BNF

BRITISH NATIONAL FORMULARY

Number 32 (September 1996)

A joint publication of the
British Medical Association and the
Royal Pharmaceutical Society of Great Britain

General Guidance

Medicines should be prescribed only when they are necessary, and in all cases the benefit of administering the medicine should be considered in relation to the risk involved. This is particularly important during pregnancy where the risk to both mother and fetus must be considered (for further details see Prescribing in Pregnancy, Appendix 4).

ABBREVIATION OF TITLES. In general, titles of drugs and preparations should be written *in full*. Unofficial abbreviations should not be used as they may be misinterpreted; obsolete titles, such as 'Mist. Expect. should not be used.

NON-PROPRIETARY TITLES. Where non-proprietary ('generic') titles are given, they should be used in prescribing. This will enable any suitable product to be dispensed, thereby saving delay to the patient and sometimes expense to the health service. The only exception is where bioavailability problems are so important that the patient should always receive the same brand; in such cases, the brand name or the manufacturer should be stated. Non-proprietary titles should **not** be invented for the purposes of prescribing generically since this can lead to confusion, particularly in the case of compound and modified-release preparations.

Titles used as headings for monographs may be used freely in Great Britain and Northern Ireland but in other countries may be subject to restriction.

Many of the non-proprietary titles used in this book are titles of monographs in the European Pharmacopoeia, British Pharmacopoeia or British Pharmaceutical Codex 1973. In such cases the preparations must comply with the standard (if any) in the appropriate publication, as required by the Medicines Act (section 65).

PROPRIETARY TITLES. Names followed by the symbol ® are or have been used as proprietary names in the United Kingdom. These names may in general be applied only to products supplied by the owners of the trade marks.

DOSES. The doses stated in the BNF are intended for general guidance and represent, unless otherwise stated, the usual range of doses that are generally regarded as being suitable for adults. In general the *doses, indications, cautions, contra-indications and side-effects* in the BNF reflect those in the manufacturers' data sheets which, in turn, reflect those in the corresponding Product Licences. On the few occasions that an unlicensed drug is included in the BNF, this is now indicated in brackets after the entry. Where a use (or route) is recommended outside the licensed indication of an available product this too is indicated. It has been noted (*Drug and Therapeutics Bulletin*, 1992, *30*, 97–99) that prescribing of licensed medicines outside the recommendations of the Product Licence alters (and probably increases) the doctor's professional responsibility.

ORAL SYRINGES. A[r]**l syringe** is supplied when oral liquid medici[n] prescribed in doses other than multiples of 5 m[L]. The oral syringe is marked in 0.5-mL divisions from 1 to 5 mL to measure doses of less than 5 mL. It is provided with an adaptor and an instruction leaflet. The *5-mL spoon* is used for doses of 5 mL (or multiples thereof).

STRENGTHS AND QUANTITIES. The strength or quantity to be contained in capsules, lozenges, tablets, etc. should be stated by the prescriber.

If a pharmacist receives an incomplete prescription for a systemically administered preparation other than a prescription for a controlled drug and considers it would not be appropriate for the patient to return to the doctor, the following procedures will apply:

(a) an attempt must always be made to contact the prescriber to ascertain the intention;
(b) if the attempt is successful the pharmacist must, where practicable, subsequently arrange for details of quantity, strength where applicable, and dosage to be inserted by the prescriber on the incomplete form;
(c) where, although the prescriber has been contacted, it has not proved possible to obtain the written intention regarding an incomplete prescription, the pharmacist may endorse the form 'p.c.' (prescriber contacted) and add details of the quantity and strength where applicable of the preparation supplied, and of the dose indicated. The endorsement should be initialled and dated by the pharmacist;
(d) where the prescriber cannot be contacted and the pharmacist has sufficient information to make a professional judgment the preparation may be dispensed. If the quantity is missing the pharmacist may supply sufficient to complete up to 5 days' treatment; except that where a combination pack (i.e. a proprietary pack containing more than one medicinal product) or oral contraceptive is prescribed by name only, the smallest pack shall be dispensed. In all cases the prescription must be endorsed 'p.n.c.' (prescriber not contacted) the quantity, the dose, and the strength (where applicable) of the preparation supplied must be indicated, and the endorsement must be initialled and dated;
(e) if the pharmacist has any doubt about exercising discretion, an incomplete prescription must be referred back to the prescriber.

ADDITIVES. Oral liquid preparations in the BNF that do not contain *fructose, glucose* or *sucrose* are labelled 'sugar-free'. Preparations containing hydrogenated glucose syrup, mannitol, or sorbitol are also marked 'sugar-free' since there is evidence that they are not cariogenic.

Where information on the presence of *aspartame, gluten, tartrazine, arachis (peanut) oil* or *sesame oil* is available, this is indicated in the BNF against the relevant preparation; the manufacturer should be contacted in the absence of information on additives in the BNF and in the product literature, if it is essential to check details.

Information is provided on *preservatives* in eye-drops and on *selected additives* in skin preparations (see section 13.1). Pressurised metered aerosols containing *chlorofluorocarbons* (CFCs) h[a]lso been identified throughout the BNF [a]lso pp. 118 and 123)

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

DRUGS AND DRIVING. Prescribers should advise patients if treatment is likely to affect their ability to drive motor vehicles. This applies particularly to drugs with sedative effects and patients should be warned that these effects are increased by alcohol. See also Appendix 9.

NOTICE CONCERNING PATENTS. In the BNF certain drugs have been included notwithstanding the existence of actual or potential patent rights. In so far as such substances are protected by Letters Patent, their inclusion in this Formulary neither conveys, nor implies, licence to manufacture.

HEALTH AND SAFETY. When handling chemical or biological materials particular attention should be given to the possibility of allergy, fire, explosion, radiation, or poisoning. Some substances, including corticosteroids, antibiotics, phenothiazines, and many cytotoxics, are irritant or very potent and should be handled with caution. Contact with the skin and inhalation of dust should be avoided.

SAFETY IN THE HOME. Patients must be warned to keep all medicines out of the reach of children. All solid dose and all oral and external liquid preparations must be dispensed in a reclosable *child-resistant container* unless:

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

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

NAME OF MEDICINE. The name of the medicine should appear on the label unless the prescriber indicates otherwise.

1. Subject to the conditions of paragraphs 4 and 6 below, the name of the prescribed medicine is stated on the label unless the prescriber deletes the letters 'NP' which appear on NHS prescription forms.
2. The strength is also stated on the label in the case of tablets, capsules, and similar preparations that are available in different strengths.
3. If it is the wish of the prescriber that a description such as 'The Sedative Tablets' should appear on the label, the prescriber should write the desired description on the prescription form.
4. The arrangement will extend to approved names, proprietary names or titles given in the BP, BPC, BNF, or DPF. The arrangement does not apply when a prescription is written so that several ingredients are given.
5. The name written on the label is that used by the prescriber on the prescription.
6. If more than one item is prescribed on one form and the prescriber does not delete the letters 'NP', each dispensed medicine is named on the label, subject to the conditions given above in paragraph 4. If the prescriber wants only selected items on such a prescription to be so labelled this should be indicated by deleting the letters 'NP' on the form and writing 'NP' alongside the medicines to be labelled.
7. When a prescription is written other than on an NHS prescription form the name of the prescribed preparation will be stated on the label of the dispensed medicine unless the prescriber indicates otherwise.
8. The Council of the Royal Pharmaceutical Society advises that the labels of dispensed medicines should indicate the total quantity of the product dispensed in the container to which the label refers. This requirement applies equally to solid, liquid, internal, and external preparations. If a product is dispensed in more than one container, the reference should be to the amount in each container.

Scope of the BNF

The BNF is intended for the guidance of medical practitioners, pharmacists, dentists, nurses, and others who have the necessary training and experience to interpret the information it provides. It is intended as a reference for the pocket, and should be supplemented by a study of more detailed publications when required.

Security and validity of prescriptions

The Councils of the British Medical Association and the Royal Pharmaceutical Society have issued a joint statement on the security and validity of prescriptions.
In particular, prescription forms should:
(i) not be left unattended at reception desks;
(ii) not left in a car where they may be visible; and
(iii) when not in use, be kept in a locked drawer within the surgery and at home.
Where there is any doubt about the authenticity of a prescription, the pharmacist should contact the prescriber. If this is [b]y telephone, the number should be obtained from the directory [t]han relying on the prescription form information, which may be [f]alse.

Prescription Writing

Shared care

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

Prescriptions[1] should be written legibly in ink or otherwise so as to be indelible[2], should be dated, should state the full name and address of the patient, and should be signed in ink by the prescriber[3]. The age of the patient should preferably be stated, and is a legal requirement in the case of prescription-only medicines for children under 12 years of age.

In general practice the following should be noted:

(a) The unnecessary use of decimal points should be avoided, e.g. 3 mg, not 3.0 mg.

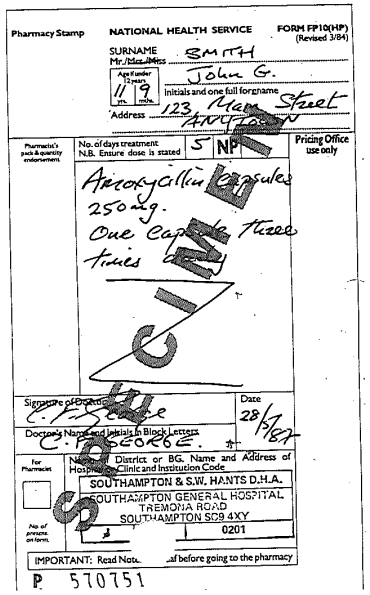
Quantities of 1 gram or more should be written as 1 g etc.

Quantities less than 1 gram should be written in milligrams, e.g. 500 mg, not 0.5 g.

Quantities less than 1 mg should be written in micrograms, e.g. 100 micrograms, not 0.1 mg.

When decimals are unavoidable a zero should be written in front of the decimal point where there is no other figure, e.g. 0.5 mL, not .5 mL.

Use of the decimal point is acceptable to express a range, e.g. 0.5 to 1 g.



(b) 'Micrograms' and 'nanograms' should **not** be abbreviated. Similarly 'units' should **not** be abbreviated.

(c) The term 'millilitre' (ml or mL)[4] is used in medicine and pharmacy, and cubic centimetre, c.c., or cm^3 should not be used.

(d) Dose and dose frequency should be stated; in the case of preparations to be taken 'as required' a **minimum dose interval** should be specified.

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

Suitable quantities:

Elixirs, Linctuses, and Paediatric Mixtures (5-mL dose), 50, 100, or 150 mL

Adult Mixtures (10-mL dose), 200 or 300 mL

Ear Drops, Eye-drops, and Nasal Drops, 10 mL (or the manufacturer's pack)

Eye Lotions, Gargles, and Mouth-washes, 200 mL

(e) For suitable quantities of dermatological preparations, see section 13.1.

(f) The names of drugs and preparations should be written clearly and **not** abbreviated, using approved titles **only** (see also advice in box on p. 5 to **avoid** creating generic titles for modified-release preparations).

(g) The symbol 'NP' on NHS forms should be deleted if it is required that the name of the preparation should not appear on the label. For full details see p. 3.

(h) The quantity to be supplied may be stated by indicating the number of days of treatment required in the box provided on NHS forms. In most cases the exact amount will be supplied. This does not apply to items directed to be used as required—if the dose and frequency are not given the quantity to be supplied needs to be stated.

When several items are ordered on one form the box can be marked with the number of days of treatment providing the quantity is added for any item for which the amount cannot be calculated.

(i) Although directions should preferably be in **English without abbreviation**, it is recognised that some Latin abbreviations are used (for details see Inside Back Cover).

(j) A prescription for a preparation that has been withdrawn or needs to be specially imported for a named patient should be handwritten. The name of the preparation should be endorsed with the prescriber's signature and the letters 'WD' (withdrawn or specially-imported drug); there may be considerable delay in obtaining a withdrawn medicine.

1. The above recommendations are acceptable for **prescription-only medicines** (PoM). For items marked CD see also Controlled Drugs and Drug Dependence p. 7.
2. It is permissible to issue carbon copies of NHS prescriptions as long as they are signed in ink.
3. Computer-generated facsimile signatures do not meet the legal requirement.
4. The use of capital 'L' in mL is a printing convention throughout the BNF; both mL and ml are recognised abbreviations for SI units.

Computer-issued Prescriptions

For computer-issued prescriptions the following recommendations of the Joint Computing Group of the General Medical Services Committee and the Royal College of General Practitioners should also be noted:

1. The computer must print out the date[1], the patient's surname, one forename, other initials, and address, and may also print out the patient's title. The age of children under 12 years must be printed in the box available; a facility may exist to print out the age of older children and adults as well.

2. The doctor's name[2] must be printed at the bottom of the prescription form; this will be the name of the doctor responsible for the prescription (who will normally sign it). The doctor's surgery address, reference number, and Health Authority (HA)[3] are also necessary. In addition, the surgery telephone number should be printed.

3. When prescriptions are to be signed by trainees, assistants, locums, or deputising doctors, the name of the doctor printed at the bottom of the form must still be that of the responsible principal. To avoid difficulties for the pharmacist checking the prescription, the name of the signing doctor may be printed in the signature box, to be signed over on prescribing.

4. Names of medicines must come from a dictionary held in the computer memory, to provide a check on the spelling and ensure that the name is written in full. The computer can be programmed to recognise both the non-proprietary and the proprietary name of a particular drug and to print out the preferred choice, but must not print out both names. For medicines not in the dictionary, separate checking mechanisms are required—the user must be warned that no check was possible and the entire prescription must be entered in the lexicon.

5. The dictionary may contain information on the usual doses, formulations, and (where relevant) pack sizes to produce standard predetermined prescriptions for common preparations, and to provide a check on the validity of an individual prescription on entry.

6. The prescription must be printed in English without abbreviation; information may be entered or stored in abbreviated form. The dose must be in numbers, the frequency in words, and the quantity in numbers in brackets, thus: 40 mg four times daily (112).

It must also be possible to prescribe by indicating the length of treatment required, see (h) above.

7. The BNF recommendations should be followed as in (a), (b), (c), (d), and (e) above.

8. Checks may be incorporated to ensure that all the information required for dispensing a particular drug has been filled in. Instructions such as 'as directed' should be avoided. For the instruction 'when required' the maximum daily dose should normally be specified.

9. Numbers and codes used in the system for organising and retrieving data must never appear on the form.

10. Supplementary warnings or advice should be written in full, should not interfere with the clarity of the prescription itself, and should usually precede any warnings or advice in the BNF; numerical codes should not be used.

11. A mechanism (such as printing a series of non-specific characters) may be incorporated to cancel out unused space, or wording such as 'no more items on this prescription' may be added after the last item. Otherwise the doctor should delete the space manually.

12. To avoid forgery the computer may print on the form the number of items to be dispensed (somewhere separate from the box for the pharmacist). The number of items per form need be limited only by the ability of the printer to produce clear and well-demarcated instructions with sufficient space for each item and a spacer line before each fresh item.

13. Handwritten alterations should only be made in exceptional circumstances—it is preferable to print out a new prescription. Any alterations that are made must be written in the doctor's own handwriting and countersigned.

14. Prescriptions for controlled drugs cannot be produced by a printer[4]. If there is a record of such a prescription in the computer, it must not be printed. Instead the computer may print out a blank form with the doctor's name[1] and other details printed at the bottom.

