Cambridgeshire Joint Prescribing Group

Recommendations to Prescribers on the Use of Unlicensed Medicines and Licensed Medicines for Unlicensed Indications In Primary Care
Executive Summary

A licensed medicine is one that has received a Marketing Authorisation which permits the manufacturer to provide a product for a limited purpose – its 'licensed indication'.

In the UK there are about 20,000 medicinal products that have a marketing authorisation. This Marketing Authorisation means that the manufacturer has submitted evidence on the safety and efficacy of the product to the regulatory body, the Medicines and Healthcare Products Regulatory Agency (MHRA), and the product has been given a Marketing Authorisation (formerly a 'licence').

Prescribers would normally be expected to prescribe a licensed product, if available, as information on the product's safety is more freely available.

There are many situations in which it is appropriate to prescribe, dispense and administer unlicensed medicines or licensed medicines for unlicensed indications. It is a practice that is already common in paediatrics and in hospitals where they see complex cases, e.g. in the area of critical care.

Liability

There is a question over who has liability when a medicine is prescribed, dispensed or administered for a purpose for which it has not been licensed.

The manufacturer would be liable for any defect in a licensed product or if it did not do what the manufacturer claimed. They would also be liable for harm caused to the patient due to adverse drug reactions and side effects.

Prescribers may also be liable for harm caused by a licensed medicine if they have made an inappropriate diagnosis, an inappropriate choice of medicine or the patient is not warned of potential adverse drug reactions and side effects.

In the case of an unlicensed medicine or unlicensed use of a licensed medicine the liability would lie with the prescriber unless the way in which the medicine was produced was defective in which case the manufacturer may be liable.

Implications for Prescribers

A risk assessment of the potential treatment with an unlicensed medicine or unlicensed use for a licensed medicine should be carried out:

- Prescribers should be aware of whether a product is licensed for the intended indication or not.
- Before prescribing, prescribers should seek additional information regarding the potential treatment and ensure that they can justify their practice as conforming with that of a responsible body of medical opinion held by practitioners skilled in the field in question, e.g. by providing evidence of peer reviewed literature, written advice from respected specialist centres or a recognised specialist clinician.
- Before prescribing an unlicensed medicine, prescribers should consider other treatments and whether there is a licensed product or use of a medicine which would be equally appropriate.
- Prescribers should source and provide information for patients and carers on the purpose and consequences of treatment.
- Prescribers should monitor treatment and report all side effects or adverse reactions to the treatment to the MHRA.
Prescribers may be called upon to justify their actions.

**Implications for Patients**

Patients should be made aware that there are situations where the prescribing or administration of an unlicensed medicine or unlicensed use of a licensed medicine is safe and clinically appropriate.

Further information for patients is available, e.g. in the BNF for Children, and clinicians are recommended to share information about the risks and benefits of treatment with unlicensed medicines or unlicensed uses of licensed medicines before prescribing.

If a patient considers that they have been harmed by an unlicensed medicine or unlicensed use of a licensed medicine they will have no redress against the manufacturer of the product unless the product can be shown to be defective. They would, however, have redress against the clinician who prescribed the medication.

Patients, who are prescribed such medicines, or their carers should be able to expect their prescriber and the pharmacist or other supplier of the medicine to ensure that they receive sufficient information to use the product safely and effectively, as such medicines are not usually supplied with a patient information leaflet.

Where a product is used off-label, i.e. an unlicensed use of a licensed medicine, patients should be made aware of the fact that the way the medicine is being used will not be reflected in any patient information leaflet provided with the medicine.

**Implications for PCTs, Hospitals and Prescribing Groups**

- Advice given to prescribers to support the prescribing of an unlicensed medicine or unlicensed use of a licensed medicine, should be evidence based.
- Recommendations must be supported by demonstration of due process.

