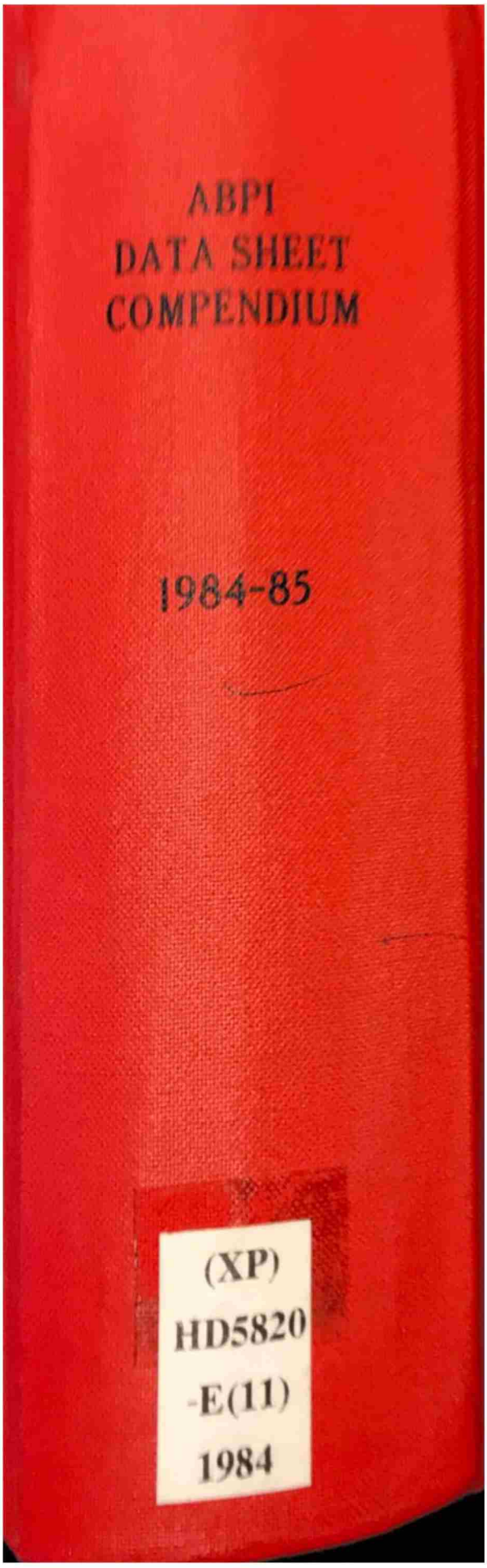

ABPI Data Sheet Compendium

1984–85

Datapharm Publications Limited
12 Whitehall, London SW1A 2DY

The Compendium

Physiological Values
Weights and Heights
Obstetric Table

For the convenience of users of the Compendium, physiological values for certain body fluids, tables of 'desirable' weights for men and women and an obstetric table can be found in the tinted section at the back of the volume.

Indexes

An alphabetical index of products, an index of non-proprietary names and a directory of participating companies (together with their telephone numbers) are provided in the tinted section at the back of the Compendium.

A list is also provided of products which are the subject of data sheets in this edition of the Compendium but which were not included in the 1983–84 edition.

Data sheets

Data sheets are supplied to practitioners in order to comply with the requirements of the Medicines Act 1968.

They are prepared by the individual companies concerned and, in consequence, vary somewhat in style. All follow, however, the requirements which are laid down by 'The Medicines (Data Sheet) Regulations 1972'.

Participation in the Compendium is open to all companies manufacturing medicinal products intended for use under medical supervision.

Further information

The regulations which relate to data sheets restrict the scope of the material which may be given under the heading 'Further information' and require insertion of the word 'Nil' in any data sheet where there is no entry under that heading. Manufacturers are, of course, none the less always willing to provide additional information on their products upon request.

Enquiries should be directed to the companies concerned.

Legal category

The following abbreviations are used under the heading 'Legal category' in entries in the Compendium.

GSL A preparation which is included in the General Sale List.

P A pharmacy sale medicine which can be sold only from a retail pharmacy.

POM A prescription only medicine.

MDA A preparation containing a substance included in Schedule 2 to the Misuse of Drugs Regulations 1973 (Misuse of Drugs Act 1971).
Doctors are reminded that the Misuse of Drugs Regulations 1973 lay down special requirements relating to the writing of prescriptions for products coming within Schedule 2.

Date of preparation

The data sheets included in this Compendium were prepared or reviewed during the final quarter of 1983 and the compendium itself was published in April 1984.

Revised data sheets

Individual participating companies may issue loose leaf data sheets which supersede those included in this Compendium.

It is advisable to retain any such revised data sheets which are received and to indicate that fact on the corresponding data sheets in the Compendium.

Trade marks

An asterisk by the name of a product indicates that the name is a trade mark. The company symbols which appear in certain participants' sections are also trade marks.

Code of Practice for the Pharmaceutical Industry

Sixth Edition (January 1984)

For many years members of the Association of the British Pharmaceutical Industry have voluntarily agreed to observe the principles set out in a *Code of Practice for the Pharmaceutical Industry*; a Code which regulates the standards of conduct to be followed in the marketing of medicines intended for use under medical supervision.

The Code was first published in 1958 and has been regularly revised to take account of changes in marketing practices. A sixth edition was introduced in 1984, publication following consultation with the British Medical Association and the Department of Health and Social Security. The Code embodies the basic principles and procedures which the pharmaceutical industry believes to be essential for the conduct of its marketing activities and for the maintenance of standards which are in the interests alike of the public, the medical and allied professions and the industry.

On occasion, the criticism has been made that members of the medical profession were not aware of the provisions of the Code and, consequently, that the Code had been less effective than might otherwise have been the case. To ensure that these provisions become better known, the sixth edition of the Code has been reproduced in its entirety below.

Those who feel that the promotion of a medical speciality product has fallen below the standards which are required by the Code may write, if they so wish, to the Secretary, Code of Practice Committee, The Association of the British Pharmaceutical Industry, 12 Whitehall, London SW1A 2DY, and ask that the matter be investigated.

INTRODUCTION

a This Code of Practice for the Pharmaceutical Industry has been drawn up after consultation with the British Medical Association and the Department of Health and Social Security.

b The Code owes its origin to the determination of the Association of the British Pharmaceutical Industry to secure the acceptance and adoption of high standards of conduct in the marketing of medical products designed for use under medical supervision.

c Medical products usually owe their existence to research carried out by their manufacturers or to the development by them of results of academic research. Before a medical product is placed on the market the manufacturer will have accumulated considerable toxicological, pharmacological and clinical evidence and will have met all the statutory requirements for the testing, manufacture and marketing of that product. Comprehensive legislation has been introduced to safeguard the public by ensuring that all products meet standards of quality, efficacy and safety which are acceptable in the state of present knowledge and experience.

d It is necessary, however, for the manufacturer, operating as he does in a keenly competitive industry and serving professions for which freedom of choice is essential, to draw attention to the existence and nature of a particular product; for example, by appropriate promotional measures and the dissemination of further knowledge and experience gained in widespread use.

e While it is possible to legislate satisfactorily for the testing, manufacture and control of medical products, the Association believes that appropriate standards of marketing conduct cannot be defined by the same means. For this reason, members of the Association have concurred in the promulgation of the Code of Practice and submitted to its restraints.

f The Code emphasises the importance in the public interest of providing the medical and allied professions with accurate, fair and objective information on medical products so that rational prescribing decisions can be made. Moreover, the Code accepts the principle that such information should be presented in a form and by ways and means which conform not only to legal requirements but also to ethical standards and canons of good taste.

The industry recognises its obligations to provide information about medical products to the pharmaceutical profession and the principles set out in this Code, therefore, apply equally to communications addressed to that profession. However, there may be instances where compliance with every provision of the Code would be inappropriate; for example, in connection with promotional material the purpose of which is to convey information of a commercial nature to pharmacists or pharmaceutical distributors.

g The Code, therefore, represents an act of self-discipline. Acceptance and observance of its provisions are a condition of membership of the Association of the British Pharmaceutical Industry. Member companies also acknowledge that the Code itself is to be applied in the spirit, as well as in the letter.

Pharmaceutical companies outside the Association are invited to accept and observe the Code because it is considered that high ethical standards should be followed throughout the whole industry if it is to maintain the confidence of all the interests which it serves.

h The Code is administered by a Committee established by the Board of Management of the Association. The Committee, with an independent legally qualified Chairman from outside the industry, consists of two independent members who are medically qualified persons not engaged in the industry, and twelve members who are drawn from the senior management of member companies, including at least four medical directors or medically qualified persons of equivalent status.

The Chairman has general authority to obtain expert assistance in any field, and has an original and a casting vote.

i The Committee meets regularly to deal with complaints, to secure compliance with the Code, and to make such recommendations as it deems fit for the amendment of the provisions of the Code.

j An outstanding feature has been the success of voluntary compliance with the provisions of the Code and acceptance of the rulings of the Committee. It has not been found necessary to apply sanctions to secure compliance because members of the Association are anxious to ensure that their marketing activities conform to the highest standard.

k It is important, therefore, that the Code should accurately reflect that standard and for this reason it is kept under constant review by the Board of Management and amended from time to time where necessary to clarify it and bring it up to date. Notes for the guidance of member companies are issued periodically to keep them informed of the rulings and recommendations of the Committee and of any alterations to the Code.

l This edition of the Code supersedes all previous issues and is the sixth edition since the Code was established in 1958. It embodies the basic principles and provisions which the pharmaceutical industry believes are essential for the conduct of its marketing activities and for the maintenance of standards which are in the interests alike of the public, the medical and allied professions and the industry.

PROVISIONS OF THE CODE

The supplementary text, which appears in italics, is intended to give guidance as to the interpretation of the Code.

1 Definition of certain terms

1.1 The term 'promotion' means those informational and marketing activities, undertaken by a pharmaceutical company or with its authority, the purpose of which is to induce the prescribing, supply or administration of its medical products.

It includes the activities of representatives and all other aspects of sales promotion in whatever form, such as journal and direct mail advertising; participation in exhibitions; the use of audio-cassettes, films, records, tapes and video recordings; the use of viewdata systems and data storage devices such as memory discs accessed and reproduced on television apparatus, visual display units and the like; the provision of samples, gifts and hospitality.

The term 'promotion' does not extend to:

(i) Replies made in response to enquiries from particular doctors or to replies in response to a specific communication, whether of enquiry or comment, including letters published in a medical journal.

(ii) Announcements of pack changes, adverse reaction warnings or recall of products provided they contain no product claims.

(iii) 'Trade advertisements' as defined in the Medicines (Advertising of Medicinal Products) Regulations 1975, i.e. catalogues, price lists or other documents issued with a view to wholesale dealing but not containing any reference to product usage other than a therapeutic classification.

By 'wholesale dealing' is meant the sale of a product to a person who, during the course of his business or professional practice, buys it for the purpose of selling it or administering it or causing it to be administered to one or more human beings.

1.2 The term 'medical product' means any unbranded or branded pharmaceutical product intended for use in humans which is promoted to the medical profession rather than directly to the lay public.

1.3 The term 'medical profession', 'practice of medicine', 'practitioner' and 'doctor' should be interpreted to extend to the dental profession and be construed accordingly.

1.4 The term 'medical representative' means a representative whose duties comprise or include calling upon members of the medical profession.

2 Methods of promotion

Methods of promotion must never be such as to bring discredit upon, or reduce confidence in, the pharmaceutical industry.

The issue of rubber stamps to doctors for use as aids to prescription writing is one of the methods of promotion barred by this clause.

3 Grant of product licence

A medical product must not be promoted prior to the grant of the product licence authorising its sale or supply.

