PCF5

PALLIATIVE CARE FORMULARY

Published by palliativedrugs.com Ltd.

Palliativedrugs.com Ltd
Hayward House Study Centre
Nottingham University Hospitals NHS Trust, City Campus
Nottingham NG5 1PB
United Kingdom

www.palliativedrugs.com

PCF4+ ePDF 2013
PCF4+ ePDF 2012
PCF4 2011, reprinted 2012 (twice), 2013
PCF3 2007, reprinted 2008, 2009
PCF2 2002, reprinted 2003
PCF1 1998

British Library Cataloguing in Publication Data

A catalogue record for this book is available from the British Library.

ISBN 978-0-9552547-9-6

Typeset by OKS Prepress Services Private Ltd, Chennai, India
Printed by Halstan Printing Group, Amersham, UK

DISCLAIMER

Every effort has been made to ensure the accuracy of this text, and that the best information available has been used. However, palliativedrugs.com Ltd neither represents nor guarantees that the practices described herein will, if followed, ensure safe and effective patient care. The recommendations contained in this book reflect the editors' judgement regarding the state of general knowledge and practice in the field as of the date of publication. Information in a book of this type can never be all-inclusive, and therefore will not cover every eventuality.

Thus, those who use this book must make their own determinations regarding specific safe and appropriate patient-care practices, taking into account the personnel, equipment, and practices available at the hospital or other facility at which they are located. Neither palliativedrugs.com Ltd nor the editors can be held responsible for any liability incurred as a consequence of the use or application of any of the contents of this book. Mention of specific product brands does not imply endorsement.

Particularly when prescribing a drug for the first time, a doctor (or other independent prescriber) should study the contents of the manufacturer's Summary of Product Characteristics (SPC), paying particular attention to indications, contra-indications, cautions, drug interactions, and undesirable effects.

EDITORIAL STAFF

CONTENTS

PREFACE

Welcome to the latest edition of the *Palliative Care Formulary* (*PCF*), written primarily for the UK. Regional adaptations include German and Japanese editions (see *www.palliativedrugs.com* for details).

The target audience comprises doctors, nurses and pharmacists involved in the care of patients receiving palliative/hospice care. *PCF* is a core textbook for medical registrars in Palliative Medicine in the UK. It is used in some areas to fulfil the NHS National Cancer Standards requirement for specialist palliative care services within a Cancer Centre and Network to have a core palliative care drug formulary and is referred to in many official healthcare documents, e.g. NICE CKS guidelines.

Although written primarily with cancer patients in mind, *PCF* contains specific material relating to a number of other life-limiting diseases, e.g. COPD, congestive heart failure, renal failure, and Parkinson's disease. *PCF* also includes a number of *Quick Clinical Guides* and *Quick Prescribing Guides* (listed inside the back cover and in the Supplementary topic index). To enhance user-friendliness, each *Guide* is limited to no more than two pages, and references are not normally included. We welcome feedback on these. We also encourage the donation of clinical guidance from other sources for posting on our website (e-mail copies to hq@palliativedrugs.com).

The production of a book of this nature depends partly on the help and advice of numerous colleagues, both past and present. We acknowledge with gratitude the support of clinical colleagues, and members of the palliativedrugs.com community who have provided feedback, particularly via surveys or by contributing to the *Syringe Driver Survey Database*.

We acknowledge with thanks the advice provided by various correspondents, including: Victoria Barnett, Claudia Bausewein, James Beattie, Christopher Blick, Ronald Elin, Bethany Foster, Philippa Hawley, Sue Hollingsworth, Aleksandra Kotlinska–Lemieszek, Louise Lynch, Mary Mihalyo, Eva Murphy, Renee Page, Russell Portenoy, Constanze Remi, Jan Rémi, John Shuster, Nigel Sykes, and by Medical Information Departments in the pharmaceutical industry.

We are grateful to Sarah Keeling for co-ordinating production, John Shaw for assistance in copy-editing, and to Karen Isaac for secretarial support.

Robert Twycross
Andrew Wilcock
Paul Howard
Editors-in-chief
July 2014

SUMMARY OF MAIN CHANGES IN PCF5

Since the publication of *PCF4* in 2011, every drug monograph has been reviewed and updated. With the anticipated demise of *Symptom Management in Advanced Cancer*, several items have been transferred into the *Formulary*:

- *Chapter 2 in Haemostatics*: a section about Haematuria, including a Table of bladder instillations and irrigations for haemorrhagic cystitis
- *Chapter 10 in Skeletal muscle relaxants*: a list of drugs which can cause cramps, and a Box detailing the use of anti-epileptics for treating cramp
- *Chapter 11 in Drugs for oral inflammation and ulceration*: a list of drugs which can cause oral ulceration.

New Chapters

25 Variability in response to drugs (replaces Cytochrome P450)
28 Drugs for pruritus

Deleted monographs

Dextropropoxyphene has been withdrawn in the UK, Europe, the USA, and other countries because of its relatively common use in intentional overdose and its potential fatal toxicity in accidental overdose. Accordingly, the monograph in earlier editions of PCF is now redundant, and has been removed.

Other monographs have been subsumed into generic drug class monographs, e.g.:

- Dalteparin and Enoxaparin (→ LMWH)
- Flecainide (→ Systemic local anaesthetics)
- Methylphenidate and Modafinil (→ Psychostimulants)
- Naloxone and Naltrexone (→ Opioid antagonists)

Monographs

Either new or amalgamations:

- Anticoagulants
- Low molecular weight heparin (LMWH)
- Haemostatics
- Gabapentin and pregabalin
- Psychostimulants
- Cannabinoids
- Opioid antagonists
- Bisphosphonates

Quick Practice Guides

These have been renamed as either *Quick Clinical Guides* (e.g. Heparin-Induced Thrombocytopenia) or *Quick Prescribing Guides* (e.g. Depression, Opioid-induced constipation). For full list, see inside the back cover.

HOW PCF IS CONSTRUCTED

There is continual review and updating of the contents of *PCF* over a three year cycle. These updates are published regularly on-line, with the whole book published in print every three years.

The *Palliative Care Formulary* (*PCF*) is a unique independent professional publication which provides essential information for prescribers and health professionals involved in palliative and hospice care. *PCF* contains authoritative independent guidance on best practice, and helps to ensure that drugs are used appropriately, safely, and optimally.