**Key Questions for Prescribers and Prescribing Advisors**

The body or individual clinician responsible for recommending the prescribing of an unlicensed medicine or off-label use of a licensed medicine is likely to be seen as reasonable and to have acted appropriately if they can answer at least one and, preferably, all three of the following three key questions:

1. Is there evidence that other prescribers, skilled in the therapeutic area being treated, would recommend this product?, e.g. is it included in the BNF or Children’s BNF, national guidelines. [Bolam Principle]
2. Can the prescriber provide a rationale for using this approach?, e.g. local evidence based guidance, considered by local Drugs and Therapeutics Committees, Local Medical Committee or Prescribing Group. [Bolitho Principle]
3. Is the decision to prescribe reasonable and not arbitrary? [Wednesbury Unreasonableness]
1. **Scope of the Recommendation**

This advice is to provide information and guidance on the clinical and prescribing responsibilities for unlicensed medicines and the off-label use of licensed medicines.

The policy is for use within Cambridgeshire PCT by General Practitioners, independent prescribers, supplementary prescribers (within a clinical management plan) and Dentists.

Pharmacists can dispense such medicines and nurses, midwives and others can administer them to patients.

2. **Introduction**

The majority of medicines have a Marketing Authorisation (formerly a product licence) issued by the Medicines and Healthcare Products Regulatory Agency (MHRA) or the European Medicines Evaluation Agency (EMEA) and are usually used in ways that are consistent with their marketing Authorisation or Summary of Product Characteristics.

A Marketing Authorisation allows for the drug manufacturers claim for the efficacy, safety and effectiveness of its product and that any failure in those claims transfers liability to the manufacturer for any defect associated with the quality of the medicine or its use in an approved clinical situation.

The Medicines Act does not prohibit the use of unlicensed medicines (medicines without a Marketing Authorisation).

The safeguards that apply to products with marketing authorisation should be extended as far as possible to the use of unlicensed medicines. The safety, efficacy and quality (including labelling) of unlicensed medicines should be assured by means of clear policies on their prescribing, purchase, supply and administration. Extra care is required with unlicensed medicines as less information may be available for the drug or its formulation.

**Liability**

There are issues associated with product liability when:

1) Medicines are used for clinical indications not covered by the Marketing Authorisation.

2) Medicines are produced extemporaneously in either a community pharmacy or a hospital pharmacy that does not have manufacturing license for that product.

3) Medicines are used which do not have a Marketing Authorisation, e.g. specials, or which have Marketing Authorisation in another country.

4) Medicines are used in a clinical trial.

This policy does not address the prescribing of medicines in relation to the conduct of clinical trials.

3. **Responsibilities**

GPs remain professionally accountable for their judgement in the prescribing of unlicensed medicines or off-label use of licensed medicines and may be called upon to justify their actions.
The decision to prescribe an unlicensed medicine or off-label use of a licensed medicine is the responsibility of the doctor accountable for the patient’s care.

Prescribers should consider other treatment options and whether there is a licensed product or use of a medicine which would be an equally appropriate treatment.

Where there are concerns regarding the level of risk (see Appendix 1) or the appropriateness of prescribing of an unlicensed medicine or off-label use of a licensed medicine, the Medicines Management team would be able to help in making a decision.

Where the use of an unlicensed medicine or off-label use of a licensed medicine does not reflect current, accepted good practice (informed by expert opinion or robust literature), the subject of an accepted Cambridgeshire PCT protocol or Shared Care Guideline, similarly detailed information should be provided by the initiating clinician before prescribing takes place.

Unlicensed medicines may be extemporaneously prepared, manufactured as specials or imported from abroad. Where the packaging does not contain full product information in English, this should be provided.

4 Frequently Asked Questions

Do I need to inform my patient that the treatment I am proposing is for an unlicensed/off label medicine?

Yes – prescribers have a responsibility to advise their patient/carer that they are being treated with an unlicensed/off-label medicine. The patient should be provided with accurate and clear information on the use and side effects of the medicine.

Where other clinical staff are involved in the treatment of a patient with an unlicensed or off-label drug the prescriber has a responsibility to ensure that:

- these staff are aware of its unlicensed/off-label status
- that they are informed of any problems and risks involved and how to deal with them
- they be given appropriate information to administer and use the product safely and correctly.