15. The strip of paper on the side of the FP10[5](Comp) may be used for various purposes but care should be taken to avoid including confidential information. It may be advisable for the patient's name to appear at the top, but this should be preceded by 'confidential'.

16. In rural dispensing practices prescription requests (or details of medicines dispensed) will normally be entered in one surgery. The prescriptions (or dispensed medicines) may then need to be delivered to another surgery or location; if possible the computer should hold up to 10 alternatives.

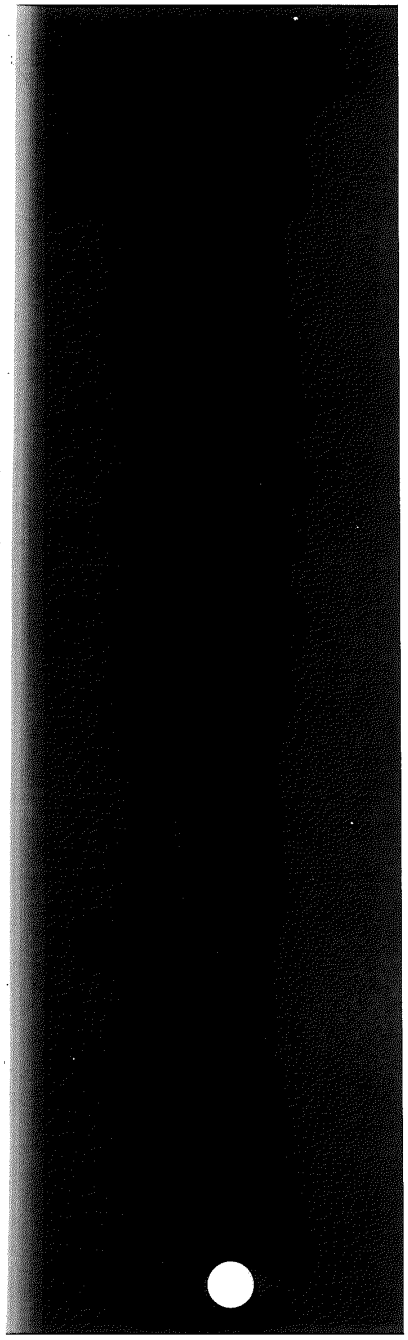
Generic names of **compound preparations** which appear in the BNF are those approved by the British Pharmacopoeia Commission; whenever possible they reflect the names of the active ingredients.

Prescribers should avoid creating their own compound names for the purposes of generic prescribing; such names do not have an approved definition and can be misinterpreted.

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

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

1. The exemption for own handwriting regulations for phenobarbitone does not apply to the date; a computer-generated date need not be deleted but the date must also be added by the prescriber.
2. Except in Scotland where it does not appear.
3. Health Board in Scotland.
4. Except in the case of phenobarbitone (but see also footnote 1) or where the prescriber has been exempted from handwriting requirements, for details see Controlled Drugs and Drug Dependence p. 7.



Emergency Supply of PoM at Patient's Request[1]

The Medicines (Products Other Than Veterinary Drugs) (Prescription Only) Order 1983, as amended, allows exemptions from the Prescription Only requirements for emergency supply to be made by a person lawfully conducting a retail pharmacy business provided:

(a) that the pharmacist has interviewed the person requesting the prescription-only medicine and is satisfied:
- (i) that there is immediate need for the prescription-only medicine and that it is impracticable in the circumstances to obtain a prescription without undue delay;
- (ii) that treatment with the prescription-only medicine has on a previous occasion been prescribed by a doctor[2] for the person requesting it;
- (iii) as to the dose which it would be appropriate for the person to take;

(b) that no greater quantity shall be supplied than will provide five days' treatment except when the prescription-only medicine is:
- (i) an ointment, cream, or preparation for the relief of asthma in an aerosol dispenser when the smallest pack can be supplied;
- (ii) an oral contraceptive when a full cycle may be supplied;
- (iii) an antibiotic in liquid form for oral administration when the smallest quantity that will provide a full course of treatment can be supplied;

(c) that an entry shall be made in the prescription book stating:
- (i) the date of supply;
- (ii) the name, quantity and, where appropriate, the pharmaceutical form and strength;
- (iii) the name and address of the patient;
- (iv) the nature of the emergency;

(d) that the container or package must be labelled to show:
- (i) the date of supply;
- (ii) the name, quantity and, where appropriate, the pharmaceutical form and strength;
- (iii) the name of the patient;
- (iv) the name and address of the pharmacy;
- (v) the words 'Emergency supply'.

(e) that the prescription-only medicine is not a substance specifically excluded from the emergency supply provision, and does not contain a Controlled Drug specified in schedules 1, 2, or 3 to the Misuse of Drugs Regulations 1985 except for phenobarbitone or phenobarbitone sodium for the treatment of epilepsy: for details see *Medicines, Ethics and Practice*, No. 16, London, Pharmaceutical Press, 1996 (and subsequent editions as available).

ROYAL PHARMACEUTICAL SOCIETY'S GUIDELINES

(1) The pharmacist should consider the medical consequences of *not* supplying.

(2) If the patient is not known to the pharmacist, the patient's identity should be established by way of appropriate documentation.

(3) It may occasionally be desirable to contact the prescriber, e.g. when the medicine requested has potential for misuse or the prescriber is not known to the pharmacist.

(4) Care should be taken to ask whether the patient's doctor has stopped the treatment, or whether the patient is taking any other medication.

(5) Except for conditions which occur infrequently (e.g. hay fever, asthma attack or migraine), a supply should not be made if the item requested was last prescribed more than 6 months ago.

(6) Consideration should be given to supplying less than 5 days' quantity if this is justified.

(7) Where a prescription is to be provided later, a record of emergency supply as required by law must still be made. It is good practice to add to the record the date that the prescription is received or. Payment for the medicine supplied is not a legal requirement, but may help to minimise the abuse of the emergency supply exemption. If an NHS prescription is to be provided, a refundable charge may be made.

1. For emergency supply at the request of a doctor see *Medicines, Ethics and Practice*, No. 16, London, Pharmaceutical Press, 1996 (and subsequent editions as available).
2. The doctor must be a UK-registered doctor.

Plasma concentrations in the BNF are expressed in mass units per litre (e.g. mg/litre). The approximate equivalent in terms of amount of substance units (e.g. micromol/litre) is given in brackets.

Approximate Conversions and Units

lb	*kg*
1	0.45
2	0.91
3	1.36
4	1.81
5	2.27
6	2.72
7	3.18
8	3.63
9	4.08
10	4.54
11	4.99
12	5.44
13	5.90
14	6.35

stones	*kg*
1	6.35
2	12.70
3	19.05
4	25.40
5	31.75
6	38.10
7	44.45
8	50.80
9	57.15
10	63.50
11	69.85
12	76.20
13	82.55
	88.90
	92.95

ml	*fl. oz*
50	1.8
100	3.5
150	5.3
200	7.0
500	17.6
1000	35.2

Mass

1 kilogram (kg)	= 1000 grams (g)
1 gram (g)	= 1000 milligrams (mg)
1 milligram (mg)	= 1000 micrograms
1 microgram	= 1000 nanograms
1 nanogram	= 1000 picograms

Volume

1 litre	= 1000 millilitres (mL)
1 millilitre	= 1000 microlitres
1 pint	≈ 568 mL

Other units

1 kilocalorie (kcal)	= 4186.8 joules (J)
1000 kilocalories (kcal)	= 4.1868 megajoules (M
1 megajoule (MJ)	= 238.8 kilo s (kc
1 millimetre of mercury (mmHg)	= 133.3 pasc)
1 kilopascal (kPa)	= 7.5 mmHg (pressure)

Controlled Drugs and Drug Dependence

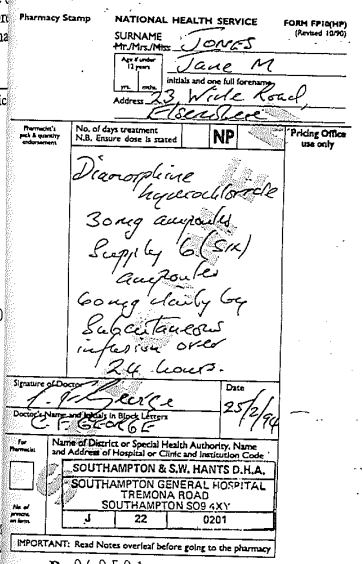
PRESCRIPTIONS. Preparations which are subject to the prescription requirements of the Misuse of Drugs Regulations 1985, i.e. preparations specified in schedules 2 and 3, are distinguished throughout the BNF by the symbol **CD** (Controlled Drugs). The principal legal requirements relating to medical prescriptions are listed below.

Prescriptions ordering Controlled Drugs subject to prescription requirements must be *signed* and *dated*[1] by the prescriber and specify the prescriber's *address*. The prescription must always state *in the prescriber's own handwriting*[2] in ink or otherwise so as to be indelible:

1. The name and address of the patient;
2. In the case of a preparation, the form[3] and where appropriate the strength[4] of the preparation;
3. The total quantity of the preparation, or the number of dose units, *in both words and figures*;[5]
4. The dose.[6]

A prescription may order a Controlled Drug to be dispensed by instalments; the amount of the instalments and the intervals to be observed must be specified.[7] Prescriptions ordering 'repeats' on the same form are **not** permitted.

It is an offence for a doctor to issue an incomplete prescription and a pharmacist is **not** allowed to dispense a Controlled Drug unless all the information required by law is given on the prescription. Failure to comply with the regulations concerning the writing of prescriptions will result in inconvenience to patients and delay in supplying the necessary medicine.


Pharmacy Stamp

NATIONAL HEALTH SERVICE — FORM FP10(HP) (Revised 10/90)

SURNAME: JONES
Mr./Mrs./Miss
Age if under 12 years
Jane M
initials and one full forename
Address: 23 Wide Road, Elsewhere

Pharmacist's pack & quantity endorsement | No. of days treatment N.B. Ensure dose is stated | NP | Pricing Office use only

Diamorphine hydrochloride
30mg ampoules
Supply by 6 (SIX) ampoules
60mg daily by Subcutaneous infusion over 24 hours.

Signature of Doctor: [signature] Date: 25/6/94
Doctor's Name and Address in Block Letters: C.F. Stocker

For Pharmacist

Name of District or Special Health Authority, Name and Address of Hospital or Clinic and Institution Code
SOUTHAMPTON & S.W. HANTS D.H.A.
SOUTHAMPTON GENERAL HOSPITAL
TREMONA ROAD
SOUTHAMPTON SO9 4XY
J | 22 | 0201

IMPORTANT: Read Notes overleaf before going to the pharmacy

B 060501

DEPENDENCE AND MISUSE. The most serious drugs of addiction are **cocaine, diamorphine** (heroin), **morphine**, and the **synthetic opioids**. For arrangements for prescribing of diamorphine, dipipanone or cocaine for addicts, see p. 9.

Despite marked reduction in the prescribing of **amphetamines** there is concern that abuse of illicitly produced amphetamine and related compounds is widespread.

Owing to problems of widespread abuse additional controlled drug requirements have been placed on **temazepam** (but it remains exempt from the additional prescribing requirements).

The principal **barbiturates** are now Controlled Drugs, but phenobarbitone and phenobarbitone sodium or a preparation containing either of these are exempt from the handwriting requirement but must fulfil all other controlled drug prescription requirements (**important:** the own handwriting exemption does **not** apply to the date; a computer-generated date need not be deleted but the date must also be added by the prescriber). Moreover, for the treatment of epilepsy phenobarbitone and phenobarbitone sodium are available under the emergency supply regulations (p. 6).

Cannabis (Indian hemp) has no approved medicinal use and cannot be prescribed by doctors (except under licence from the Home Secretary). Its use is illegal but has become widespread in certain sections of society. Cannabis is a mild hallucinogen seldom accompanied by a desire to increase the dose; withdrawal symptoms are unusual. **Lysergide** (lysergic acid diethylamide, LSD) is a much more

1. A prescription is valid for 13 weeks from the date stated thereon.
2. Does not apply to prescriptions for temazepam. Otherwise applies unless the prescriber has been specifically exempted from this requirement or unless the prescription contains no controlled drug other than phenobarbitone or phenobarbitone sodium or a preparation containing either of these; the exemption does **not** apply to the date—a computer-generated date need not be deleted but the date must also be added by the prescriber.
3. The dosage form (e.g. tablets) must be included on a Controlled Drugs prescription irrespective of whether it is implicit in the proprietary name (e.g. *MST Continus*) or of whether only one form is available.
4. When more than one strength of a preparation exists the strength required must be specified.
5. Does not apply to prescriptions for temazepam.
6. The instruction 'one as directed' constitutes a dose but 'as directed' does not.
7. A special form, FP10(HP)(ad), in Scotland HBP(A), is available to doctors in NHS drug treatment centres for prescribing cocaine, dextromoramide, diamorphine, dipipanone, methadone, morphine, or pethidine by instalments for addicts (see also Terms of Service, paragraph 43). In Scotland general practitioners can prescribe by instalments on form GP10. In England and Wales forms FP10 and FP10(HP) are not suitable for this purpose but form FP10(MDA) is available. **Important:** in all cases a special licence is necessary to prescribe cocaine, diamorphine, or dipipanone for addicts except for tr t of organic disease or injury, for details see p.

potent hallucinogen; its use can lead to severe psychotic states in which life may be at risk.

PRESCRIBING DRUGS LIKELY TO CAUSE DEPENDENCE OR MISUSE. The prescriber has three main responsibilities:

1. To avoid creating dependence by introducing drugs to patients without sufficient reason. In this context, the proper use of the morphine-like drugs is well understood. The dangers of other controlled drugs are less clear because recognition of dependence is not easy and its effects, and those of withdrawal, are less obvious. Perhaps the most notable result of uninhibited prescribing is that a very large number of patients in the country take tablets which do them neither much good nor much harm, but are committed to them indefinitely because they cannot readily be stopped.
2. To see that the patient does not gradually increase the dose of a drug, given for good medical reasons, to the point where dependence becomes more likely. This tendency is seen especially with hypnotics and anxiolytics (for CSM advice see section 4.1). The prescriber should keep a close eye on the amount prescribed to prevent patients from accumulating stocks that would enable them to arrange their own dosage or even that of their families and friends. A minimal amount should be prescribed in the first instance, or when seeing a new patient for the first time.
3. To avoid being used as an unwitting source of supply for addicts. Methods include visiting more than one doctor, fabricating stories, and forging prescriptions. A doctor should therefore be wary of prescribing for strangers and may be able to get information about suspected opioid addicts from the Home Office (for details see p. 9).

Patients under temporary care should be given only small supplies of drugs unless they present an unequivocal letter from their own doctors. Doctors should also remember that their own patients may be doing a collecting round with other doctors, especially in hospitals. It is sensible to decrease dosages steadily or to issue weekly or even daily prescriptions for small amounts if it is apparent that dependence is occurring.

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

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

TRAVELLING ABROAD. Prescribed drugs listed in schedules 4 and 5 to the Misuse of Drugs Regulations 1985 are subject to import or export licensing but c , are advised that patients intending to carry schedule 2 and 3 drugs abroad may require an export licence. This is dependent upon the amount of drug to be exported and further details may be obtained from the Home Office by telephoning 0171-273 3806. Applications for licences should be sent to the Home Office, Drugs Branch, Queen Anne's Gate, London SW1H 9AT.