This prohibition does not apply to any product which is exempt from the need to be the subject of a product licence.

4 Nature and availability of information

4.1 Upon reasonable request, the company concerned shall promptly provide members of the medical profession with accurate and relevant information about the medical products which the company markets.

4.2 Information about medical products should accurately reflect current knowledge or responsible opinion.

4.3 Information about medical products must be accurate, balanced and must not mislead either directly or by implication.

Claims for superior potency per unit weight are meaningless and best avoided unless they can be linked with some practical advantage, e.g. reduction in side-effects or cost of effective dosage.

4.4 Information must be capable of substantiation, such substantiation being provided without delay at the request of members of the medical profession.

5 Claims and comparisons

5.1 Claims for a medical product must be based on an up-to-date evaluation of all the evidence and must reflect this evidence accurately and clearly.

5.2 Exaggerated or all-embracing claims must not be made and superlatives must not be used. Claims should not imply that a medical product, or an active ingredient, has some special merit, quality or property unless this can be substantiated.

5.3 Any statement about side-effects should be specific and based on data submitted with the licence application or notified to the licensing authority, or on published data to which references are given. It should not be stated that a product has no side-effects, toxic hazards or risks of addiction. The word 'safe' must not be used without qualification.

5.4 The word 'new' should not be used to describe any product or presentation which has been generally available, or any therapeutic indication which has been generally promoted, for more than twelve months in the United Kingdom.

5.5 Comparisons of products must be factual, fair, and capable of substantiation. In presenting a comparison, care must be taken to ensure that it does not mislead by distortion, by undue emphasis, or in any other way.

'Hanging' comparatives, which merely claim that a product is 'better' or 'stronger' etc, must not be used.

5.6 Brand names of products of other companies must not be used unless the prior consent of the proprietors has been obtained.

6 Disparaging references

6.1 The products or services of other companies should not be disparaged either directly or by implication.

Substantiated comparative claims inviting fair comparisons with a group of products or with other products in the same field are permissible, provided that such claims are not presented in a way which is likely to mislead, whether by distortion, undue emphasis or otherwise.

6.2 The clinical and scientific opinions of members of the medical and allied professions should not be disparaged either directly or by implication.

7 Printed promotional material

7.1 The Medicines Act 1968 requires a pharmaceutical company to provide a practitioner with a data sheet before promoting a product directly to him. The content of such data sheets is determined by Regulations made under the Medicines Act.

Data Sheets for many prescription products are published in the ABPI Data Sheet Compendium which is issued at regular intervals. Copies of the Compendium are supplied to members of the medical and pharmaceutical professions.

7.2 All other printed material (including journal advertising) which is issued for promotional purposes by the product licence holder or with his authority must include certain information specified in this Code.

The requirements of Clause 7.3 or 7.4, as appropriate, must be complied with in any advertising directed towards the medical profession even if it is of a general nature, e.g. prestige advertisements listing a company's products.

An advertisement which would not otherwise conform with the Code should not be regarded as doing so by reason only of the fact that the content of the data sheet is reproduced as part of the advertisement or because a data sheet is sent with the advertisement.

7.3(i) Except for 'abbreviated advertisements', as defined in Clause 7.4, the following information must be given clearly and concisely on printed promotional material:

a The number of the relevant product licence and the name and address of the holder of the licence, or the business name and address of the part of his business responsible for the sale of the product.

b A quantitative list of the active ingredients, using approved names where such exist, or other non-proprietary names; alternatively, the non-proprietary name of the product if it is the subject of an accepted monograph.

Attention is drawn to the fact that the Medicines (Advertising to Medical and Dental Practitioners) Regulations 1978 (SI 1978 No. 1020) impose additional requirements which relate to the position and type size of this information.

c At least one authorised indication for use consistent with the data sheet.

d A succinct statement of the information in the data sheet relating to the dosage and method of use relevant to the indications quoted in the advertisement and, where not otherwise obvious, the route of administration.

e A succinct statement of the side-effects, precautions and contra-indications relevant to the indications in the advertisement, giving, in an abbreviated form, the substance of the relevant information in the data sheet.

f Any warning issued by the Medicines Commission, a committee appointed under Section 4 of the Medicines Act 1968 or the licensing authority, which is required to be included in advertisements.

g The cost of a product, except in the case of advertisements in journals which have an appreciable proportion of their circulation outside the United Kingdom.

The cost of a product is the cost (excluding value added tax) of either a specified package of the product, or a specified quantity or recommended daily dose, calculated by reference to any specified package of the product.

Attention is drawn to the fact that the Medicines (Advertising to Medical and Dental Practitioners) Regulations 1978 (SI 1978 No. 1020) impose a specific requirement to that proportion of the circulation of a journal which has to be outside the United Kingdom in order to qualify for the exception to this requirement.

7.3(ii) The information required by Clause 7.3 (i) (d), (e) and (f) must be printed in such type and in such a position that its relationship to the claims and indications is readily appreciated by the reader.

7.4(i) The requirements of Clause 7.3 do not apply in the case of an 'abbreviated advertisement'. An 'abbreviated advertisement' is one, the text of which contains in relation to the product no more than:

a The brand name of the product.

b The approved names of the active ingredients, where such names exist, or other non-proprietary names; alternatively, the non-proprietary name of the product if it is the subject of an accepted monograph.

Attention is drawn to the fact that the Medicines (Advertising to Medical and Dental Practitioners) Regulations 1978 (SI 1978 No. 1020), impose additional requirements which relate to the position and type of this information.

c The name and address of the product licence holder, or the business name and address of the part of his business responsible for the sale of the product.

d One indication for use, or more than one indication provided that these are related, consistent with the data sheet.

e A concise statement, consistent with the data sheet, giving the reason why the product is recommended for such indication or indications.

f A form of words which indicates clearly that further information is available on request to the licence holder or is to be found in the data sheet relating to the product.

7.4(ii) An 'abbreviated advertisement' must always contain the information required by Clause 7.4(i) (a), (b), (c) and (f). The information required by Clause 7.4(i) (d) and (e) is optional. An 'abbreviated advertisement' must not include any illustration which is likely to convey any information about the product or imply claims which are additional to those provided in accordance with Clause 7.4(i) (a) to (e) inclusive.

7.4(iii) An 'abbreviated advertisement' directed towards a doctor is permissible only when it constitutes an advertisement appearing in a publication sent or delivered wholly or mainly to doctors. A loose insert included in such a publication cannot be an 'abbreviated advertisement'.

Attention is drawn to the fact that the Medicines (Advertising to Medical and Dental Practitioners) Regulations 1978 (SI 1978 No. 1020) impose additional requirements which relate to the maximum permitted size of an 'abbreviated advertisement'.

7.4(iv) An 'abbreviated advertisement' is not permissible where the Medicines Commission, a committee appointed under Section 4 of the Medicines Act 1968 or the licensing authority, have required a warning to be included in any advertisement relating to the medical product, and the licensing authority have issued a direction that 'abbreviated advertisements' should not be issued.

7.5 Promotional material, such as mailings and journal advertisements, must not be designed to disguise its real nature.

Doctors rightly resent receiving promotional material in the guise of personal communications, as when advertisements are enclosed in a plain envelope or are addressed in real or facsimile handwriting on letters or postcards.

Envelopes should not be used for the dispatch of promotional material if they bear words implying that the contents are non-promotional, e.g. that the contents provide information relating to safety.

It is advisable to use first class mail only for important communications of a non-promotional nature such as notifications of warnings or cautions or the withdrawal or recall of a product.

Advertisements in journals should not be designed so as to resemble editorial matter.

7.6 Promotional material should conform, both in text and illustration to canons of good taste and should recognise the professional standing of the recipients.

Representations of the nude female form (even in silhouette) or partly clothed figures should not be used in promotional material in such a way as to arouse a visual or emotional response in order to attract attention to the text.

Displays of part of the naked body which are necessary to illustrate pictorially the message of the text are permissible provided that they conform to the dictates of decency and good taste.

7.7 Doctors' names or photographs must not be used in a prominent manner in promotional material or in any other way that is contrary to the ethical code of the medical profession.

7.8 Promotional material should not imitate the devices, copy, slogans or general layout adopted by other companies in a way that is likely to mislead or confuse.

7.9 Where appropriate, for example, in technical and other informative material, the date of printing or the last review should be stated.

7.10 Extremes of format, size or cost of printed material should be avoided.

Large size mailings which cannot be put through letter boxes are a source of irritation to doctors and should be avoided as far as possible.

7.11 Postcards, other exposed mailings, envelopes or wrappers should not carry matter which might be regarded as advertising to the lay public or which could be considered unsuitable for public view.

Postcards and other exposed mailings should not contain copy or illustrations which ought not to be read or seen by lay persons.

7.12 'Telemessages' and 'Telex' must not be used for promotional purposes.

7.13 In a multi-page press advertisement only one page need include the information required by Clause 7.3 of the Code, provided that each of the other pages (except the page on which, or facing which, the information is printed) includes a reference, on an outer edge, in at least 8 point type, indicating on which page that information appears. No initial recto or final verso must be false or misleading if read in isolation.

A loose insert included in a journal is not regarded as a 'multi-page press advertisement' for the purpose of this clause.

By 'multi-page press advertisement' is meant an advertisement in a journal in which the pages follow on from one another without interruption. It does not include, for example, promotional material which appears on a series of successive right-hand pages. Where the pages of an advertisement do not follow on without interruption each individual page, or uninterrupted group of pages, is to be regarded as a separate advertisement.

7.14 In a multi-page advertisement other than a press advertisement, the information required by Clause 7.3 of the Code must appear on one or more continuous pages and, where such an advertisement consists of more than four pages, the advertisement must include a clear indication as to where this information may be found.

8 References to official bodies

Promotional material should not include any reference to the Medicines Commission, a committee appointed under Section 4 of the Medicines Act 1968 or the licensing authority, unless this is specifically required by the licensing authority.

9 References to the National Health Service

9.1 Where reference is made to the prescribing of a product under the National Health Service, the phrase

'freely prescribable' or similar phrases suggesting a lack of restriction or restraint must not be used.

This clause was inserted in the first edition of the Code in deference to the wishes of the then Ministry of Health. 'Freely' in this context means 'without restriction or restraint'.

Although NHS doctors are free to prescribe whatever medicines they consider necessary for the treatment of a patient, they are nevertheless required to exercise due economy.

9.2 Reproductions of official documents, such as prescription form FP 10, should not be used for promotional purposes unless the agreement of the appropriate Government department has been received.

The term 'reproduction' includes any depiction which simulates or might be taken to simulate the document in question.

10 Artwork, graphs, illustrations, etc.

10.1 Illustrations must not mislead as to the nature of the claims or comparisons being made, nor as to the purposes for which the product is used; nor should illustrations detract from warnings or contra-indications.

10.2 Artwork and graphs must conform to the letter and the spirit of the Code. Graphs and tables should be presented in such way as to give a clear, fair, balanced view of the matters with which they deal, and should only be included if they are strictly relevant to the claims or comparisons being made.

10.3 Graphs and tables must not be used in any way which might mislead; for example, by their incompleteness or by the use of suppressed zeros or unusual scales.

11 Reprints, abstracts and quotations

This clause is included to accord with the views of the Ethical Committee of the British Medical Association; its object is to avoid the risk of contravention of the BMA Code of Ethics.

11.1 Reprints of articles by members of the medical profession must not be included in mailings but may be supplied to individual doctors on request. It is permissible to include in promotional material reasonably brief abstracts of, or quotations from, articles by members of the medical profession and to include in such material reference to doctors' names in a bibliography of published works. In no case, however, should doctors' names be used in a prominent manner in promotional material.

Quotations from public broadcasts, e.g. radio and television, may not be used in promotional material. It is permissible to use quotations from private occasions, e.g. medical conferences or symposia, with the written permission of the speaker.