Do I need to obtain consent from patients when supplying an unlicensed medicine or off label use of a licensed medicine?

Yes – as with any product, it should be ensured that the patient or their carer/guardian is able to make a balanced judgement on whether to give or withhold consent. The patient or their carer/guardian should be informed of any material or significant risks in the proposed treatment, any alternatives to the proposed treatment and the risks incurred by doing nothing.

The patient’s individual needs and priorities should be established before providing information about treatment options but it should be noted that an individual patient’s preference for a treatment should be secondary to clinical appropriateness.

It is recommended that consent for the prescribing of an unlicensed medicine should be recorded in the patients’ notes.

Is there any occasion where consent would not be required?

Where the proposed treatment is to be used in an emergency situation and it is not possible to gain consent.
Or

Where a medicine has an established use outside its licensed indication, e.g. in the case of intermittent use of PPIs or use of aspirin for secondary prevention of cardiovascular disease.

**When is it appropriate for me to prescribe an unlicensed medicine or off label use of a licensed medicine?**

An unlicensed medicine or off-label use of a licensed medicine may be recommended where there is no licensed alternative to meet the clinical needs of the patient.

Or

Where the clinical and pharmaceutical needs of the patient cannot be met by a suitably licensed product and where the benefits of treatment using the unlicensed or off-label product are considered to outweigh the potential risks, for example where a patient has an intolerance or allergy to an ingredient in a licensed product or an inability to tolerate the formulation of the licensed product e.g. if they need an unlicensed liquid formulation of a drug as they are not able to ingest a licensed solid oral dosage form.

**What evidence do I need to provide to support my prescribing of an unlicensed medicine or off label use of a licensed medicine?**

A prescriber should be able to justify their practice as conforming with that of a responsible body of medical opinion held by practitioners skilled in the field in question, e.g. by providing evidence of peer reviewed literature, written advice from respected specialist centres or a recognised specialist clinician, e.g. in the case of buccal Midazolam for the treatment of cluster seizures in children.

**When is it not appropriate to prescribe an unlicensed medicine or off label use of a licensed medicine?**

If the choice is being made purely on the grounds of cost.

**What should I do if requested to prescribe an unlicensed medicine or off-label use of a licensed medicine by a secondary care clinician?**

When considering whether to accept clinical and legal responsibility for prescribing of such medicines it would be advisable to take into account the level of risk involved. (see Appendix 1).

Secondary care clinicians are expected to request the agreement of the primary care clinician to prescribe and inform them of the unlicensed or off-label status of the proposed treatment and the level of risk attached to the prescribing of the medicine. The secondary care clinician also has a responsibility to ensure that the requested treatment has been approved by the relevant Drugs and Therapeutics Committee.

The primary care clinician should be provided with a copy of any shared care protocol (approved by Cambridgeshire Joint Prescribing Group (CJPG)) or detailed information regarding how the medicine is used, the risks involved, any monitoring arrangements and where to obtain supplies of the product.

A primary care prescriber is under no obligation to take on prescribing of a secondary care initiated drug if they feel it to be inappropriate or feel unable to take on clinical responsibility. The
• implications for the patient of not prescribing should be considered and information gathered from secondary care clinicians and/or PCT Pharmacists to help inform the final choice of treatment.

**What information should I provide when prescribing an unlicensed medicine or off label use of a licensed medicine?**

Patient information leaflets are not required for unlicensed medicines and manufacturers’ patient information leaflets for licensed medicines do not contain information about off-label uses for these medicines. This should be explained to the patient to avoid misunderstandings.

It may take longer to obtain some unlicensed medicines and the patient or their carer should be made aware of this. Some imported medicines or specially manufactured medicines can take up to 2 weeks to obtain.

