric (p.2252).

Pharmacopoeias. In *Chin.* and *Jpn.*

Eur. (see p.vii) includes Saffron for Homeopathic Preparations. **Ph. Eur. 6.8 (Saffron for Homeopathic Preparations). The dried stigmas of *Crocus sativus* usually joined by the base to a short style. It has a characteristic, aromatic odour. Protect from light.**

Profile

Saffron consists of the dried stigmas and tops of the styles of *Crocus sativus* (Iridaceae), containing crocins, crocetin, and picrocrocin. Saffron is used to colour medicines, foods, and cosmetics. It is also used as a flavouring agent. Saffron has been included in preparations for teething pain. It is being investigated for the treatment of depression. There have been reports of poisoning with saffron, but in some cases these may have been due to meadow saffron, *Colchicum autumnale*.

Homeopathy. Saffron has been used in homeopathic medicines under the following names: Croci stigma; Crocus sativus; Crocus; Croc. s.