Recommended International Non-proprietary Names (rINN) are used for drugs. The order of drug monographs broadly follows that of the *British National Formulary* (*BNF*).

Editorial team

The *PCF* editorial team is co-ordinated by three medically qualified Editors-in-chief who are (or have been) accredited specialists in Palliative Medicine and a specialist palliative care pharmacist. For each print edition, every section of *PCF* is reviewed and updated with the help of an Editorial Board. Suggestions for new monographs are discussed by the *PCF* editorial team, and experts identified to assist in the preparation of new documents.

The Editorial Board

The Editorial Board mainly comprises palliative care physicians appointed on the basis of their clinical knowledge and expertise. Editorial Board members have committed to reviewing one or more drug monographs or chapters, and work in liaison with the editorial team. Responsibilities include scrutinizing literature databases such as PubMed, and accessing and studying relevant new publications.

Correspondents

Correspondents are drawn from a range of medical specialties. They include doctors, pharmacists, nurses, and others who provide advice on the text by:

- checking amendments for scientific accuracy, and to enhance clarity
- providing additional expert opinion in areas of controversy or when reliable evidence is lacking
- advising on areas when the *PCF* diverges from a manufacturer's Summary of Product Characteristics (SPC)
- providing additional validation and clinical evidence about unauthorized (off-label) use.

Sources of *PCF* information

PCF uses various sources for its information, including:

Summary of product characteristics (SPC)

The SPCs are the principal source of product information and are carefully reviewed to ensure that *PCF* monographs are fully up-to-date in this respect.

Literature

Research papers and reviews relating to the drugs featured in *PCF* are carefully processed. When a difference between the advice in the *PCF* and a paper is noted, the new information is evaluated for reliability and relevance to UK clinical practice. If necessary, new text is drafted and thoroughly reviewed by the editorial team with support, as needed, from the Editorial Board and/or Correspondents.

PCF also has access to many on-line information resources (see p.xviii). For example, www.azcert.org is used to flag drugs which have the potential to prolong QT interval to a

clinically relevant degree, and www.psychotropical.com is used to help adjudicate whether a report about serotonin toxicity is reliable.

Systematic reviews

PCF monitors various databases of systematic reviews, including the *Cochrane Library* and several other web-based resources. Reviews published in *Clinical Evidence* are used to validate *PCF* advice.

Consensus guidelines

The advice in *PCF* is checked against consensus guidelines produced by expert bodies including the National Institute for Health and Care Excellence (NICE), the Scottish Medicines Consortium (SMC), and the Scottish Intercollegiate Guidelines Network (SIGN).

PCF also takes note of other expert bodies which produce clinical guidelines relevant to palliative care, e.g. Association for Palliative Medicine, British Lymphology Society.

Statutory information

PCF routinely processes relevant information from various Government bodies, including Statutory Instruments and regulations affecting the Prescription only Medicines Order, Controlled Drugs and from the Medicines and Healthcare products Regulatory Agency (MHRA). Safety warnings issued by the Commission on Human Medicines (CHM) and guidelines on drug use issued by the UK health departments are routinely processed.

Relevant professional statements issued by the Royal Pharmaceutical Society (RPS), Nursing and Midwifery Council (NMC) and General Medical Council (GMC) are included in *PCF* as are guidelines from the medical Royal Colleges.

Pricing information

Drug prices are net prices based on those in the online edition of the *BNF* at the time of the monograph update. For products not included in the *BNF*, prices are checked directly with suppliers. However, particularly in hospitals, heavily discounted contract prices radically alter both the absolute and relative acquisition costs.

Prices worked out for 28 days' supply are generally based on the most convenient strength for the patient and cheapest pack size. Costs for broken bulk, dispensing/sourcing fees and delivery charges are *not* included. Costs under £5 have been rounded up to the next 50p; prices over £5 are rounded up to the next full pound.

Comments from industry

Manufacturers are contacted directly if there are queries about the content of an SPC.

GETTING THE MOST OUT OF PCF

Information in a book of this type can never be all-inclusive, and thus will not cover every eventuality. Readers should satisfy themselves as to the appropriateness of the information before applying it in practice.

Particularly when prescribing a drug for the first time, a doctor (or other independent prescriber) should study the contents of the manufacturer's Summary of Product Characteristics (SPC), paying particular attention to indications, contra-indications, cautions, drug interactions, and undesirable effects (also see p.xvii).

PCF often refers to the use of drugs beyond the scope of their marketing authorization (product licence). The use of drugs in this way clearly has implications for the prescriber (see p.xix).

A cautious approach is always necessary when prescribing for the frail, the elderly, and patients with hepatic impairment, renal impairment or respiratory insufficiency (see Chapter 14, p.639). Further, if caring for a woman who is pregnant or breast-feeding, or for someone with porphyria, it is crucial to double-check a drug's suitability in both the *BNF* and its SPC.

The literature on the pharmacology of pain and symptom management in end-stage disease is growing continually, and it is impossible for anyone to be familiar with all of it. This is where a book like *PCF* comes into its own as a major accessible resource for prescribing clinicians involved in palliative care.

PCF is not an easy read, indeed it was never intended that it would be read from cover to cover. It is essentially a reference book – to study the monograph of an individual drug, or class of drugs, with specific questions in mind.

In Part 1, the sections generally follow the systematic order of the *British National Formulary* (*BNF*). Drugs marked with an asterisk (*) should generally be used only by, or after consultation with, a specialist palliative care service.

Part 2 and the appendices deal with themes that transcend the drug monographs, e.g. pre-emptive prescribing in the community, continuous subcutaneous infusions, administering drugs via enteral tubes, the use of nebulized drugs.

Reliable knowledge, levels of evidence and strength of recommendations

Research is the pursuit of reliable knowledge. The gold standard for drug treatment is the randomized controlled trial (RCT) or, better, a systematic review of homogeneous RCTs.

Over the last 20–30 years, numerous systems have been published for categorizing levels of evidence and the strength of the derived recommendations. Box A reproduces the system used by the British Medical Journal. This checklist is based on material published by three main sources, namely the US Agency for Health Care Policy and Research, the NHS Management Executive, and the North of England Guidelines Group.[1–3]

However, it is important to recognize that the RCT is *not* the only source of reliable knowledge. Broadly speaking, sources of knowledge can be conveniently grouped under three headings:

- *instrumental*, includes RCT data and data from other high-quality studies
- *interactive*, refers to anecdotal data (shared clinical experience), including retrospective and prospective surveys
- *critical*, data unique to the individual in question (e.g. personal choice) and societal/cultural factors (e.g. financial and logistic considerations).[5]

Relying on one type of knowledge alone is *not* good practice. All three sources must be exploited in the process of therapeutic decision-making.