11.2 Quotations from medical literature, or from personal communications received from doctors, must accurately reflect the meaning of the author and the significance of the study.

11.3 The utmost care must be taken to avoid ascribing claims or views to medical authors when such claims or views no longer represent, or may not represent, the current views of the author concerned.

12 Distribution of printed promotional material

12.1 Promotional material should only be sent or distributed to those categories of persons whose need for, or interest in, the particular information can reasonably be assumed.

12.2 Any information designed to encourage the use of medical products in clinics, industrial concerns, clubs or schools must be addressed to the medical adviser or medical officer or to medical auxiliary staff.

12.3 Restraint should be exercised on the frequency of distribution and on the volume of promotional material distributed.

The style of mailings is relevant to their acceptability to doctors and criticism of their frequency is most likely to arise where their informational content is limited or where they appear to be elaborate and expensive. A higher frequency rate will be accepted for mailings on 'new' products than for others.

12.4 Mailing lists must be kept up to date. Requests from doctors to be removed from promotional mailing lists must be complied with promptly and no name may be restored except at the doctor's request or with his permission.

13 Audio-visual material

13.1 Audio-visual material must comply with all relevant requirements of the Code, with the exception of Clause 7.3.

13.2 When audio-visual material is used to promote a product, copies of the relevant data sheet, or a document with the same content, should be made available to all persons present or to whom the material is sent or delivered.

The expression 'audio-visual material' is to be interpreted as including material which consists either of sound only or of projected moving or still pictures only. It includes sound recordings, cinematograph films, tape-slide presentations, video-recordings and sound or television broadcasting. It does not include information reproduced on television apparatus, visual display units and the like which comes within the scope of Clause I.

13.3 Audio-visual promotional material is subject to the certification requirements of Clause 15.

14 Material reproduced on television apparatus, visual display units and the like

14.1 Promotional material which is made available to hospitals, doctors, pharmacists etc., by systems which enable the material to be accessed and reproduced on to television apparatus, visual display units and the like, must comply with all relevant requirements of the Code, with the exception of Clauses 7.3 and 7.14.

14.2 Such material includes viewdata systems, memory discs and the like, but not video-tapes, which come within the scope of Clause 13.

14.3 The obligatory information required by Clause 7.3(1)(a)–(f) must be available through the system conveying the promotional material and instructions for accessing that information must be displayed with the promotional material

14.4 Promotional material made available in this way is subject to the certification requirements of Clause 15.

Copies of promotional information made available in this way must be made in permanent form and retained for not less than three years.

15 Certification of printed promotional material

15.1 No promotional material shall be issued unless the final text and layout have been certified by two persons on behalf of the member company in the manner

provided by this Clause. One of the two persons shall be a doctor. The other shall be a pharmacist or some other appropriately qualified person or a senior official of the company. The doctor, pharmacist or other qualified person must be a senior employee of the company or an appropriately qualified person whose services are retained for that purpose.

15.2 The names of those nominated, together with their qualifications, shall be notified in advance to the licensing authority. The names and qualifications of designated alternative signatories must also be given. Changes in the names of nominees must be promptly notified.

15.3 The certificate shall certify that the signatories have examined the material in its final form and that in their belief it is in accordance with the requirements of the relevant advertising regulations and this Code of Practice, is consistent with the product licence and the data sheet, and is a fair and truthful presentation of the facts about the product.

15.4 Companies shall preserve all certificates, together with the material in the form certified, for not less than three years and produce them upon request from the licensing authority or the Association at the instance of the Code of Practice Committee.

15.5 The foregoing procedure shall apply, with the necessary variations, to audio-visual material prepared by or on behalf of companies in accordance with Clause 13, to promotional material provided by or with the authority of companies for reproduction on television apparatus, visual display units and the like in accordance with Clause 14 and to briefing material for representatives prepared in accordance with Clause 17.12.

16 Suspension of advertisements

In the event of the Code of Practice Committee requiring a company either:

(i) to suspend the use of an advertisement pending its decision on a complaint by the licensing authority relevant to the safe or proper use of the product, in accordance with paragraph 8 of the 'Constitution and Procedure for the Code of Practice Committee', or,

(ii) to discontinue a practice or suspend the use of an advertisement until a review has been completed, in accordance with paragraph 13 of the 'Constitution and Procedure for the Code of Practice Committee',

the member company shall at once make every possible endeavour to comply.

17 Medical representatives

17.1 Medical representatives must be adequately trained and possess sufficient medical and technical knowledge to present information on the company's products in an accurate and responsible manner.

17.2 Medical representatives should at all times maintain a high standard of ethical conduct in the discharge of their duties.

17.3 The requirements of the Code which aim at accuracy, fairness, balance, and good taste apply to oral representations as well as printed material.

17.4 Unfair or misleading comparisons or comparisons implying a therapeutic advantage which is not in fact justified must be avoided by medical representatives.

17.5 Claims made for products by medical representatives must be limited to the indications permitted by the product licence.

17.6 Medical representatives must not employ any inducement or subterfuge to gain an interview. No payment of a fee should be made for the grant of an interview.

The practice of gaining or extending an interview on the pretext of carrying out a survey is to be avoided. This does not preclude the use of medical representatives to obtain bona fide survey information, but it is essential that the survey should be devised and conducted so as to leave no doubt in the doctor's mind that the survey will produce medically useful information.

17.7 Medical representatives must ensure that the frequency, timing and duration of calls on doctors, or on hospitals, together with the manner in which they are made, do not cause inconvenience. The wishes of an individual doctor, or the arrangements in force at any particular establishment, must be observed by medical representatives.

The number of calls made on a medical practitioner and the intervals between successive visits are relevant to the determination of frequency.

Companies should arrange that intervals between visits do not cause inconvenience to practitioners and the number of calls made by a medical representative each year should not normally exceed, on average, three visits to each doctor.

Averages are to be calculated separately for general practitioners and other members of the medical profession to whom visits are made.

The calculation should exclude:

(i) Attendance by a medical representative at a scientific meeting or an audio-visual presentation given to a group of doctors.

(ii) A visit which is requested by a doctor or a call which is made in order to respond to a specific enquiry.

(iii) A visit to follow up a report of an adverse reaction.

A medical representative should not stay in a surgery in which another medical representative is already waiting, except with the doctor's or receptionist's approval.

Medical representatives must always endeavour to treat the doctor's time with the utmost respect and give him no cause to believe that his time might have been wasted. If, for any unavoidable reasons, an appointment with a doctor cannot be kept, the longest possible notice must be given.

Calls on hospital medical staff should generally be limited to matters likely to be of specific interest to them. The majority are specialists and medical representatives should ensure that their specialised interests are borne in mind. It is preferable for most hospital staff to be seen only after making a prior appointment, at which time subjects for discussion should be identified.

17.8 Medical representatives must take adequate precautions to ensure the security of medical products in their possession.

17.9 Medical representatives must not use the telephone to promote products to the medical profession unless prior arrangement has been made with individual doctors.

17.10 Medical representatives should be paid on the basis of a fixed basic salary, and any addition proportional to sales of prescription medicines should not constitute an undue proportion of their remuneration.

17.11 When discussion about a product is initiated by a medical representative, he should place before the

doctor for reference either a data sheet in respect of that product or another document with the same content. If, however, the doctor asks a question about a different product, then the medical representative will not be required to produce such data in respect of that other product.

17.12 Companies must prepare detailed briefing material for medical representatives on the technical aspects of any product which the medical representative is to promote. A copy of such material must be made available to the licensing authority on request. Briefing material must comply with the relevant requirements of the Code and, in particular, is subject to the certification requirements of Clause 15.

17.13 Medical representatives should not make a claim for a product based on the regulatory treatment of that product, or of competing products, or based on any warnings issued in relation to other products, unless in accordance with a specific requirement. However, a medical representative may refer to such matters in answer to a specific question.

17.14 A company may only employ as medical representatives persons who have passed the examination established by the Association except that:

(i) Persons with an acceptable professional qualification, e.g. in pharmacy, medicine or nursing will be exempt from this requirement.

(ii) Persons employed as medical representatives on 1 October 1979, the date upon which this provision of the Code came into operation, are exempt from this requirement.

(iii) Trainee medical representatives may be employed for a period of up to two years from the date of commencing training as a medical representative.

18 Samples

18.1 Samples should be provided to a doctor only in response to a signed request unless intended solely for identification or demonstration purposes.

A company may make available to a doctor a pre-printed request form or card; such a form or card may bear no more than the doctor's name, the company's name and address and an identifying reference, together with guidance as to the further information which the doctor himself must add. This limitation as to the provision of information on a pre-printed request form or card does not apply, however, in the case of a product controlled under the Misuse of Drugs Act 1971.

If such a pre-printed form or card is presented by a representative, then the doctor himself must complete the form by inserting the requisite information.

Wherever practicable, an individual sample should not represent more than four days treatment for a single patient. When samples are provided to assist doctors in the recognition or identification of a product, or to demonstrate the use of a particular apparatus or equipment, only the minimum quantity necessary for this purpose should be supplied.

18.2 Where samples of products restricted by law to supply on prescription are distributed by a representative, the sample must be handed direct to the doctor or given to a person authorised to receive the sample on his behalf. A similar practice must be adopted for products which it would be unsafe to use except under medical supervision.

18.3 Samples of products restricted by law to supply on prescription, which are made available to representatives for distribution, should be strictly limited in quantity and an adequate system of accountability should be established.

18.4 Samples sent by post must be packed so as to be reasonably secure against the package being opened by young children.

18.5 Distribution of samples in hospitals should comply with individual hospital regulations, if any.

19 Gifts and inducements

19.1 Subject to Clause 19.2 no gift or financial inducement shall be offered or given to members of the medical profession for purposes of sales promotion.

Schemes designed to test the extent to which mailings are opened and read and which involve a reward, e.g. a reward for the return of a voucher included in the mailing, are unacceptable if the gift is one which would not come within Clause 19.2.

19.2 Gifts in the form of articles designed as promotional aids, whether related to a particular product or of general utility, may be distributed to members of the medical and allied professions provided the gift is inexpensive and relevant to the practice of medicine or pharmacy.

Amongst other items, nail brushes, book matches and pens have been held to be reasonable gifts. Gifts of table mats have been held to be in contravention of the Code as being irrelevant to the practice of medicine or pharmacy.

19.3 The requirements of Clause 7.3 or Clause 7.4 do not apply if a promotional aid of the type mentioned in Clause 19.2 bears no more than one or more of the following particulars:

(i) The name of the product.

(ii) The name of the product licence holder or the name of that part of his business responsible for the sale of the product.

(iii) The address of the product licence holder or the address of the part of his business responsible for the sale of the product.

(iv) An indication that the product name is a trade mark.

If a promotional aid consists of a note pad in which the individual pages bear advertising material, there is no need for the individual pages to comply with Clause 7 provided that the information required by the clause is given elsewhere in the pad; for example, on the cover.

20 Hospitality

Entertainment or other hospitality offered to members of the medical and allied professions for purposes of sales promotion should always be secondary to the main purpose of the meeting. It should not extend beyond members of the professions. The level of hospitality should be appropriate and not out of proportion to the occasion; its cost should not exceed that level which the recipients might normally adopt when paying for themselves.

Medical and group meetings are desirable and are to be encouraged. Both the British Medical Association and the Association share the opinion that such meetings should only take place if the advertising content is supported by a clear educational content. If hospitality is offered at meetings attendance should be restricted to members of the medical and allied professions.

It follows, therefore, that invitations to such medical

and group meetings should not be extended to wives or husbands unless they themselves are practising members of the medical or allied professions.

