GOOD PRACTICE GUIDELINES
for the management of unlicensed medicines

Prescribing unlicensed drugs or using products outwith the terms of their licence (off-label) is common but raises questions about appropriateness of therapy, liability and consent. NHS Greater Glasgow has devised a policy which should provide a helpful system to promote safe prescribing of unlicensed drugs. Dr Jennifer Burns of Glasgow Royal Infirmary led the policy development and explains some of the issues. The full document is available on hospital intranets and the ADTC website.

The Medicines and Healthcare Products Regulatory Agency (MHRA) grants UK marketing authorisations (previously known as product licences) to medicinal products that meet appropriate standards of safety, quality and efficacy for a specific use. Most prescribed medicines have a marketing authorisation and are known as licensed medicines.

The Medicines Act 1968 allows doctors to use unlicensed medicines where appropriate. Such use is so widespread that treatment of patients with unusual conditions or who are refractory to licensed treatment would be seriously impeded if the practice were to be curtailed. This issue covers two distinct categories of prescribing; use of unlicensed medicines and unlicensed (off-label) use of licensed medicines.

Unlicensed medicines have no marketing authorisation for human use in the UK. This classification encompasses:

- **products being considered by the MHRA for granting of a marketing authorisation**
- **products used in clinical trials**
- **products whose UK marketing authorisation has been suspended, revoked or not renewed, eg thalidomide**
- **products derived from licensed medicine; including any form of extemporaneous dispensing (preparation from base ingredients), eg 1% coal tar in aqueous cream or production of liquid formulations.**

Pharmaceutical companies are only obliged to seek a marketing authorisation if they intend to promote the product for that specific indication. There may be evidence that a drug is effective for a condition other than those covered by the licence. Prescribing other than in accordance with the licence is referred to as off-label use. This is relatively common; well recognised examples include amitriptyline for neuropathic pain and valproate for migraine prophylaxis. Some off-label use may be less established but might be considered when other therapeutic choices have been exhausted. This should be subject to careful prescribing and professional review as there are greater risks with less well established options.

Particular issues are evident in paediatrics; up to 40% of drugs prescribed for children in hospital are used outwith the licensed indication or dosage. A joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacist Group produced guidance which states that informed use of licensed medicines for unlicensed indications is necessary in paediatric practice. Divisions should support such practices as long as they are advocated by a respectable, responsible body of professional opinion, eg local formularies or the Medicines for Children book.

Given this background, a group covering primary and secondary care was convened to provide guidance on the safe use of unlicensed medicines. Key features are:

1. Licensed products should be used wherever possible.
2. Unlicensed medicines should be used only if there is no equivalent licensed medicine to satisfy a patient's specific needs.
3. Those involved in the prescribing, distribution or administration of an unlicensed medicine should, wherever possible, be aware of its unlicensed status and any relevant known adverse effects associated with its use.
4. Hospitals will implement a system for request and approval of new unlicensed medicine use. This will be monitored by the Medicines Management Committee or Drug and Therapeutics Committee.
5. For medicines used outwith their licensed indications, it is more difficult to maintain a comprehensive approach to secure approval, but the guidance will provide a clear route for approval to be granted in selected situations.
6. When using unlicensed medicines, the informed consent of the patient is required. Adequate information must be provided to ensure appropriate awareness of the problems that may be associated with their use and continuity of supply.
7. All significant adverse drug reactions to an unlicensed medicine should be reported to the CSM Scotland and documented in the patient's notes. All medication errors and any significant adverse drug reaction should also be reported via the hospital's clinical incident reporting scheme.

There is a spectrum of risk associated with prescribing. Legal responsibility for the effect of a prescribed medicine lies with the doctor who signs a prescription. If an untoward incident is caused by a product defect or occurs with use of a licensed

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Web site
http://www.show.scot.nhs.uk/ggnhsb/adtc

Incremental alphabetical list of published SMC advice on which Glasgow decisions have recently been taken.
For further information and a full list of SMC advice, visit **www.scottishmedicines.org**