Box A A scheme for categorizing evidence and grading recommendations[4]

Category	*Level of evidence*	*Grade*	*Strength of recommendations*
Ia	Evidence obtained from a meta-analysis of RCTs	A	Directly based on Category I evidence without extrapolation
Ib	Evidence from at least one RCT		
IIa	Evidence obtained from at least one well-designed controlled study without randomization	B	Directly based on Category II evidence or by extrapolation from Category I evidence
IIb	Evidence obtained from at least one other well-designed quasi-experimental study		
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies	C	Directly based on Category III evidence or by extrapolation from Category I or II evidence
IV	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities	D	Directly based on category IV evidence or by extrapolation from Category I, II, or III evidence This grading indicates that directly applicable clinical studies of good quality are absent or not readily available

Pharmaceutical company information

Although the manufacturer's SPC is an important source of information about a drug, it is important to remember that many published studies are sponsored by the drug company in question. This can lead to a conflict of interest between the desire for objective data and the need to make one's own drug as attractive as possible.[6] It is thus best to treat information from company representatives as inevitably biased. The information provided by *PCF* is commercially independent, and should serve as a counterbalance to manufacturer bias.

Remember: it is often safer to stick with an 'old favourite', and not seek to be among the first to prescribe a newly released product – which may simply be a 'me-too' drug rather than true innovation.[6]

Generic drugs

PCF encourages generic prescribing.[7] Apart from occasional exceptions, e.g. m/r formulations of diltiazem, nifedipine, theophylline and some anti-epileptics, there is little reliable evidence that different preparations of the same drug are significantly different in terms of bio-availability and efficacy.[8] However, particularly for oral morphine preparations, the Department of Health (London) recommends including the brand name of opioid analgesics on the prescription and dispensing label, to avoid unwittingly switching brands and confusing the patient.[9]

Indications

PCF often refers to the use of drugs beyond the scope of their marketing authorization (product licence). The use of drugs in this way clearly has implications for the prescriber (see p.xix). As always, readers should satisfy themselves as to the appropriateness of the information before applying it in practice.

In *PCF* generally, only those indications which are relevant to palliative care are listed, with unauthorized indications or uses preceded by a † sign. However, a succinct summary is not always

possible because the Marketing Authorization reflects what the manufacturer applied for. Thus, authorized indications can vary between drugs within a therapeutic class or for the same drug by different:

- manufacturers
- routes of administration, e.g. haloperidol tablets and injection
- formulations, e.g. buprenorphine TD patches, desmopressin tablets
- pack sizes, e.g. buprenorphine tablets.

We have endeavoured to indicate such circumstances with the statement: 'Authorized indications vary between products; consult SPC for details'. In any event, before using a product for the first time, the SPC should be studied.

Contra-indications and cautions

Contra-indications and cautions listed in SPCs sometimes vary between different manufacturers of the same drug. Thus, a contra-indication in one SPC may be styled a caution in another, and *vice versa*.

In *PCF*, we do *not* include universal contra-indications (e.g. history of hypersensitivity to the drug), and have generally *not* included a contra-indication from the SPC if the use of the drug in the stated circumstance is accepted prescribing practice in palliative care.

Advice regarding dosing a drug in renal impairment can vary. When this occurs, *PCF* favours the opinion of the independent *Renal Drug Handbook* over the manufacturer's SPC.

However, as always, a cautious approach is necessary when prescribing for the frail, the elderly, and patients with organ impairment or respiratory insufficiency (see Chapter 14, p.639). If caring for a woman who is pregnant or breast-feeding, or for someone with porphyria, it is crucial to check a drug's suitability in both the *BNF* and SPC.

Pharmacokinetics

Generally, pharmacokinetic data are taken from *Martindale: the complete drug reference*[10] or from a manufacturer's SPC. Other sources are referenced in the text.

Drug interactions

Generally, information on drug interactions is taken from *Stockley's drug interactions*[11] or from a manufacturer's SPC. Other sources are referenced in the text.

It is assumed that clinicians are aware of the risk of commonsense pharmacodynamic interactions, e.g. that the concurrent prescription of two or more drugs with sedative properties is likely to result in more sedation than if each drug was prescribed alone. On the other hand, pharmacokinetic interactions (leading to either increased or reduced effect) are generally covered in individual drug monographs and in Chapter 25, p.767.

Undesirable effects of drugs

As recommended by the European Commission, the term 'undesirable effect' is used rather than 'side effect' or 'adverse drug reaction'. Wherever possible, undesirable effects are categorized as:

- very common ($>10\%$)
- common ($<10\%$, $>1\%$)
- uncommon ($<1\%$, $>0.1\%$)
- rare ($<0.1\%$, $>0.01\%$)
- very rare ($<0.01\%$).

PCF generally includes information on the very common and common undesirable effects. Selected other undesirable effects are also included, e.g. uncommon or rare ones which may have serious consequences. The manufacturer's SPC should be consulted for a full list of undesirable effects.

Supply

The list of products in the Supply section is *not* exhaustive. Generally, generic products and selected proprietary ones are included, e.g. an alternative proprietary formulation not available as a generic.

Literature references

In choosing references, articles in hospice and palliative care journals have frequently been selected preferentially. Such journals are likely to be more readily available to our readers, and often contain detailed discussion.

It is not feasible to reference every statement in *PCF*. However, readers are invited to enter into constructive dialogue with the Editors via the Bulletin Board on *www.palliativedrugs.com*. This is currently accessed by >25,000 health professionals worldwide.

Online sources of information

Website references are not routinely given for articles available in traditionally published journals. However, various full-text core journals are available free to UK NHS staff with an Athens password through the NHS Evidence Services website at https://www.evidence.nhs.uk.

Information from the *BNF* and *BNFc* is freely available, after registration, from www.bnf.org.uk for users in the UK and the HINARI group of developing countries. References to manufacturer's SPCs and PILs are generally *not* included. However, most can be freely accessed from www.medicines.org.uk or obtained directly from the manufacturer.