When organising a meeting at which hospitality will be offered, a factor to be taken into account is the impression which will be created in the minds of the recipients or those who hear about it. Hospitality which becomes little more than pure entertainment has limited value in terms of the provision of information and promotion; such hospitality can only be regarded, therefore, as irrelevant and wasteful.

21 Marketing research

Marketing research is the collection and analysis of information and must be unbiased and non-promotional. The use to which the statistics or information is put may well be promotional. The two phases should be kept distinct.

21.1 Methods used for marketing research must never be such as to bring discredit upon, or to reduce confidence in, the pharmaceutical industry. The following provisions apply whether the research is carried out directly by the company concerned or by an organisation acting on the company's behalf.

21.2 The following information must be made available to the informant at first approach:

(i) The nature of the survey.

(ii) The name and address of the organisation carrying out the work.

(iii) The identity of the interviewer.

(iv) The nature and length of the interview.

The requirement in Clause 21.2(ii) does not mean that the organisation is also obliged to reveal the identity of its client. This must depend upon the contract between the client and the organisation.

21.3 Questions intended to solicit disparaging references to competing products or companies must be avoided.

21.4 Any written or oral statement given or made to an informant in order to obtain co-operation must be both factually correct and honoured.

21.5 Any incentives offered to the informants should be kept to a minimum and be commensurate with the work involved.

21.6 Marketing research must not in any circumstances be used as a disguised form of sales promotion and the research *per se* must not have as a direct objective the influencing of the opinions of the informant.

21.7 The identity of an informant must be treated as being confidential, unless he has specifically agreed otherwise.

In the absence of this agreement it follows that the information provided (as distinct from the overall results of the research) must not be used as the basis upon which a subsequent approach is made to that informant for the purpose of sales promotion.

21.8 Precautions should be taken to ensure that no embarrassment results for informants following on from an interview, or from any subsequent communication concerning the research project.

22 Relations with the general public and lay communication media

22.1 Requests from individual members of the public for information or advice on personal medical matters must always be refused and the enquirer recommended to consult his or her own doctor.

22.2 Medicines which cannot legally be sold or supplied to the public otherwise than in accordance with a prescription, or which are legally limited to promotion for sale or supply only on prescription, must not be advertised to the general public.

Posters or notices issued for display in doctor's surgeries, pharmacies or anywhere to which the public have access must not include any message likely to arouse a demand for any particular product.

22.3 Statements must never be designed or made for the purpose of encouraging members of the public to ask their doctor to prescribe a product.

22.4 Information about medical products or matters related thereto, including scientific discoveries or advances in treatment, should not in general be made available to the general public either directly or through any lay medium.

The intention is to ensure that arrangements made for a press conference, or the extent of a press release, are such as to confine the disclosure of information about medical products or matters relating thereto to persons who are capable of evaluating the information responsibly and not concerned to exaggerate or even sensationalise its significance.

22.5 The importance of such information and the existence of legitimate public interest in acquiring it may exceptionally justify holding a press conference or the issue of a press release.

Invitations to attend such a conference, or the distribution of such a press release, should be confined to persons who are either medically qualified or established as the representatives of the medical, pharmaceutical or scientific press, or as the medical correspondents of a responsible medium.

In the circumstances set out above as to the significance of the information, and in response to an unsolicited enquiry from a person of the standing described, information may also be released in an informal manner.

22.6 A further exception may arise when there exists a genuine mutual interest of a financial or commercial nature justifying the disclosure of information about medical products or related matters privately or to a restricted public. Examples are the interests of shareholders, financial advisers, employees and creditors.

When releasing information, it is essential to bear in mind the provisions of Clause 5.3 and, in particular, the extreme caution required in any reference to side-effects; it should also be emphasised that the treatment of a particular individual is solely a matter for decision by his medical practitioner.

22.7 On all occasions the information whether written, or communicated by other means, must be presented in a balanced way so as to avoid the risk of raising unfounded hopes of successful treatment or stimulating the demand for prescription of the particular product.

22.8 An announcement of the introduction of a new medical product must not be made by press conference or formal press release until the appropriate steps have been taken to inform the medical profession of its availability.

23 Operative date

This Sixth Edition of the Code shall take effect on 1 January 1984.

Abbott Laboratories Limited
Queenborough
Kent ME11 5EL

ABBOCIN*

Presentation Each yellow, sugar-coated tablet contains 250 mg Oxytetracycline Dihydrate BP.

Uses Organisms sensitive to oxytetracycline include a large number of Gram-negative and Gram-positive pathogenic bacteria. Those organisms that are sensitive to tetracycline in the concentrations usually achieved in the body during treatment are *Bacillus anthracis.* bordetella spp., brucella spp., *Escherichia coli.* haemophilus spp., klebsiella spp., *Proteus vulgaris,* staphylococci, streptococci, mycoplasma, *Entamoeba histolytica, Trichomonas vaginalis,* certain rickettsias and larger viruses. *Pseudomonas aeruginosa,* salmonella spp., and *Mycobacterium tuberculosis* are less susceptible.

Dosage and administration For adults and older children the dose is 250 mg four times daily taken orally. In severe infections this dose may be doubled or trebled.

Contra-indications, warnings, etc
Contra-indications: Hypersensitivity to the tetracyclines.

Precautions and side-effects: As with other tetracyclines, Abbocin should be administered with great care to individuals with renal or hepatic dysfunction. Because of the staining of teeth and effects on bone development, tetracyclines should not be given in pregnancy or to children under 12 years of age. Tetracyclines should not be administered simultaneously with milk, antacids or preparations containing iron, calcium or magnesium.

Side-effects include nausea, diarrhoea and symptoms resulting from the overgrowth of non-susceptible organisms. Overgrowth of *Candida albicans* in the mouth may cause glossitis and stomatitis which may extend into the trachea and bronchi; overgrowth of *C albicans* in the bowel results in pruritis ani; overgrowth of resistant coliform organisms such as pseudomonas and proteus may also cause diarrhoea. Occasionally resistant staphylococci may give rise to a fulminating enterocolitis. Allergic reactions and skin rashes are rare.

Treatment of overdosage: Gastric lavage. Intensive supportive therapy. In cases of overdosage, allergic reactions such as drug fever, anaphylactic shock and rash may occur. For treatment of anaphylaxis immediate administration of adrenaline, oxygen and artificial respiration is necessary.

Adrenaline is given subcutaneously as 0.5–1 ml adrenaline Injection BP 0.1%. For dyspnoea, aminophylline, calcium and antihistamines may be given. General measures, such as administration of plasma, blood, vasopressor drugs or hydrocortisone (100 mg IV) may be necessary.

Incompatible with alkalis and chloramphenicol.

Pharmaceutical precautions Store below 25°C. Keep container tightly closed.

Legal category POM.

Package quantities Abbocin is supplied in containers of 1,000 sugar-coated tablets.

Further information Metabolisable carbohydrate content approx 0.29 g per tablet.

Product licence number 0037/0095.

ABBOKINASE*

Presentation Abbokinase is a highly purified sterile lyophilised formulation of urokinase obtained from cultures of human kidney cells. Urokinase is a plasminogen activator excreted in the urine of normal healthy individuals. Each vial of Abbokinase contains in excess of 250,000 iu so that, following reconstitution with 5.2 ml sterile water for injection, each ml of the 5 ml which can be withdrawn will contain 50,000 iu urokinase, 5 mg mannitol and 5 mg sodium chloride.

Uses Abbokinase *in-vivo* and *in-vitro* produces the release of plasmin by an enzymatic action on human plasminogen.

Abbokinase has only minimal activity in reducing fibrinogen levels but blood plasminogen levels are reduced, the effect being dose-dependent.

Abbokinase is virtually non-antigenic to humans and, in therapeutic doses, is thromboplastin-free.

Thrombolytic therapy is indicated in the treatment of vascular occlusions caused by forming or recently formed fibrin clots. Theoretically the best results will be obtained with thrombi less than 24 hours old.

Abbokinase is indicated as a thrombolytic agent in pulmonary embolism.

Dosage and administration Abbokinase is administered intravenously by continuous infusion, usually for a period of 12 hours.

It is recommended that Abbokinase be given in a solution of normal saline by constant infusion. An initial loading dose to be given during the first ten minutes of therapy is advocated.

This loading dose should be equal to the amount which it is planned to administer over each succeeding period of one hour. Ideally, an infusion pump should be used to maintain a constant rate of infusion.

Abbokinase is reconstituted with 5.2 ml sterile water for injection, without preservatives.

For administration the reconstituted solution should be further diluted with normal saline. It is strongly recommended that the total volume after dilution should be 195 ml, irrespective of the number of vials used, since this provides for a bolus dose of 15 ml followed by the infusion of 15 ml per hour over 12 hours. However, choice of another volume is possible, the physician being

Armour Pharmaceutical Company Limited
St. Leonards House
St. Leonards Road
Eastbourne
East Sussex BN21 3YG

ARVIN®

Presentation A sterile clear colourless aqueous solution of ancrod for intravenous and subcutaneous injection. Each ml contains 70 international units put up in isotonic saline. pH is 6.8, phosphate content approximately 0.0025M and chlorbutol approximately 0.005%.

The international unit is defined as the specific biological activity contained in 0.307 mg of the international standard for ancrod.

Uses *Controlled defibrination for:*

1. The prevention of deep vein thrombosis following surgical repair of fractured neck of femur and hip replacement.
2. The treatment of deep vein thrombosis, central retinal and branch vein thrombosis, priapism, pulmonary hypertension of embolic origin, embolism after insertion of prosthetic cardiac valves, rethrombosis after thrombolytic therapy and rethrombosis after vascular surgery.
3. Peripheral arterial insufficiency.

Dosage and administration

Subcutaneous dosage:

1. Prophylaxis of deep vein thrombosis in:

(a) Patients undergoing surgical repair for fractured neck of femur – 4 × 1 ml ampoules as a single s.c. injection immediately after surgery then 1 ampoule daily for the next 4 days.

(b) Hip replacement – 4 × 1 ml ampoules as a single s.c. injection immediately after surgery then 1 ampoule daily for the next 8 days.

With these prophylactic regimes, Arvin normally produces predictable defibrination. Occasionally however, the clinical situation may warrant the measurement of fibrinogen levels.

2. peripheral arterial insufficienty – 1 unit/kg body weight as a single injection into the anterior abdominal wall or thigh each day for four days to lower the plasma fibrinogen to 50 mg% or more; then 4 units/kg as a single injection every three or four days to maintain the fibrinogen at this level. This subcutaneous regimen may be used for up to one month in patients with chronic peripheral arterial insufficiency. Fibrinogen levels should be monitored prior to administration of the next dose.

Intravenous dosage:

Treatment of established thrombo-embolic conditions:

Induction dose: 2–3 units/kg body weight in 50–500 ml Sodium Chloride Injection BP by slow intravenous drip over a period of four to twelve hours. Administration of this dose should not take place over a period of less than 4 hours.

Maintenance doses: 2 units/kg body weight in 10–50 ml Sodium Chloride Injection BP by intravenous injections at twelve-hour intervals, given slowly, taking about five minutes over each injection. Fibrinogen levels should be monitored daily by standard laboratory procedures to facilitate accurate control of dosage.

Contra-indications, warnings, etc

Contra-indications: Severe infections and diffuse intravascular coagulation.

Pregnancy.

Gastro-intestinal ulcers liable to bleed such as peptic ulcer, ulcerative colitis.

Ulcerogenic drugs.

Haematological defects which interfere with haemostasis such as platelet count of < 100,000/cu mm.

Patients in receipt of plasma expanders such as dextrans or antifibrinolytic agents such as EACA should not be treated with Arvin.

Precautions: Pretreatment investigations such as blood film, platelet count and fibrinogen should be made before treatment.

