Policy for the prescribing and supply of unlicensed and off-label medication

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Title	Policy for the prescribing and supply of unlicensed and off – label medicinal products
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Associated documents	
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Sponsoring Director	

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This document was developed with permission from NHS Dorset Clinical Commissioning Group Medicines Code Chapter 6: Policy for Prescribing Unlicensed and Off Label Medicines.

1. INTRODUCTION

1.1. This policy details the Nottingham and Nottinghamshire Integrated Care Board (ICB) approach to the use of unlicensed medicinal products, and medicinal products used outside the terms of their licence (off-licence or off-label).

1.2. This document is underpinned by, and should be read in conjunction with, the documents listed in the references.

2. PURPOSE

2.1. To safeguard patients against the risk of injury and minimise the likelihood of claims against an organisation or individual prescriber contracted by the Nottingham and Nottinghamshire ICB, arising from the use of medicines in an unlicensed or off-label manner.

3. SCOPE

3.1. The policy is to be followed by all medical staff, nursing and other health care professionals who prescribe medication as a contractor or as part of a service commissioned by the ICB.

3.2. This policy covers the use of the following within the ICB:

- Unlicensed medicines (ULM): These may be imported, or alternatively produced as a “special” in the UK by large reputable companies, small independent companies or within hospital pharmacies.

- Off-label prescribing (OLP): This includes prescribing for unlicensed indications, at higher than licensed doses, by routes and to age groups not included in the licence, etc. Also included are those situations where the form of a preparation is changed before administration (e.g. tablets needing to be dispersed, capsules opened, etc).

- Products where the licence has been suspended, revoked or not renewed (usually for commercial reasons), but where the company continues to make the product available for named individuals, e.g. co-proxamol.

- Products that are not a medicine but are being used to treat a rare condition (e.g. a metabolic disease).

3.3. The use of unlicensed medicinal products in clinical trials is outside the scope of this policy.

4. DEFINITIONS

4.1. A licensed medicine has been given a marketing authorisation (product licence) by a medicine's regulator. It has been assessed for efficacy, safety, and quality; has been manufactured to appropriate quality standards and when placed on the market is accompanied by appropriate product information and labelling.
The Summary of Product Characteristics (SPC) also specifies the licensed indications (uses) of a medicinal product and how it is to be used (e.g. doses, frequency, route, form, reconstitution, dilution etc) and when it is not to be used (contra-indications) or used with caution (special precautions).

4.2. An unlicensed medicine is a medicine that does not have a UK marketing authorisation (or product licence). These are manufactured by a licensed manufacturer but are not for sale in the UK.

4.3. A medicine may be unlicensed for a variety of reasons for example:

- New medicines, post-clinical trial, awaiting a marketing authorisation.
- It has been imported from another country.
- It has been prepared extemporaneously.
- It has been prepared under a specials licence (e.g. liquid preparations, low dose products for children, or preservative free formulations).

4.4. An off-label (or off-licence) medicine is a medicine with a product licence, but which is being used outside the terms of that licence. This may include being used for an unlicensed indication or dose, or in a patient population which has not been studied in clinical trials. In neonatal or paediatric medicine, medicines are often used 'off-label' because the cost and ethical considerations for clinical trials in children discourage manufacturers from applying for the appropriate licence for use in these age groups.

4.5. Off-label and unlicensed medicines can fall into many categories. These may include:

- products derived from licensed indications (e.g. low dose formulations for children, higher than normally recommended doses in psychiatry);
- product 'specials' (e.g. liquid products for patients unable to swallow, products free of sensitising agents).
- medicines used when the product licence has been suspended.
- compassionate use of newly developed medicines (e.g. to treat cancer).

4.6. Throughout this policy, "ULM" refers to an unlicensed medicine and "OLP" refers to Off-label prescribing.

5. LICENSING, LEGISLATION and LIABILITY

5.1. In the UK in 1971, product licensing became mandatory, and all new medicinal products entering clinical trials or proposed for marketing had to be assessed by the licensing authority for quality, safety, and efficacy.