Online sources of information are referenced when this is the usual route of publication and access is freely available, e.g. UK Department of Health guidelines, MHRA Drug Safety Updates, NICE guidance, SIGN guidance. The website address quoted is for the homepage or the page from which the guidance can be found and downloaded.

Whenever possible, subscription websites have been avoided. However, to ensure that the most current information is included when revising *PCF*, the following standard reference texts are consulted from subscribed access to Medicines Complete (www.medicinescomplete.com):

- *Amercian Hospital Formulary Service (AHFS)*
- *Handbook of drug administration via enteral feeding tubes*
- *Handbook on injectable drugs*
- *Martindale: the complete drug reference*
- *Stockley's drug interactions*.

These are available in all UK Medicines Information Services.

1 Eccles M, *et al.* (1996) North of England evidence based guidelines development project: methods of guideline development. *British Medical Journal*. **312**: 762–762.

2 DoH (1996) *Clinical Guidelines: Using Clinical Guidelines to Improve Patient Care Within the NHS*. Department of Health: NHS Executive, Leeds.

3 Agency for Health Care Policy and Research (1992) Acute pain management, operative or medical procedures and trauma 0032–0032. In: *Clinical Practice Guideline Quick Ref Guide for Clinicians*. AHCPR Publications, Rockville, Maryland, USA, pp. 22–22.

4 BMJ Publishing Group (2009) Resources for authors. Checklists and forms: clinical management guidelines. Available from: http://resources.bmj.com/bmj/authors/checklists-forms/clinical-management-guidelines

5 Aoun SM and Kristjanson LJ (2005) Challenging the framework for evidence in palliative care research. *Palliative Medicine*. **19**: 465–465.

6 Angell M (2004) *The Truth About the Drug Companies: how they deceive us and what to do about it*. Random House, New York.

7 National Prescribing Centre (2011) Generic prescribing in primary care. *MeReC Bulletin*. **21**: 6–6.

8 National Prescribing Centre (2000) Modified-release preparations. *MeReC Bulletin*. **11**: 16–16.

9 Smith J (2004) Building a Safer NHS for Patients - Improving Medication Safety. pp. 111–111. Department of Health, London. Available from: www.dh.gov.uk/assetRoot/04/08/49/61/04084961.pdf

10 Sweetman SC. *Martindale: The Complete Drug Reference*. London: Pharmaceutical Press www.medicinescomplete.com

11 Baxter K and Preston CL. *Stockley's Drug Interactions*. London:- Pharmaceutical Press www.medicinescomplete.com

THE USE OF DRUGS BEYOND (OFF-LABEL) AND WITHOUT MARKETING AUTHORIZATION

The use of drugs for off-label purposes is widespread. Surveys suggest that up to one quarter of all prescriptions in palliative care come into this category.[1,2] In *PCF*, the symbol † is used to indicate such use. However, it is impractical to highlight all cases of off-label use, particularly when it is simply a matter of the route or dose being different from those in the manufacturer's Summary of Product Characteristics (SPC).

It is important for prescribers to understand that *marketing authorization* for drugs regulates the *marketing activities* of pharmaceutical companies, and not the prescriber's clinical practice. Even so, off-label use does have implications for prescribers, and these are discussed in this section.

Definitions

Marketing authorization

Marketing authorization (MA) means that a drug has been approved by a regulatory body for use in humans and authorized for specific indications, and can be marketed by the relevant pharmaceutical company.

Off-label use

Off-label describes the use of a drug beyond the specifications of its MA, e.g. for an unauthorized indication, or in doses, preparations, patient population or route not covered by the MA.

Unauthorized drug

There is no simple definition of an unauthorized drug. Essentially it is a drug which does not have MA for medicinal use in humans. Unauthorized drugs include:

- the final product when two or more drugs are mixed together for administration e.g. in a syringe for CSCI (see below and Chapter 20, p.697)
- 'specials' obtained from a commercial company with a 'specials' manufacturing licence, e.g. alfentanil solution for nasal/buccal administration (see Alfentanil, p.385)
- preparations made in a local pharmacy at the request of a prescriber for an individual named patient
- drugs that have had a MA withdrawn but special provision has been made by the MHRA for a continued supply, e.g. co-proxamol or for which MA has been abandoned, suspended or revoked, e.g. cisapride, oxetacaine, thioridazine
- drugs that are authorized in another country but not in the UK and are imported into the UK by a specialist importing company, e.g. hydromorphone injection
- new drugs undergoing clinical trials or awaiting a MA, e.g. if a patient wishes to continue an investigational product after a clinical trial.

The authorization (licensing) process

Before a drug can be marketed in the UK, it requires MA (previously product licence). There are four application procedures in the European Union:

- *centralized*, application evaluated by the European Medicines Agency (EMEA); the European Commission grants a single MA valid for the whole European Union
- *decentralized*, simultaneous application made by several member states, with one taking the lead; if successful, national MA then being granted in each state

- *mutual recognition*, application for authorization in a member state when MA exists in another member state; the new member state relies on the original member state's evaluation as a basis for its decision
- *national*, application for MA in only one member state; in the UK the application is evaluated by the Medicines and Healthcare products Regulatory Agency (MHRA) on behalf of the Licensing Authority, a body consisting of UK health ministers.[3]

Certain drugs, e.g. for HIV/AIDS, cancer, neurodegenerative diseases, must be authorized through the centralized procedure. The UK Parallel Import Licensing Scheme also allows a drug authorized in other European Union states to be imported and marketed in the UK, if it has labels and a Patient Information Leaflet (PIL) in English.

In the UK, the MHRA evaluation comprises an evaluation of the efficacy, safety and quality of the drug from a medical, pharmaceutical and scientific viewpoint to ensure that it satisfies predefined criteria. Advice is sought from the Commission on Human Medicines (CHM), an independent advisory body, which in turn is assisted by specialist expert advisory groups.

At a European level, the Committee for Medicinal Products for Human Use (CHMP) fulfils a similar role to the CHM. New drugs will have relatively limited safety information and the pharmaceutical company is generally required to outline a risk management plan.