**What are my responsibilities regarding adverse drug reactions in relation to the prescribing of an unlicensed medicine or off label use of a licensed medicine?**

All adverse drug reactions that occur in patients treated with unlicensed medicines or unlicensed uses of licensed medicines should be reported to the Committee on Safety of Medicines (CSM) using the Yellow Card Scheme. Report card available at [www.yellowcard.gov.uk](http://www.yellowcard.gov.uk)

**Can Unlicensed Medicines be supplied on a long-term basis?**

If a pharmaceutically equivalent licensed product is not available through normal distribution channels in a reasonable time then it may be necessary to supply an unlicensed product, however, long-term supply should be avoided, if possible.

Unlicensed products should not be included in repeat dispensing schemes but be dealt with on a case by case basis.

It should be noted that liability for prescribing of unlicensed medicines or off-label use of licensed medicines lies with the prescriber (unless the medicine can be shown to be defective) and prescribers may wish to check with their medical defence organisation before prescribing any unlicensed products.

**5. Supply of Unlicensed Medicines or Medicines for which the Use Will be Unlicensed**

**As a supplying, procuring pharmacist, do I have any liability for the supply of an unlicensed medicine or the off-label use of a licensed medicine?**

Yes - pharmacists who supply a licensed medicine for an unlicensed use or an unlicensed product are professionally accountable for any harm caused by a defect in the medicine that is attributable to their own actions or omissions.

They should take reasonable steps to satisfy themselves that the prescriber is fully aware of the unlicensed status of the product and that its unlicensed use is appropriate in the circumstances.

A pharmacist has a duty of care to the patient when supplying them with any medicinal product.
How should Unlicensed products be Obtained or Supplied?

Supplies of unlicensed medicines should be obtained from appropriately licensed manufacturers or wholesalers (either with a specials manufacturing licence or an importer’s licence) or be otherwise prepared in a registered pharmacy.

The pharmacist or dispensing doctor should be satisfied that that the importer has made the necessary written notifications to the MHRA.

Unlicensed medicines should be labelled in English and supplied with patient information in English (applies especially to unlicensed medicines imported from abroad).

Prescribers, dispensing doctors and pharmacists should keep adequate records relating to purchase, preparation and supply of unlicensed products. Such records should be kept for at least five years.

When ordering an unlicensed medicine the pharmacist should declare their professional status and confirm that the supply of the unlicensed medicine is in accordance with a prescription from an authorised prescriber.

There is no requirement to give the supplier the name and/or address of the patient.

Are there any variations to the guidance for dispensing doctors?

Where medicines are extemporaneously prepared, there are exemptions to the licensing requirements for products prepared in a registered pharmacy under the supervision of a pharmacist, in accordance with:

- A medical prescription for an individual patient
- The specification or monograph of a pharmacopoeia and intended to be supplied directly to patients of a Pharmacy.
- A specification furnished by the person to whom the product is to be sold where the product is prepared or dispensed for administration to that person or a person under his care.

A marketing authorisation or manufacturer’s licence is not required to produce and supply such products. These exemptions do not apply to dispensing doctors.

Where dispensing doctors and pharmacists procure an unlicensed medicine, adequate records relating to the purchase, preparation and supply of the unlicensed medicinal products, including the source of the product, the person to whom the product was sold or supplied, the quantity of each sale or supply, the batch number of the product and details of any adverse reactions to the product sold or supplied should be kept. These details should be retained for five years.
Produced with acknowledgement to Nottingham County PCT, Havering PCT and Addenbrooke's and Papworth Hospitals Policies for Unlicensed and Unlicensed uses of medicines.
Appendix 1

Potential Risks Associated With The Prescribing And Supply Of Unlicensed Medicines or Off-label Use of Licensed Medicines

This guidance is an aid to prescribers in making decisions as to the risk:benefit profile associated with the use of unlicensed or off-label use of licensed medicines.

It is recommended that in considering the information available to establish the level of risk for an unlicensed medicine or the off-label use of a licensed medicine and where there is no currently accepted protocol or guidance within Cambridgeshire PCT, that advice is sought from the Medicines Management Team.

