Procedure for the use of unlicensed medicines

Purpose of this procedure:

The aim of this procedure is to provide details of the steps involved in the safe procurement, supply and use of unlicensed medicines. It is applicable to patients being treated with unlicensed medicines within primary care and secondary care across NHS Lothian. It describes good practice and provides support for prescribers in the use of unlicensed medicines.

The objectives of this procedure are to:

- Provide guidance on the prescribing and use of unlicensed medicines in adults and children across NHS Lothian.
- Provide support for primary and secondary care prescribers in the use of unlicensed medicines, including continuity of supply when transferring patients between the sectors.
- Describe the responsibilities of healthcare professionals when prescribing an unlicensed medicine.
- Describe the system of categorisation of unlicensed medicines and formulary classification in NHS Lothian.

For the purposes of this procedure an 'unlicensed medicine' is a medicine without a marketing authorisation as defined by the Medicines and Healthcare Products Regulatory Agency (MHRA).[1]

Definitions are detailed in Appendix 1

Medicines legal position is detailed in Appendix 2

Professional guidance is detailed in Appendix 3

Liability

If an untoward incident occurs with a licensed medicine that is the result of a product defect, or a problem with its use in an approved clinical situation (as defined in the marketing authorisation) any liability arising may in part or whole be transferred to the manufacturer.

Should a patient suffer harm as a result of the effects of an unlicensed medicine then the manufacturer is not liable , unless the medicine was shown to be defective.

Prescribing medicines outside the recommendations of their marketing authorisation increases the prescriber's professional responsibility and potential liability. The prescriber should be able to justify and feel competent in using such medicines, and inform the patient or the patient's carer that the prescribed medicine is unlicensed.[2]

Prescribers should pay particular attention to the risks associated with using unlicensed medicines or using a licensed medicine off-label. 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).[3] Prescribers are responsible for prescribing within their sphere of clinical competence and for the ongoing monitoring and review of the patient. All unlicensed medicines will be categorised as **green**, **amber** or **red** when placed on an approved list of unlicensed medicines. All Formulary Decisions on unlicensed medicine indications are published on the Formulary website.

A pharmacist will share liability with the prescriber; as the purchaser of the product, particularly where this involves defining the specification of the product to be purchased, especially if his or her actions or omissions have contributed to the harm.[4]

Indemnity
NHS Indemnity applies to staff in the course of their NHS employment. It does not apply to independent contractors under contract for services.[5]

The Procedure:

Roles and Responsibilities are described as a series of steps .

Patients, Relatives and Carers

1
Informing the specialist team, GP or other healthcare professional, if they do not have a clear understanding of the treatment.

2
Reporting any adverse effects to the specialist team, GP or other healthcare professional involved in their care.

3
Sharing any concerns about their treatment and compliance with the specialist team, GP or other healthcare professional involved in their care.

4
Carers have a responsibility to support the patient in fulfilling their roles and responsibilities as outlined above.

Prescribers

Includes non-medical prescribers.[6,7]

 **1**

Unlicensed medicines should only be used where their use is clearly justified and their clinical and pharmaceutical benefits are considered to outweigh the risks involved. The prescriber is professionally accountable for this judgement and may be called upon to justify their actions. An unlicensed medicine not on formulary should not be prescribed without direct consultant instruction. An unlicensed medicine or off-label use of a medicine that is flagged within the Formulary as Specialist Initiation (SI) or Specialist Use Only (SUO) should also not be prescribed without direct consultant instruction. Formulary flags which relate to unlicensed medicines are detailed in the table below.

SI	Specialist Initiation: may be continued in a primary care setting
SUO	Specialist Use Only: must only be prescribed by a specialist
UM	Unlicensed Medicine: a medicine with no UK marketing authorisation
UI	Unlicensed Indication: licensed medicine being used outside the terms of its licence

 **2**

It is the responsibility of the prescriber to ensure patients (or their parents or carers) are provided with sufficient information about the unlicensed medicines being prescribed; including information on side effects, to allow them to make an informed decision on consent.[3,7] In line with the NHS Lothian consent policy.