Restrictions are imposed if evidence of safety and efficacy is unavailable in particular patient groups, e.g. children. MA is granted for up to 5 years and then renewed following re-evaluation of the risks and benefits.[3]

Thus, the process ensures that in relation to the drug's authorized uses, there has been due consideration of its efficacy, safety and quality, that the benefits outweigh the potential risks, and that there is appropriate accompanying product information and labelling.[4] The MA defines the conditions and patient groups for which a pharmaceutical company can market and supply the drug, with more information about the drug's authorized uses provided by the manufacturer in the Summary of Product Characteristics (SPC).

However, the MA does not limit what the drug could be used for (i.e. off-label use), and clinical experience may reveal other indications. For these to receive a MA, additional evidence would need to be gathered and submitted. The considerable expense of this, perhaps coupled with a small market for a new indication, often means that a revised application is not made.

Prescribing for off-label indications or unauthorized drugs

In the UK, the following may legally prescribe authorized drugs for off-label indications and unauthorized drugs:[5–7]

- doctors, specifically safeguarded in the UK Medicines Act 1968
- nurses, pharmacists, podiatrists, physiotherapists and radiographers who are registered as *supplementary prescribers*, provided it is done within the framework of an agreed Clinical Management Plan for a specific patient in partnership with a doctor or dentist
- nurses or pharmacists who are registered as *independent prescribers* if this is accepted clinical practice and within their clinical competence.

These prescriptions can be dispensed by pharmacists[8] and administered by nurses or midwives.[9]

In addition to clinical trials, such prescriptions may be justified:

- when prescribing generic formulations for which indications are not described
- with established drugs for proven but unauthorized indications
- with drugs for conditions for which there are no other treatments (even in the absence of strong evidence)
- when using drugs in individuals not covered by the MA, e.g. children
- when mixing drugs before administration, e.g. two or more drugs in a syringe for administration by continuous infusion.[10,11]

Any *independent prescriber,* including non-medical prescribers, can mix drugs and direct others to mix, as can *supplementary prescribers* when the preparation is part of the Clinical Management Plan for an individual patient. Legislation on mixing now extends to controlled drugs. Existing good practice recommendations should be followed in relation to mixing all drugs.[10] Preparations resulting from mixing drugs, other than when one product is a vehicle for the administration of the other, cannot be supplied or administered under Patient Group Direction arrangements.

The responsibility for the consequences of prescribing a drug under such circumstances lies with the prescriber, who must be competent, operate within the professional codes and ethics of their statutory bodies and the prescribing practices of their employers.[4–6] The prescriber must be

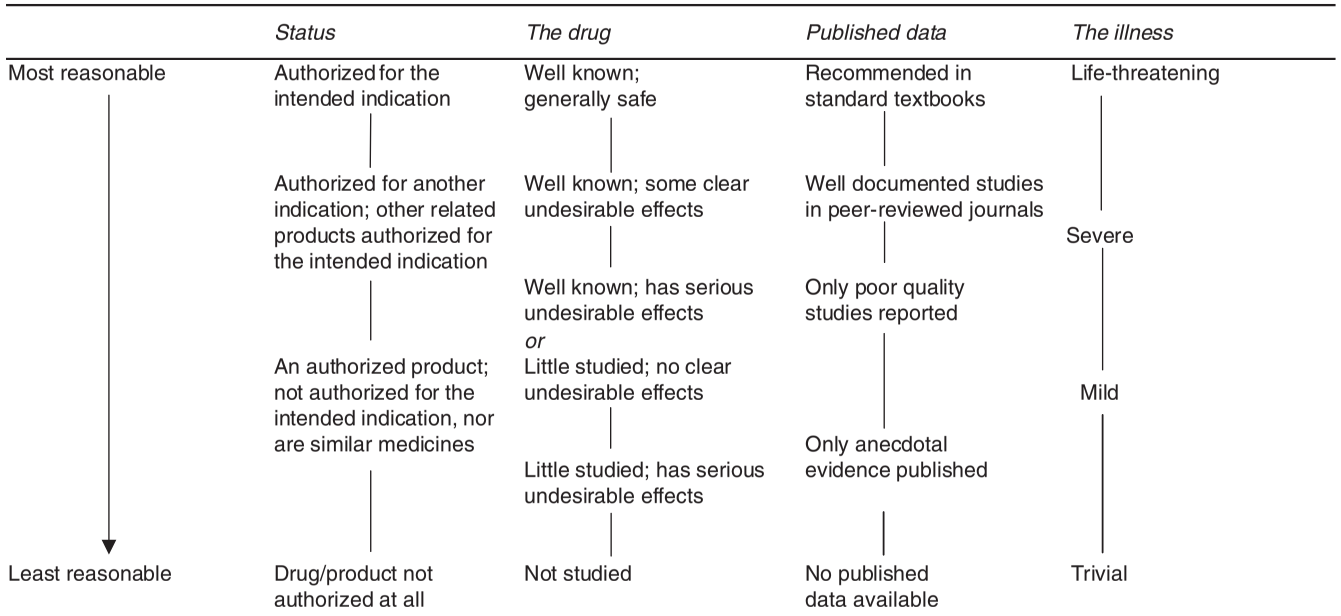

Figure 1 Factors influencing the reasonableness of prescribing decisions.

fully informed about the actions and uses of the drug, be assured of the quality of the particular product, and in the light of published evidence, balance both the potential good and the potential harm which might ensue.

It is possible to draw a hierarchy of degrees of reasonableness relating to off-label and unauthorized drug use (Figure 1). The more dangerous the medicine and the more flimsy the evidence the more difficult it is to justify its prescription.

The PIL will not contain information about unauthorized indications. Thus, it is important that prescribers (or those authorizing treatment on their behalf) provide sufficient information to patients about the drug's expected benefits and potential risks (undesirable effects, drug interactions, etc.) to enable them to make an informed decision (Box A). The GMC also recommends that when prescribing a drug off-label, doctors should:

- be satisfied that such use would better serve the patient's needs than an authorized alternative (if one exists)
- be satisfied that there is sufficient evidence/experience of using the drug to show its safety and efficacy, seeking the necessary information from appropriate sources
- record in the patient's clinical notes the drug prescribed and, when not following common practice, the reasons for the choice
- take responsibility for prescribing the drug and for overseeing the patient's care, including monitoring the effects of the drug, or arrange for another suitable doctor to do so.[12]

Non-medical prescribers should ensure that they are familiar with their own profession's prescribing standards, e.g. NMC. Although the advice is broadly similar to that of the GMC, there are some differences.[13,14]

Box A Providing information for patients about the use of drugs beyond and without marketing authorization[12]

Patients (or their proxy) should be given sufficient information about any proposed drug treatment to allow them to make an informed decision. Questions must be answered fully and honestly.