5.2. The national regulatory authority responsible for regulating the supply and sales of medicinal products in the UK is the Medicines and Healthcare products Regulatory Agency (MHRA). The equivalent organisation in Europe is the EMEA, European Agency for the Evaluation of Medicinal Products.

5.3. Registration of medicinal products has evolved to ensure the safety of the patient by controlling the quality and efficacy of all medicinal products on the market. Registration protects the patient from false medical claims, ensures medicine purity and prevents the incorrect use of medicines.

5.4. A marketing authorisation (or product licence) is held by the company responsible for the composition of the medicine or for placing the medicine on the UK market. It guarantees the quality, efficacy and safety of the medicine and the holders of the licence are responsible for these aspects and liable for any adverse effects resulting from the use of the product.

5.5. An ULM or OLP may be recommended in secondary care with an expectation that prescribing will continue in primary care. Prescribers should take into account the category of risk involved (see Appendix 1) when considering whether to accept clinical and legal responsibility.

5.6. In the case of ULMs and OLP, if an adverse incident were to occur, clinical responsibility and legal liability rests with the prescriber.

5.7. Exceptions to the general rule for which certain healthcare professionals can sell, supply, and/or administer medicines to patients under Schedule 17 of the Human Medicines Regulation 2012 are also known as exemptions.
Medicines intended to be used for an off-label indication (only when clearly justified and supported by best clinical practice) can be administered under the Schedule 17 exemptions. Further information on exemptions can be found on the MHRA website.

6. RISK MANAGEMENT (also see Appendix 1)

Prescribers should pay particular attention to the risks associated with using ULM or OLP. These risks may include adverse reactions, product quality or discrepant product information or labelling (e.g. absence of information for some unlicensed medicines, information in a foreign language for unlicensed imports, and potential confusion for patients or carers when the patient information leaflet is inconsistent with a medicine's off-label use).

Those involved in the prescribing, supply or administration should be aware of:

- The status of the product in question
- Relevant risks associated with the proposed use
- Their position with regard to legal liability. **Prescribers should check with their professional defence organisation, if they have concerns, before prescribing any unlicensed products.**

7. PRINCIPLES OF PRESCRIBING UNLICENSED MEDICINAL PRODUCTS (also see Appendix 2)

7.1. There are clinical situations when the use of ULMs or OLP may be judged by the prescriber to be in the best interest of the patient based on available evidence.

7.2. However, all healthcare professionals who prescribe off-licence or unlicensed medicines must do so within:

- their individual clinical competence
- the professional codes and ethics of their statutory bodies
- the prescribing policies of their employers

7.3. The responsibility that falls on healthcare professionals when prescribing an ULM or an OLP may be greater than when prescribing a licensed medicine within the terms of its licence.

8. ADVICE FOR PRESCRIBERS

8.1. The MHRA guidance states that:

- Before prescribing an unlicensed medicine, prescribers should be satisfied that an alternative, licensed medicine would not meet the patient's needs.

- Before prescribing a medicine off-label, the prescriber should be satisfied that such use would better serve the patient's needs than an appropriately licensed alternative.

8.2. Furthermore, before prescribing an ULM or OLP, prescribers should:

- Be satisfied that there is a sufficient evidence base and/or experience of using the medicine to show its safety and efficacy.
- Take responsibility for prescribing the medicine and for overseeing the patient's care, including monitoring and follow-up.
- Record the medicine prescribed and, where common practice is not being followed, the reasons for prescribing this medicine.
- Have given patients, or those authorising treatment on their behalf, sufficient information about the proposed treatment, including known serious or common adverse reactions, to enable them to make an informed decision.