Higher Risk – these products are unlikely to suitable for use within Primary Care for one or more of the following reasons:
- They have very limited evidence to support their use.
- There is limited evidence of toxicity or other risks.
- They have been withdrawn from the market due to concerns over safety.
- There is little or no assurance of pharmaceutical quality.
- Where the product is a vaccine, blood product or other biological.
- Where the product is of animal origin.

Intermediate Risk - could be considered for use in primary care but should be supported by either a Cambridgeshire Joint Prescribing Group agreed shared care protocol, other Cambridgeshire PCT protocol or guidance, or protocols and guidance developed by hospitals and approved by Cambridgeshire PCT. These may include:
- Drugs being used in a complicated disease area or where there are requirements for monitoring beyond those normally dealt with in primary care.
- Drugs never licensed in the UK or discontinued on economic grounds.
- Drugs where there is limited assurance of pharmaceutical quality due to potentially sub UK standard quality assurance in the exporting country or an inadequate supply chain environment.
- Extemporaneously prepared products for which there is no quality control testing before the product is supplied to the patient, e.g. those prepared in a pharmacy.

Lower Risk – prescribing should be suitable for GPs and other primary care prescribers. This may include:
- Off-label use of licensed products where consideration has been given to any precautions or warnings.
- Off-label use of licensed products where consideration has been given to the quality aspect of intended use of a product in relation to an alternative route of administration.
- Specials manufactured in premises licensed by the MHRA.

When considering these levels of risk, precedence should be given to the highest category of potential risk in determination of the overall risk.
Appendix 2

Definitions

**Licensed medicines** are medicines with a UK marketing authorisation. When prescribed within the terms of the marketing authorisation the manufacturer is likely to be found liable for any harm caused by that medicine.

**Off-label medicines** are medicines where the prescriber elects for an indication, age group, dose and/or route of administration that is outside those recommended in the licence or which override any of the contra-indications, precautions or warnings. If a patient is harmed by such use of a medicine then the manufacturer is unlikely to be found liable, unless the harm is directly attributable to a defect in the medicine, rather than the way in which it was prescribed, e.g. sodium valproate as a mood stabiliser or use of medicines licensed for use only in adults, for the treatment of children.

**Unlicensed medicines** are medicines, or substances used as medicines without a UK marketing authorisation and include:

- Medicines prepared by a UK manufacturer but not for sale in the UK and may include medicines undergoing clinical trial, medicines awaiting a UK marketing authorisation, medicines withdrawn from the UK market, or medicines manufactured for export. Such medicines are usually available on an “individual patient basis”, e.g. Primidone tablets, Pyrazinamide tablets, Naproxen suspension.

- Medicines prepared outwith the UK with a marketing authorisation from the country of origin. Such medicines are imported into the UK, e.g. Formepizole (ethylene glycol antidote)

- “Specials” obtained from a hospital or commercial supplier with a manufacturer’s “specials” licence. Such medicines can be supplied against an unsolicited order or prescription e.g. Sodium chloride 1mmol/ml solution (salt replacement for cystic fibrosis patients), Captopril suspension.

- Extemporaneously dispensed medicines prepared for a specific patient under the supervision of a pharmacist in accordance with a practitioner’s prescription, including TPN compounding, IV additive & cytotoxic reconstitutions, e.g. Azathioprine suspension.

- Re-packed medicines. These are medicines which are removed from their original containers and re-packed during dispensing, e.g. Flucloxacillin capsules 250mg for a 5 day treatment course packed down from a larger manufacturers pack.

- Chemicals used to treat rare metabolic disorders, e.g. Dichloracetic acid for Leigh’s encephalopathy, L-Arginine Powder for Urea cycle disorder, Copper Histidine injection for Menkes disease / syndrome

Some of the above examples are common practice (e.g. repackaged medicines) and raise little concern for prescribers or patients, whereas others, though sometimes accompanied by published evidence of efficacy, raise concerns over unfamiliarity with prescribing, quality assurance and liability.