The intravenous induction dose of Arvin must not be given in less than 4 hours as if given rapidly the fibrin degradation products may produce a rise in blood viscosity.

Warnings: Haemorrhage may occur and can be rapidly reversed by the specific antidote although this is rarely necessary as fibrinogen levels return to haemostatic values within a few hours of cessation of therapy.

Defibrination may complicate malignant hypertension; acute pericarditis, sub-acute bacterial endocarditis, retinopathy (grade 3 or worse), diabetic retinopathy, resting diastolic pressure > 120 mm Hg and may cause bleeding in uraemia > 100 mg%, renal colic with calculus, cerebrovascular accidents, history of neurosurgery.

Migraine – a few patients with a history of migraine have experienced headaches after Arvin injections.

ESR – during treatment with Arvin, the erythrocyte sedimentation rate falls to about 1 mm/hour and cannot be used as an index of pathological activity.

Platelets – although Arvin has no specific effect on platelets the fibrin degradation products produce reduced platelet aggregation.

Treatment of overdosage or excessive bleeding: A specific antidote has been prepared of which 1 ml neutralises 70 units of Arvin *in vivo*.

The following procedure is recommended for the use of the antidote.

1. 1 in 1,000 adrenaline should be available on the giving tray.
2. Give 0.2 ml antidote subcutaneously and observe for an erythematous reaction for half hour.

Sodium Chloride BP	0.20 g
Potassium Chloride BP	0.30 g
Sodium Bicarbonate BP	0.30 g
Glucose BP	8.00 g

Uses Oral correction of fluid and electrolyte loss in infants, children and adults.

Treatment of watery diarrhoea of varying aetiologies, including gastroenteritis, in all age groups.

Dosage and administration *Reconstitution:* The contents of each sachet should be dissolved in 200 ml (approximately 7 fluid ounces) of drinking water. Use fresh drinking water for adults and children. For infants, and where drinking water is unavailable, the water should be freshly boiled and cooled. The solution should be made up immediately before use. If refrigerated, the solution may be stored for up to 24 hours, otherwise any solution remaining an hour after reconstitution should be discarded. The solution must not be boiled.

The actual volume of reconstituted Dioralyte which should be taken should be decided by the clinician, taking into consideration the weight of the patient and the stage and severity of the condition. A basic principle of treatment of diarrhoea is to replace lost fluid and then to maintain sufficient fluid intake to replace fluid loss from stools.

Daily intake may be based on a volume of 150 ml/kg body weight for infants and 20–40 ml/kg body weight for adults and children. A reasonable approximation is:

Infants – One to one and a half times the usual feed volume.

Children – One sachet after every loose motion.

Adults – One or two sachets after every loose motion.

More may be required initially to ensure early and full volume repletion.

In the initial stages of treatment of diarrhoea all foods, including cow's or artificial milk, should be stopped. However, breast milk need not be witheld. In breast fed infants it is suggested that the infant is given the same volume of Dioralyte as the normal feed and then put to the breast until satisfied. Expression of residual milk from the breasts may be necessary during this period. After 24–48 hours, when symptoms have subsided, the normal diet should be resumed but this should be gradual to avoid exacerbation of the condition. A suggested regimen for the treatment of severe infantile diarrhoea based on body weight in kilograms is given below.

Day	*Volume of Dioralyte solution (ml)*	*Volume of artificial milk feed (ml)*	*Total volume in 24 hours (ml)*
1	150 × wt*	0	150 × wt
2	120 × wt	30 × wt	150 × wt
3	90 × wt	60 × wt	150 × wt
4	60 × wt	90 × wt	150 × wt
5	30 × wt	120 × wt	150 × wt
6	0	150 × wt	150 × wt

* Weight in kilograms.

Where vomiting is present with the diarrhoea it is advisable that small amounts of Dioralyte be taken frequently. However, it is important that the whole of the required volume of Dioralyte is taken. Where the kidneys are functioning normally, it is difficult to overhydrate by mouth and where there is doubt about the exact dosage, more rather than less should be taken.

Contra-indications, warnings, etc There are no known contra-indications to Dioralyte. However, there may be a number of conditions where treatment with Dioralyte will be inappropriate eg intestinal obstruction requiring surgical intervention.

Precautions: For oral administration only.

Dioralyte should not be reconstituted in diluents other than water.

Each sachet should always be dissolved in 200 ml of water. A weaker solution than recommended will not contain the optimal glucose and electrolyte concentration and a stronger solution than recommended may give rise to electrolyte imbalance.

If the diarrhoea does not improve promptly, the patients should be reassessed.

Warning: Cow's milk and artificial milk feeds in infants should be stopped for 24 hours and gradually reintroduced when the diarrhoea has lessened. However, breast feeding should be continued.

Pharmaceutical precautions The sachet should be stored in a cool, dry place. Shelf-life 3 years.

Legal category P.

Package quantities Packs of 4 and 20 sachets.

Further information The composition of Dioralyte is based on the observation that a correctly balanced, isotonic solution of glucose and sodium stimulates intestinal water absorption.

A litre of made up solution (5 sachets, 5 × 200 ml quantities) contains: 35 mmol Sodium (Na^+); 20 mmol Potassium (K^+); 37 mmol Chloride (Cl^-); 18 mmol Bicarbonate (HCO_3); 200 mmol Dextrose.

The total osmolarity is 310 mmol per litre.

Each sachet of Dioralyte contains 8 g of glucose which is equivalent to 30.5 kcal.

Product licence numbers

Dioralyte	0231/0043.
Dioralyte Cherry	0231/0067

FACTORATE*

Presentation Dried Human Antihaemophilic Fraction Factorate is a stable lyophilised concentrate of Factor VIII (AHF, AHG) prepared from pooled human plasma.

Each vial contains the labelled amount of antihaemophilic activity in International Units (one International Unit is the activity equivalent to the average Factor VIII content of 1 ml aliquots of 167 samples of fresh normal plasma, as determined in an international collaborative study). Each vial also contains sufficient sodium chloride to make the reconstituted solution approximately isotonic when sterile Water for Injections BP is added as directed.

Uses For use in therapy of classic haemophilia (Haemophilia A).

Dosage and administration Factorate is for intravenous administration only. As a general rule one unit of Factor VIII activity per kg will increase by 2% the circulating Factor VIII level, and although dosage must be adjusted according to the needs of the patient (weight, severity of haemorrhage, presence of inhibitors) the following general dosages are suggested.

1. Overt bleeding: Initially 20 units per kg of body weight followed by 10 units per kg every eight hours for the first 24 hours and the same dose every 12 hours for

the next 3 or 4 days. For massive wounds, give until bleeding stops and maintain with 20 units per kg 8-hourly to achieve a minimum Factor VIII level of 40%.

2. Muscle haemorrhages: (a) Minor haemorrhages in extremities or non-vital areas: 10 units per kg once a day for 2 or 3 days.

(b) Massive haemorrhages in non-vital areas: 10 units per kg by infusion at 12 hour intervals for 2 days and then once a day for 2 more days.

(c) Haemorrhages near vital organs (neck, throat, subperitoneal): 20 units per kg, initially; then 10 units per kg every 8 hours. After 2 days the dose may be reduced by one-half.

3. Joint haemorrhages: 10 units per kg every 8 hours for a day; then twice daily for 1 or 2 days. If aspiration is carried out, 10 units per kg just prior to aspiration with additional infusions of 10 units per kg 8 hours later and again on the following day.

4. Surgery: Dosages of 30 to 40 units per kg body weight prior to surgery are recommended. After surgery 20 units per kg every 8 hours should be administered. Close laboratory control to maintain the blood level of Factor VIII above 40% of normal for at least 10 days post-operatively is suggested.

5. Dental extractions: For simple extractions a pre-operative dose of 20–25 units per kg sufficient to raise the Factor VIII level to 50% should be given, followed by intravenous administration of epsilon aminocaproic acid. For multiple extractions further doses of Factor VIII may be advisable 24 or 36 hours after the operation.

Recommended reconstitution: Reconstitute Factorate using 20 ml sterile Water for Injections BP using standard aseptic precautions.

Warm both diluent and Factorate vials to between 20°C and 25°C. Direct diluent down the side of the vial and gently rotate the vial until contents are dissolved. DO NOT SHAKE VIAL. Vigorous shaking will cause frothing and prolong the reconstitution time. Complete solution usually takes less than 5 minutes. The solution is now ready for administration. If a gel forms on reconstitution, the preparation should not be used.

Administration: Standard aseptic techniques should be used at all times.

Intravenous injection: Plastic disposable syringes are recommended with Factor VIII solution. The ground glass surfaces of all-glass syringes tend to stick with solutions of this type.

1. Attach a filter needle to a sterile disposable syringe. Insert filter needle into stopper of Factor VIII vial; inject air and withdraw the reconstituted solution from the vial.
2. Discard the filter needle and attach a suitable intravenous needle.
3. Administer solution by slow intravenous injection (20 ml in about five minutes).

Intravenous infusion: The infusion equipment used should comply with that described in sections 3 or 4 of British Standard 2463:1962, Transfusion Equipment for Medical Use.

1. Prepare solution of Factorate as recommended under '*Reconstitution*'.
2. Attach suitable infusion set.
3. If more than one vial is to be administered to the same patient the infusion set may be transferred to a second vial.
4. When infusion of Factorate is complete, the infusion set may be flushed with sterile isotonic saline to avoid loss of any of the reconstituted solution.
5. After use, discard infusion set, needles and vials together with any unused solution.

Contra-indications, warnings, etc

Warning: Factor VIII is prepared from human plasma, each donation of which has been found negative for hepatitis B surface antigen (HBsAg) by the radio-immunoassay (RIA) method. In addition, each batch, after reconstitution as recommended, has been tested and found negative by the RIA method. However, since no completely reliable laboratory test is yet available to detect all potentially infectious plasma donations, the risk of transmitting viral hepatitis is still present.

Side-effects: Products of this type are known to cause mild chills, nausea or stinging at the infusion site.

Contra-indications: There are no known contra-indications to antihaemophilic fraction.

Precautions: Factor VIII contains low levels of group A and B isohaemagglutinins. When large volumes are given to patients of blood groups A, B or AB, the possibility of intravascular haemolysis should be considered. Such patients should be monitored by means of a haematocrit and direct Coombs test for signs of progressive anaemia.

Pharmaceutical precautions Factorate is to be stored at refrigerator temperature (2°C–6°C). When stored as directed, it will maintain its labelled potency for the dating period indicated on the label but within this period may be stored at room temperature (not exceeding 30°C or 86°F) for up to six months.

Legal category POM.

Package quantities Factorate is supplied in single dose vials (potency is stated on each vial label).

Further information Haemophilia A, a hereditary disorder of blood coagulation occurring almost exclusively in males results in profuse bleeding in joints, muscles or internal organs as a result of minor trauma. The disease appears to be due to a deficiency of a specific plasma protein, antihaemophilic factor, Factor VIII: Factorate provides temporary replacement of the missing clotting factor.

Affected individuals frequently require therapy following minor trauma. Surgery, when required in such individuals must be preceded by temporary correction of the clotting abnormality with fresh plasma transfusions, cryoprecipitate or by injections of Factor VIII concentrates. Obvious advantages of the use of concentrates of Factor VIII are the avoidance of hyper-proteinaemia, overloading the circulatory system and possible kidney dysfunction resulting from large volume transfusions.

Several different concentrations of Factor VIII have been used successfully. These range from Fraction 1 of Cohn to highly purified potent preparations. Dried Human Antihaemophilic Fraction – Factorate is in an intermediate category, being purified cryoglobulin complying with the standards of the BP.

Product licence number 0231/0038.