8.3. Where current practice supports the use of a medicine outside the terms of its licence, it may not be necessary to draw attention to the licence when seeking consent. However, it is good practice to give as much information as patients/carers/guardians require or which they may see as relevant.

8.4. Prescribers should explain the reasons for prescribing an ULM or OLP where there is little evidence to support its use, or where the use of a medicine is innovative.

8.5. Suspected adverse reactions should be reported to the Medicines and Healthcare Regulatory Authority (MHRA) and Commission on Human Medicines (CHM) via the Yellow Card Scheme (see www.yellowcard.gov.uk). Such reporting is equally important for unlicensed medicines or those used off-label as for those that are licensed.

8.6. In cases of suspected adverse or unexpected reactions, clinicians should use the Yellow Card System to notify the (MHRA) and the pharmaceutical company concerned. In addition, a significant event form should also be completed and sent to the ICB.

8.7. The prescriber's responsibility and potential liability are increased when prescribing 'off-label'.

9. REQUESTS TO PRESCRIBE UNLICENSED / OFF LABEL MEDICINES FROM SECONDARY CARE

9.1. Any specialist who asks a GP to prescribe an ULM or OLP should clearly state the licence status of the medicine. The specialist initiating therapy must ensure that the GP is aware of their responsibilities in relation to prescribing the medicine on an unlicensed or off-

label basis. Where this information is not provided by the specialist the GP should seek clarity from them before taking over prescribing.

9.2. The specialist must present the case for using this medicine and justify its use in preference to licensed alternatives. The evidence base behind the recommendation must be given and it should be made clear whether the treatment recommended is a peer-supported option. Where this information is not provided by the specialist the GP should seek clarity from them before taking over prescribing.

9.3. The specialist initiating therapy must inform the patient of the unlicensed / off-label use of the medicine and obtain their informed consent for its use.

9.4. The specialist must ensure that the patient is aware of the known side-effects of the medicine and that there may be other unknown side-effects.

9.5. It should not be assumed that GPs will take on responsibility for prescribing ULMs or OLP. Unless there is a mutual agreement for the GP to take over prescribing responsibility, this should continue to rest with the specialist initiating treatment.

9.6. The GP should reassure themselves that a body of medical opinion supports the use of the medicine in these circumstances e.g., check in an appropriate formulary for paediatric use.

9.7. The GP should keep detailed notes of the reasons for using an ULM or OLP, documentation of patient consent and consultation notes. The GP must also satisfy their selves that the patient has been informed about known side effects and is aware that there may be other unknown side-effects.

9.8. Prescribing responsibilities between the specialist and the GP must be clearly documented and state the specific responsibilities of each party. Shared-care agreements, where available, should be used to assist in this process.

9.9. In addition, the patient must be reviewed regularly to assess benefit and adverse effects. Outcomes of these reviews must be shared with the GP, wherever possible.

9.10. Secondary care clinicians should not recommend the use of medicines to GPs or patients that are categorised as “red” or “grey” within the Nottinghamshire Joint Formulary traffic light system.

9.11. It is important that patients are not led to expect that their GP will follow a particular course of action. It is also important that there is appropriate dialogue between the specialist and GP to prevent conflicting messages being given to patients and carers.

9.12. Where there is a financial concern in terms of the impact on primary care medicine budgets, this needs to be clarified before treatment is initiated.

10. NON-MEDICAL PRESCRIBERS (NMPs)

10.1. Independent prescribers

Under current legislation independent prescribers such as nurses, optometrists, physiotherapists, therapeutic radiographers, podiatrists, paramedics, and pharmacists can prescribe an unlicensed or off-label medicine. However, to do so these NMP’s must ensure the following conditions are met:

- The NMP is satisfied that it would better serve the patient/client's needs than an appropriately licensed alternative.
- The NMP is satisfied that there is a sufficient evidence base and/or experience of using the medicine to demonstrate its safety and efficacy. Where information from the manufacturer is of limited help, the necessary information must be sought from another source (for example, a Medicines Information Centre).
- The NMP should explain to the patient/carer/guardian in broad terms, the reasons why the medicines are not licensed for their proposed use.
- The NMP must make a clear, accurate, and legible record of all medicines prescribed and the reasons for prescribing an 'off-label or unlicensed medicine.