 **3**

If the intention is to prescribe unlicensed medicines where the treatment is not routine or if there are suitably licensed alternatives available, this should be explained to the patient, including the reasons for doing so.[8]

 **4**

In emergencies it may not be practical to explain the details of unlicensed medicines being used. In other cases, where prescribing unlicensed medicines is supported by authoritative clinical guidance or protocol, it is still necessary to explain the use of the unlicensed medicine. Questions from patients (or their patients or carers) about medicines must always be answered fully and honestly. [3,7]

 **5**

Prescribing a medicine off-label or prescribing an unlicensed medicine where there is little evidence to support its use, or where the use of a medicine is innovative this must be explained to the patient

or carer and explicit informed consent should be obtained. In line with the NHS Lothian consent policy.

 6

When handing over prescribing responsibilities during transition of care, the indication and reasons for choosing the unlicensed medicine are important and must be shared so that the new prescriber, supported by a pharmacist, can consider alternative available products as the patient's needs change.

 7

If the unlicensed medicine is not included in the formulary (this includes when the unlicensed medicine is not included for the indication and patient group in question), the clinician must complete (jointly with the pharmacist) a non-formulary medicine request form for the individual patient. This applies for individual patients at treatment initiation and until the unlicensed medicine is classified as routinely available on the formulary, see Appendix 4.

Clinical teams can apply for the use of an unlicensed medicine in a patient group using either a Formulary Amendment Form or a Formulary Application Form (FAF3) as appropriate. Forms are completed jointly by a clinician and pharmacist on behalf of the clinical team and submitted to formulary committee for approval, see Appendices 5 & 6 respectively.

Medicines governance processes are detailed in Medicines Governance Applications & Forms Flowcharts, see Appendix 7.

Pharmacy Staff

 1

Pharmacy staff should:

- Notify prescribers of licensed alternative products becoming available where appropriate
- Notify clinicians of any serious problems that they are alerted to with individual unlicensed medicines
- Report any defect in an unlicensed medicine through the relevant reporting routes
- Ensure that individual patients are given information regarding the availability of unlicensed medicines to pass on to the community pharmacist to ensure continuity of supply
- Inform primary care pharmacists, where available, at transition of care.

 2

Pharmacists work closely with patients and other health professionals to reach a joint decision on which treatment option best suits an individual patient's needs. This is based on the risks and benefits of each option and supported by high quality information that includes the licensed status of the chosen treatment.[9]


3

Pharmacy staff will ensure, as far as is practicable, that the prescriber is aware that a medicine they have requested is only available on an unlicensed basis, and will provide advice on alternative licensed products.


4

If in the professional opinion of a pharmacist the use of an unlicensed medicine would be unsafe for a given patient and would not be supported by a peer group review it is their professional responsibility not to supply it. Such cases will be referred to the relevant Drug and Therapeutics Committee for local review.


5

If the unlicensed medicine is not included in the formulary (this includes when the unlicensed medicine is not included for the indication and patient group in question), the pharmacist jointly with clinician must complete a non-formulary medicine request form for the individual patient. This applies for individual patients at treatment initiation and until the unlicensed medicine is classified as routinely available on the formulary, see Appendix 4.

Clinical teams can apply for the use of an unlicensed medicine in a patient group using either a Formulary Amendment Form or a Formulary Application Form (FAF3) as appropriate. The form to be completed by the pharmacist jointly with a clinician on behalf of the clinical team and submitted to formulary committee for approval, see Appendices 5 & 6 respectively.

Medicines governance processes are detailed in Medicines Governance Applications & Forms Flowcharts, see Appendix 7.

When a patient transfers from one care setting to another; there is a need for the original prescriber and pharmacist to share information on the unlicensed medicine in a timely manner with new prescribers and pharmacists.

Medicines Governance

Prescribers

Includes non-medical prescribers[6,10]


1

When an unlicensed medicine is to be recommended for use in a patient group, and it has not previously been used within NHS Lothian or where the medicine is not yet included on the formulary for the indication, the clinician, with support from clinical pharmacist, should follow Medicines

Governance Applications & Forms Flowchart and complete a request form to use an unlicensed medicine before the product can be supplied.

If the medicine is a new off-label use for a UK licensed product the Medicines Governance Applications & Forms Flowchart should be followed.