HIGH POTENCY FACTORATE*

Presentation Dried Human Antihaemophilic Fraction High Potency Factorate is a stable lyophilised concentrate of Factor VIII (AHF, AHG) prepared from pooled

human plasma. It conforms to the monograph for Dried Human Antihaemophilic Factor BP.

Each vial contains the labelled amount of antihaemophilic activity in International Units (one International Unit is the activity equivalent to the average Factor VIII content of 1 ml aliquots of 167 samples of fresh normal plasma, as determined in an international collaborative study). Each vial also contains sufficient sodium chloride to make the reconstituted solution approximately isotonic when Water for Injections BP is added as directed.

Uses For use in therapy of classic haemophilia (Haemophilia A).

Dosage and administration High Potency Factorate is for intravenous administration only. As a general rule one unit of Factor VIII activity per kg will increase by 2% the circulating Factor VIII level, and although dosage must be adjusted according to the needs of the patient (weight, severity of haemorrhage, presence of inhibitors) the following general dosages are suggested.

1. Overt bleeding: Initially 20 units per kg of body weight followed by 10 units per kg every eight hours for the first 24 hours and the same dose every 12 hours for the next 3 or 4 days. For massive wounds, give until bleeding stops and maintain with 20 units per kg 8-hourly to achieve a minimum Factor VIII level of 40%.

2. Muscle haemorrhages: (a) Minor haemorrhages in extremities or non-vital areas: 10 units per kg once a day for 2 or 3 days.

(b) Massive haemorrhages in non-vital areas: 10 units per kg by infusion at 12 hour intervals for 2 days and then once a day for 2 more days.

(c) Haemorrhages near vital organs (neck, throat, subperitoneal), 20 units per kg, initially; then 10 units per kg every 8 hours. After 2 days the dose may be reduced by one-half.

3. Joint haemorrhages: 10 units per kg every 8 hours for a day; then twice daily for 1 or 2 days. If aspiration is carried out, 10 units per kg just prior to aspiration with additional infusions of 10 units per kg 8 hours later and again on the following day.

4. Surgery: Dosages of 30 to 40 units per kg body weight prior to surgery are recommended. After surgery 20 units per kg every 8 hours should be administered. Close laboratory control to maintain the blood level of Factor VIII above 40% of normal for at least 10 days post-operatively is suggested.

5. Dental extractions: For simple extractions a pre-operative dose of 20–25 units per kg sufficient to raise the Factor VIII level to 50% should be given, followed by intravenous administration of tranexamic acid. For multiple extractions further doses of Factor VIII may be advisable 24 or 36 hours after the operation.

Recommended reconstitution: Reconstitute High Potency Factorate using 30 ml sterile Water for Injections BP using standard aseptic precautions.

Warm both diluent and High Potency Factorate vials to between 20°C and 30°C. Direct diluent down the side of the vial and gently rotate the vial until contents are dissolved. DO NOT SHAKE VIAL. Vigorous shaking will cause frothing and prolong the reconstitution time. Complete solution usually takes approximately 10 minutes. The solution is now ready for administration. If a gel forms on reconstitution, the preparation should not be used. The solution should be used within 3 hours of reconstitution.

Administration: Standard aseptic techniques should be used at all times.

Intravenous injection: Plastic disposable syringes are recommended with Factor VIII solution. The ground glass surfaces of all-glass syringes tend to stick with solutions of this type.

1. Attach a filter needle to a sterile disposable syringe. Insert filter needle into stopper of Factor VIII vial; inject air and withdraw the reconstituted solution from the vial.
2. Discard the filter needle and attach a suitable intravenous needle.
3. Administer solution by slow intravenous injection, at a rate comfortable to the patient, and not exceeding 2 ml per minute.

Intravenous infusion: The infusion equipment used should comply with that described in sections 3 or 4 of British Standard 2463:1962, Transfusion Equipment for Medical Use.

1. Prepare solution of High Potency Factorate as recommended under '*Reconstitution*'.
2. Attach suitable infusion set.
3. If more than one vial is to be administered to the same patient the infusion set may be transferred to a second vial.
4. When infusion of High Potency Factorate is complete, the infusion set may be flushed with sterile isotonic saline to avoid loss of any of the reconstituted solution.
5. After use, discard infusion set, needles and vials together with any unused solution.

Contra-indications, warnings, etc

Warning: Factor VIII is prepared from human plasma, each donation of which has been found negative for hepatitis B surface antigen (HBsAg) by the radioimmunoassay (RIA) method. In addition, each batch, after reconstitution as recommended, has been tested and found negative by the RIA method. However, since no completely reliable laboratory test is yet available to detect all potentially infectious plasma donations, the risk of transmitting viral hepatitis is still present.

Side-effects: Products of this type are known to cause mild chills, nausea or stinging at the infusion site.

Contra-indications: There are no known contra-indications to antihaemophilic fraction.

Precautions: Factor VIII contains low levels of group A and B isohaemagglutinins. When large volumes are given to patients of blood groups A, B or AB, the possibility of intravascular haemolysis should be considered. Such patients should be monitored by means of a haematocrit and direct Coombs test for signs of progressive anaemia.

Pharmaceutical precautions High Potency Factorate is to be stored at refrigerator temperature (2°C–6°C). When stored as directed, it will maintain its labelled potency for the period indicated on the label but within this period it may be stored at room temperature (not exceeding 30°C or 86°F) for up to six months.

Legal category POM.

Package quantities High Potency Factorate is supplied in single dose vials (potency is stated on each vial label).

Further information Haemophilia A, a hereditary disorder of blood coagulation occurring almost exclusively in males results in profuse bleeding in joints, muscles or internal organs as a result of minor trauma.

The disease appears to be due to a deficiency of a specific plasma protein, antihaemophilic factor, Factor VIII; High Potency Factorate provides temporary replacement of the missing clotting factor.

Affected individuals frequently require therapy following minor trauma. Surgery, when required in such individuals must be preceded by temporary correction of the clotting abnormality with fresh plasma transfusions, cryoprecipitate or by injections of Factor VIII concentrates. Advantages of the use of concentrates of Factor VIII are the avoidance of hyperproteinaemia, overloading the circulatory system and possible kidney dysfunction resulting from large volume transfusions. Several different concentrations of Factor VIII have been used successfully. These range from Fraction 1 of Cohn to highly purified potent preparations. Dried Human Antihaemophilic Fraction – High Potency Factorate is a purified preparation with lower levels of fibrinogen and other non-AHF protein per international unit than 'Intermediate Purity' AHF preparations.

Product licence number 0231/0044.

KALSPARE* ▼

Presentation Orange film coated tablet marked 'A' on one side and with a breakline on the reverse. Each tablet contains 50 mg Chlorthalidone BP and 50 mg Triamterene BP. Presented in calendar packs.

Uses Kalspare is a long acting potassium sparing diuretic and antihypertensive of particular value in conditions where potassium conservation is an important consideration.

Management of mild to moderate hypertension, oedema associated with congestive cardiac failure, nephrosis, corticosteroid or oestrogen therapy and ascites associated with hepatic cirrhosis.

Dosage and administration

Hypertension: Usually one tablet daily taken after breakfast. If necessary the dose may be increased to two tablets taken once daily.

Oedema: The usual dose is one tablet daily taken after breakfast. If oedema persists after seven to ten days the dose may be increased to two tablets daily.

Dosage in children has not been established and Kalspare is recommended for the treatment of adults only.

Contra-indications, warnings, etc

Contra-indications: Hypersensitivity to the individual components or to other sulphonamide-derived drugs.

Progressive renal failure (see also Precautions).

Concomitant lithium therapy.

Kalspare should not be used in the presence of hyperkalaemia (plasma potassium above 5.0 mmol/litre) or in patients receiving other potassium-sparing agents, such as spironolactone or amiloride.

Warnings: Caution should be exercised in patients with severe kidney disease, impaired liver function or progressive liver disease.

As with thiazide diuretics and chlorthalidone, treatment with Kalspare may result in hyperuricaemia or the precipitation of acute gout in certain patients.

Potassium supplements should not be given with Kalspare except in the presence of hypokalaemia.

Chlorthalidone has, in common with other sulphonamide diuretics, occasionally aggravated or precipitated Diabetes mellitus. This effect is usually reversible on cessation of therapy.

Chlorthalidone and related drugs may decrease serum protein bound iodine levels without signs of thyroid disturbance.

Triamterene may cause a decreasing alkali reserve, with the possibility of metabolic acidosis.

Precautions: Although no clinically significant hyperkalaemia has occurred in studies with Kalspare, all potassium conserving diuretic combinations can cause an abnormal elevation of plasma potassium. It is recommended that measurements of potassium are made at the time of dosage adjustments and at appropriate intervals during therapy, particularly in elderly or diabetic patients with confirmed or suspected renal insufficiency.

Signs or symptoms of hyperkalaemia include paraesthesia, muscular weakness, fatigue, flaccid paralysis of the extremities, bradycardia, shock and ECG abnormalities. If hyperkalaemia occurs in patients taking Kalspare, the drug should be withdrawn, a diuretic substituted and potassium intake restricted. If the plasma potassium level exceeds 6.5 mmol per litre, active measures should be taken to reduce it. Such measures include the intravenous administration of sodium bicarbonate solution or oral or parenteral glucose with a rapid-acting insulin preparation.

If progressive renal impairment becomes evident, Kalspare therapy should be withdrawn and alternative therapy instituted if necessary.

Use in pregnancy and lactation: Thiazide diuretics have been shown to cross the placenta and also to appear in breast milk. In rare instances, thrombocytopenia, pancreatitis or hypokalaemia have been reported in newborn infants of mothers treated with thiazide diuretics. The use of Kalspare in pregnant women or nursing mothers should therefore be avoided unless essential.

Side effects: Side-effects are similar to those that have been associated with thiazide therapy and include nausea, dry mouth, constipation, leg cramp, headaches, dizziness and fatigue.

Rare cases of megaloblastic anaemia have been reported in association with triamterene.

Drug interactions: Kalspare may add to or potentiate the action of other antihypertensive drugs.

Any tendency to orthostatic hypotension on Kalspare treatment may be aggravated by concomitant alcohol, barbiturates or narcotics.

Chlorthalidone and related drugs may increase the responsiveness to tubocurarine.

Overdose: The stomach contents should be emptied immediately. Treatment should be symptomatic and supportive with correction of electrolyte imbalance and fluid depletion. No specific antidote exists for Kalspare.

Pharmaceutical precautions Store in a cool dry place. Protect from light.

Legal category POM.

Package quantities Calendar packs of 2 × 14 tablets.

Further information The potassium conserving action of Kalspare has been shown to reduce the need for additional potassium in the maintenance of normal plasma levels. It is therefore particularly valuable where dietary potassium intake is low, and for patients on digitalis. Kalspare is highly effective baseline therapy for hypertension and may be used with other antihypertensive drugs such as beta-blockers. Its prolonged duration

Bayer UK Limited
Pharmaceutical Division
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Newbury, Berkshire, RG13 1JA

ADALAT®

Presentation *Adalat/Adalat 5:* Orange, soft gelatin capsules containing a yellow viscous liquid. Adalat capsules contain 10 mg nifedipine. Adalat 5 capsules contain 5 mg nifedipine.

Adalat Retard: Pink-grey lacquered tablets one side marked 1U, the reverse side with the Bayer Cross each containing 20 mg nifedipine.

Uses *Mode of action:* Adalat is a potent calcium antagonist. Its most important effect is to protect the heart against excessive oxygen utilisation during physical activity. There is a reduction in cardiac work and in myocardial oxygen demand. Adalat also causes peripheral vasodilatation and thus reduces peripheral resistance and heart work load. Adalat has no therapeutic anti-arrhythmic effect. Since Adalat does not cause a rise in intraocular pressure, it can be used in patients with glaucoma.