There is no standard application form but applications must be supported by a letter from a doctor giving details of:

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

Ten days should be allowed for processing the application.

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

These import/export licences for named individuals do not have any legal status outside the UK and are only issued to comply with the Misuse of Drugs Act and facilitate passage through UK Customs control. For clearance in the country to be visited it would be necessary to approach that country's embassy or High Commission in the UK.

Misuse of Drugs Act

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

Class A includes: alfentanil, cocaine, dextromoramide, diamorphine (heroin), dipipanone, lysergide (LSD), methadone, morphine, opium, pethidine, phencyclidine, and class B substances when prepared for injection
Class B includes: oral amphetamines, barbiturates, cannabis, cannabis resin, codeine, ethylmorphine, glutethimide, pentazocine, phenmetrazine, and pholcodine
Class C includes: certain drugs related to the amphetamines such as benzphetamine and chlorphentermine, buprenorphine, diethylpropion, mazindol, meprobamate, pemoline, pipradrol, most benzodiazepines, androgenic and anabolic steroids, clenbuterol, chorionic gonadotrophin (HCG), non-human chorionic gonadotrophin, somatotropin, somatrem, and somatropin

The Misuse of Drugs Regulations 1985 define the classes of person who are authorised to supply and possess controlled drugs while acting in their professional capacities and lay down the conditions under which these activities may be carried out. In the regulations drugs are divided into five schedules each specifying the requirements gov such activities as import, export, production, , possession, prescribing, and record keeping which apply to them.

Schedule 1 includes drugs such as cannabis and lysergide which are not used medicinally. Possession and supply are prohibited except in accordance with Home Office authority.
Schedule 2 includes drugs such as diamorphine (heroin), morphine, pethidine, quinalbarbitone, glutethimide, amphetamine, and cocaine and are subject to the full controlled drug requirements relating to prescriptions, safe custody (except for quinalbarbitone), the need to keep registers, etc. (unless exempted in schedule 5).
Schedule 3 includes the barbiturates (except quinalbarbitone, now schedule 2), buprenorphine, diethylpropion, mazindol, meprobamate, pentazocine, phentermine, and temazepam. They are subject to the special prescription requirements (except for phenobarbitone and temazepam, see p. 7) but not to the safe custody requirements (except for buprenorphine, diethylpropion, and temazepam) nor to the need to keep registers (although there are requirements for the retention of invoices for 2 years).
Schedule 4 includes in Part II 33 benzodiazepines (temazepam is now in schedule 3) and pemoline which are subject to minimal control. Part I includes androgenic and anabolic steroids, clenbuterol, chorionic gonadotrophin (HCG), non-human chorionic gonadotrophin, somatotropin, somatrem, and somatropin. Controlled drug prescription requirements do not apply and Schedule 4 Controlled Drugs are not subject to safe custody requirements.
Schedule 5 includes those preparations which, because of their strength, are exempt from virtually all Controlled Drug requirements other than retention of invoices for two years.

Notification of Addicts

The Misuse of Drugs (Notification of and Supply to Addicts) Regulations 1973 require that any doctor who attends a person who the doctor considers or has reasonable grounds to suspect, is addicted to any of the 14 notifiable drugs (see below) shall, within seven days of the attendance, furnish in writing particulars of that person to:

Chief Medical Officer,
Home Office, Drugs Branch,
Queen Anne's Gate,
London SW1H 9AT.

The drugs to which the Regulations apply are:

Cocaine	Methadone
Dextromoramide	Morphine
Diamorphine	Opium
Dipipanone	Oxycodone
Hydrocodone	Pethidine
Hydromorphone	Phenazocine
Levorphanol	Piritramide

Note. Dipipanone is only legally available as Diconal® Tablets. These have been much misused by opioid addicts in recent years; only medical practitioners with a special licence may now prescribe them for addicts to treat addiction. Doctors and others should be suspicious of young people who ask for them, especially as temporary residents.

Particulars[1] to be notified to the Chief Medical Officer are:

Name and address
Sex
Date of birth
National Health Service number (if known)
Date of attendance
Name of drugs of addiction
Whether patient injects any drug (whether or not notifia-

Notification must be confirmed annually in writing if the patient is still being treated by the practitioner. Notified information is incorporated in an Index of Addicts which is maintained in the Home Office and information from this is available on a confidential basis to doctors; in fact, it is good medical practice to check all new cases of addiction or suspected addiction with the Index before prescribing or supplying controlled drugs since this is a safeguard against addicts obtaining supplies simultaneously from two or more doctors. Enquiries can be made either in writing to the Chief Medical Officer or, preferably, by telephoning 0171-273 2213. To keep notified information confidential, such enquiries are normally answered by means of a return telephone call. The reply will come from lay staff who are not qualified to give guidance on the clinical handling of cases; a recorded telephone service is available for out-of-office hours.

The preceding paragraph applies only to medical practitioners in England, Scotland, and Wales. In Northern Ireland notification should be sent to:

Chief Medical Officer,
Department of Health and Social Services,
Dundonald House,
Belfast BT4 3SB.
Enquiries should also be made to that Department, telephone (01232) 520000 extension 24323.

Prescribing of diamorphine (heroin), dipipanone, and cocaine for addicts

The Misuse of Drugs (Notification of and Supply to Addicts) Regulations 1973 also provide that only medical practitioners who hold a special licence issued by the Home Secretary may prescribe diamorphine, dipipanone (Diconal®), or cocaine for addicts; other practitioners must refer any addict who requires these drugs to a treatment centre. Whenever possible the addict will be introduced by a member of staff from the treatment centre to a pharmacist whose agreement has been obtained and whose pharmacy is conveniently sited for the patient. Prescriptions for weekly supplies will be sent to the pharmacy by post and will be dispensed on a daily basis as indicated by the doctor. If any alterations of the arrangements are requested by the addict, the portion of the prescription affected must be represcribed and not merely altered. *General practitioners and other doctors may still prescribe diamorphine, dipipanone, and cocaine for patients (including addicts) for relief of pain due to organic disease or injury without a special licence.*

For prescription-writing guidelines, see p. 7.

1. Only the particulars of which the doctor has knowledge need be notified immediately; the remainder may be notified at a later date. Private doctors, police surgeons and prison medical officers may continue to notify the Home Office using form HS2A /1(Rev), available from their Health Authority (HA) or their Health Board in Scotland.

All othe rs, including general practitioners, hospital doct those practising in treatment centres, should use notification forms which can be obtained from their Regional Health Authority Drugs Misuse

Adverse Reactions to Drugs

Any drug may produce unwanted or unexpected adverse reactions. Detection and recording of these is of vital importance. Doctors are urged to help by reporting adverse reactions to:

CSM
Freepost
London SW8 5BR
(0171-627 3291)

Yellow prepaid lettercards for reporting are available from the above address or by dialling 100 and asking for 'CSM Freefone'; also, forms are bound in this book (inside back cover).

A 24-hour Freefone service is now available to all parts of the United Kingdom, for doctors seeking advice and information on adverse reactions; it may be obtained by dialling 100 and asking for 'CSM Freefone'. Outside office hours a telephone-answering machine will take messages.

The following regional centres also collect data:

CSM Mersey
Freepost
Liverpool L3 3AB
(0151-236 4620 Extn 2126)

CSM Wales
Freepost
Cardiff CF4 1ZZ
(01222 744181
Direct Line)

CSM Northern
Freepost 1085
Newcastle upon Tyne
NE1 1BR
(0191-232 1525 Direct Line)

CSM West Midlands
Freepost SW2991
Birmingham B18 7BR
[No telephone number]

Suspected adverse reactions to *any* therapeutic agent should be reported, including drugs (those taken for *self medication* as well as those *prescribed*), blood products, vaccines, X-ray contrast media, dental or surgical materials, intra-uterine devices, and contact lens fluids.

ADROIT

Adverse Drug Reactions On-line Information Tracking (ADROIT) has now been introduced to facilitate the monitoring of adverse drug reactions.

NEWER DRUGS. These are indicated by the sign ▼. Doctors are asked to report *all* suspected reactions (i.e. any adverse or any unexpected event, however minor, which could conceivably be attributed to the drug). Reports should be made despite uncertainty about a causal relationship, irrespective of whether the reaction is well recognized, and even if other drugs have been given concurrently.

ESTABLISHED DRUGS. Doctors are asked to report *all* serious suspected reactions, including those that are fatal, life-threatening, disabling, incapacitating, or which result in or prolong hospitalisation; they should be reported even if the effect is well recognised.

Examples include anaphylaxis, blood disorders, endocrine disturbances, effects on fertility, haemorrhage from any site, renal impairment, jaundice, ophthalmic disorders, severe CNS effects, severe skin reactions, reactions in pregnant women, and any drug interactions. Reports of serious adverse reactions are required to enable risk/benefit ratios to be compared with other drugs of a similar class. For established drugs doctors are asked not to report well-known, relatively minor side-effects, such as dry mouth with tricyclic antidepressants, constipation with opioids, or nausea with digoxin.

Special problems

Delayed drug effects. Some reactions (e.g. cancers, chloroquine retinopathy, and retroperitoneal fibrosis) may become manifest months or years after exposure. Any suspicion of such an association should be reported.

The elderly. Doctors are asked to be particularly alert to adverse reactions in the elderly.

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

Vaccines. Doctors are asked to report all suspected reactions to both new and established vaccines. The balance between risks and benefits needs to be kept under continuous review.

Prevention of adverse reactions

Adverse reactions may be prevented as follows:

1. Never use any drug unless there is a good indication. If the patient is pregnant do not use a drug unless the need for it is imperative.
2. It is very important to recognise allergy and idiosyncrasy as causes of adverse drug reactions. Ask if the patient had previous reactions.
3. Ask if the patient is already taking other drugs *including self-medication*; remember that interactions may occur.
4. Age and hepatic or renal disease may alter the metabolism or excretion of drugs, so that much smaller doses may need to be prescribed. Pharmacogenetic factors may also be responsible for variations in the rate of metabolism, notably of isoniazid and the tricyclic antidepressants.
5. Prescribe as few drugs as possible and give very clear instructions to the elderly or any patient likely to misunderstand complicated instructions.
6. When possible use a familiar drug. With a new drug be particularly alert for adverse reactions or unexpected events.
7. If serious adverse reactions are liable to occur warn the patient.

Defective Medicines

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

The Defective Medicines Report Centre operates a 24-hour service to assist with the investigation of problems arising from licensed medicinal products thought to be defective, and to co-ordinate any necessary protective action. Reports on suspect defective medicinal products should include the brand or the non-proprietary name, the name of the manufacturer or supplier, the strength and dosage form of the product, the product licence number, the batch number or numbers of the product, the nature of the defect, and an account of any action already taken in consequence. The Centre can be contacted at:

The Defective Medicines Report Centre
Medicines Control Agency
Room 1801, Market Towers
1 Nine Elms Lane
London SW8 5NQ
0171-273 0574 (weekdays 9.00 am–5.00 pm)
or 0171-210 5368 or 5371 (any other time)

Prescribing for Children

All children, and particularly neonates, differ from adults in their response to drugs. Special care is needed in the neonatal period (first 30 days of life) and doses should always be calculated according to weight. At this age, the risk of toxicity is increased by inefficient renal filtration, relative enzyme deficiencies, differing target organ sensitivity, and inadequate detoxifying systems causing delayed excretion. In childhood dosage should be adjusted for weight until 50 kg or puberty is reached.

Whenever possible painful intramuscular injections should be **avoided** in children.

PRESCRIPTION WRITING. Prescriptions should be written according to the guidelines in Prescription Writing (p. 4). Inclusion of age is a legal requirement in the case of prescription-only medicines for children under 12 years of age, but it is preferable to state the age for **all** prescriptions for children.

It is particularly important to state the strengths of capsules or tablets. Although liquid preparations are particularly suitable for children, many contain sucrose which encourages dental decay. When taken over a long period, sugar-free tablets and liquid medicines should be used when possible.

When a prescription for a liquid oral preparation is written and the dose ordered is smaller than 5 mL, the preparation will no longer be diluted. Instead an **oral syringe** will be supplied, for full details, see p. 2. Parents should be advised not to add any medicines to the contents of the infant's feeding bottle, since the drug may interact with the milk or other liquid in it; moreover the ingested dosage may be reduced, if the child does not drink all the contents.

Parents must be warned to keep **all** medicines out of the reach of children, see Safety in the Home, p. 3.

Rare paediatric conditions

Information on substances such as *biotin* and *sodium benzoate* used in rare metabolic conditions can be obtained from:

Drug Information Centre, Alder Hey Children's Hospital, Liverpool L12 2AP (Tel. 0151-252 5381);
Pharmacy, Hospital for Sick Children, Great Ormond St, London, WC1N 3JH (Tel. 0171-405 9200)

Dosage in Children

Children's doses in the BNF are stated in the individual drug entries as far as possible, except where paediatric use is not recommended or there are special hazards.

Doses are generally based on body-weight (in kilograms) or the following age ranges:

first month (neonate)
up to 1 year (infant)
1–5 years
6–12 years

Where a single dose is quoted for a given range, it applies to the middle of the age range and some extrapolation may be necessary to obtain doses for ages at the lower and upper limits of the stated range.

DOSE CALCULATION. Children's doses may be calculated from adult doses by using age, body-weight, or body-surface area, or by a combination of these factors. The most reliable methods are those based on body-surface area.

Body-weight may be used to calculate doses expressed in mg/kg. Young children may require a higher dose per kilogram than adults because of their higher metabolic rates. Other problems need to be considered. For example, calculation by body-weight in the obese child would result in much higher doses being administered than necessary; in such cases, dose should be calculated from an ideal weight, related to height and age.

Body-surface area (BSA) estimates are more accurate for calculation of paediatric doses than body-weight since many physical phenomena are more closely related to body-surface area. The average body-surface area of a 70-kilogram human is about 1.8 m^2. Thus, to calculate the dose for a child the following formula may be used:

Approximate dose for patient =

$$\frac{\text{surface area of patient } (m^2) \times \text{adult dose}}{1.8}$$

The **percentage method** below may be used to calculate paediatric doses of commonly prescribed drugs that have a wide margin between the therapeutic and the toxic dose

Age	Ideal body-weight kg	Ideal body-weight lb	Height cm	Height in	Body-surface m^2	Percentage of adult dose
Newborn*	3.4	7.5	50	20	0.23	12.5
1 month*	4.2	9	55	22	0.26	14.5
3 months*	5.6	12	59	23	0.32	18
6 months	7.7	17	67	26	0.40	22
1 year	10	22	76	30	0.47	25
3 years	14	31	94	37	0.62	33
5 years	18	40	108	42	0.73	40
7 years	23	51	120	47	0.88	50
12 years	37	81	148	58	1.25	75
Adult						
Male	68	150	173	68	1.80	100
Female	56	123	163	64	1.60	100

* The figures relate to full term and not preterm infants who may need reduced dosage according to their clinical condition.

More precise body-surface values may be calculated from height and weight by means of a nomogram (e.g. J. Insley, *A Paediatric Vade-Mecum*, 12th Edition, London, Edward Arnold, 1990).

DOSE FREQUENCY. Doses for antibiotics are usually stated as every 6 hours. Some flexibility should be allowed in children to avoid waking them during the night. For example, the night-time dose may be given at the [illegible] bedtime.