10.2. Supplementary prescribers

Supplementary prescribers (prescribing in partnership with an independent prescriber such as a doctor or a dentist) must not prescribe an unlicensed medication independently. However, they may prescribe unlicensed medication as a supplementary prescriber as part of a clinical management plan providing:

- The doctor/dentist and NMP acting as a supplementary prescriber have agreed the plan with the patient in a voluntary relationship.
- The NMP is satisfied an alternative, licensed medication would not meet the patient's need.
- The NMP is satisfied there is a sufficient evidence base and/or experience to demonstrate the medications safety and efficacy for that particular patient.
- The doctor/dentist is prepared to take the responsibility for prescribing the unlicensed medicine and has agreed the patient's clinical management plan to that effect.
- The patient agrees to a prescription in the knowledge that the medicine is unlicensed and understands the implications of this.
- The medication chosen and the reason for choosing it is documented in the clinical management plan.

11. INFORMATION TO PATIENTS AND/OR PARENTS AND CARERS

11.1. Healthcare professionals must respect the rights of patients and where appropriate carers to be involved in any discussion relating to their care and ensure that any decisions are properly informed. Individual patients and carers must be made aware that an ULM or OLP is being prescribed and of the potential risks (e.g., possible side effects).

11.2. In general, no additional steps, beyond those taken when prescribing licensed medicines, are required to obtain the consent of patients. However, it is good practice to seek consent and include an appropriate record of any discussion in the patient's notes, particularly if the risk of harm is significant or unknown, the evidence in support of the product use is minimal or the product has previously been withdrawn from the market because of serious toxicity problems. The patient should also be advised that sometimes it may take longer to source an unlicensed medication.

11.3. Patients and/or carers should be given clear written information (or a form which is suitable to their needs) on the use of the unlicensed or off label medicines. A generic information leaflet can be provided to help patients understand what an unlicensed medication is. It is noteworthy that the manufacturer's patient information leaflet may be inappropriate for OLP use and may be non-existent for ULMs or "specials".

12. OBTAINING SUPPLIES

12.1. It should be noted that unlicensed medicines may be 'specials' that community pharmacies may have difficulty in obtaining.

12.2. Unlicensed medicines need to be obtained from the 'special-order' manufacturers and specialist-importing companies on a named-patient basis.

12.3. Adequate time must be allowed for products to be obtained. Until a regular supply is established in primary care, secondary care should continue to obtain supplies for the patient.

13. TRAINING AND CONTINUING PROFESSIONAL DEVELOPMENT

13.1. All Health Professionals contracted to provide services to the ICB are responsible for maintaining their own CPD, and seeking updates when alerts arise. The ICB will provide direction to suitable resources if appropriate.

14. REFERENCES

- The supply of unlicensed medicinal products ("specials). MHRA Guidance Note 14. Medicines and Healthcare Products regulatory Agency. 6 May 2014.
- Off-label or unlicensed use of medicines: prescribers' responsibilities. Medicine Safety Update. April 2009: 2(9): 6-7. Medicines and Health care products Regulatory Agency.
- Nurse and midwife independent prescribing of unlicensed medicines. Nursing and Midwifery Council circular. 10 March 2010
- The Royal Pharmaceutical Society. Prescribing Specials Guidance for the prescribers of Specials, April 2016
- Use of off-label or unlicensed products under Human Medicines Regulations 2012 Schedule 17 exemptions – SPS - Specialist Pharmacy Service – The first stop for professional medicines advice
- Unlicensed medicines – information leaflet for patients SFH
- Prescribing unlicensed medicines - ethical guidance - GMC (gmc-uk.org)
- The Human Medicines Regulations 2012 (legislation.gov.uk)
- Non-medical prescribing | Advice guides | Royal College of Nursing (rcn.org.uk)
- Medicines for children - Unlicensed medicines – Medicines For Children