Some drugs are routinely used beyond their licence, e.g. when treating children and in palliative care.

In emergencies, or when there is no realistic alternative treatment and such information is likely to cause distress, it may not be practical or necessary to draw attention to the licence.

In other situations, when the prescription of an unauthorized drug is supported by authoritative clinical guidance, it may be sufficient to describe in general terms why the drug is not authorized for the proposed use.

When prescribing a drug which is unauthorized or off-label in a non-routine way, or when suitable authorized alternatives exist, the reason for this should be explained to the patient.

In palliative care, off-label drug use is so widespread that concerns have been expressed that a detailed explanation on every occasion is impractical, would be burdensome for the patient and increase anxiety, and could result in the refusal of beneficial treatment.[15] A UK survey of over 220 palliative medicine doctors showed that, when using a drug for a routine off-label indication, $<5\%$ *always* mention this to their patients, and 20% *never* do. However, in situations where there is little evidence and limited clinical experience to support a drug's off-label use, these figures change to 75% and 5% respectively.[16]

This is a grey area and each clinician must decide how explicit to be; an appropriate level of counselling and a sensitive approach is essential. Some NHS Trusts and other institutions have policies in place and have produced information cards or leaflets for patients and caregivers (Box B). A joint position statement has also been produced by the British Pain Society and the Association for Palliative Medicine (Box C),[17] together with a patient information booklet.[18]

Box B Example of a patient information leaflet about the off-label use of a drug

Use of medicines beyond their licence (off-label)

This leaflet contains important information about your medicines, so please read it carefully.

Generally, medicines prescribed by your doctor or bought over-the-counter from a pharmacist are licensed for use by the Medicines and Healthcare products Regulatory Agency (MHRA).

The licence (or marketing authorization) specifies the conditions and patient groups for which the medicine should be used, and how it should be given.

Patient Information Leaflets (PILs) supplied with medicines reflect the licensed uses. When a medicine is used beyond its licence, the information in the PIL may not be relevant to your circumstances.

In palliative care, medicines are commonly used for conditions or in ways that are not specified on the licence.

Your doctor will use medicines beyond the licence only when there is research and experience to back up such use.

Medicines used very successfully beyond the licence include some antidepressants and anti-epileptics (anti-seizure drugs) when given to relieve some types of pain. Also, instead of injecting into a vein or muscle, medicines are often given subcutaneously (under the skin) because this is more comfortable and convenient.

If you would like more information, please ask your doctor or pharmacist.

Alternatively, contact:

Dr/Nurse .....

Hospital .....

.....

.....

Tel .....

1 Atkinson C and Kirkham S (1999) Unlicensed uses for medication in a palliative care unit. *Palliative Medicine*. **13**: 152–152.
2 Todd J and Davies A (1999) Use of unlicensed medication in palliative medicine. *Palliative Medicine*. **13**: 466.
3 Anonymous (2009) The licensing of medicines in the UK. *Drug and Therapeutics Bulletin*. **47**: 48–48.
4 Anonymous (2009) Off-label or unlicensed medicines: prescribers' responsibilities. *MHRA Drug Safety Update*. **2 (9)**: 7–7.
5 Department of Health (2005) Supplementary prescribing by nurses, pharmacists, chiropodists/podiatrists, physiotherapists and radiographers within the NHS in England: a guide for implementation. HMSO, London. Available from: *www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4110032*
6 Department of Health (2006) Improving patients' access to medicines: a guide to implementing nurse and pharmacist independent prescribing within the NHS in England. HMSO, London. Available from: *www.dh.gov.uk/assetRoot/04/13/37/47/04133747.pdf*
7 Department of Health (2010) Changes to medicines legislation to enable Mixing of Medicines prior to administration in clinical practice. Available from: *www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Prescriptions/TheNon-MedicalPrescribing-Programme/DH_110765*
8 Royal Pharmaceutical Society of Great Britain (2007) Fitness to practise and legal affairs directorate fact sheet: five. The use of unlicensed medicines in pharmacy. Royal Pharmaceutical Society of Great Britain. Available from: *www.rspgb.org/pdfs/factsheet5.pdf*
9 Anonymous (1992) Prescribing unlicensed drugs or using drugs for unlicensed indications. *Drug and Therapeutics Bulletin*. **30**: 99–99.
10 Department of Health (2010) Mixing of medicines prior to administration in clinical practice: medical and non-medical prescribing. HMSO, London. Available from: *www.gov.uk*
11 National Prescribing Centre (2010) Mixing of medicines prior to administration in clinical practice - responding to legislative changes. Liverpool. Available from: *www.npc.nhs.uk*
12 General Medical Council (2013) Good practice in prescribing medicines. Available from: *www.gmc-uk.org*

Box C Recommendations of the Association for Palliative Medicine of Great Britain and Ireland and the British Pain Society[17]

Use of medicines beyond (off-label) and without (unlicensed) Marketing Authorization (MA) in palliative care and pain medicine

1 This statement should be seen as reflecting the views of a responsible body of opinion within the clinical specialties of palliative medicine and pain medicine

2 The use of medicines beyond and without a MA in palliative care and pain medicine practice is both necessary and common and should be seen as a legitimate aspect of clinical practice.

3 Organizations providing palliative care and pain medicine services should support therapeutic practices that are underpinned by evidence and advocated by a responsible body of professional opinion.

4 Health professionals involved in prescribing medicines beyond or without MA should select those medicines that offer the best balance of benefit against harm for any given patient.

5 Choice of treatment requires partnership between patients and health professionals, and informed consent should be obtained, whenever possible, before prescribing any medicine.

6 Patients should be offered accurate, clear and specific information that meets their needs about the use of medicines beyond or without a MA in accordance with professional regulatory body guidance. The information needs of carers and other health professionals involved in the care of the patient should also be considered and met as appropriate. The use of information cards or leaflets may help with this. It is often unnecessary to take additional steps when recommending medicines beyond or without MA.

7 Health professionals should inform, change and monitor their practice with regard to medicines beyond or without MA in the light of evidence from audit and published research.

8 The Department of Health should work with health professionals and the pharmaceutical industry to enable and encourage the extension of product licences where there is evidence of benefit in circumstances of defined clinical need.