2

A Formulary Application Form (FAF3) or a formulary amendment request form should be completed by the responsible clinician, with the support of the appropriate clinical pharmacists in the following circumstances:

- When the treatment is **not** for a 'one off' use
- When the treatment is for a patient group

Completed forms should be submitted to East Region Working Group (ERWG) for support prior to being submitted to the East Region Formulary Committee (ERFC).

3

Other clinical staff involved in the treatment of a patient with an unlicensed/off-label medicine should, where appropriate (and particularly for unlicensed medicines in the red category) be:

- Made aware of its unlicensed/off-label status
- Informed of any problems and risks involved and how to deal with them
- Given sufficient information to administer and use the product safely and correctly.

4

In clinical areas where there is a requirement for high levels of usage of such medicines (i.e. neonatal units, critical care, etc.) staff should be aware of the issues surrounding unlicensed drug usage and approach the use of medicines in their areas accordingly.

5

General practice recommendations – the consultant recommending the unlicensed medicine use is responsible for ensuring that the GP is given sufficient information about the product and its availability to allow safe and appropriate prescribing. At transition of care and handover of prescribing responsibilities the indication and reasons for choosing the product must be provided so that the GP can consider switching to alternative licensed product if the patient's needs change.

6

Whilst the decision to prescribe an unlicensed medicine ultimately rests with the individual prescriber, it is anticipated that, in general, GPs would be expected to prescribe medicines assigned to the green category. In some circumstances a GP may be asked to continue a supply following advice and provision of information from the initiating clinician with support from pharmacy team. Medicines assigned to the amber category may require a shared care approach to prescribing. GPs are not expected to prescribe medicines assigned to the red category. See 'Medicines Governance Committees' below.

Adverse drug reactions and medication incidents involving unlicensed medicines should be reported in the same manner as for licensed medicines via the Yellow Card Scheme – Yellow Card Centre Scotland www.yccscotland.scot.nhs.uk or telephone 0131 242 2919.

Pharmacy Staff

The Royal Pharmaceutical Society's professional standards for hospital pharmacy services states that governance arrangements should be consistent with the MHRA position on unlicensed medicines.[8]

A risk assessment is undertaken to determine the suitability and quality of the unlicensed medicine before a clinical decision is made to recommend its use in a patient population. A risk assessment for an unlicensed medicine form (Appendix 5) must be completed. This should be a collaborative process between the Clinical pharmacist and QA and will enable documentation of actions to be taken to mitigate any risks, for example over labelling of foreign labelled packages and insertion of translated information. If deemed suitable for use then after procurement the medicine must be assessed before supply to ensure that it meets an acceptable standard in accordance with the relevant medicines policies and following any additional guidance from the NHS Pharmaceutical Quality Assurance Committee[3] and the MHRA.[11]

A Formulary Application Form (FAF3) should be completed by the responsible clinician, with the support of the appropriate clinical pharmacists in the following circumstances:

- When the treatment is **not** for a 'one off' use
- When the treatment is for a patient group

The FAF3 should be submitted to East Region Working Group (ERWG) for support prior to being submitted to the East Region Formulary Committee (ERFC).

Medicines Governance Committees

Secondary care Drug and Therapeutics Committees will review submissions and where deemed appropriate will forward to the East Region Working Group (ERWG) for support prior to being submitted to the East Region Formulary Committee (ERFC), who will provisionally categorise it **green**, **amber** or **red**. The Formulary flags of Specialist Initiation SI or Specialist Use Only SUO will be applied to unlicensed medicines when incorporated into the formulary.

In general, only new medicines or new indications for existing medicines will be assigned to one of the three categories. However, medicines in current use may be considered if a specific request is made or concerns are raised, for instance, if a GP practice is asked to prescribe an existing unlicensed medicine for the first time.

If appropriate (**green** or **amber**), the submission would be forwarded to the General Practice Prescribing Committee (GPPC) for consideration. GPPC would either endorse the proposed category or discuss the submission further with the East Region Formulary Committee before agreeing the category. For some medicines categorised as **amber**, a request for a shared care arrangement may be made.