Drug	Reason for consideration	Indication/pharmacology	SMC decision	Glasgow decision
Atazanavir (Reyataz®)	New medicine	Treatment of HIV-1 infected adults who have undergone antiretroviral treatment, used in combination with other antiretroviral medicinal products. Therapy should be initiated by a physician experienced in the treatment of HIV infection.	Accepted for restricted use within NHS Scotland. Restricted to use in combination with other antiretroviral medicinal products in those patients who do not require concomitant statin use.	*Formulary.* SMC restrictions apply.
Bortezomib (Velcade®)	New medicine	Treatment of patients with multiple myeloma who have already received at least two therapies, have seen their disease progress on the last therapy and who are unresponsive to alternative licensed treatments for this stage of the disease. Treatment must be initiated and administered under the supervision of a physician qualified and experienced in the use of chemotherapeutic agents.	Accepted for use within NHS Scotland.	SMC recommendation accepted. Non-*Formulary* until development of Haematology Managed Clinical Network protocol and review by Prescribing Management Group.
Buprenorphine (Transtec®) patch	New medicine	Moderate to severe cancer pain and severe pain that does not respond to non-opioid analgesics.	Not recommended for use within NHS Scotland.	Non-*Formulary.*
Duloxetine (Yentreve®)	New medicine	Treatment of moderate to severe stress urinary incontinence (SUI).	Accepted for restricted use within NHS Scotland. Restricted to use only as part of an overall management strategy for SUI in addition to pelvic floor muscle training. Patients should be reviewed after 12 weeks of therapy to assess progress and determine whether it is appropriate to continue treatment.	*Formulary.* SMC restrictions apply. Use subject to GGNHSB protocol (currently under development).
Esomeprazole IV formulation (Nexium® IV)	New formulation	Treatment of GORD in patients with oesophagitis and/or severe symptoms of reflux as an alternative to oral therapy when oral intake is not appropriate.	Accepted for use within NHS Scotland.	Non-*Formulary.*
Ibandronic acid (Bondronat®)	New medicine	Prevention of skeletal events in patients with breast cancer and bone metastases.	Accepted for use within NHS Scotland.	*Formulary.* Restricted to prescribing by specialist oncologists for prevention of skeletal events in patients with breast cancer and bone metastases.
Ibandronic acid (Bondronat®) HCM	New medicine	Treatment of tumour induced hypercalcaemia with or without metastases. Should only be used by physicians experienced in the treatment of hypercalcaemia.	Accepted for use within NHS Scotland.	*Formulary.* Restricted to prescribing by consultants treating tumour-induced hypercalcaemia.
Oxycodone IV (OxyNorm®)	New formulation	Treatment of moderate to severe pain in patients with cancer.	Accepted for restricted use within NHS Scotland. Restricted to patients who have difficulty in tolerating morphine or diamorphine therapy.	*Formulary.* Acknowledge new formulation. SMC restrictions apply.
Pimecrolimus cream (Elidel®)	Following Independent Review Panel Assessment	Short-term treatment of signs and symptoms and intermittent long-term treatment for prevention of progression to flares of mild to moderate atopic dermatitis (eczema) in patients aged 2 years and over.	Not recommended for use within NHS Scotland. NICE guidance subsequently approved this product for second line treatment restricted to initiation by physicians experienced in the management of eczema. Restricted to management of moderate eczema on the face and neck of children aged 2 to 16 years that has not been controlled by topical steroids where there is a serious risk of important adverse effects from further corticosteroid use, particularly irreversible skin atrophy.	*Formulary.* Restricted to initiation by physicians experienced in the management of eczema and as per NICE guidance.
Rabeprazole (Pariet®)	New indication	On-demand therapy in the symptomatic treatment of moderate to severe gastro-oesophageal reflux disease (symptomatic GORD) after resolution of symptoms in patients without oesophagitis.	Accepted for use within NHS Scotland.	Non-*Formulary.*
Sumatriptan Succinate tablets (Imigran Radis®)	New formulation	Acute relief of migraine attacks, with or without aura, provided there is a clear diagnosis of migraine.	Accepted for use within NHS Scotland.	*Formulary.* Acknowledge new formulation.
Teriparatide (Forsteo®)	New medicine	Treatment of established (severe) osteoporosis in postmenopausal women.	Accepted for restricted use within NHS Scotland. Restricted to initiation by specialists experienced in the treatment of osteoporosis following assessment of fracture risk including measurement of bone mineral density.	*Formulary.* Restricted to initiation by specialists experienced in the treatment of osteoporosis according to GGNHSB prescribing protocol. Prescribing by secondary care specialists only.
Valsartan / Hydrochlorothiazide (Co-Diovan®)	New medicine	Treatment of essential hypertension, in patients whose blood pressure is not adequately controlled on valsartan monotherapy.	Accepted for use within NHS Scotland.	Non-*Formulary.*
Clobetasol propionate, neomycin and nystatin (Dermovate NN®)	ADTC appeal	Short course treatment of recalcitrant eczemas, neurodermatoses, and other conditions which do not respond satisfactorily to less active steroids where secondary bacterial or candidal infection is present, suspected or likely to occur.	N / A	*Formulary.*
Palivizumab (Synagis®)	ADTC *Formulary* review	Prevention of serious lower respiratory tract disease requiring hospitalisation caused by respiratory syncytial virus (RSV) in children at high risk for RSV disease.	N / A	*Formulary*, restricted to use under GGNHSB protocol. Current programme to be consolidated into routine practice.