Where new or potentially toxic drugs are used, the manufacturers' recommended doses should be

Prescribing in Palliative Care

In recent years there has been increased interest in providing better treatment and support for patients with terminal illness. The aim is to keep them as comfortable, alert, and free of pain as possible. It may also be necessary to direct attention to emotional, financial, social, or family problems. The patient's minister or the hospital chaplain may give invaluable help.

DOMICILIARY CARE. If they wish, whenever possible, patients should end their days in their own homes. Although families may at first be afraid of caring for the patient at home, they will usually do so if extra support from district nursing services, social services and voluntary agencies is provided. Families may be reassured if an assurance is given that the patient will be admitted to a hospital or hospice if they cannot cope.

HOSPITAL OR HOSPICE CARE. The most important lesson to be drawn from the experience of hospices is that both doctors and nurses must give time to listen to the patient. This gives great support and comfort to a patient who may otherwise suffer intolerable loneliness. Often problems come to light that can easily be dealt with—adjusting a blind in the late afternoon, an irritating noise to be avoided, drinks to be placed in easier reach, someone to read the newspaper, or the TV to be replaced by radio. The staff should not exclude the family from contributing to the patient's care; if prevented they may be resentful or subsequently suffer a feeling of guilt.

DRUG TREATMENT. The number of drugs should be as few as possible, for even the taking of medicine may be an effort. Oral medication is usually satisfactory unless there is severe nausea and vomiting, dysphagia, weakness, or coma, in which case parenteral medication may be necessary.

PAIN

Analgesics are always more effective in preventing the development of pain than in the relief of established pain.

The **non-opioid** analgesics **aspirin** or **paracetamol** given regularly will often make the use of opioids unnecessary. Aspirin (or other NSAIDs if preferred) may also control the pain of *bone secondaries*; naproxen, flurbiprofen, and indomethacin (see section 10.1.1) are valuable and if necessary can be given rectally. **Corticosteroids, radiotherapy** or radioactive isotopes of **strontium** (Metastron® available from Amersham) are also often useful for pain due to bone metastases.

Morphine is the most useful of the **opioid analgesics**. In addition to relief of pain, it confers a state of euphoria and mental detachment.

ORAL ROUTE. M ıe is given *by mouth* as an oral solution re ı every 4 hours, the initial dose depending largely on the patient's previous treatment. A dose of 5–10 mg is enough to replace a weaker analgesic (such as paracetamol or co-proxamol), but 10–20 mg or more is required to replace a strong one (comparable to morphine itself). If the first dose of morphine is no more effective than the previous analgesic it should be increased by 50%, the aim being to choose the lowest dose which prevents pain. Although a dose of 5–20 mg is usually adequate there should be no hesitation in increasing it to 30–60 mg or occasionally to 90–150 mg or higher if necessary. If pain occurs between doses the next dose due is increased; in the interim an additional dose is given.

Modified-release tablets of morphine (MST Continus® tablets or Oramorph® SR tablets) are an alternative to the oral solution; they have the advantage that they need only be taken every 12 hours. The starting dose of MST Continus® tablets or Oramorph® SR tablets is usually 10–20 mg every 12 hours if no other analgesic (or only paracetamol) has previously been taken, but to replace a weaker opioid analgesic (such as co-proxamol) the starting dose is usually 20–30 mg every 12 hours. Increments should be made to the dose, not to the frequency of administration, which should remain at every 12 hours.

The effective dose of MST Continus® tablets or Oramorph®SR tablets can alternatively be found by giving the oral solution of morphine every 4 hours in increasing doses until the pain has been controlled, and then transferring the patient to the same total 24-hour dose of morphine given as the modified-release tablet (divided into two portions for 12-hourly administration). The first dose of the modified-release tablet is given 4 hours after the last dose of the oral solution[1].

Modified-release capsules of morphine sulphate (MXL®) are available which need to be taken only once every 24 hours. This may aid compliance, but the patient's 24-hour morphine requirements should be found before starting this preparation; morphine as oral solution or tablets, should be prescribed for breakthrough pain.

PARENTERAL ROUTE. If the patient becomes unable to swallow, the equivalent intramuscular dose of morphine is half the oral solution dose; in the case of the modified-release tablets it is half the total 24-hour dose (which is then divided into 6 portions to be given every 4 hours). **Diamorphine** is preferred for injection because being more soluble it can be given in a smaller volume. The equivalent intramuscular (or subcutaneous) dose of diamorphine is only about a quarter to a third of the oral dose of morphine; *subcutaneous infusion via syringe driver* can be useful (for details, see p. 14).

RECTAL ROUTE. Morphine is also available for *rectal administration* as suppositories; alternatively **oxycodone** suppositories can be obtained on special order.

1. Studies have indicated that administratio. ıe la dose of the *oral solution* with the first dose of the *modified-release tablets* is not necessary

TRANSDERMAL ROUTE. Transdermal preparations of fentanyl are now available, see section 4.7.2. Careful conversion from oral morphine to transdermal fentanyl is necessary; a 25 micrograms/hr patch is equivalent to a total dose of morphine up to 135 mg/24 hours

GASTRO-INTESTINAL PAIN. The pain of *bowel colic* may be reduced by loperamide 2–4 mg 4 times daily. Hyoscine hydrobromide may also be helpful, given sublingually at a dose of 300 micrograms 3 times daily as Kwells® (Roche Consumer Health) tablets. For the dose by *subcutaneous infusion* using a syringe driver, see p. 14.

Gastric distension pain due to pressure on the stomach may be helped by a preparation incorporating an antacid with an antiflatulent (see section 1.1.1) and by domperidone 10 mg 3 times daily before meals.

MUSCLE SPASM. The pain of muscle spasm can be helped by a muscle relaxant such as diazepam 5–10 mg daily or baclofen 5–10 mg 3 times daily.

NERVE PAIN. Pain due to *nerve compression* may be reduced by a corticosteroid such as dexamethasone 8 mg daily, which reduces oedema around the tumour, thus reducing compression.

Dysaesthetic or stabbing pain resulting from *nerve irritation* may be reduced by amitriptyline 25–75 mg at night, or by carbamazepine 200 mg 3 times daily.

Nerve blocks may be considered when pain is localised to a specific area. **Transcutaneous electrical nerve stimulation (TENS)** may also provide useful relief of pain.

MISCELLANEOUS CONDITIONS

Non-licensed indications or routes

Several recommendations in this section involve non-licensed indications or routes.

RAISED INTRACRANIAL PRESSURE. Headache due to *raised intracranial pressure* often responds to a high dose of a corticosteroid, such as dexamethasone 16 mg daily for 4 to 5 days, subsequently reduced to 4–6 mg daily if possible.

INTRACTABLE COUGH. *Intractable cough* may be relieved by moist inhalations or may require regular administration of an oral morphine hydrochloride (or sulphate) solution in an initial dose of 5 mg every 4 hours. Methadone linctus should be avoided as it has a long duration of action and tends to accumulate.

DYSPNOEA. *Dyspnoea* may be relieved by regular oral morphine hydrochloride (or sulphate) solution in carefully titrated doses, starting at 5 mg every 4 hours. Diazepam 5–10 mg daily may be helpful; a corticosteroid, such as dexamethasone 4–8 mg daily, may also be helpful if there is *bronchospasm* or *partial obstruction*.

EXCESSIVE RESPIRATORY SECRETION. *Excessive respiratory secretion* (death rattle) may be reduced by subcutaneous injection of hyoscine hydrobromide 400–600 micrograms every 4 to 8 hours; care must however be taken to avoid the discomfort of dry mouth. For the dose by *subcutaneous infusion* using a syringe driver, see next page.

RESTLESSNESS AND CONFUSION. *Restlessness and confusion* may require treatment with haloperidol 1–3 mg by mouth every 8 hours. Chlorpromazine 25–50 mg by mouth every 8 hours is an alternative, but causes more sedation. Methotrimeprazine is also used occasionally for restlessness. For the dose by *subcutaneous infusion* using a syringe driver, see next page

HICCUP. *Hiccup due to gastric distension* may be helped by a preparation incorporating an antacid with an antiflatulent (see section 1.1.1). If this fails, metoclopramide 10 mg every 6 to 8 hours by mouth or by intramuscular injection can be added; if this also fails, chlorpromazine 10–25 mg every 6 to 8 hours can be tried.

ANOREXIA. *Anorexia* may be helped by prednisolone 15–30 mg daily or dexamethasone 2–4 mg daily.

CONSTIPATION. *Constipation* is a very common cause of distress and is almost invariable after administration of an opioid. It should be prevented if possible by the regular administration of laxatives; a faecal softener with a peristaltic stimulant (e.g. co-danthramer), or lactulose solution with a senna preparation should be used (see sections 1.6.2 and 1.6.3).

FUNGATING GROWTH. *Fungating growth* may be treated by cleansing with a mixture of 1 part of 4% povidone-iodine skin cleanser solution and 4 parts of liquid paraffin. Oral administration of metronidazole (see section 5.1.11) may eradicate the anaerobic bacteria responsible for the odour of fungating tumours; topical application (see section 13.10.1.2) is also used.

CAPILLARY BLEEDING. *Capillary bleeding* may be reduced by applying gauze soaked in adrenaline solution (1 in 1000).

DRY MOUTH. *Dry mouth* may be associated with candidiasis which can be treated by nystatin oral suspension or pastilles, amphotericin lozenges, or miconazole oral gel after food (see section 12.3.2); alternatively, fluconazole can be given by mouth (see section 5.2). Morphine sulphate and antimuscarinic drugs (such as hyoscine) may cause dry mouth.

PRURITUS. *Pruritus*, even when associated with *obstructive jaundice*, often responds to simple measures such as emollients. In the case of obstructive jaundice, further measures include administration of cholestyramine or an anabolic steroid, such as stanozolol 5–10 mg daily; antihistamines can be helpful (see section 3.4.1).

CONVULSIONS. Patients with *cerebral tumours* or *uraemia* may be susceptible to convulsions. Prophylactic trea with phenytoin or carbamazepine (see sectic 5.1) should be considered. When oral medication is no longer possible, diazepam as

phenobarbitone by injection 50–200 mg twice daily is continued as prophylaxis. For the use of midazolam by *subcutaneous infusion* using a syringe driver, see next page.

DYSPHAGIA. A corticosteroid such as dexamethasone 8 mg daily may help, temporarily, if there is an obstruction due to *tumour*. See also under Dry Mouth.

NAUSEA AND VOMITING. *Nausea and vomiting* are very common in patients with advanced cancer. The cause should be diagnosed before treatment with anti-emetics (see section 4.6) is started. Octreotide (see section 8.3.4.3), which stimulates water and electrolyte absorption and inhibits water secretion in the small bowel, can be used by subcutaneous infusion, in a dose of 300–600 micrograms/24 hours to reduce intestinal secretions and vomiting.

Nausea and vomiting may also occur in the initial stages of morphine therapy but can be prevented by giving an anti-emetic such as haloperidol or prochlorperazine. An anti-emetic is usually only necessary for the first 4 or 5 days therefore fixed-combination opioid preparations containing an anti-emetic are not recommended since they lead to unnecessary anti-emetic therapy (often with undesirable drowsiness). For the administration of anti-emetics by *subcutaneous infusion* using a syringe driver, see below.

INSOMNIA. Patients with advanced cancer may not sleep because of discomfort, cramps, night sweats, joint stiffness, or fear. There should be appropriate treatment of these problems before hypnotics are used. Benzodiazepines, such as temazepam, may be useful (see section 4.1.1).

HYPERCALCAEMIA. See section 9.5.1.2.

SYRINGE DRIVERS

Although drugs can usually be administered *by mouth* to control the symptoms of advanced cancer, the parenteral route may sometimes be necessary. If the parenteral route is necessary, repeated administration of *intramuscular injections* can be difficult in a cachectic patient. This has led to the use of a portable syringe driver to give a *continuous subcutaneous infusion*, which can provide good control of symptoms with little discomfort or inconvenience to the patient.

Indications for the **parenteral route** are:

- the patient is unable to take medicines by mouth owing to *nausea and vomiting, dysphagia, severe weakness*, or *coma*;
- there is *malignant bowel obstruction* in patients for whom further surgery is inappropriate (avoiding the need for an intravenous infusion or for insertion of a nasogastric tube);
- occasionally when the patient *does not wish* to take regular medication by mouth.

NAUSEA AND VOMITING. **Haloperidol** is given in a *subcutaneous infusion* dose of 2.5–10 mg/24 hours.

Methotrimeprazine causes sedation in about 50% of patients; it is given in a *subcutaneous infusion dose* of 25–[illegible] /24 hours.

Cyclizine is particularly liable to precipitate if mixed with diamorphine or other drugs (see under Mixing and Compatibility, below); it is given in a *subcutaneous infusion dose* of 150 mg/24 hours.

Metoclopramide may cause skin reactions; it is given in a *subcutaneous infusion dose* of 30–60 mg/24 hours.

BOWEL COLIC OR EXCESSIVE RESPIRATORY SECRETIONS. **Hyoscine hydrobromide** effectively reduces respiratory secretions and is sedative (but occasionally causes paradoxical agitation); it is given in a *subcutaneous infusion dose* of 0.6–2.4 mg/24 hours.

Hyoscine butylbromide is effective in bowel colic, is less sedative than hyoscine hydrobromide, but is not always adequate for the control of respiratory secretions; it is given in a *subcutaneous infusion dose* of 20–60 mg/24 hours (**important:** this dose of *hyoscine butylbromide* must not be confused with the much lower dose of *hyoscine hydrobromide*, above).

RESTLESSNESS AND CONFUSION. **Haloperidol** has little sedative effect; it is given in a *subcutaneous infusion dose* of 5–30 mg/24 hours.

Methotrimeprazine has a sedative effect; it is given in a *subcutaneous infusion dose* of 50–200 mg/24 hours.

Midazolam is a sedative and an antiepileptic, and is therefore suitable for a very restless patient; it is given in a *subcutaneous infusion dose* of 20–100 mg/24 hours.

CONVULSIONS. If a patient has previously been receiving an antiepileptic *or* has a primary or secondary cerebral tumour *or* is at risk of convulsion (e.g. owing to uraemia) antiepileptic medication should not be stopped. **Midazolam** is the benzodiazepine antiepileptic of choice for *continuous subcutaneous infusion*, and is given in a dose of 20–40 mg/24 hours.

PAIN CONTROL. **Diamorphine** is the preferred opioid since its high solubility permits a large dose to be given in a small volume (see under Mixing and Compatibility, below). The table on the next page gives the approximate doses of *morphine by mouth* (as oral solution or standard tablets or as modified-release tablets) equivalent to *diamorphine by injection* (intramuscularly or by subcutaneous infusion).

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

In theory injections dissolved in **water for injections** are more likely to be associated with pain (possibly owing to their hypotonicity). Use of **physiological saline** (sodium chloride 0.9%) however increases the likelihood of precipitation when

more than one drug is used; moreover subcutaneous infusion rates are so slow (0.1–0.3 mL/hour) that pain is not usually a problem when water is used as a diluent.