All medicines categorised **green**, **amber** or **red** are placed on an approved list of unlicensed medicines. Formulary Decisions are published on the Formulary website.

The ADTC endorses this process and manages appeals from prescribers.

List of Appendices

Appendix 1
Definitions

Licensed medicines: medicines with a UK marketing authorisation are referred to as a 'licensed drug', 'licensed medicine' or a 'licensed product'[1], when prescribed within the terms of their marketing authorisation the manufacturer is likely to be found liable for any harm caused by that medicine.

Unlicensed medicines: medicines without a UK marketing authorisation are referred to as 'unlicensed medicines'[1], may include medicines undergoing clinical trial, medicines awaiting UK marketing authorisation, medicines withdrawn from the UK market, or medicines manufactured for export.

'Specials': medicines obtained from a hospital or commercial supplier with a manufacturer's 'specials' licence which have been specially manufactured or imported to the order of a doctor, dentist, nurse independent prescriber, pharmacist independent prescriber or supplementary prescriber for the treatment of individual patients.[3, 10]

Off-label medicines: licensed medicines, prescribed for an indication not covered by the licence, or via a different route that is out with the terms of the marketing authorisation. 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. The GMC, in its document 'Good practice in prescribing and managing medicines and devices (2013)',

revised its guidance; where licensed medicines that are used outside the terms of their UK licence (i.e. used off-label), are described as 'unlicensed medicines'.

Medicines prepared out with the UK with a licence in the country of origin: medicines imported into the UK.

Extemporaneously dispensed medicines: prepared for a specific patient under the supervision of a pharmacist in accordance with a practitioner's prescription, including Total Parenteral Nutrition compounding, intravenous additive and cytotoxic reconstitutions.

Re-packed medicines: medicines removed from their original containers and repacked during dispensing or ward stock 'packdown' procedures.

Chemicals used to treat rare metabolic disorders: chemicals used for a medicinal purpose and treated as medicines for the clinical treatment of patients; these agents have not been approved for safety, quality and efficacy; any such agents purchased for treating patients should be of an appropriate quality.

Non-Medical Prescribers: Independent prescribing is defined as 'a practitioner, who is responsible and accountable for the assessment of patients with undiagnosed or diagnosed conditions and can make prescribing decisions to manage the clinical condition of the patient.' Supplementary prescribing is defined as, 'a voluntary partnership between an independent prescriber (doctor/dentist) and a supplementary prescriber, to implement an agreed patient/client-specific Clinical Management Plan (CMP) with the patients agreement.'[6].

Appendix 2
Legal Position

The Medicines and Healthcare Products Regulatory Agency (MHRA) is responsible for ensuring that medicines and medical devices meet applicable standards of safety, quality and efficacy. The regulation of medicines in the UK market is undertaken by MHRA in accordance with the Human Medicines Regulations 2012 (SI 2012/1916).[11]

A Marketing Authorisation (MA) or product licence defines a medicine's terms of use. A licensed medicine has been assessed for efficacy, safety and quality, has been manufactured to appropriate high standards, and when placed on the market is accompanied by appropriate product information and labelling.[1] The MHRA accepts that when a licenced medicine is prescribed and/or used by a healthcare professional out with its MA, this does not create an unlicensed medicine and falls under the scope of off-label use. However, if placed on the market, for a new indication the product would require a new or extended MA, or an exemption from the need for one.[1]

Updated MHRA guidance on the supply of unlicensed medicinal products ('specials') better known as MHRA Guidance Note 14 was published in May 2014.[10] This guidance was updated following the consolidation of medicines legislation into the Human Medicines Regulations 2012 and takes into account the outcomes of relevant European court cases. It provides advice on the manufacture, importation, distribution and supply of unlicensed medicinal products for human use (commonly described as 'specials') which have been specially manufactured or imported to the order of a doctor, dentist, nurse independent prescriber, pharmacist independent prescriber or supplementary prescriber for the treatment of individual patients.