Indications: For the treatment and prophylaxis of angina pectoris and for the treatment of hypertension.

Dosage and administration For oral administration, the capsules should be taken with a little fluid during or after meals. The recommended dose is one 10 mg capsule three times daily. If necessary, up to two capsules three times daily may be taken.

If an immediate effect is required, the capsule should be bitten open and the liquid contents allowed to remain in the mouth.

Adalat 5 capsules permit titration of initial dosage in the elderly and those patients on concomitant medication. The recommended dose is one Adalat 5 capsule three times daily.

In the treatment of hypertension the recommended dose of Adalat Retard is one 20 mg tablet twice daily swallowed after food with a little fluid. If necessary the dose may be increased to 40 mg twice daily.

Treatment may be continued indefinitely.

Contra-indications, warnings, etc

Contra-indications: Must not be given to women capable of child-bearing.

Warnings and precautions: Adalat is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker, preferably over 8–10 days.

Adalat may be used in combination with beta-blocking drugs and other antihypertensive agents, but the possibility of an additive effect resulting in postural hypotension should be borne in mind. Adalat will not prevent possible rebound effects after cessation of anti-hypertensive therapy.

Adalat should be used with caution in patients whose cardiac reserve is poor.

Ischaemic pain has been reported in some patients, commonly within 30 minutes of the introduction of Adalat therapy. Patients experiencing this effect should discontinue Adalat.

The use of Adalat in diabetic patients may require adjustment of their control. There is no known drug incompatibility.

Side-effects: Adalat is well tolerated. Minor side-effects, usually associated with vasodilatation are mainly headache, flushing and lethargy. These are transient and invariably disappear with continued treatment.

Overdosage: Standard measures such as atropine and noradrenaline may be used for resultant bradycardia and hypotension. Intravenous calcium gluconate may be of benefit.

Pharmaceutical precautions The capsules should be protected from strong light and stored in the manufacturer's original container.

Legal category POM.

Package quantities Adalat and Adalat 5 capsules are available in foil strips of 10 in packs of 100.

Adalat Retard tablets are also available in foil strips of 10 in packs of 100.

Further information As a specific calcium antagonist, Adalat's main action is to relax arterial smooth muscle both in the coronary and peripheral circulation.

In angina pectoris Adalat capsules relax peripheral arteries so reducing the load of the left ventricle. Additionally Adalat dilates submaximally both clear and atherosclerotic coronary arteries, thus protecting the heart against coronary artery spasm and improving perfusion to the ischaemic myocardium.

Adalat capsules reduce the frequency of painful attacks and the ischaemic ECG changes irrespective of the relative contribution from coronary artery spasm or atherosclerosis. In normotensive individuals Adalat has little or no effect on blood pressure.

In hypertension Adalat Retard twice daily provides smooth 24 hour control of raised blood pressure. Adalat Retard causes a reduction in blood pressure such that the percentage lowering of blood pressure is directly related to its initial height.

In long-term treatment, none of these formulations have been shown to cause serious adverse reactions. Metabolic disturbance, failure of ejaculation, increased incidence of Raynaud's phenomenon and bronchospasm

Immuno Ltd
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Dunton Green, Nr. Sevenoaks,
Kent, TN14 5HB

GAMMABULIN*
Normal Immunoglobulin Injection BP.

Presentation Gammabulin is a concentrate of antibodies present in the IgG fraction of human plasma and is available in liquid or lyophilised forms. It is produced from pooled human plasma obtained from suitable human donors† whose donations are shown by RIA to be free from HB_sAg. Pooled plasma and the final product are also tested for freedom from HB_sAg.

Gammabulin liquid is a clear solution varying in colour from pale yellow to light brown. It has a protein content of 16% of which at least 90% is gamma globulin. Glycine is added at a strength of 2.25% as a stabiliser and Merthiolate at a strength of 0.01% as a preservative.

Gammabulin lyophilised is a white to slightly yellowish powder or solid friable mass completely soluble in Water for Injections BP.

When the lyophilised powder is reconstituted with the amount of Water for Injections BP indicated on the label, it has a protein content of 16% of which at least 90% is gamma globulin. Glycine is added at a strength of 6% as a stabiliser and Merthiolate at a strength of 0.01% as a preservative.

Uses Gammabulin is used in the treatment of:

Antibody deficiency syndrome and recurring bacterial infections in dys-, hypo- and agammaglobulinaemia.

Hepatitis A prophylaxis.

Prevention or modification of measles infection.

Treatment of susceptible pregnant women exposed to Rubella infection who will not consider therapeutic abortion.

Dosage and administration Gammabulin must be administered by the intramuscular route.

All recommendations and doses given below refer to the 16% solution and are expressed in ml.

Antibody deficiency syndrome in dys-, hypo- and agammaglobulinaemia: By intramuscular administration of Gammabulin antibody concentrate the frequency and severity of recurring bacterial infections can be reduced. For treatment of gamma globulin deficiency, it is necessary to achieve and maintain a gamma globulin level of approximately 200 mg per 100 ml serum.

Initial dosage: 1.8 ml per kg bodyweight e.g. in three single administrations of 0.6 ml/kg bodyweight each at intervals of 24 hours.

Maintenance dose: 0.6 ml per kg bodyweight, monthly.

Hepatitis A: Gammabulin is an efficient agent for the prevention or modification of hepatitis A. It must be pointed out that after gamma globulin administration an anicteric course of hepatitis has been observed. Because of this, regular monitoring of transaminase levels may be warranted.

Dosage for children: 0.02–0.04 ml per kg bodyweight. If exposure continues, repeat the dose after 4–6 months.

Dosage for adults:

(a) for a short period of exposure of less than 2 months: 0.02 to 0.04 ml per kg bodyweight.
(b) for longer periods of exposure 0.08 to 0.12 ml per kg bodyweight. If exposure continues, repeat the dose after 4 to 6 months

Note: No benefit may be expected if administered after the onset of clinical symptoms.

Measles: Gammabulin should be given as soon as possible at a dose of 0.25 ml/kg to prevent or modify measles in a susceptible person exposed less than six days previously. Gammabulin may be especially indicated for susceptible household contacts of measles patients, particularly with children under one year of age or children who are immunosuppressed or have an immune deficiency disease and should not receive measles vaccine or any other live viral vaccine.

Prophylaxis: 0.2 ml per kg bodyweight with continued or repeated exposure repeat after 3 weeks.

Mitigation without influence on the immunising effect: 0.04 ml per kg bodyweight.

Rubella: (German Measles) The routine use of Gammabulin prophylaxis of Rubella in early pregnancy is of dubious value and cannot be justified. Some studies suggest that the use of Gammabulin in exposed, susceptible women can lessen the likelihood of infection and foetal damage, therefore, 20 ml of Gammabulin may benefit those women who will not consider a therapeutic abortion.

Contra-indications, warnings, etc Gammabulin is generally well tolerated without reactions. On very rare occasions (e.g. in special forms of a- or hypogammaglobulinaemia) anaphylactoid reactions may occur in patients who have antibodies against Immune Globulin A (IgA) or who have shown atypical reaction after blood transfusion or following administration of blood derivatives.

Gammabulin must not be administered intravenously.

Pharmaceutical precautions Gammabulin liquid should be stored between +2° and +8°C when it will have a shelf life of 3 years.

Gammabulin lyophilised should be stored at room temperature (+2° to +25°C) when it will have a shelf life of 5 years.

Both preparations should be protected from the light.

Legal category POM.

† Human donors as described in the British Pharmacopoeia 1980 Vol. II under Albumin.

antibodies, particularly isoagglutinins, is achieved. It can therefore be given to patients regardless of their blood group or rhesus factor. It will not interfere with subsequent blood investigations.

Product licence number 0215/0009.

KRYOBULIN* – DRIED FACTOR VIII FRACTION BP

Presentation Dried Factor VIII Fraction BP is a white to yellowish amorphous powder or friable solid without any characteristic odour.

It is prepared from the plasma of suitable human donors† whose donations are shown by RIA to be free from HB_sAg. Pooled plasma and the final product are also tested for freedom from HB_sAg.

It is packed in vials each containing approximately 250, 500 or 1,000 International Units of Factor VIII. Separate vials of Water for Injections BP are provided for reconstitution.

1 International Unit is the amount of Factor VIII activity contained in 12.745 mg of the 2nd International Standard for Blood Coagulation Factor VIII Human. It is approximately equivalent to the Factor VIII activity in 1 ml of average normal plasma.

Uses Kryobulin corrects Factor VIII deficiency, and is used in the treatment of bleeding due to such deficiency in:

Haemophilia A
von Willebrand's disease
Haemophilia complicated by Factor VIII inhibitors.

Dosage and administration Frequent tests of the patient's plasma level of Factor VIII must be made to allow correction of the deficiency by administration of Kryobulin, but for guidance an estimation of the required dosage can be made by the following calculation:

To achieve an increase of Factor VIII concentration of 1% it is necessary to administer 1 i.u. of Kryobulin per kg bodyweight, both for adults and children.

Initial treatment requires doses to be given at shorter intervals than in maintenance therapy, to provide an initial high level of activity and to replenish the extravascular compartment.

Bleeding from skin, nose and oral mucous membrane: Initial dose should be 10 i.u./kg at intervals of 6 to 12 hours.

Haemarthrosis: The initial dose should be approximately 10 i.u./kg and the maintenance dose 5 to 10 i.u. per kg at intervals of 6 to 12 hours. Combined with immobilisation of the affected joint for several days, the treatment should be sufficient to restore function.

Bruising: In most cases a single dose of 10 i.u./kg is sufficient. For widespread bruising, repeated administration of 5 to 10 i.u./kg at intervals of 6 to 12 hours may be required.

Heavy bleeding into muscles: Immediate treatment is required to prevent permanent deformity and loss of function, and initial immobilisation of the affected area is important. An initial dose of 15 to 20 i.u./kg should be given, the maintenance dose to be 10 i.u./kg at intervals of 6 hours from the first to the second day, and at intervals of 12 hours from the third to the fifth day.

Haematuria: The initial dose should be 15 to 20 i.u./kg, and the maintenance dose 10 i.u./kg at intervals of 12 hours.

Major surgery on haemophilic patients: The initial dose should be at least 25 to 50 i.u./kg, and the maintenance dose 20 to 40 i.u./kg at intervals of 4 hours from the first to the fourth day, of 8 hours from the fifth to the eighth day, and of 12 hours until all wounds are healed.

The effect of treatment must be checked daily. Factor VIII activity should not be allowed to fall below 50% of the normal 100% average value. It is important that treatment be continued until all wounds have healed completely, as the risk of haemorrhage persists till then.

In addition to monitoring Factor VIII activity, tests for the development of Factor VIII inhibitors should also be made.

Dental extractions: The required dosage depends on the number and type of teeth to be extracted, and on the severity of the haemophilia. If *one or two teeth* are to be extracted from a patient with severe haemophilia, an initial dose of 10 to 20 i.u./kg should be given.

Maintenance treatment with this dosage at intervals of 6 hours from the first to the third day, and 8 hours from the fourth to the eighth day after extraction, should be given. If *more than two teeth are to be extracted from patients with severe haemophilia* a minimum initial dose of 20 to 30 i.u./kg should be given, and a maintenance dose of 10 to 20 i.u./kg at intervals of 6 hours from the first to the third day, and of 8 hours for twelve more days. The plasma concentration of Factor VIII should not be allowed to fall below 10% of the normal 100% average value.

Factor VIII assays should be used to monitor the effectiveness of treatment, as partial thromboplastin time gives a less accurate value when large quantities of Kryobulin are being used.

Solutions of Kryobulin must be administered intravenously, at a rate not exceeding 10 ml in 3 minutes.