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

The following can be mixed with *diamorphine:*

Cyclizine[1]
Dexamethasone[2]
Haloperidol[3]
Hyoscine butylbromide
Hyoscine hydrobromide
Methotrimeprazine
Metoclopramide[4]
Midazolam

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

PROBLEMS ENCOUNTERED WITH SYRINGE DRIVERS. The following are problems that may be encountered with syringe drivers and the action that should be taken:

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

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

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

Equivalent doses of morphine sulphate by mouth (as oral solution or standard tablets *or* as modified-release tablets) *or* of diamorphine hydrochloride by intramuscular injection *or by* subcutaneous infusion

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

ORAL MORPHINE		PARENTERAL DIAMORPHINE	
Morphine sulphate oral solution or standard tablets	Morphine sulphate modified-release tablets	Diamorphine hydrochloride by intramuscular injection	Diamorphine hydrochloride by subcutaneous infusion
every 4 hours	**every 12 hours**	**every 4 hours**	**every 24 hours**
5 mg	20 mg	2.5 mg	15 mg
10 mg	30 mg	5 mg	20 mg
15 mg	50 mg	5 mg	30 mg
20 mg	60 mg	7.5 mg	45 mg
30 mg	90 mg	10 mg	60 mg
40 mg	120 mg	15 mg	90 mg
60 mg	180 mg	20 mg	120 mg
80 mg	240 mg	30 mg	180 mg
100 mg	300 mg	40 mg	240 mg
130 mg	400 mg	50 mg	300 mg
160 mg	500 mg	60 mg	360 mg
200 mg	600 mg	70 mg	400 mg

If breakthrough pain occurs give a subcutaneous (preferable) or intramuscular injection of diamorphine equivalent to one-sixth of the total 24-hour subcutaneous infusion dose. It is kinder to give an intermittent bolus injection *subcutaneously*—absorption is smoother so that the risk of adverse effects at peak absorption is avoided (an even better method is to use a subcutaneous butterfly needle).

To minimise the risk of infection no individual subcutaneous [illegible] solution should be used for longer than 24 hours.

▼ PoM **Lamictal®** (Wellcome)

Tablets, all yellow, lamotrigine 25 mg, net price 21-tab pack (*'Valproate Add-on therapy' Starter Pack*) = £7.49, 42-tab pack (*'Monotherapy' Starter Pack*) = £14.97, 56-tab pack = £19.97; 50 mg, 42-tab pack (*'Non-valproate Add-on therapy' Starter Pack*) = £25.46, 56-tab pack = £33.95; 100 mg, 56-tab pack = £58.57; 200 mg, 56-tab pack = £99.56. Counselling, driving (see notes above)

Dispersible tablets, lamotrigine 5 mg (scored), net price 28-tab pack = £7.96; 25 mg, 56-tab pack = £19.97; 100 mg, 56-tab pack = £58.57. Label: 13, counselling, driving (see notes above)

PHENOBARBITONE AND OTHER BARBITURATES

Phenobarbitone is effective for tonic and partial seizures but may be sedative in adults and cause behavioural disturbances and hyperkinesia in children. It may be tried for atypical absence, atonic, and tonic seizures. Rebound seizures may be a problem on withdrawal. Monitoring plasma concentrations is less useful than with other drugs because tolerance occurs. **Methylphenobarbitone** is largely converted to phenobarbitone in the liver and has no advantages. **Primidone** is largely converted to phenobarbitone and this is probably responsible for its antiepileptic action. A small starting dose of primidone (125 mg) is essential, and the drug should be introduced over several weeks.

PHENOBARBITONE

(Phenobarbital)

Indications: all forms of epilepsy except absence seizures; status epilepticus, section 4.8.2

Cautions: elderly, debilitated, children, impaired renal or hepatic function, respiratory depression (avoid if severe), pregnancy and breast-feeding (see notes above); avoid sudden withdrawal; see also notes above; avoid in porphyria (see section 9.8.2); **interactions:** see p. 203 and Appendix 1 (barbiturates and primidone)

Side-effects: drowsiness, lethargy, mental depression, ataxia and allergic skin reactions; paradoxical excitement, restlessness and confusion in the elderly and hyperkinesia in children; megaloblastic anaemia (may be treated with folic acid); overdosage: see Emergency Treatment of Poisoning, p. 23

Dose: *by mouth*, 60–180 mg at night; CHILD 5–8 mg/kg daily

By intramuscular or intravenous injection, 50–200 mg, repeated after 6 hours if necessary; max. 600 mg daily; dilute injection 1 in 10 with water for injections before intravenous administration; status epilepticus, section 4.8.2

Note. For therapeutic purposes phenobarbitone and phenobarbitone sodium may be considered equivalent in effect. Plasma concentration for optimum response 15–40 mg/litre (60–180 micromol/litre)

CD [1]Phenobarbitone Tablets, phenobarbitone 15 mg, net price 20 = 7p; 30 mg, 20 = 6p; 60 mg, 20 = 11p. Label: 2, counselling, driving (see notes above)

CD [1]Phenobarbitone Elixir, phenobarbitone 15 mg/5 mL in a suitable flavoured vehicle, containing alcohol 38%. Net price 100 mL = 52p. Label: 2, counselling, driving (see notes above)

Note. Some hospitals supply alcohol-free formulations

CD [1]Phenobarbitone Injection, phenobarbitone sodium 200 mg/mL in propylene glycol 90% and water for injections 10%. Net price 1-mL amp = 86p

Note. Must be diluted before intravenous administration (see under Dose)

Available from Rhône-Poulenc Rorer (**CD** [1]Gardenal Sodium®), Martindale; other strengths also available from Martindale.

1. See p. 7 for prescribing requirements for phenobarbitone

METHYLPHENOBARBITONE

(Methyphenobarbital)

Indications; Cautions; Side-effects: see under Phenobarbitone

Dose: 100–600 mg daily

CD Prominal® (Sanofi Winthrop)

Tablets, methylphenobarbitone 30 mg, net price 20 = 78p; 60 mg, 20 = £1.03; 200 mg, 20 = £2.20. Label: 2, counselling, driving (see notes above)

PRIMIDONE

Indications: all forms of epilepsy except absence seizures; essential tremor (section 4.9.3)

Cautions; Side-effects: see under Phenobarbitone. Drowsiness, ataxia, nausea, visual disturbances, and rashes, particularly at first, usually reversible on continued administration; **interactions:** see p. 203 and Appendix 1 (barbiturates and primidone)

Dose: epilepsy, initially, 125 mg daily at bedtime, increased by 125 mg every 3 days to 500 mg daily in 2 divided doses then increased by 250 mg every 3 days to a max. of 1.5 g daily in divided doses; CHILD under 2 years, 250–500 mg daily in 2 divided doses; 2–5 years, 500–750 mg daily in 2 divided doses; 6–9 years 0.75–1 g daily in 2 divided doses

Note. Monitor plasma concentrations of derived phenobarbitone. Optimum range as for phenobarbitone.

PoM **Mysoline®** (Zeneca)

Tablets, scored, primidone 250 mg. Net price 100-tab pack = £1.77. Label: 2, counselling, driving (see notes above)

Oral suspension, primidone 250 mg/5 mL. Net price 250-mL pack = £1.01. Label: 2, counselling, driving (see notes above)

PHENYTOIN

Phenytoin is effective in tonic-clonic and partial seizures. It has a narrow therapeutic index and the relationship between dose and plasma concentra-

tion is non-linear; small dosage increases in some patients may produce large rises in plasma concentrations with acute toxic side-effects. Monitoring of plasma concentration greatly assists dosage adjustment. A few missed doses or a small change in drug absorption may result in a marked change in plasma concentration.

Phenytoin may cause coarse facies, acne, hirsutism, and gingival hyperplasia and so may be particularly undesirable in adolescent patients.

PHENYTOIN

Indications: all forms of epilepsy except absence seizures; trigeminal neuralgia (see also section 4.7.3)

Cautions: hepatic impairment (reduce dose), pregnancy (**important:** see notes above and Appendix 4), breast-feeding (see notes above); avoid sudden withdrawal; manufacturer recommends blood counts (but evidence of practical value unsatisfactory); avoid in porphyria (see section 9.8.2); see also notes above; **interactions:** see p. 203 and Appendix 1 (phenytoin)

BLOOD, or SKIN DISORDERS. Patients or their carers should be told how to recognise signs of blood, or skin disorders, and advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, bruising, or bleeding develop. Leucopenia which is severe, progressive or associated with clinical symptoms requires withdrawal (if necessary under cover of suitable alternative)

Side-effects: nausea, vomiting, mental confusion, dizziness, headache, tremor, transient nervousness, insomnia occur commonly; rarely dyskinesias, peripheral neuropathy; ataxia, slurred speech, nystagmus and blurred vision are signs of overdosage; rashes (discontinue, if mild re-introduce cautiously but discontinue immediately if recurrence), coarse facies, acne and hirsutism, fever and hepatitis; lupus erythematosus, erythema multiforme (Stevens-Johnson syndrome), toxic epidermal necrolysis, polyarteritis nodosa; lymphadenopathy; gingival hypertrophy and tenderness; rarely haematological effects, including megaloblastic anaemia (may be treated with folic acid), leucopenia, thrombocytopenia, agranulocytosis, and aplastic anaemia; plasma calcium may be lowered (rickets and osteomalacia)

Dose: *by mouth*, initially 3–4 mg/kg daily *or* 150–300 mg daily (as a single dose *or* in two divided doses) increased gradually as necessary (plasma monitoring, see notes above); usual dose 300–400 mg daily; max. 600 mg daily; CHILD 5–8 mg/kg daily (in 1 or 2 doses)

By intravenous injection—section 4.8.2

Note. Plasma concentration for optimum response 10–20 mg/litre (40–80 micromol/litre)

COUNSELLING. Take preferably with or after food

PoM **Phenytoin** (Non-proprietary)

Capsules, phenytoin sodium 50 mg, net price 20 = 40p; 100 mg, 20 = 56p. Label: 27, counselling, administration, blood or skin disorder symptoms (see above), driving (see notes above)

Tablets, coated, phenytoin sodium 50 mg, net price 20 = 26p; 100 mg, 20 = 31p. Label: 27, counselling, administration, blood or skin disorder symptoms (see above), driving (see notes above)

Available from APS, Berk (Pentran®), Cox

Note. On the basis of single dose tests there are no clinically relevant differences in bioavailability between available phenytoin sodium tablets and capsules but some clinics prefer patients to remain on the same brand whenever possible

PoM **Epanutin®** (P-D)

Capsules, phenytoin sodium 25 mg (white/purple), net price 20 = 39p; 50 mg (white/pink), 20 = 40p; 100 mg (white/orange), 20 = 56p; 300 mg (white/green), 20 = £1.69. Label: 27, counselling, administration, blood or skin disorder symptoms (see above), driving (see notes above)

Infatabs® (= tablets, chewable), yellow, scored, phenytoin 50 mg. Net price 20 = £1.10. Label: 24, counselling, blood or skin disorder symptoms (see above), driving (see notes above)

Note. Contain phenytoin 50 mg (as against phenytoin sodium) therefore care is needed on changing to capsules or tablets containing phenytoin sodium

Suspension, red, phenytoin 30 mg/5 mL. Net price 100 mL = 71p. Counselling, administration, blood or skin disorder symptoms (see above), driving (see notes above)

Note. Suspension of phenytoin 90 mg in 15 mL may be considered to be approximately equivalent in therapeutic effect to capsules or tablets containing phenytoin sodium 100 mg, but nevertheless care is needed in making changes

VALPROATE

Sodium valproate is effective in controlling tonic-clonic seizures, particularly in primary generalised epilepsy. It is a drug of choice in primary generalised epilepsy, generalised absences and myoclonic seizures, and may be tried in atypical absence, atonic, and tonic seizures. Controlled trials in partial epilepsy suggest that it has similar efficacy to that of carbamazepine and phenytoin, but more evidence is awaited. Plasma concentrations are not a useful index of efficacy, therefore routine monitoring is unhelpful. The drug has widespread metabolic effects, and may have dose-related side-effects. There has been concern over severe hepatic or pancreatic toxicity, although these effects are rare.

SODIUM VALPROATE

Indications: all forms of epilepsy

Cautions: monitor liver function before therapy and during first 6 months especially in patients most at risk (see also below), ensure no undue potential for bleeding before starting and before major surgery; severe renal impairment; pregnancy (**important** see notes above and Appendix 4 (neural tube screening)); breast-feeding; systemic lupus erythematosus; may give false-positive urine tests for ketones; avoid sudden withdrawal; porphyria (see section 9.8.2); see also notes above; **interactions:** see p. 203 and Appendix 1 (valproate)

LIVER TOXICITY. Liver dysfunction (including fatal hepatic failure) has occurred in association with valproate (especially in children under 3 years of age and those with metabolic or degenerative disorders, organic brain disease or severe seizure disorders associated with

mental retardation) usually in the first 6 months of therapy and usually involving multiple antiepileptic therapy (monotherapy preferred). Raised liver enzymes are not uncommon during valproate treatment and are usually transient but patients should be reassessed clinically and liver function (including prothrombin time) monitored until return to normal—an abnormally prolonged prothrombin time (particularly in association with other relevant abnormalities) requires discontinuation of treatment. Any concomitant use of salicylates should be stopped.

BLOOD OR HEPATIC DISORDERS. Patients or their carers should be told how to recognise signs of blood or liver disorders, and advised to seek immediate medical attention if symptoms develop (advice is given on patient information leaflet).

Contra-indications: active liver disease, family history of severe hepatic dysfunction

Side-effects: gastric irritation, nausea, ataxia and tremor; hyperammonaemia, increased appetite and weight gain; transient hair loss (regrowth may be curly), oedema, thrombocytopenia, and inhibition of platelet aggregation; impaired hepatic function leading rarely to fatal hepatic failure (see also under Cautions—withdraw treatment immediately if vomiting, anorexia, jaundice, drowsiness, or loss of seizure control occurs); rashes; sedation reported (rarely lethargy and confusion associated with too high an initial dose) and also increased alertness (occasionally aggression, hyperactivity and behavioural disturbances); rarely pancreatitis (measure plasma amylase in acute abdominal pain), leucopenia, red cell hypoplasia, fibrinogen reduction; irregular periods and amenorrhoea also reported, also gynaecomastia

Dose: *by mouth*, initially, 600 mg daily given in 2 divided doses, preferably after food, increasing by 200 mg/day at 3-day intervals to a max. of 2.5 g daily in divided doses, usual maintenance 1–2 g daily (20–30 mg/kg daily); CHILD up to 20 kg, initially 20 mg/kg daily in divided doses, may be increased provided plasma concentrations monitored (above 40 mg/kg daily also monitor clinical chemistry and haematological parameters); over 20 kg, initially 400 mg daily in divided doses increased until control (usually in range of 20–30 mg/kg daily); max. 35 mg/kg daily

By intravenous injection (over 3–5 minutes) or *by intravenous infusion*, continuation of valproate treatment when oral therapy not possible, same as current dose by oral route

Initiation of valproate therapy (when oral valproate not possible), *by intravenous injection* (over 3–5 minutes), 400–800 mg (up to 10 mg/kg) followed by *intravenous infusion* up to max. 2.5 g daily; CHILD, usually 20–30 mg/kg daily, may be increased provided plasma concentrations monitored (above 40 mg/kg daily also monitor clinical chemistry and haematological parameters)

PoM **Sodium Valproate** (Non-proprietary)

Tablets, e/c, sodium valproate 200 mg, net price 20 = £1.20; 500 mg, 20 = £3.01. Label: 5, 25, counselling, blood or hepatic disorder symptoms (see above), driving (see notes above)

Available from Cox, CP (Orlept®), Hillcross, Norton

Oral solution, sodium valproate 200 mg/5 mL. Net price 100 mL = £1.80. Counselling, blood or hepatic disorder symptoms (see above), driving (see notes above)

Available from CP, (Orlept®, sugar-free), Hillcross, Norton (sugar-free)

PoM **Epilim®** (Sanofi Winthrop)

Tablets (crushable), scored, sodium valproate 100 mg. Net price 20 = 78p. Counselling, blood or hepatic disorder symptoms (see above), driving (see notes above)

Note. Sodium valproate crushable tablets also available from Hillcross

Tablets, both e/c, lilac, sodium valproate 200 mg, net price 20 = £1.28; 500 mg, 20 = £3.21. Label: 5, 25, counselling, blood or hepatic disorder symptoms (see above), driving (see notes above)

Liquid, red, sugar-free, sodium valproate 200 mg/5 mL. Net price 300-mL pack = £5.89. Counselling, blood or hepatic disorder symptoms (see above), driving (see notes above)

Syrup, red, sodium valproate 200 mg/5 mL. Net price 300-mL pack = £5.89. Counselling, blood or hepatic disorder symptoms (see above), driving (see notes above)

PoM **Epilim Chrono®** (Sanofi Winthrop)

Tablets, m/r, all lilac, sodium valproate 200 mg (as sodium valproate and valproic acid), net price 100-tab pack = £7.70; 300 mg, 100-tab pack = £11.55; 500 mg, 100-tab pack = £19.25. Label: 25, counselling, blood or hepatic disorder symptoms (see above), driving (see notes above)

Dose: ADULT and CHILD over 20 kg, as above, total daily dose given in 1–2 divided doses

PoM **Epilim® Intravenous** (Sanofi Winthrop)

Injection, powder for reconstitution, sodium valproate. Net price 400-mg vial (with 4-mL amp water for injections) = £8.77

Valproic acid

PoM **Convulex®** (Pharmacia)

Capsules, e/c, valproic acid 150 mg, net price 100-cap pack = £3.85; 300 mg, 100-cap pack = £7.70; 500 mg, 100-cap pack = £12.83. Counselling, blood or hepatic disorder symptoms (see above), driving (see notes above)

Dose: ADULT and CHILD initially 15 mg/kg daily in 2–4 divided doses, gradually increasing in steps of 5–10 mg/kg up to 30 mg/kg daily

EQUIVALENCE TO SODIUM VALPROATE. Manufacturer advises that Convulex® has a 1:1 dose relationship with products containing sodium valproate, but nevertheless care is needed in making changes.