medicine in an approved clinical situation, any liability arising may, in part or whole, be transferred to the licence holder. This is not the case with unlicensed medicines or off-label use of licensed products. NHS Greater Glasgow could bear some responsibility for any harm resulting from prescribing of an unlicensed medicine, even when this is done in accordance with instructions or advice of a consultant and when all policies and procedures have been adhered to.

Interface with primary care

Where treatment is to be continued after hospital discharge, clear arrangements must be agreed between primary and secondary care regarding clinical and prescribing responsibility. The final decision should depend primarily on the best interests of the patient in terms of safety and convenience.

General practitioners should not normally be asked to prescribe any medicine which does not possess a marketing authorisation. Exceptions might include commonly used extemporaneous products such as GTN ointment for anal fissures, dermatological topical products, liquid medicines for patients with swallowing problems and paediatric preparations. GPs who initiate or continue unlicensed prescribing should ensure they have assessed the evidence for use of that drug, the risks and benefits for the individual patient and have obtained full informed consent. These are the recommendations of the MDDUS who can provide members with further advice if necessary.

GPs may be asked to prescribe medicines outwith their licensed indications, eg amitriptyline for neuropathic pain. Only consultants experienced in the particular speciality should recommend off-label use. They should ensure that the GP is given sufficient clinical and prescribing information about the product to allow safe and appropriate prescribing. A GP should be able to refuse such a request if they do not feel confident and competent to prescribe.

Wherever possible, GPs and hospital pharmacists should ensure that community pharmacists have sufficient information to continue to provide pharmaceutical care to patients being treated with unlicensed medicines. Community pharmacists should normally source unlicensed medicines through NHS licensed manufacturers, eg the Western Infirmary pharmacy production unit.

CFC-free beclometasone inhaler (Qvar®)

Qvar® has been added to the *Glasgow Formulary* and the standard metered dose inhaler (MDI) is being considered for designation as the formulation of choice for inhaled beclometasone. It is competitively priced and should provide reduced prescribing costs when prescribed at half the dose of beclometasone MDIs.

The link between CFCs and the depletion of the earth's ozone layer has led to the phasing out of CFC-containing medicines. This is due to be completed by 2005. Inhaled medicines have been reformulated in hydrofluoroalkane-134a (HFA) which has not been an easy process for beclometasone.

Qvar® has been available since 1998. The HFA formulation produces a solution rather than the suspension obtained in the CFC formulation, resulting in much smaller particle size. The HFA formulation has better penetration and patterns of disposition. **It is equivalent to approximately twice the dose of CFC beclometasone inhalers.** The BNF notes that, in well controlled patients, initially a 100 microgram dose of Qvar should be substituted for 200-250 micrograms of either beclometasone or budesonide or 100 micrograms of fluticasone. The British Guideline on the Management of Asthma / SIGN Guideline 63 recommends a period of close monitoring to ensure adequate control after a change from CFC beclometasone to Qvar®.

The original ADTC advice was that two equipotent MDIs should be available before CFC-free formulations would be added to the *Formulary*. It now seems increasingly unlikely that two equipotent formulations of CFC-free beclometasone will be licensed in the near future, if at all.

For all article references, contact Mrs A Lee, Principal Pharmacist, Medicines Information, Royal Infirmary, Glasgow G4 0SF tel: 0141 211 4776 fax: 0141 552 8170 e-mail: med.info@northglasgow.scot.nhs.uk or check our website.

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PostScript Primary Care is a monthly newsletter aimed at GPs and community pharmacists. You can also view this on the ADTC website or join the mailing list to receive every edition as it is published by sending a blank e-mail to pspc-subscribe@smartgroups.com

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