13 Nursing and Midwifery Council (2006) Standards of proficiency for nurse and midwife prescribers. Available from: *www.nmc-uk.org*

14 Royal Pharmaceutical Society of Great Britain (2010) Professional Standards and Guidance for Pharmacist Prescribers. Available from: *www.rpharms.com/archived-documents/archived-documents.asp#law*

15 Pavis H and Wilcock A (2001) Prescribing of drugs for use outside their licence in palliative care: survey of specialists in the United Kingdom. *British Medical Journal*. **323**: 485–485.

16 Culshaw J *et al.* (2013) Off-label prescribing in palliative care: a survey of independent prescribers. *Palliative Medicine*. **27**: 319–319.

17 British Pain Society (2012) Use of medicines outside of their UK Marketing Authorization in pain management and palliative care. Available from: *www.britishpainsociety.org*

18 British Pain Society (2012) Use of medicines outside of their UK Marketing Authorisation in pain management and palliative medicine - information for patients. Available from: *www.britishpainsociety.org*

DRUG NAMES

All drugs marketed in Europe are now known by their recommended International Non-proprietary (generic) Name (rINN). In the past, most publications in the UK used the now outdated British Approved Name (BAN). To aid understanding of the older literature, significant differences between BANs and rINNs are listed in Table 1. However, when the difference is simply, e.g. 'f' instead of 'ph', 'e' instead of 'oe', or 't' instead of 'th', these generally have *not* been included.

In the USA, United States Adopted Names (USANs) take precedence over rINNs. USANs are also included in Table 1 where these differ significantly from rINNs.

Note: in the UK, the BANs **adrenaline** and **noradrenaline** are still used in conjunction with the corresponding rINNs, i.e. **adrenaline (epinephrine)** and **noradrenaline (norepinephrine).**

Care should be taken with proprietary drug names in different countries. Some proprietary names are similar in spelling or pronunciation but contain different drugs. Further, some products with identical proprietary names contain different drugs, e.g. Urex® in the USA contains **methenamine** but, in Australia, **furosemide**.[1]

Table 1 Drug names relevant to palliative care for which the rINN, BAN and/or USAN differ

rINN	*BAN*	*USAN*
Alimemazine	Trimeprazine	Trimeprazine
Amobarbital	Amylobarbitone	
Bendroflumethiazide	Bendrofluazide	Bendroflumethiazide
Benzylpenicillin		Penicillin G
Calcitonin (salmon)	Salcatonin	Calcitonin
Carmellose		Carboxymethylcellulose
Chlorphenamine	Chlorpheniramine	Chlorpheniramine
Clomethiazole	Chlormethiazole	
Dexamfetamine	Dexamphetamine	Dextroamphetamine
Dextropropoxyphene		Propoxyphene
Dicycloverine	Dicyclomine	Dicyclomine
Diethylstilbestrol	Stilboestrol	Diethylstilbestrol
Dosulepin	Dothiepin	Dothiepin
Epinephrine	Adrenaline	Epinephrine
Glibenclamide		Glyburide
Glycerol	Glycerine	Glycerin
Glyceryl trinitrate		Nitroglycerin
Hyoscine		Scopolamine
Isoprenaline		Isoproterenol
	Ispaghula	Psyllium
Levomepromazine	Methotrimeprazine	
Levothyroxine	Thyroxine	
Liquid paraffin		Mineral oil
Methenamine hippurate	Hexamine hippurate	
Paracetamol		Acetaminophen
Pethidine		Meperidine

continued

Table 1 Continued

rINN	*BAN*	*USAN*
Phenobarbital	Phenobarbitone	
Phenoxymethylpenicillin		Penicillin V
Phytomenadione		Phytonadione
Retinol	Vitamin A	Vitamin A
Rifampicin		Rifampin
Salbutamol		Albuterol
Simeticone[a]	Simethicone	Simethicone
Sodium cromoglicate	Sodium cromoglycate	Cromolyn sodium
Tetracaine	Amethocaine	
Trihexyphenidyl	Benzhexol	Trihexyphenidyl

a. silica-activated dimeticone; known in some countries as activated dimethylpolysiloxane.

1 FDA (2006) Consumers filling U.S. prescriptions abroad may get the wrong active ingredient because of confusing drug names. *Public Health Advisory.* www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm173134.htm

ABBREVIATIONS

Drug administration

In 2005, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) in the USA published National Patient Safety Goals. These include a series of recommendations about ways in which confusion (and thus errors) can be reduced by avoiding the use of certain abbreviations on prescriptions. The full set of recommendations is available at http://www.jointcommission.org/standards_information/npsgs.aspx.

Although some traditional abbreviations remain acceptable (e.g. Table 1), other commonly used ones are not. Thus, it is now recommended that the following are written in full:

- at bedtime
- once daily
- each morning
- every other day.

These four recommendations have also been adopted in *PCF*.

Although the following conventions have *not* been adopted in PCF, readers should be aware of the following recommendations for handwritten and printed prescriptions, and other printed medical matter, e.g. packaging, patient records:

- include a space between the drug dose and the unit of measure, e.g. 25 mg, not 25mg
- write 'per' instead of an oblique (mistaken for a figure 1), e.g. 200 mg per day, not 200mg/day
- use 'subcut' or 'subcutaneous' instead of SC (mistaken for SL)
- write 'less than' or 'greater than' instead of $<$ and $>$ (mistaken for a letter L or figure 7; or written the wrong way round and thus signifying the opposite of the intended meaning).

Further, although it has been recommended in the UK that 'PR' (prolonged-release) should become the generic term for 'slow-release', 'extended-release' etc., PR is a time-honoured abbreviation for 'per rectum'. It is in this latter sense that PR will be used in *PCF*. As in earlier editions, 'm/r' (modified-release) will be used.

Note: in earlier editions, 'normal-release' was used for non-modified products. However, because of international popular usage, in this edition the term 'immediate-release' is used (without abbreviation).