VIGABATRIN

Vigabatrin is effective for use in chronic epilepsy not satisfactorily controlled by other antiepileptics. It is useful in tonic-clonic and partial seizures but has prominent behavioural side-effects in some patients.

VIGABATRIN

Indications: epilepsy not satisfactorily controlled by other antiepileptics, monotherapy for management of infantile spasms (West's syndrome)

ACETAZOLAMIDE

Indications: see notes above

Cautions; Side-effects: see section 11.6

Dose: 0.25–1 g daily in divided doses; CHILD 8–30 mg/kg daily; max. 750 mg daily

Preparations

See section 11.6

GABAPENTIN

Indications: adjunctive treatment of partial seizures with or without secondary generalisation not satisfactorily controlled with other antiepileptics

Cautions: avoid sudden withdrawal (taper off over at least 1 week); mixed seizure disorders that include absence seizures (which may be exacerbated); elderly (may need to reduce dose), renal impairment (reduce dose), false positive readings with some urinary protein tests; pregnancy and breast-feeding; **interactions:** Appendix 1 (gabapentin)

Side-effects: somnolence, dizziness, ataxia, fatigue, nystagmus, headache, tremor, diplopia, nausea and vomiting, rhinitis, amblyopia; also convulsions, pharyngitis, dysarthria, weight gain, dyspepsia, amnesia, nervousness, coughing

Dose: 300 mg on first day, then 300 mg twice daily on second day, then 300 mg 3 times daily on third day, then increased according to response to 1.2 g daily (in 3 equally divided doses); if necessary may be further increased in steps of 300 mg daily (in 3 divided doses) to max. 2.4 g daily, usual range 0.9–1.2 g daily; max. period between doses should not exceed 12 hours; CHILD not recommended

▼ PoM **Neurontin®** (P-D)

Capsules, gabapentin 100 mg (white), net price 100-cap pack = £22.86; 300 mg (yellow), 100-cap pack = £53.00; 400 mg (orange), 100-cap pack = £61.33. Label: 3, 5, counselling, driving (see notes above)

PIRACETAM

Section 4.9.3

TOPIRAMATE

Indications: adjunctive treatment of partial seizures with or without secondary generalisation not satisfactorily controlled with other antiepileptics

Cautions: avoid abrupt withdrawal; ensure adequate hydration (especially if predisposition to nephrolithiasis); pregnancy (see notes above); renal impairment; **interactions:** see p. 203 and Appendix 1 (topiramate)

Contra-indications: breast-feeding

Side-effects: ataxia, impaired concentration, confusion, dizziness, fatigue, paraesthesia, somnolence, abnormal thinking, agitation, emotional lability (with abnormal behaviour), depression; nephrolithiasis (see Cautions); also amnesia, anorexia, aphasia, diplopia, nausea, nystagmus, speech disorder, taste alteration, abnormal vision, weight loss

Dose: initially 100 mg daily as a single dose for a week (lower dose may be used) *then* increased to 200 mg daily in 2 divided doses for a further week, *further dose increments* of 200 mg daily should be made at weekly intervals; usual dose 200–600 mg daily in 2 divided doses; max. 800 mg daily; CHILD not recommended

▼ PoM **Topamax®** (Janssen-Cilag)

Tablets, f/c, topiramate 50 mg (light yellow), net price 60-tab pack = £36.17; 100 mg (yellow), 60-tab pack = £64.80; 200 mg (salmon), 60-tab pack £125.83. Label: 3, counselling, driving (see notes above)

4.8.2 Drugs used in status epilepticus

Major status epilepticus should be *treated initially* with intravenous **diazepam**, used with caution because of the risk of respiratory depression; in situations where facilities for resuscitation are not immediately available, *small doses* of diazepam can be given intravenously or the drug can be administered as a rectal solution. Absorption from intramuscular injection or from suppositories is too slow for treatment of status epilepticus. When diazepam is given intravenously there may be a high risk of venous thrombophlebitis which is minimised by using an emulsion (Diazemuls®). **Clonazepam** and **lorazepam** are also used; lorazepam has the advantage of a long duration of action.

To *prevent recurrence* **phenytoin sodium** may be given by slow intravenous injection, with ECG monitoring in a dose of 15 mg/kg at a rate of not more than 50 mg/minute (in adults) followed by the maintenance dosage. Intramuscular use of phenytoin is not recommended (absorption is slow and erratic). Alternatively, **phenobarbitone sodium** (section 4.8.1) can be given by intravenous injection in a dose of 15 mg/kg at a rate of not more than 100 mg/minute. Other drugs which can be tried include **chlormethiazole edisylate**, given by intravenous infusion. Chlormethiazole has a short half-life, and the rate of infusion can be titrated against the patient's clinical condition (see **cautions** on next page).

Paraldehyde also remains a valuable drug. Given rectally (or occasionally by deep intramuscular injection) it causes little respiratory depression and is therefore useful where facilities for resuscitation are poor.

If the above measures fail to control seizures, anaesthesia with **thiopentone** or **a non-barbiturate anaesthetic** should be instituted with full intensive care support.

DIAZEPAM

Indications: status epilepticus; convulsions due to poisoning (see Emergency Treatment of Poisoning); other indications, see sections 4.1.2, 10.2.2, 15.1.4.1

Cautions; Contra-indications; Side-effects: see section 4.1.2; hypotension and apnoea may occur; when given intravenously facilities for reversing respiratory depression with mechanical ventilation must be at hand (but see also notes above); intravenous infusion, see also below

SPECIAL CAUTIONS FOR INTRAVENOUS INFUSION. Intravenous infusion of diazepam is potentially hazardous (especially if prolonged), calling for close and constant observation and best carried out in specialist centres with intensive care facilities. Special cautions required on prolonged intravenous infusion are as for Chlormethiazole, see below

Dose: *by intravenous injection*, 10–20 mg at a rate of 0.5 mL (2.5 mg) per 30 seconds, repeated if necessary after 30–60 minutes; may be followed by *intravenous infusion* to max. 3 mg/kg over 24 hours; CHILD 200–300 micrograms/kg *or* 1 mg per year of age

By rectum as rectal solution, ADULT and CHILD over 3 years 10 mg; CHILD 1–3 years and ELDERLY 5 mg; repeat after 5 minutes if necessary

PoM **Diazepam** (Non-proprietary)

Injection (solution), diazepam 5 mg/mL. See Appendix 6. Net price 2-mL amp = 25p

Available from CP, Roche (Valium®)

Injection (emulsion), diazepam 5 mg/mL (0.5%). See Appendix 6. Net price 2-mL amp = 76p

Available from Dumex (Diazemuls®)

Rectal tubes (= rectal solution), diazepam 2 mg/mL. Net price 2.5-mL (5-mg) tube = £1.27; 4 mg / mL, 2.5-mL (10-mg) tube = £1.62

Available from CP (Diazepam Rectubes®), Dumex (Stesolid®), Lagap

Oral preparations, section 4.1.2

CLONAZEPAM

Indications: status epilepticus; other forms of epilepsy, and myoclonus, section 4.8.1

Cautions; Contra-indications; Side-effects: see section 4.8.1. Hypotension and apnoea may occur and resuscitation facilities must be available; intravenous infusion, see also below

SPECIAL CAUTIONS FOR INTRAVENOUS INFUSION. Intravenous infusion of clonazepam is potentially hazardous (especially if prolonged), calling for close and constant observation and best carried out in specialist centres with intensive care facilities. Special cautions required on prolonged intravenous infusion are as for Chlormethiazole, see below

Dose: *by intravenous injection* into a large vein (over 30 seconds) *or by intravenous infusion*, 1 mg, repeated if necessary; CHILD all ages, 500 micrograms

PoM **Rivotril®** (Roche)

Injection, clonazepam 1 mg/mL in solvent, for dilution with 1 mL water for injections immediately before injection or as described in Appendix 6. Net price 1-mL amp (with 1 mL water for injections) = 71p

Oral preparations, section 4.8.1

CHLORMETHIAZOLE

(Clomethiazole)

Indications: status epilepticus; other indications, see sections 4.1.1, 4.10, 15.1.4.1; eclampsia, see data sheet

Cautions: see section 4.10 for general cautions; resuscitation facilities must be available; maintain clear airway (risk of mechanical obstruction in deep sedation); *rapid infusion* to be given only under direct medical supervision (risk of apnoea and hypotension—special care in those susceptible to cerebral or cardiac complications, e.g. the elderly); during *continuous infusion* sleep induced may lapse into deep unconsciousness and patient must be kept under close and constant observation; *prolonged infusion* may lead to accumulation and delay recovery, may also cause electrolyte imbalance (infusion contains only Na^+ 32 mmol/litre and no other electrolytes); **interactions:** Appendix 1 (anxiolytics and hypnotics)

LENNOX GASTAUT SYNDROME. Paradoxical worsening of epilepsy may occur in the Lennox Gastaut syndrome

Contra-indications: acute pulmonary insufficiency

Side-effects: nasal congestion and irritation (with sneezing), conjunctival irritation, headache; localised thrombophlebitis, tachycardia and transient fall in blood pressure (apnoea and hypotension on rapid infusion, see cautions); see also section 4.10

Dose: *by intravenous infusion*, as a 0.8% solution of chlormethiazole edisylate, initially 5–15 mL (40–120 mg)/minute up to a max. total dose of 40–100 mL (320–800 mg); may then be continued if necessary at a reduced rate according to response (see notes above); usual rate 0.5–1 mL (4–8 mg)/minute

CHILD initially 0.01 mL (80 micrograms)/kg/minute, then dose increased every 2–4 hours if necessary until seizures controlled or drowsiness occurs; if no seizure for 2 days dose gradually reduced every 4–6 hours (if seizures recur dose increased to previous level)

IMPORTANT. See cautions for intravenous infusion under Cautions (above)

PoM **Heminevrin®** (Astra)

Intravenous infusion 0.8%, chlormethiazole edisylate 8 mg/mL. Net price 500-mL bottle = £5.12

Oral preparations, section 4.10

LORAZEPAM

Indications: status epilepticus; other indications, section 4.1.2

Cautions; Contra-indications; Side-effects: see section 4.1.2; hypotension and apnoea may occur and resuscitation facilities must be available

Dose: *by intravenous injection* (into large vein), 4 mg; CHILD 2 mg

Preparations

Section 4.1.2

PARALDEHYDE

Indications: status epilepticus

Cautions: bronchopulmonary disease, hepatic impairment; avoid intramuscular injection near sciatic nerve (causes severe causalgia)

INTRAVENOUS INFUSION. Paraldehyde has been given by intravenous infusion (diluted in physiological saline) in specialist centres with intensive care facilities but this method of administration is no longer recommended

Side-effects: rashes; pain and sterile abscess after intramuscular injection; rectal irritation after enema

Dose: by deep intramuscular injection, as a single dose, 5–10 mL; usual max. 20 mL daily with not more than 5 mL at any one site; CHILD up to 3 months 0.5 mL, 3–6 months 1 mL, 6–12 months 1.5 mL, 1–2 years 2 mL, 3–5 years 3–4 mL, 6–12 years 5–6 mL

By intravenous infusion, formerly given in a dose of up to 4–5 mL diluted to a 4% solution with sodium chloride intravenous infusion 0.9%, but **no longer recommended**

By rectum, 5–10 mL, administered as a 10% enema in physiological saline (some centres mix paraldehyde with an equal volume of arachis (peanut) oil instead); CHILD as for intramuscular dose

Note. Do not use paraldehyde if it has a brownish colour or an odour of acetic acid. Avoid contact with rubber and plastics.

PoM **Paraldehyde** (Non-proprietary)

Injection, sterile paraldehyde 5-mL and 10-mL amp

Note. May temporarily be unavailable

PHENYTOIN SODIUM

Indications: status epilepticus; seizures in neurosurgery; arrhythmias, see section 2.3.2

Cautions: hypotension and heart failure; resuscitation facilities must be available; injection solutions alkaline (irritant to tissues); see also section 4.8.1; **interactions:** see p. 203 and Appendix 1 (phenytoin)

Contra-indications: sinus bradycardia, sino-atrial block, and second- and third-degree heart block; Stokes-Adams syndrome; porphyria (see section 9.8.2)

Side-effects: intravenous injection may cause cardiovascular and CNS depression (particularly if injection too rapid) with arrhythmias, hypotension, and cardiovascular collapse; alterations in respiratory function (including respiratory arrest)

Dose: by slow intravenous injection or infusion (with blood pressure and ECG monitoring), status epilepticus, 15 mg/kg at a rate not exceeding 50 mg per minute, as a loading dose (see also notes above). Maintenance doses of about 100 mg should be given thereafter at intervals of every 6–8 hours as the injection—not exceeding 50 mg/minute, for further details of the infusion, see Appendix 6). To avoid local venous irritation each injection or infusion should be both preceded and followed by an injection of sterile physiological saline through the same needle or or catheter

By intramuscular injection, not recommended (see notes above)

PoM **Epanutin Ready Mixed Parenteral®** (P-D)

Injection, phenytoin sodium 50 mg/mL with propylene glycol 40% and alcohol 10% in water for injections. Net price 5-mL amp = £4.07

Note. Phenytoin injection also available from Antigen, David Bull

Oral preparations, section 4.8.1

4.8.3 Febrile convulsions

Brief febrile convulsions need only simple treatment such as tepid sponging or bathing, or antipyretic medication, e.g. **paracetamol** (section 4.7.1). *Prolonged febrile convulsions* (those lasting 15 minutes or longer), *recurrent convulsions*, or those occurring in a child at known risk must be treated more actively, as there is the possibility of resulting brain damage. **Diazepam** is the drug of choice given either by slow intravenous injection in a dose of 250 micrograms/kg (section 4.8.2) or preferably rectally in solution (section 4.8.2) in a dose of 500 micrograms/kg (max. 10 mg), repeated if necessary (for full details of dose, see p. 212). The rectal route is preferred as satisfactory absorption is achieved within minutes and administration is much easier. Suppositories are not suitable because absorption is too slow.

