The British Pain Society

Use of medicines outside of their UK marketing authorisation in pain management and palliative medicine

This is a consensus document prepared on behalf of the British Pain Society in consultation with the the Association for Palliative Medicine of Great Britain and Ireland.

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Contents

Definitions

Marketing Authorisation (MA)
Marketing Authorisation means that a medicine has been approved by a regulatory body for use in humans and licensed for specific indications and patient populations, and can be marketed for these purposes by the relevant pharmaceutical company.

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

Unlicensed medicine
There is no simple definition of an unlicensed medicine. Essentially it is a drug which does not have MA for medicinal use in humans. Unlicensed medicines include:

- a mixture of two or more medicines in a syringe for administration by continuous infusion
- 'specials' obtained from a commercial company with a 'specials' manufacturing licence
- preparations made in a local pharmacy at the request of a prescriber for an individual named patient
- medicines from a licensed manufacturer in the UK without MA in the UK, e.g. new medicines awaiting MA, or medicines for which MA has been abandoned, suspended or revoked, e.g. cisapride, thioridazine
- medicines with MA in another country, but not the UK, which are imported
- new drugs undergoing clinical trials.

Introduction

The use of medicines beyond their Marketing Authorisation (MA) is widespread, particularly in specialties such as paediatrics, pain medicine and palliative care, with surveys in the latter suggesting that up to one quarter of all prescriptions come into this category[1,2]. Specialist texts, such as the *Palliative Care Formulary*, highlights such use[3]. However, identifying *every* instance of off-label use is challenging, 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).

The use of unlicensed medicines is also widespread in pain medicine and palliative care because the mixing of two or more licensed medicines is now officially considered to produce an unlicensed preparation (see below).

The Royal College of Paediatrics and Child Health considers the use of medicines beyond (off-label) or without (unlicensed) MA as a necessary part of paediatric practice and have already issued their own guidance[4]. This joint statement by the British Pain Society and the Association for Palliative Medicine of Great Britain and Ireland similarly regards such use of medicines in palliative care and pain medicine *to be in the best interests of the patient and generally represents standard practice*. Nonetheless, there are implications for prescribers which are outlined below.

The authorisation (licensing) process

Before a medicine can be marketed in the UK, it requires MA (previously the product licence). Depending on the application procedure followed, the MA is issued either by the European Commission via the European Medicines Agency (EMEA) or by the UK Licensing Authority via the Medicines and Healthcare product Regulatory Agency (MHRA)[5].

The process ensures that in relation to the medicine's authorised 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[6]. The MA defines the conditions and patient groups for which a pharmaceutical company can market the medicine, with more information about the medicine's authorised uses provided by the manufacturer in the SPC.

However, the MA does not limit what the medicine could be used for (i.e. off-label use), and clinical experience may reveal other indications. For these to receive 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 unlicensed medicines

The MA regulates the marketing activities of pharmaceutical companies, and not the prescriber's clinical practice. In the UK, the following may legally prescribe medicines beyond or without MA: [7–9]

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

Legally, prescriptions for medicines used beyond or without MA can be dispensed by pharmacists[10] and administered by nurses or midwives[11]. In addition to clinical trials, such prescriptions may be justified:

- when prescribing generic formulations for which indications are not described
- with established medicines for proven but unlicensed indications

- with medicines for conditions for which there are no other treatments (even in the absence of strong evidence)

- when using medicines in individuals not covered by the MA, e.g. children

- when mixing medicines prior to administration, e.g. two or more medicines in a syringe for administration by continuous infusion.

The mixing of two or more licensed medicines prior to administration is considered to produce a new, unlicensed preparation [12,13]. Common examples of this include the mixing of a local anaesthetic with a depot corticosteroid prior to injection, and the mixing of two or more medicines in a syringe for administration by continuous infusion. Legally, any *independent prescriber*, including non-medical prescribers, can mix medicines and direct others to mix medicines, as can *supplementary prescribers* when the preparation is part of the Clinical Management Plan for an individual patient. Current legislation on mixing does not extend to controlled drugs, although the necessary amendments are under consideration. Meantime, existing good practice arrangements should be followed in relation to mixing controlled drugs[12]. Products resulting from the mixing of medicines, other than where 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 medicine beyond or without MA 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[6–8]. The prescriber must be fully informed about the actions and uses of the medicine, 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.

