

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 (EMEA, 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

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. An 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 sulpham, ‘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-’.

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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