APPENDIX ONE

CATEGORISATION OF POTENTIAL RISKS ASSOCIATED WITH PRESCRIBING AND SUPPLY OF UNLICENSED MEDICINES

This categorisation is NOT intended to be prescriptive but is provided as an aid to developing an understanding of the risk/benefit profile of unlicensed medicines or off-label use of licensed medicines. A greater degree of caution should be exercised with increasing risk.

HIGHER RISK – unlikely to be suitable for use within primary care

- Very limited evidence in support of proposed product and/or its use
- Limited evidence of toxicity and other risks
- Medicines withdrawn from the market due to concerns with safety
- Little or no assurance of pharmaceutical quality
- Vaccines, blood products or other biologicals
- Any product containing material of animal origin
- Examples may include those medicines listed as RED in the traffic light system, medicines administered by an unusual route e.g. intra-thecal, intra-occular or nebulised or a preparation that needs to be specially manufactured.

INTERMEDIATE RISK – could be considered for use in primary care, but should be considered and approved by the Area Prescribing Committee as appropriate i.e. Amber 1 or an Amber 2 medicine

- Complicated disease area or requirements for monitoring
- Medicines never licensed in the UK or discontinued on economic grounds
- Limited assurance of pharmaceutical quality [For example, products imported from abroad, where quality will only be as good as standards applying in the exporting country (no testing to UK standards on entry). The potential for the supply chain environment (hot/cold/humidity) to impact adversely on product stability should be considered.]
- Extemporaneously prepared products (where there is no Quality Control testing before release to patient), e.g. a suspension of crushed tablets
- Examples may include azathioprine for Inflammatory bowel disease or rheumatology, lamotrigine for bi-polar disorder

LOWER RISK – prescribing could be initiated by GP

- Off-label use of licensed products [assuming no reckless disregard for precautions and warnings], BUT do still need to consider whether quality is appropriate to intended use, particularly if different route of administration
- “Specials” manufactured in premises licensed by the MHRA
- Established practice endorsed by a national reference e.g. BNF, BNFc, Medicines for Children, Palliative Care Formulary, Royal College/Society guidelines
- Examples may include nortriptyline for neuropathic pain.

N.B. More than one of the above situations could apply. In which case, the highest category of potential risk should take precedence in any determination of overall risk. [For example, a special, with very limited evidence to support its use in a complicated disease area, would fall into the higher risk category.]

APPENDIX TWO

MHRA RISK HIERARCHY FOR THE USE OF UNLICENSED MEDICINES

• An unlicensed product should not be used where a product available and licensed within the UK could be used to meet the patient's special need.

• Although the MHRA does not recommend "off label" (outside of the licensed indications) use of products, if the UK licensed product can meet the clinical need, even "off-label", it should be used in preference to an unlicensed product. Licensed products available in the UK have been assessed for quality safety and efficacy. If used "off-label" some of this assessment may not apply, but much will still be valid. This is a better risk position than in the use of an unassessed, unlicensed product. The fact that the intended use is outside of the licensed indications is therefore not a reason to use an unlicensed product. It should be understood that the prescriber’s responsibility and potential liability are increased when prescribing off-label.

• If the UK product cannot meet the special need, then another (imported) medicinal product should be considered, which is licensed in the country of origin.

• If none of these options will suffice, then a completely unlicensed product may have to be used, for example, UK manufactured "specials", which are made in GMP inspected facilities, but which are otherwise unassessed (GMP inspection of specials manufacturers is not product specific). There may also be other products available which are unlicensed in the country of origin.