Key points from MHRA Guidance Note 14[10]

An unlicensed medicinal product may only be supplied in order to meet the special needs of an individual patient. An unlicensed medicinal product should not be supplied where an equivalent licensed medicinal product can meet the special needs of the patient. Responsibility for deciding whether an individual patient has 'special needs' which a licensed product cannot meet should be a matter for the doctor, dentist, nurse independent prescriber, pharmacist independent prescriber or supplementary prescriber responsible for the patient's care. Examples of 'special needs' include an intolerance or allergy to a particular ingredient, or an inability to ingest solid oral dosage forms. These examples are not exhaustive.

The requirement for a 'special need' relates to the special clinical needs of the individual patient. It does not include reasons of cost, convenience or operational needs. Anyone supplying an unlicensed medicinal product, where an equivalent licensed medicinal product is available must be satisfied as to the existence of a special need for the unlicensed medicinal product. MHRA expects that documentary evidence of this special need should be obtained by manufacturers, importers or distributors and that this evidence should be made available on request of the Licensing Authority. This may take the form of a prescriber's letter, however an alternative fully documented audit trail through the supply chain confirming special need may be acceptable.

Although MHRA does not recommend 'off-label' (outside the licensed indications) use of products, if a UK licensed product can meet the clinical need, even off-label, it should be used instead of an unlicensed product.

Guidance on the hierarchy for the use of unlicensed medicines is included as an appendix to Guidance Note 14. This is provided for guidance only and each case should be considered on its individual merit.

Appendix 3
Professional Guidance

General Medical Council guidance
General Medical Council guidance[7] recommends that doctors should '**usually prescribe licensed medicines in accordance with the terms of their licence. However, they may prescribe unlicensed or off-label medicines where, on the basis of an assessment of the individual patient, they conclude, for medical reasons, that it is necessary to do so to meet the specific needs of the patient**.'

The GMC offered a further elaboration: **'For clarity, in GMC guidance the term 'unlicensed medicines' refers to both medicines with no UK licence, and those being used outside of the terms of their licence (commonly referred to as 'off-label').[12]**

Royal Pharmaceutical Society professional standards
The Royal Pharmaceutical Society's professional standards for hospital pharmacy services[8] states:

Governance arrangements, aligned to medicines regulations, are in place for the management of all medicines. This includes off-label use of medicines, unlicensed medicines, radiopharmaceuticals, Investigational Medicinal Products and Advanced Therapy Medicinal Products.

The use of any type of unlicensed medicine, including those that are aseptically or extemporaneously prepared is clinically justified and consistently in line with regulatory requirements, adhering to the principles of risk-benefit to the patient and using licensed medicines wherever possible.

Nursing and Midwifery Council guidance -
The RPS; A Competency Framework for all Prescribers was adopted by NMC 28 January 2019; defines unlicensed medicines.
Unlicensed Medicines (also known as specials): A medicinal product without a valid UK marketing authorisation. These may be medicinal products that are imported, procured or manufactured under a UK specials manufacturing licence. They are prescribed to meet the special clinical needs of an individual patient on the direct personal responsibility of the prescriber.[5]

Appendix 4

Request Form to Use an Unlicensed Medicine

Links are provided to Policy Online [under the Safe Use of Medicines Policy]
https://policyonline.nhslothian.scot/Policies/Pages/safe-use-of-medicines-policy.aspx#tab5

Appendix 5

Use of Unlicensed Medicines - Risk Assessment Form

Links are provided to Policy Online [under the Safe Use of Medicines Policy]
https://policyonline.nhslothian.scot/Policies/Pages/safe-use-of-medicines-policy.aspx#tab5

Appendix 6

Formulary Application Form 3

Links are provided to forms Online [under Lothian Joint Formulary]
Formulary | Lothian Joint Formulary (nhs.scot)

Appendix 7

Medicines Governance Applications & Forms Flowchart

Links are provided to Policy Online [under the Safe Use of Medicines Policy]
https://policyonline.nhslothian.scot/Policies/Pages/safe-use-of-medicines-policy.aspx#tab6