Contra-indications, warnings, etc Although the danger of volume overload is small with Kryobulin, during major surgery monitoring of the patient's central venous pressure and blood pressure, and serial chest X-rays, may be advisable.

In disseminated intravascular coagulation associated with low Factor VIII levels, Heparin should be given to interrupt intravascular coagulation before therapy with Kryobulin is started.

A low incidence of adverse reactions is experienced with Kryobulin, but the following may occur:

1. *Allergic reactions:* All forms of allergic reaction from mild and transient urticaria to severe anaphylactic shock are possible when human plasma derivatives are administered. If such reactions occur, treatment with Kryobulin must be interrupted at once. Allergic reactions should be controlled with antihistamines and corticosteroids and routine treatment given for anaphylactic shock.

Monitoring of pulse rate and blood pressure is essential. If the pulse rate increases and/or blood pressure falls transfusion of 5% Dextrose should be started.

2. *Hepatitis:* Despite the precautions taken in the selection and testing of donors and donations, the risk of transmitting hepatitis cannot be entirely excluded.

3. *Factor VIII Inhibitors:* The appearance of a circulating Factor VIII inhibitor is possible. Its appearance cannot be predicted as it does not relate to the amount of Kryobulin administered, nor to the frequency of administration. As far as is known neither corticosteroids

† Human donors as described in the British Pharmacopoeia 1980 Vol II under Albumin.

nor immunosuppressive agents significantly influence the formation of inhibitors.

Pharmaceutical precautions Kryobulin must be stored between +2°C and +6°C, and protected from the light. It then has a shelf-life of two years. When stored between +20°C and +30°C it has a life of six months.

Legal category POM.

Package quantities
Kryobulin Home Treatment Pack (Standard)
Each pack contains:
1 rubber capped vial containing 250 or 500 i.u. Dried Factor VIII Fraction BP
1 rubber capped vial containing Water for Injections BP
This pack also contains a syringe, I/V needles, winged adaptor needle, filter needle, venting needle and swabs.

Kryobulin Home Treatment Pack (Multipack):
Each pack contains:
5 rubber capped vials containing 250 or 500 i.u. Dried Factor VIII Fraction BP.
5 rubber capped vials containing Water for Injections BP
The equipment is packed in a separate box and consists of: Syringes, I/V needles, winged adaptor needles, filter needles, venting needles and swabs.
There is sufficient equipment for reconstituting 5 packs of Kryobulin (1 multipack).

Kryobulin Hospital Pack
Each pack contains:
1 rubber capped vial containing 1,000 i.u. Dried Factor VIII Fraction BP
1 rubber capped vial containing Water for Injections BP.
The pack also contains a filter needle and venting needle.

Further information Kryobulin is especially suitable for Home Treatment. Packs contain all requirements and can be stored in a domestic refrigerator for two years and for up to six months at room temperatures not exceeding 30°C.

Product licence number 0215/0003.

PLASMA PROTEIN FRACTION BP 4.3% IMMUNO (Human Albumin Fraction Saline)

Presentation Plasma Protein Fraction BP 4.3% Immuno is a clear amber liquid, presented as a solution for intravenous administration to human beings. It is prepared from the plasma of suitable human donors† whose donations are shown by RIA to be free from HB_sAg. Pooled plasma and the final product are also tested by RIA for freedom from HB_sAg.

Plasma Protein Fraction BP 4.3% Immuno contains 4.3% protein of which at least 96% is albumin, the rest being heat stable alpha – and beta – globulins. As stabilisers sodium caprylate and sodium acetyltryptophanate have been added, both at a concentration of 3.44 mmol/L.

Uses Plasma Protein Fraction BP 4.3% Immuno is indicated for volume replacement in hypovolaemic shock (e.g. following crush injury, severe trauma, surgery, burns and abdominal emergency) and for use whenever a predominant loss of plasma fluid has occurred.

Dosage and administration Adult dosage of Plasma Protein Fraction BP 4.3% Immuno for hypovolaemic shock is in the range of 250 to 500 ml. A flow rate of up to 16 ml/min (1 litre/hr) has been well tolerated in adults. The rate of infusion, which can be increased in emergency treatment, depends on response. In hypoproteinaemia the usual dosage range is 1,500 to 2,000 ml daily (equivalent to 65 to 85 g plasma protein), but larger amounts can be given in severe hypoproteinaemia with continuing loss. The flow rate should not exceed 5 to 8 ml/min.

Dosage for infants and young children in whom Plasma Protein Fraction BP 4.3% Immuno is indicated for shock due to dehydration or infection, should be in the range of 20 to 30 ml/kg bodyweight, infused at a rate of 10 ml/min. The infusion rate should be adjusted in accordance with the clinical response. Administration is by intravenous infusion. A site should be chosen away from the area of injury or infection.

Contra-indications, warnings, etc Careful monitoring of the patient's clinical condition is necessary so that hypervolaemia is not caused. Signs to be watched for are dyspnoea, pulmonary oedema, rise of blood pressure and central venous pressure.

Careful selection of donors and the inclusion of filtration and heating at 60°C for 10 hours in the preparation of the product have virtually eliminated the risk of Serum Hepatitis. As with all blood products, however, this risk cannot be absolutely excluded.

A turbid solution must not be given. Once set up, the entire contents of the infusion bottle should be administered within 4 hours.

Pharmaceutical precautions Plasma Protein Fraction BP 4.3% Immuno should be stored at +2°C to +25°C. It must be protected from light. The shelf life is 5 years.

Legal category POM.

Package quantities Plasma Protein Fraction BP 4.3% Immuno is supplied in 50 ml, 100 ml, 250 ml, and 400 ml infusion bottles.

Further information Plasma Protein Fraction BP 4.3% Immuno is processed in such a way that removal of all isoagglutinins and other antibodies is achieved. It can therefore be given without restriction to patients, regardless of blood group. It will not interfere with subsequent blood investigations.

Product licence number 0215/0002.

PROTHROMPLEX* Partial Prothrombin Complex (Human)

Presentation Prothromplex contains coagulation Factors II, IX and X and is a white, amorphous freeze-dried powder or friable solid without any characteristic odour. It is packed in rubber-capped vials containing 200 units or 500 units each of Factor II, IX & X.

It is prepared from the plasma of suitable human donors† whose donations are shown by RIA to be free from HB_sAg. Pooled plasma and the final product are also tested by RIA for freedom from HB_sAg. Prothromplex

† Human donors as described in the British Pharmacopoeia 1980 Vol II under Albumin.

† Human donors as described in the British Pharmacopoeia 1980 Vol II under Albumin.

is also tested to discount the likelihood of causing disseminated intravascular coagulation.

Uses Treatment of cases of Factor IX deficiency (Haemophilia B).

By administering an appropriate dose of Prothromplex, it is possible to achieve a prompt and sufficient rise of Factor IX in the patient's plasma.

The effectiveness of treatment can be checked by simple laboratory tests. The activity of Factor IX is assayed through determination of the Partial Thromboplastin Time (PTT), however the most reliable results are obtained by quantitative activity assays of Factor IX.

Dosage and administration Immediately before use Prothromplex must be dissolved in 10 ml of the solvent provided.

After sterilising the cap of the solvent bottle remove 10 ml using the disposable syringe and one of the needles provided. Next sterilise the cap of the Prothromplex bottle and introduce the solvent using the second disposable needle. Reconstitute by gently shaking to and fro, thus avoiding frothing. Withdraw the reconstituted Prothromplex, then remove the syringe from the needle and attach the third disposable needle.

Prothromplex is now ready for slow intravenous injection taking about ten minutes.

Only general directions can be given for the dosage of Prothromplex. It is dependent upon the severity of the coagulation defect and the degree of the traumatic and haemorrhagic tissue damage. The suggested dosage for the treatment of Factor IX deficiency is given in the guide below.

Dosage guide for the treatment of severe and semi-severe cases of Factor IX deficiency: Formula for the calculation of the necessary quantity of Factor IX:

One unit of Factor IX/kg bodyweight = 1% increase of Factor IX in the patient's plasma.

Prothromplex dosage table (Factor IX)

Clinical Manifestation	*Minimum Factor IX level required*	*Initial dose in units Factor IX per kg bodyweight*	*Maintenance dose at intervals of 6 to 12 (24) hours in units per kg bodyweight*
Surface haemorrhage from the skin and mucosae Superficial or deep haematoma Haemarthroses Slight bleeding following injuries Uncomplicated dental extractions Severe muscle haematoma	5–10%	15 U	7–15 U
Moderate bleeding following injuries Gastric and intestinal haemorrhages Bone fractures Cerebral bleeding Haematuria Complicated dental extractions Minor surgery	15–30%	20–30 U	15–30 U
Major surgery	more than 50%	75 U	50–75 U

It is suggested that a high initial dosage be chosen to ensure a rapid and sufficient increase of Factor IX thus achieving a reliable cessation of bleeding. Here, as well as with the subsequent maintenance therapy the initial short half-life of the coagulation factors has to be considered. Depending on the in-vivo half-life of Factor IX, which is approx 12–30 hours, a successful result will be achieved by repeated administration of Prothromplex at intervals of 6–12 hours. To assure absolute control of treatment, determination of the PTT should be made and, where possible, quantitative assays of Factor IX activity. Treatment should be maintained up to the resorption of the tissue haemorrhage or until the wounds have healed completely, thus ensuring a complication-free post-operative course. The special advantage of Prothromplex lies in the fact that by application of small volumes of fluid and a low amount of protein a high concentration of circulating coagulation Factor IX is achieved. The danger of volume or protein overloading of the patient is avoided even with the administration of high doses.

Contra-indications, warnings, etc With patients suffering from disseminated intravascular coagulation, (DIC), Prothromplex should not be given unless consumption of the coagulation factors has been previously interrupted by Heparin.

Side-effects are rarely observed during treatment with Prothromplex though the following reactions may occur:

1. *Allergic reactions:* All forms of allergic reactions from mild and temporary urticarial rashes to severe anaphylactic shock are possible when human plasma derivatives are administered. If these occur, treatment with Prothromplex must be interrupted at once. Allergic reactions should be controlled with antihistamines and glucocorticoids and routine shock-treatment given for anaphylactic shock. Careful and frequent recording of pulse rate and blood pressure is essential. If the pulse rate increases and/or the blood pressure falls a transfusion of 5% Dextrose should be started.

2. Despite the precautions taken in the checking of donors, donations and the final product, the transmission of hepatitis cannot be entirely excluded following the administration of coagulation factors. This should be taken into account before using Prothromplex to control haemorrhage in non life saving situations in liver disease patients and those undergoing anticoagulant therapy.

3. During every type of therapy involving blood or coagulation factor concentrates, the occurrence of a circulating coagulation factor inhibitor is a possibility. The time at which such an inhibitor is produced cannot be predicted and depends neither on the amount of the plasma preparation administered nor on the frequency of the administration. As far as is known neither corticosteroids nor immunosuppressive agents significantly influence the formation of inhibitors.

Pharmaceutical precautions Prothromplex has a shelf life of two years when stored between +2°C and +6°C, and should be protected from light.

Legal category POM.

Package quantities 200 units or 500 units of Factors II, IX and X in each container.

1 rubber-capped vial containing lyophilised Prothromplex.

1 rubber-capped vial containing 10 ml Water for Injections BP.

1 10 ml disposable syringe.

3 disposable needles.

Further information Prothromplex can be stored in a domestic refrigerator, and can therefore be kept available for home treatment.

Prothromplex can be given in small volume injections, and is therefore suitable for home treatment.

Prothromplex can be moved in insulated containers to a refrigerator at some other location, giving a patient a greater degree of mobility.

Product licence number
0215/0006 – 200 U
0215/0007 – 500 U

**Trade Mark*