• The least acceptable products are those that are unlicensed in the country of origin, and which are not classed as medicines in the country of origin (but are in the UK). Hence, for example, the use of melatonin products from the USA, where melatonin products are classed as supplements, not pharmaceuticals and may not be made to expected standards of pharmaceutical GMP should be avoided whenever possible.

APPENDIX THREE

Use Of Unlicensed Medicines Or Licensed Medicines For Unlicensed Applications

The use of unlicensed medicines or licensed medicines for unlicensed applications in paediatric practice | RCPCH (December 2017).

- Those who prescribe for a child should choose the medicine which offers the best prospect for that child, aware that such prescribing may be constrained by the availability of resources. Children should be able to receive medicines that are safe, effective, appropriate for their condition, palatable and available with minimal clinical risk.
- The informed use of some unlicensed medicines or licensed medicines for unlicensed applications is necessary in paediatric practice.
- Health professionals should have ready access to sound information on any medicine they prescribe, dispense or administer, and its availability.
- In general, it is not necessary to take additional steps, beyond those taken when prescribing licensed medicines, to obtain the consent of parents, carers and child patients to prescribe or administer unlicensed medicines or licensed medicines for unlicensed applications.
- NHS Trusts and Health Authorities should support therapeutic practices that are advocated by a respectable, responsible body of professional opinion.
- Where available an appropriate licenced product should be prescribed and supplied in preference to an unlicensed product.

Suggested procedure when prescribing medication 'off-label' (Royal College of Psychiatrists, December 2017)

1. Check that medicines with a product licence have either had a proper therapeutic trial or been considered but excluded on clinical grounds (such as contraindications and risk of interactions).
2. Familiarise yourself with the evidence about the proposed medicine, including any possible medicine interactions and potential adverse effects.
3. If the medicine to be used does not have a substantial evidence-base supporting its use for the proposed indication, or if you are not sufficiently expert in this field, or have particular concerns, obtain the advice of another doctor or specialist pharmacist.
4. Consider the risks and benefits of the proposed treatment. Particular consideration is needed with children, elderly patients, and in those with impaired insight and judgement. Document this.
5. Give the patient (or his/her relative, carer - when relevant) a full explanation, including the information that the medicine will be used outside its product license. Document this explanation.
6. If agreement from the patient (or his/her relative, when needed) is obtained, document this approval. If a patient is unable to consent to a necessary treatment, note that it has not been possible to obtain consent.
7. Begin a cautious trial of treatment with the medicine. In out-patients, consider sending the patient a copy of any letter sent to his/her general practitioner, summarising why this approach has been adopted. Start with low dose. If medication is well tolerated but not effective consider a slow dose increase.
8. Monitor the patient closely. Continue with full documentation of its effectiveness and tolerance.
9. If the treatment proves unsuccessful, withdraw it, gradually if needed. Document the reason for the withdrawal of treatment, then consider alternatives, using the same process.
10. Consider writing up the case, to add to the available knowledge about the medicine and its use.

Version Control- Policy for the prescribing and supply of unlicensed and off-label medication			
Version	Author(s)	Date	Changes
1.1	Michalina Ogejo – Medicine Optimisation and Interface Pharmacist	April 2023	Updated front page (logo and table content) Updated table of contents (page 2) Changed CCG to ICB (throughout the document) 4.1. Added information about SPC. 4.2. Added details about unlicensed medicine. 4.3. Amendment to the listed examples. 5.7. Added section 5.7. 8.7. Added section 8.7. 10.1. Added other IPs: physiotherapists, therapeutic radiographers, podiatrists, paramedics. 10.2. Added *Supplementary prescribers (prescribing in partnership with an independent prescriber such as a doctor or a dentist)* 11.3. Added patient information leaflet and link to it. 14. Added new and updated current references links. Appendix 1 – lower risk, nortriptyline instead of amitriptyline. Appendix 3 – updated links and added *Where available an appropriate licenced product should be prescribed and supplied in preference to an unlicensed product.*