Appendix 8

Members of Short-Life Working Group

Andrew Parker (Research & Coordination)	Specialist Pharmacist
Anne Gilchrist	Lead Pharmacist, Medicines Governance and Guidance
Tracy Duff	Senior Pharmacist, Royal Infirmary of Edinburgh
Mr James McDade	Principal Pharmacist, Quality Risk and Governance Services
Julie Harrold	Purchasing and Medicines Supply Manager, Royal Infirmary of Edinburgh
Joanne Webster	Specialist Pharmacist, Medicines Management Team
Jenny Scott	Lead Clinical Pharmacist, NHS Lothian
Lesley Macher, Professional Secretary to ADTC	Specialist Clinical Pharmacist, Western General Hospital

Appendix 9

Medicines Governance Committees involved in Consultation

Committee	
General Practice Prescribing Committee (GPPC)	Alison MacRae Gillian Brunton Helen Christie-Thom
East Region Formulary Project Team	Jane Browning Kirsty Macfarlane
Medicines Policies Subcommittee	Jenny Scott Mary Purves
Cancer and Therapeutics Advisory Committee (CTAC)	Sally Clive Heather Dalrymple
Paediatric and Neonatal Drug and Therapeutics Committee (P&N DTC)	Rosalyn Ardill Karen Burke Erin Heaney
University Hospitals Division Drug and Therapeutics Committee (UHD DTC)	Iain MacIntyre Tracy Duff Alexander Kiker
Medicines Utilisation Review Group (MURG)	Dervilla Bray Lynne Merchant Helen Christie-Thom
Royal Edinburgh Hospital and Associated Services Drug and Therapeutics Committee (REAS DTC)	Andrew Watson Sharon Smith Joan Kelly
Patient Group Direction Committee (PGD Committee)	Garry Todd Veronica Phillips

Associated materials/references:

This procedure relates to the NHS Lothian Safe Use of Medicines Policy

[1] Off-label or unlicensed use of medicines: prescribers' responsibilities. Drug Safety Update. April 2009. Medicines and Healthcare Products Regulatory Agency. www.gov.uk/drug-safety-update/off-label-or-unlicensed-use-of-medicines-prescribers-responsibilities

[2] British National Formulary. British Medical Association and Royal Pharmaceutical Society. BNF NICE 2021. (Accessed November 2021) Guidance on prescribing | Medicines guidance | BNF content published by NICE

[3] GUIDANCE FOR THE PURCHASE AND SUPPLY OF UNLICENSED MEDICINAL PRODUCTS; Notes For Prescribers And Pharmacists: NHS Pharmaceutical Quality Assurance Committee Yellow Cover Document, Third Edition June 2004

[4] Clinical negligence and other risks indemnity scheme (CNORIS). NHS MEL (2000)18. Scottish Executive Health Department. 20 April 2000. https://www.scot.nhs.uk/sehd/mels/2000_18.pdf

[5] The Royal Pharmaceutical Society's Competency Framework for all Prescribers adopted 28 January 2019. https://www.nmc.org.uk/standards/standards-for-post-registration/standards-for-prescribers/standards-of-proficiency-for-nurse-and-midwife-prescribers/

[6] Framework for independent and supplementary prescribing. NHS Lothian. April 2020. https://policyonline.nhslothian.scot/Policies/Document/Independent%20and%20Supplementary%20Prescribing%20Framework.pdf

[7] Good practice in prescribing and managing medicines and devices. Published 5 April 2021; came into effect on 25 February 2013. General Medical Council. www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/good-practice-in-prescribing-and-managing-medicines-and-devices

[8] RPS Professional Standards for Hospital Pharmacy Services For providers of pharmacy services in or to acute hospital, mental health, private, community service, prison, hospice and ambulance settings Version 3 | December 2017 Hospital Standards-2017.pdf (rpharms.com)

[9] The Royal Pharmaceutical Society's Competency Framework for all Prescribers adopted 28 January 2019. https://www.nmc.org.uk/standards/standards-for-post-registration/standards-for-prescribers/standards-of-proficiency-for-nurse-and-midwife-prescribers/

[10] The supply of unlicensed medicinal products ('specials'). MHRA Guidance Note 14. Medicines and Healthcare Products Regulatory Agency. 6 May 2014. www.mhra.gov.uk/Howweregulate/Medicines/Medicinesregulatorynews/CON413521

[11] Human Medicines Regulations 2012 (SI 2012/1916). **The Human Medicines Regulations 2012 (legislation.gov.uk)**