Table 1 Abbreviations used in *PCF* for the times of drug administration

Times	*UK*	*Latin*
Twice per day	b.d.	*bis die*
Three times per day	t.d.s.	*ter die sumendus*
Four times per day	q.d.s.	*quarta die sumendus*
Every 4 hours etc.	q4h	*quaque quarta hora*
Rescue medication (as needed/required)	p.r.n.	*pro re nata*
Give immediately	stat	

a.c.	ante cibum (before food)
amp	ampoule containing a single dose (cf. vial)
CD	preparation subject to prescription requirements under the Misuse of Drugs Act (UK); for regulations see BNF
CIVI	continuous intravenous infusion

CSCI	continuous subcutaneous infusion
e/c	enteric-coated (gastroresistant)
ED	epidural
IM	intramuscular
IT	intrathecal
IV	intravenous
IVI	intravenous infusion
m/r	modified-release; alternatives, controlled-release, extended-release, prolonged-release, slow-release, sustained-release
~~NHS~~	not prescribable on NHS prescriptions
OTC	over the counter (i.e. can be obtained without a prescription)
p.c.	post cibum (after food)
PO	per os, by mouth
POM	prescription-only medicine
PR	per rectum
PV	per vaginam
SC	subcutaneous
SL	sublingual
TD	transdermal
TM	transmucosal
vial	sterile container with a rubber bung containing either a single or multiple doses (cf. amp)
WFI	water for injections

General

*	specialist use only
†	unlicensed use
ACBS	Advisory Committee on Borderline Substances
AHFS	American Hospital Formulary Service
BNF	British National Formulary
BP	British Pharmacopoeia
CHM	Commission on Human Medicines
CSM	Committee on Safety of Medicines (now part of CHM)
DH	Department of Health (UK)
EMEA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
FDA	Food and Drug Administration (USA)
IASP	International Association for the Study of Pain
IDIS	International Drug Information Service
MCA	Medicines Control Agency (now MHRA)
MHRA	Medicines and Healthcare products Regulatory Agency (formerly MCA)
NICE	National Institute for Health and Care Excellence
NPF	Nurse Prescribers' Formulary
NPSA	National Patient Safety Association
NYHA	New York Heart Association
PCS/PCU	palliative care service/unit
PEG	percutaneous endoscopic gastrostomy
PIL	Patient Information Leaflet (UK)
rINN	recommended International Non-proprietary Name
RPS	Royal Pharmaceutical Society
SIGN	Scottish Intercollegiate Guidelines Network
SPC	Summary of Product Characteristics (UK)
UK	United Kingdom
UKMI	UK Medicines Information
USA	United States of America
USP	United States Pharmacopoeia
VAS	visual analogue scale, 0–100mm
WHO	World Health Organization

Medical

ACE	angiotensin-converting enzyme
ADH	antidiuretic hormone (vasopressin)
ATP	adenosine triphosphate
AUC	area under the plasma concentration-time curve
β_2	beta 2 adrenergic (receptor)
CHF	congestive heart failure
C_{max}	maximum plasma drug concentration
CNS	central nervous system
COX	cyclo-oxygenase; alternative, prostaglandin synthase
COPD	chronic obstructive pulmonary disease
CKD	chronic kidney disease
CRP	C-reactive protein
CSF	cerebrospinal fluid
CT	computed tomography
δ	delta-opioid (receptor)
D_2	dopamine type 2 (receptor)
DIC	disseminated intravascular coagulation
DVT	deep vein thrombosis
ECG (EKG)	electrocardiogram
EFT	enteral feeding tube
ERCP	endoscopic retrograde cholangiopancreatography
FBC	full blood count
FEV_1	forced expiratory volume in 1 second
FRC	functional residual capacity
FSH	follicle-stimulating hormone
FVC	forced vital capacity of lungs
GABA	gamma-aminobutyric acid
GI	gastro-intestinal
Hb	haemoglobin
HIV	human immunodeficiency virus
H_1, H_2	histamine type 1, type 2 (receptor)
Ig	immunoglobulin
INR	international normalized ratio
κ	kappa-opioid (receptor)
LABA	long-acting β_2-adrenergic receptor agonist
LFTs	liver function tests
LH	luteinizing hormone
LMWH	low molecular weight heparin
MAOI	mono-amine oxidase inhibitor
MARI	mono-amine re-uptake inhibitor
MRI	magnetic resonance imaging
MSU	mid-stream specimen of urine
μ	mu-opioid (receptor)
NaSSA	noradrenergic and specific serotoninergic antidepressant
NDRI	noradrenaline (norepinephrine) and dopamine re-uptake inhibitor
NG	nasogastric
NJ	nasojejunal
NMDA	N-methyl D-aspartate
NNH	number needed to harm, i.e. the number of patients needed to be treated in order to harm one patient sufficiently to cause withdrawal from a drug trial
NNT	number needed to treat, i.e. the number of patients needed to be treated in order to achieve 50% improvement in one patient compared with placebo
NO	nitric oxide
NRI	noradrenaline (norepinephrine) re-uptake inhibitor
NSAID	non-steroidal anti-inflammatory drug
$PaCO_2$	arterial partial pressure of carbon dioxide
PaO_2	arterial partial pressure of oxygen

PCA	patient-controlled analgesia
PE	pulmonary embolus/embolism
PEF	peak expiratory flow
PG	prostaglandin
PPI	proton pump inhibitor
RCT	randomized controlled trial
RIMA	reversible inhibitor of mono-amine oxidase type A
RTI	respiratory tract infection
SaO_2	oxygen saturation
SNRI	serotonin and noradrenaline (norepinephrine) re-uptake inhibitor
SRE	skeletal-related events
SSRI	selective serotonin re-uptake inhibitor
TCA	tricyclic antidepressant
TIBC	total iron-binding capacity; alternative, plasma transferrin concentration
TI_{CO}	transfer factor of the lung for carbon monoxide
T_{max}	time to reach C_{max}
UTI	urinary tract infection
VEGF	vascular endothelial growth factor
VIP	vaso-active intestinal polypeptide
WBC	white blood cell
w/v	weight of solute (g) per 100mL

Units

cm	centimetre(s)
cps	cycles per sec
dL	decilitre(s)
g	gram(s)
Gy	Gray(s), a measure of radiation
h	hour(s)
Hg	mercury
kcal	kilocalories
kg	kilogram(s)
L	litre(s)
mg	milligram(s)
microL	microlitre(s)
micromol	micromole(s)
mL	millilitre(s)
mm	millimetre(s)
mmol	millimole(s)
min	minute(s)
mosmol	milli-osmole(s)
msec	millisecond
nm	nanometre(s)
nmol	nanomole(s); alternative, nM
sec	second(s)