Intermittent prophylaxis (i.e. the anticonvulsant administered at the onset of fever) is possible in only a small proportion of children. Again **diazepam** is the treatment of choice, orally or rectally.

The exact role of continuous prophylaxis in children at risk from prolonged or complex febrile convulsions is controversial. It is probably indicated in only a small proportion of children, including those whose first seizure occurred at under 14 months or who have pre-existing neurological abnormalities or who have had previous prolonged or focal convulsions. Thus long-term anticonvulsant prophylaxis is rarely indicated.

4.9 Drugs used in parkinsonism and related disorders

In idiopathic Parkinson's disease, progressive degeneration of pigment-containing cells of the

tion' cephalosporin cefuroxime, has the same antibacterial spectrum as the parent compound.

Cefixime has a longer duration of action than the other cephalosporins that are active by mouth. It is presently only licensed for acute infections. **Ceftibuten** is similar to cefixime but is less active against pneumococci.

Cefpodoxime proxetil, is more active than the other oral cephalosporins against respiratory bacterial pathogens and it is licensed for upper and lower respiratory-tract infections.

CEFACLOR

Indications: infections due to sensitive Gram-positive and Gram-negative bacteria, but see notes above

Cautions: penicillin sensitivity; renal impairment (see Appendix 3); pregnancy and breast-feeding (but appropriate to use); false positive urinary glucose (if tested for reducing substances) and false positive Coombs' test; **interactions:** Appendix 1 (cephalosporins)

Contra-indications: cephalosporin hypersensitivity; porphyria (see section 9.8.2)

Side-effects: diarrhoea and rarely pseudomembranous colitis (CSM has warned both more likely with higher doses), nausea and vomiting, abdominal discomfort, headache; allergic reactions including rashes, pruritus, urticaria, serum sickness-like reactions with rashes, fever and arthralgia, and anaphylaxis; erythema multiforme, toxic epidermal necrolysis reported; disturbances in liver enzymes, transient hepatitis and cholestatic jaundice; other side-effects reported include eosinophilia and blood disorders (including thrombocytopenia, leucopenia, agranulocytosis and aplastic anaemia); reversible interstitial nephritis, hyperactivity, nervousness, sleep disturbances, confusion, hypertonia, and dizziness

Dose: 250 mg every 8 hours, doubled for severe infections; max. 4 g daily; CHILD over 1 month, 20 mg/kg daily in 3 divided doses, doubled for severe infections, max. 1 g daily; *or* 1 month–1 year, 62.5 mg every 8 hours; 1–5 years, 125 mg; over 5 years, 250 mg; doses doubled for severe infections

PoM **Cefaclor** (Non-proprietary)

Capsules, cefaclor (as monohydrate) 250 mg, net price 21-cap pack = £9.60; 500 mg 21-cap pack = £22.74. Label: 9

Available from Hillcross, Kent

PoM **Distaclor®** (Dista)

Capsules, cefaclor (as monohydrate) 500 mg (violet/grey), net price 20 = £21.66. Label: 9

Suspension, both pink, cefaclor (as monohydrate) for reconstitution with water, 125 mg/5 mL, net price 100 mL = £5.16; 250 mg/5 mL, 100 mL = £10.32. Label: 9

PoM **Distaclor MR®** (Dista)

Tablets, m/r, both blue, cefaclor (as monohydrate) 375 mg, net price 14-tab pack = £6.93; 500 mg, 7-tab pack = £5.95. Label: 9, 21, 25

Dose: 375 mg every 12 hours with food, dose doubled for pneumonia

Lower urinary-tract infections, 375 mg every 12 hours with food *or* 500 mg at night

CEFADROXIL

Indications: see under Cefaclor; see also notes above

Cautions; Contra-indications; Side-effects: see under Cefaclor

Dose: patients over 40 kg, 0.5–1 g twice daily; skin, soft tissue, and simple urinary-tract infections, 1 g daily; CHILD under 1 year, 25 mg/kg daily in divided doses; 1–6 years, 250 mg twice daily; over 6 years, 500 mg twice daily

PoM **Baxan®** (Bristol-Myers)

Capsules, cefadroxil 500 mg (as monohydrate). Net price 20 = £5.64. Label: 9

Suspension, cefadroxil (as monohydrate) for reconstitution with water, 125 mg/5 mL, net price 60 mL = £1.75; 250 mg/5 mL, 60 mL = £3.48; 500 mg/5 mL, 60 mL = £5.21. Label: 9

CEFIXIME

Indications: see under Cefaclor and notes above

Cautions; Contra-indications; Side-effects: see under Cefaclor

Dose: ADULT and CHILD over 10 years, 200–400 mg daily as a single dose or in 2 divided doses; CHILD over 6 months 8 mg/kg daily as a single dose or in 2 divided doses *or* 6 months–1 year 75 mg daily; 1–4 years 100 mg daily; 5–10 years 200 mg daily

PoM **Suprax®** (Rhône-Poulenc Rorer)

Tablets, f/c, scored, cefixime 200 mg. Net price 20 = £27.39. Label: 9

Paediatric oral suspension, cefixime 100 mg/5 mL when reconstituted with water. Net price 37.5 mL (with double-ended spoon for measuring 3.75 mL or 5 mL since dilution not recommended) = £6.53; 75 mL = £11.72. Label: 9

CEFODIZIME

Indications: see under Dose

Cautions; Contra-indications; Side-effects: see under Cefaclor

Dose: by intramuscular or intravenous injection or by intravenous infusion, lower respiratory-tract infection (including pneumonia and bronchopneumonia), 1 g every 12 hours

Upper and lower urinary-tract infections (including acute and chronic pyelonephritis and cystitis), 1 g every 12 hours *or* 2 g daily (as a single dose); single doses over 1 g intravenous route only

PoM **Timecef®** (Roussel)

Injection, powder for reconstitution, cefodizime (as sodium salt), net price 1-g vial = £11.04

Electrolytes: Na^+ 3.18 mmol/g

CEFOTAXIME

Indications: see under Cefaclor; surgical prophylaxis; Haemophilus epiglottitis and meningitis (see section 5.1 table 1); see also notes above

Cautions; Contra-indications; Side-effects: see under Cefaclor

Dose: *by intramuscular or intravenous injection or by intravenous infusion*, moderate to serious infection, 1 g every 8 hours; life-threatening infection, 2 g every 8 hours; exceptionally, for life-threatening infections due to organisms less sensitive to cefotaxime, up to 12 g daily; NEONATE, 50 mg/kg daily in 2–4 divided doses increased to 150–200 mg/kg daily in severe infections; CHILD, 100–150 mg/kg daily in 2–4 divided doses; increased up to 200 mg/kg daily in severe infections

Urinary-tract and mild to moderate infections, 1 g every 12 hours

Gonorrhoea, 1 g as a single dose

PoM **Claforan®** (Roussel)

Injection, powder for reconstitution, cefotaxime (as sodium salt). Net price 500-mg vial = £2.41; 1-g vial = £4.85; 2-g vial = £9.65

Electrolytes: Na^+ 2.09 mmol/g

CEFOXITIN

Indications: see under Cefaclor; surgical prophylaxis; more active against Gram-negative bacteria

Cautions; Contra-indications; Side-effects: see under Cefaclor

Dose: *by deep intramuscular or by slow intravenous injection or by infusion*, 1–2 g every 6–8 hours, increased up to 12 g daily in divided doses for infections requiring higher doses; CHILD up to 1 week 20–40 mg/kg every 12 hours, 1–4 weeks 20–40 mg/kg every 8 hours, over 1 month 20–40 mg/kg every 6–8 hours, increased up to 200 mg/kg daily in divided doses (max. 12 g daily) in severe infections; intravenous route recommended for children

Uncomplicated urinary-tract infection, *by deep intramuscular injection*, 1 g every 12 hours for 10 days

Uncomplicated gonorrhoea, *by deep intramuscular injection*, 2 g as a single dose with probenecid 1 g by mouth

Surgical prophylaxis, *by deep intramuscular injection or by intravenous injection or infusion*, 2 g 30–60 minutes before surgery, dose repeated every 6 hours for usual max. 24 hours; CHILD 30–40 mg/kg 30–60 minutes before surgery, dose repeated every 6 hours for usual max. 24 hours (second and third doses every 8–12 hours in NEONATES); intravenous route recommended for children

PoM **Mefoxin®** (MSD)

Injection, powder for reconstitution, cefoxitin (as sodium salt). Net price 1-g vial = £4.92; 2-g vial = £9.84

Electrolytes: Na^+ 2.3 mmol/g

CEFPIROME

Indications: see under Cefaclor and notes above

Cautions; Contra-indications; Side-effects: see under Cefaclor; interference with creatinine assays using picrate method; taste disturbance shortly after injection reported

Dose: *by intravenous injection or infusion*, complicated upper and lower urinary-tract, skin and soft-tissue infections, 1 g every 12 hours increased to 2 g every 12 hours in very severe infections

Lower respiratory-tract infections, 1–2 g every 12 hours

Severe infections including bacteraemia and septicaemia and infections in neutropenic patients, 2 g every 12 hours

CHILD under 12 years not recommended

▼ PoM **Cefrom®** (Roussel)

Injection, powder for reconstitution, cefpirome (as sulphate), net price 1-g vial = £10.75; 2-g vial = £21.50

CEFPODOXIME

Indications: respiratory-tract infections but in pharyngitis and tonsillitis reserved for infections which are recurrent, chronic, or resistant to other antibiotics

Cautions; Contra-indications; Side-effects: see under Cefaclor

Dose: upper respiratory-tract infections, 100 mg twice daily with food (200 mg twice daily in sinusitis)

Lower respiratory-tract infections (including bronchitis and pneumonia), 100–200 mg twice daily with food

CHILD under 15 days not recommended, 15 days–6 months 8 mg/kg daily in 2 divided doses, 6 months–2 years 40 mg twice daily, 3–8 years 80 mg twice daily, over 9 years 100 mg twice daily

PoM **Orelox®** (Roussel)

Tablets, f/c, cefpodoxime 100 mg (as cefpodoxime proxetil). Net price 10-tab pack = £9.26. Label: 5, 9, 21

Oral suspension, cefpodoxime (as proxetil) for reconstitution with water, 40 mg/5 mL, net price 50 mL = £6.50, 100 mL = £10.89. Label: 5, 9, 21

Note. Suspension contains aspartame (see section 9.4.1)

CEFTAZIDIME

Indications: see under Cefaclor; see also notes above

Cautions; Contra-indications; Side-effects: see under Cefaclor

Dose: *by deep intramuscular injection or intravenous injection or infusion*, 1 g every 8 hours *or* 2 g every 12 hours; 2 g every 8–12 hours in severe infections; single doses over 1 g intravenous route only; elderly usual max. 3 g daily; CHILD, up to 2 months 25–60 mg/kg daily in 2 divided doses, over 2 months 30–100 mg/kg daily in 2–3 divided doses; up to 150 mg/kg daily (max. 6 g daily) in 3 divided doses if immunocompromised or meningitis; intravenous route recommended for children

Urinary-tract and less serious infections, 0.5–1 g every 12 hours

5.3 Antiviral drugs

The specific therapy of virus infections is generally unsatisfactory and treatment is, therefore, primarily symptomatic. Fortunately, the majority of infections resolve spontaneously. For **interferon** preparations used in hepatitis B and C infections, see section 8.2.4.

HERPES SIMPLEX AND VARICELLA–ZOSTER

Aciclovir is active against herpes viruses but does not eradicate them. It is effective only if started at the onset of infection. Uses of aciclovir include the systemic treatment of varicella–zoster (chickenpox–shingles) and the systemic and topical treatment of herpes simplex infections of the skin and mucous membranes (including initial and recurrent genital herpes); it is also used topically in the eye. It can be life-saving in herpes simplex and varicella–zoster infections in the immunocompromised, and is also used in the immunocompromised for prevention of recurrence and prophylaxis. Aciclovir may also be given by mouth to immunocompetent adults and older adolescents with chickenpox; it is not generally indicated for immunocompetent children in whom the disease is milder. See also section 11.3.3 (eye) and section 13.10.3 (skin, including herpes labialis).

Famciclovir, a prodrug of penciclovir, is similar to aciclovir and it is recommended for herpes zoster and genital herpes; unlike aciclovir it only needs to be given 3 times daily (or as a single daily dose in herpes zoster). Penciclovir itself is used as a cream for herpes simplex labialis (see section 13.10.3).

Valaciclovir is an ester of aciclovir which is licensed for herpes zoster and for herpes simplex infections of the skin and mucous membranes (including initial and recurrent genital herpes).

Idoxuridine is also only effective if started at the onset of infection; it is too toxic for systemic use. It has been used topically in the treatment of herpes simplex lesions of the skin and external genitalia with variable results; it has also been used topically in the treatment of zoster, but evidence of its value is dubious. See also section 13.10.3 (skin, including herpes labialis).

Inosine pranobex has been used by mouth for herpes simplex infections; its effectiveness has not been established.

Amantadine has been used by mouth for herpes zoster but, again, its effectiveness has not been established. Amantadine may be used for prophylaxis during an outbreak of influenza A in:

- unimmunised patients in 'at risk' groups (see under Influenza vaccine, section 14.4), for 2 weeks while the vaccine takes effect
- patients in 'at risk' groups for whom immunisation is contra-indicated, for the duration of the outbreak
- health care workers and other key personnel (to prevent disruption of service), during an epidemic.