Specialist services recommending such use of medicines to other clinicians to prescribe, e.g. General Practitioners, should provide appropriate levels of information and ongoing support. Other clinicians are not obliged to prescribe in these circumstances and can decline. However, this is rarely seen in practice, as specialist advice is generally sought by clinicians when a patient under their care has difficult to manage symptoms.

The Product Information Leaflet prepared by the manufacturer will only contain information about licensed indications. Thus, it is important that prescribers (or those authorizing treatment on their behalf) provide sufficient information to patients about the expected benefits and potential risks of using a medicine beyond or without MA (undesirable effects, drug interactions, etc.) to enable them to make an informed decision (Box A). The General Medical Council (GMC) also recommends that when prescribing a medicine off-label, doctors should:

- be satisfied that such use would better serve the patient's needs than an authorised alternative (if one exists)

- be satisfied that there is sufficient evidence/experience of using the medicine to show its safety and efficacy, seeking the necessary information from appropriate sources

- record in the patient's clinical notes the medicine prescribed and, when not following common practice, the reasons for the choice

- take responsibility for prescribing the medicine and for overseeing the patient's care, including monitoring the effects of the medicine.

For off-label prescribing, monitoring can be delegated to another doctor, but not if the medicine is completely unlicensed[14]. Medical defence organisations echo the GMC guidance.

Non-medical prescribers should ensure that they are familiar with the legislative framework and their own profession's prescribing standards, e.g. Nursing and Midwifery Council. Although the advice is broadly similar to that of the GMC, there are some differences[15,16].

Box A Providing information for patients about the use of medicines beyond and without MA[14]

Some drugs are routinely used beyond their licence, e.g. when treating children. When current practice supports the use of a drug in this way, it may not be necessary to draw attention to the licence when recommending it.

However, it is good practice to give as much information as patients or those authorizing treatment on their behalf, require or which they may see as significant.

When patients or their carers express concern, you should also explain in broad terms the reasons why the drug is not licensed for its proposed use. Such explanations may be supported by written information.

However, you must explain the reasons for prescribing a drug that is unlicensed or being used off-label when there is little research or other evidence of current practice to support its use, or when the use of the drug is innovative.

In palliative care, off-label medicine 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[17]. A recent UK survey of over 220 palliative medicine doctors showed that, when using a medicine for a routine off-label indication, only 5% always mention this to their patients, and 31% never do. However, in situations where there is little evidence and limited clinical experience to support a medicine's off-label use, these figures change to 57% and 7% respectively[18].

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

Recommendations of the British Pain Society and Association for Palliative Medicine of Great Britain and Ireland

Taking the above into account, a number of recommendations can be made (Box B).

Box B Recommendations of the British Pain Society and Association for Palliative Medicine of Great Britain and Ireland

Use of medicines beyond (off-label) and without (unlicensed) Marketing Authorisation (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. Organisations 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.

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Declaration of competing interests

William Campbell has attended advisory panels for Grünenthal and Lilly. In addition, he has received invitations to National and European educational meetings by Napp and Pfizer.

Andrew Wilcock is a co-director of palliativedrugs.com Ltd. and an Editor-in-Chief of the Palliative Care Formulary.

Sam Ahmedzai-no conflicts of interests declared.

Nick Allcock has attended advisory panels for Grünenthal relating to pain in older adults and patient information and has met with pharmaceutical representatives.

John Goddard has attended advisory boards with Grünenthal, and met with company medical advisors, relating to paediatric practice as pharmaceutical representatives not able to discuss off-label prescribing.

Roger Knaggs has attended advisory boards and educational meetings organised or supported by Grünenthal, Napp, Reckitt Benckiser Healthcare, Astra Zeneca UK, Astellas Pharma and Pfizer although none have been to discuss off-label use of medicines specifically.

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