ACICLOVIR

(Acyclovir)

Indications: herpes simplex and varicella–zoster (see also under Dose)

Cautions: maintain adequate hydration; renal impairment (see Appendix 3); pregnancy and breast-feeding; **interactions:** Appendix 1 (aciclovir and famciclovir)

Side-effects: rashes; gastro-intestinal disturbances; rises in bilirubin and liver enzymes, increases in blood urea and creatinine, decreases in haematological indices, headache, neurological reactions (including dizziness), fatigue; on intravenous infusion, severe local inflammation (sometimes leading to ulceration), also confusion, hallucinations, agitation, tremors, somnolence, psychosis, convulsions and coma

Dose: by mouth,

Herpes simplex, treatment, 200 mg (400 mg in the immunocompromised or if absorption impaired) 5 times daily, usually for 5 days; CHILD under 2 years, half adult dose, over 2 years, adult dose

Herpes simplex, prevention of recurrence, 200 mg 4 times daily *or* 400 mg twice daily possibly reduced to 200 mg 2 or 3 times daily and interrupted every 6–12 months

Herpes simplex, prophylaxis in the immunocompromised, 200–400 mg 4 times daily; CHILD under 2 years, half adult dose, over 2 years, adult dose

Varicella and herpes zoster, treatment, 800 mg 5 times daily for 7 days; CHILD, varicella, 20 mg/kg (max. 800 mg) 4 times daily for 5 days *or* under 2 years 200 mg 4 times daily, 2–5 years 400 mg 4 times daily, over 6 years 800 mg 4 times daily

By intravenous infusion over 1 hour, herpes simplex or recurrent varicella–zoster 5 mg/kg every 8 hours; doubled in primary and recurrent varicella–zoster in the immunocompromised, and in simplex encephalitis (for which it should be continued for at least 10 days); CHILD up to 3 months 10 mg/kg every 8 hours; 3 months–12 years, 250 mg/m^2 every 8 hours, dose doubled in the immunocompromised and in simplex encephalitis (for which it should be continued for at least 10 days)

By topical application, herpes simplex (*cream* or *eye ointment* as appropriate) every 4 hours (5 times daily), see sections 13.10.3 and 11.3.3

Note. Cream should not be used on mucous membranes

PoM **Aciclovir** (Non-proprietary)

Tablets, aciclovir 200 mg, net price 25-tab pack = £28.80; 400 mg, 56-tab pack = £105.90; 800 mg, 35-tab pack £107.25. Label:9

Available from CP

Dispersible tablets, aciclovir 200 mg, net price 25-tab pack = £28.89; 400 mg, 56-tab pack = £105.95; 800 mg, 35-tab pack = £107.30. Label: 9

Available from Cox, Hillcross, Norton

PoM **Zovirax®** (Wellcome)

Tablets, all dispersible, aciclovir 200 mg (blue), net price 25-tab pack = £28.89; 400 mg (pink), 56-tab pack = £105.95; 800 mg (scored, *Shingles Treatment Pack*), 35-tab pack = £107.30. Label: 9

Suspension, both off-white, sugar-free, aciclovir 200 mg/5 mL, net price 125 mL = £28.89; 400 mg/5 mL (*Chickenpox Treatment*) 50 mL = £16.14. Label: 9

Intravenous infusion, powder for reconstitution, aciclovir (as sodium salt). Net price 250-mg vial = £10.91; 500-mg vial = £20.22
Electrolytes: Na^+ 1.1 mmol/250-mg vial
Cream, see section 13.10.3
Eye ointment, see section 11.3.3

AMANTADINE HYDROCHLORIDE

Indications: see under Dose and notes above; parkinsonism, see section 4.9.1
Cautions; Contra-indications; Side-effects: see section 4.9.1
Dose: herpes zoster, 100 mg twice daily for 14 days, if necessary extended for a further 14 days for post-herpetic neuralgia
Influenza A_2, ADULT and CHILD over 10 years, treatment, 100 mg daily for 4–5 days; prophylaxis, 100 mg daily usually for 6 weeks *or* with influenza vaccination for 2–3 weeks after vaccination
ELDERLY over 65 years, less than 100 mg daily *or* 100 mg at intervals of more than 1 day

Preparations

See section 4.9.1

FAMCICLOVIR

Indications: treatment of herpes zoster and genital herpes simplex
Cautions: renal impairment; pregnancy and breast-feeding; **interactions:** Appendix 1 (aciclovir and famciclovir)
Side-effects: nausea; headache
Dose: herpes zoster, 250 mg 3 times daily for 7 days *or* 750 mg once daily for 7 days
Genital herpes, first episode, 250 mg 3 times daily for 5 days; recurrent infection, 125 mg twice daily for 5 days
CHILD not recommended

▼ PoM **Famvir®** (SmithKline Beecham)
Tablets, both f/c, famciclovir 125 mg, net price 10-tab pack = £25.56; 250 mg, 15-tab pack = £76.68, 21-tab pack = £107.35. Label: 9

IDOXURIDINE

See section 13.10.3 (skin including herpes labialis)

INOSINE PRANOBEX

Indications: see under Dose
Cautions: avoid in renal impairment; history of gout or hyperuricaemia
Side-effects: reversible increases in serum and urinary uric acid
Dose: mucocutaneous herpes simplex, 1 g 4 times daily for 7–14 days
Adjunctive treatment of genital warts, 1 g 3 times daily for 14–28 days

PoM **Imunovir®** (Nycomed)
Tablets, inosine pranobex 500 mg. Net price 100 = £39.50. Label: 9

VALACICLOVIR

Note. Valaciclovir is a pro-drug of aciclovir
Indications: treatment of herpes zoster and of herpes simplex infections of skin and mucous membranes including initial and recurrent genital herpes
Cautions: maintain adequate hydration; renal impairment (see Appendix 3); pregnancy and breast-feeding; **interactions:** Appendix 1 (aciclovir and famciclovir)
Side-effects: as a pro-drug of aciclovir it is anticipated that side-effects will be comparable; nausea and headache reported
Dose: herpes zoster, 1 g 3 times daily for 7 days
Herpes simplex, first episode, 500 mg twice daily for 5 days (up to 10 days if severe); recurrent infection, 500 mg twice daily for 5 days
CHILD not recommended

▼ PoM **Valtrex®** (Wellcome)
Tablets, valaciclovir (as hydrochloride) 500 mg. Net price 10-tab (*HS Treatment*) pack = £23.50, 42-tab (*Shingles Treatment*) pack = £98.50. Label: 9

HUMAN IMMUNODEFICIENCY VIRUS

Zidovudine inhibits the human immunodeficiency virus (HIV) but does not eradicate it from the body; it is not therefore a cure for AIDS but may delay progression of the disease. It is now also being recommended for asymptomatic HIV antibody positive individuals. Zidovudine is toxic and expensive and should only be prescribed by those experienced in its use.

Didanosine is indicated for the treatment of symptomatic HIV infection in adult patients who are intolerant of zidovudine *or* who have shown significant clinical or immunological deterioration during zidovudine therapy *or* when zidovudine is inappropriate. **Zalcitabine** is a recently introduced anti-HIV drug with similar indications.

A combination of zidovudine with either didanosine or zalcitabine is more effective than zidovudine alone and can delay the emergence of HIV strains resistant to zidovudine.

ZIDOVUDINE

(Azidothymidine, AZT)
Note. The abbreviation AZT which has sometimes been used for zidovudine has also been used for another drug
Indications: management of advanced human immunodeficiency virus (HIV) disease such as acquired immunodeficiency syndrome (AIDS) or AIDS-related complex; early symptomatic or asymptomatic HIV infection with markers indicating risk of disease progression; symptomatic or asymptomatic HIV-infected children with markers indicating significant immune suppression; consider for prevention of maternal-fetal HIV transmission (by treating pregnant women and their newborn infants)
Cautions: haematological toxicity (blood tests at least every 2 weeks for first 3 months then at least once a month, early disease with good bone mar-

15.1.4.1 ANXIOLYTICS AND NEUROLEPTICS

Anxiolytic benzodiazepines are widely used whereas neuroleptics (e.g. chlorpromazine) are now rarely used.

BENZODIAZEPINES

Oral premedication with benzodiazepines is increasing in popularity, a short-acting oral benzodiazepine now being the most common premedicant.

Benzodiazepines are also of particular value for the production of light sedation during unpleasant procedures or during operations under local anaesthesia (including dentistry). The resultant amnesia is such that the patient is unlikely to have any unpleasant memories of the procedure (however, benzodiazepines, particularly when used for deep sedation, can sometimes induce sexual fantasies).

Diazepam is relatively insoluble in water and preparations formulated in organic solvents are painful on intravenous injection and followed by a high incidence of venous thrombosis (which may not be noticed until a week after the injection); they are also painful on intramuscular injection, and absorption from the injection site is erratic. An emulsion preparation for intravenous injection is less irritant and is followed by a negligible incidence of venous thrombosis; it is not suitable for intramuscular injection. Diazepam is also available as a rectal solution.

Benzodiazepines are also of particular value for sedation of patients in intensive care units, particularly those having assisted ventilation. Since they have no analgesic action they are often given in conjunction with opioid analgesics.

Benzodiazepines may on occasion cause marked respiratory depression and facilities for treatment of this are essential.

Diazepam is used to produce light sedation with amnesia. The 'sleep' dose shows too great an individual variation to recommend it for induction of anaesthesia. It is a long-acting drug with active metabolites, and a second period of drowsiness can occur 4–6 hours after its administration.

Temazepam is given by mouth and has a shorter action and a relatively more rapid onset than diazepam by mouth. Used as a premedicant, anxiolytic and sedative effects are produced which continue for one and a half hours. After this period patients are usually fully alert but there may be residual drowsiness. It has proved useful as a premedicant in inpatient and day-case surgery.

Lorazepam produces more prolonged sedation than temazepam. In addition amnesia is commonplace. It is used as a premedicant the night before major surgery. A further, smaller, dose may be required the following morning if any delay in starting surgery is anticipated. Alternatively the first dose may be given in the early morning of the day of operation.

Midazolam is a water-soluble benzodiazepine which is often used in preference to diazepam. Recovery is faster than with diazepam. The incidence of side-effects is low but the CSM has received reports of respiratory depression (sometimes associated with severe hypotension) following intravenous administration. It is also associated with some major interactions (see below).

DIAZEPAM

Indications: premedication; sedation with amnesia, and in conjunction with local anaesthesia; other indications, see sections 4.1.2, 4.8.2, 10.2.2

Cautions; Contra-indications; Side-effects: see notes above and sections 4.1.2, 4.8.2

Dose: *by mouth*, 5 mg at night, 5 mg on waking, and 5 mg 2 hours before minor or dental surgery

By intravenous injection, into a large vein 10–20 mg over 2–4 minutes as sedative cover for minor surgical and medical procedures; premedication 100–200 micrograms/kg

By rectum in solution, ADULT and CHILD over 3 years 10 mg; CHILD 1–3 years and ELDERLY 5 mg

Preparations

See section 4.1.2

LORAZEPAM

Indications: sedation with amnesia; as pre-medication; other indications, see sections 4.1.2, 4.8.2

Cautions; Contra-indications; Side-effects: see under Diazepam

Dose: *by mouth*, 2–3 mg the night before operation; 2–4 mg 1–2 hours before operation

By slow intravenous injection, preferably diluted with an equal volume of sodium chloride intravenous infusion 0.9% or water for injections, 50 micrograms/kg 30–45 minutes before operation

By intramuscular injection, diluted as above, 50 micrograms/kg 1–1½ hours before operation

PoM **Ativan®** (Wyeth)

Injection, lorazepam 4 mg/mL. Net price 1-mL amp = 40p

Tablets, see section 4.1.2

MIDAZOLAM

Indications: sedation with amnesia, and in conjunction with local anaesthesia; premedication, induction

Cautions; Contra-indications; Side-effects: see under Diazepam; see notes above for CSM warning; **important:** profound sedation with erythromycin and possibly other drugs, see **interactions:** Appendix 1 (anxiolytics and hypnotics)

Dose: sedation, *by intravenous injection* over 30 seconds, 2 mg (elderly 1–1.5 mg) followed after 2 minutes by increments of 0.5–1 mg if sedation not adequate; usual range 2.5–7.5 mg (about 70 micrograms/kg), elderly 1–2 mg

Premedication, *by intramuscular injection*, 70–100 micrograms/kg 30–60 minutes before surgery; usual dose 5 mg (2.5 mg in elderly)

Induction, *by slow intravenous injection*, 200–300 micrograms/kg (elderly 100–200 micrograms/kg); CHILD over 7 years, 150 micrograms/kg

Sedation of patients receiving intensive care, *by intravenous infusion*, initially 30–300 micrograms/kg given over 5 minutes, then 30–200 micrograms/kg/hour; reduce dose (or omit initial dose) in hypovolaemia, vasoconstriction, or hypothermia; low doses may be adequate if opioid analgesic also used; avoid abrupt withdrawal after prolonged administration (safety after more than 14 days not established)

PoM **Hypnovel®** (Roche)

Injection, midazolam (as hydrochloride) 2 mg/mL, net price 5-mL amp = £1.01; 5 mg/mL, 2-mL amp = 85p

TEMAZEPAM

Indications: premedication before minor surgery; anxiety before investigatory procedures; hypnotic, see section 4.1.1

Cautions; Contra-indications; Side-effects: see under Diazepam

Dose: *by mouth*, premedication, 20–40 mg (elderly, 10–20 mg) 1 hour before operation; CHILD 1 mg/kg (max. 30 mg)

Preparations

See section 4.1.1

CHLORMETHIAZOLE

Chlormethiazole is licensed for use as an intravenous infusion to maintain sleep during surgery carried out under regional anaesthesia, but is no longer in current use for this purpose.

CHLORMETHIAZOLE

(Clomethiazole)

Indications: sedative during regional anaesthesia (but see also notes above); other indications, see sections 4.1.1, 4.8.2, 4.10

Cautions; Contra-indications; Side-effects: see section 4.10

Dose: *by intravenous infusion*, as a 0.8% solution of chlormethiazole edisylate, induction 25 mL (200 mg)/minute for 1–2 minutes; maintenance 1–4 mL (8–32 mg)/minute

IMPORTANT. See special cautions for intravenous infusion, section 4.10

Preparations

See section 4.10

PHENOTHIAZINES AND RELATED

Neuroleptics such as **chlorpromazine** and **droperidol** are rarely used in the UK for premedication; although chlorpromazine is licensed to prevent shivering in induction of hypothermia, it is no longer in current use for this purpose. **Trimeprazine** is used as a premedicant for children.

CHLORPROMAZINE HYDROCHLORIDE

Indications: see under Dose (but see also notes above), other indications, see section 4.2.1

Cautions; Contra-indications; Side-effects: see section 4.2.1

Dose: induction of hypothermia (to prevent shivering), *by deep intramuscular injection*, 25–50 mg every 6–8 hours; CHILD 1–12 years, initially 0.5–1 mg/kg, followed by maintenance 500 micrograms/kg every 4–6 hours

Preparations

See section 4.2.1

DROPERIDOL

Indications: anti-emetic, pre-operative sedation; other indications, see section 4.2.1

Cautions; Contra-indications; Side-effects: see section 4.2.1

Dose: premedication, *by intramuscular injection*, up to 10 mg 60 minutes before operation; CHILD 200–500 micrograms/kg

Neuroleptanalgesia, *by intravenous injection*, 5–15 mg at induction with an opioid analgesic; CHILD 200–300 micrograms/kg

PoM **Droleptan®** (Janssen)

Injection, droperidol 5 mg/mL. Net price 2-mL amp = 90p

PROMETHAZINE HYDROCHLORIDE

Indications: pre-operative sedative and antimuscarinic; anti-emetic, see section 4.6; other indications, see sections 3.4.1, 3.4.3

Cautions; Contra-indications; Side-effects: see section 4.6

Dose: premedication, *by mouth*, CHILD under 2 years not recommended, 2–5 years 15–20 mg, 5–10 years 20–25 mg

By deep intramuscular injection, 25–50 mg 1 hour before operation; CHILD 5–10 years, 6.25–12.5 mg

Preparations

See sections 3.4.1 and 15.1.4.3 (with pethidine)

TRIMEPRAZINE TARTRATE

(Alimemazine Tartrate)

Indications: pre-operative sedation, anti-emetic; other indications, see section 3.4.1

Cautions; Contra-indications; Side-effects: see notes above and section 3.4.1

Dose: *by mouth*, premedication, CHILD 2–7 years up to 2 mg/kg 1–2 hours before operation

Preparations

See section 3.4.1