

Prescribing licensed medicines for unlicensed indications

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Introduction

Doctors have traditionally exercised their clinical freedom in prescribing licensed drugs for unlicensed indications for the patient's benefit. However, if they decide to go beyond the limits set out in the licence they should only do so after careful thought.

The licensing process

In the United Kingdom, the Medicines Act 1968 makes the possession at a licence necessary for anyone who sets out to manufacture or market a product for which therapeutic claims are made. The Licensing Authority, working through the Medicines Control Agency, can grant Manufacturer's Licences, and can issue a Marketing Authorisation (previously a Product Licence) allowing a company to market and supply a product for specified indications (reasons for treatment). Applications are judged on the product's efficacy, quality and safety in normal use for the specified indications; cost is not taken into account. Since the beginning of 1995 a European Union (EU) system for licensing medicines has been in operation; it must be used for certain compounds and can be used by manufacturers' choice.

The law requires that the licensed indications for proprietary medicines be listed in the Product Data Sheet (available, for example, in the Data Sheet Compendium). Under new EU regulations, a product will not be required to have a Data Sheet if it has an approved Summary of Product Characteristics (SPC). The initial marketing of a drug is usually founded on very restricted indications, for which evidence is presented to the Licensing Authority. Wider indications which come to light after further clinical trials and experience need additional submission and specific approval; in some cases a licence for a new indication may never be sought. Although doctors usually prescribe according to the licensed indications, they are not obliged to.

Prescribing outside the licence

There are several circumstances in which the prescription may go beyond the licensed indications: some of these are now discussed.

Two products containing the same active ingredient may have clear but different indications. For example, a modified-release formulation of propranolol hydrochloride (160 mg), Bedranol SR, is licensed for the treatment of hypertension and angina, whilst Inderal-LA is licensed not only for those indications, but also for the treatment of essential tremor and anxiety, for the symptoms of thyrotoxicosis, and for prophylaxis in portal hypertension and migraine. A prescription might, however, specify Bedranol SR for one of the wider indications for some concrete reason: the other product being unavailable; cost differential; or perhaps patient preference (if subjective preference meant good compliance). Alternatively, if “modified-release propranolol 160 mg” were prescribed for a patient with hyperthyroidism, the pharmacist might dispense Bedranol SR instead of Inderal-LA, and the doctor could then be said effectively to have prescribed outside the licensed indications.

In some cases the licensed indications are so broadly drawn that it may be difficult to know their limits. For example, Amfipen is proprietary ampicillin licensed for “the treatment of a wide range of infections caused by ampicillin-sensitive organisms”. However, ampicillin is often justifiably prescribed before the sensitivity of an infecting organism is known.

If a medicine is available in a generic formulation, in which case there is generally no Data Sheet available, the prescriber has to suppose that the indications are the same as for the leading branded formulation—a fair assumption, and one surely implicit in any demand to prescribe generically and not by brand.

A well-established drug may be well documented as effective in a condition for which it is not licensed, for example, amitriptyline for neuropathic pain; prescription is then justifiable.

The prescriber may be aware of evidence that a drug is effective for a new indication, for example, hydroxyurea in sickle-cell disease. He or she then has to decide, given the quality of the evidence, whether it is reasonable to prescribe the drug. In some cases, general practitioners will have received advice from a hospital consultant, and then they must either trust that advice or refuse to prescribe.

Sometimes a doctor may want to prescribe for a type of patient not described in the Data Sheet, such as a child, an elderly person, or a pregnant or breast-feeding woman. For example, the Data Sheet for Ventolin (salbutamol) syrup does not describe its use in children aged under two years. If there is published evidence of efficacy and safety in such cases, prescribing may well be judged reasonable under the criteria indicated below.

In conditions for which there is no treatment of proven efficacy from randomised clinical trials, other scientific evidence may justify the use of an unlicensed drug. This is essentially the basis on which dicobalt edetate was introduced for the treatment of cyanide poisoning: cyanide ions chelate to cobalt more avidly than to the iron in cytochromes.

Sensible prescribing

A Data Sheet may contain a bland disclaimer saying that if the product is to be used in some particular circumstance, the prescriber should weigh the benefits and risks of treatment. This simply means that the onus is on the doctor to ensure that the prescription is a sensible one, which is of course, true for all prescribing.

There are a few simple general rules that ought to govern prescribing decisions. The clinician should consider whether the patient has a condition that merits treatment, whether there is a treatment that might be expected to help, and whether the benefits of prescribing for this individual patient outweigh the risks. Before prescribing any medicine for any patient he or she should think carefully about the potential good and the possible harm that might ensue (ie, the benefit:risk ratio) in the light of published evidence.

The prescriber's decision may have to be defended against a claim for negligence, and one defence is to show that the action was reasonable in the circumstances, and that a reputable group of peers would have behaved in the same way. In this context, it is possible to draw a hierarchy of degrees of reasonableness: this is expressed in the Figure. The more dangerous the medicine, and the flimsier the evidence on which the treatment is based, the more difficult it will be to justify a decision to prescribe it. Considered and reasonable decisions, especially when recorded in the case-notes, will protect both the patient and the doctor.

When prescribing licensed drugs for unlicensed indications, doctors should inform their patients and their carers of what they are doing and why. It is also important to remember that Patient Information Leaflets (PILs) will not contain any information about unlicensed indications, and to explain that to the patient. Ideally, others involved in the patient's care should also be informed, so that misunderstandings will be avoided, although that may not always be possible. Best practice is to record in the patient's notes the reasons for any decision to prescribe outside licensed indications, and to make the patient or carer, the pharmacist, and the nursing staff all aware of the decision.

Conclusion

- It is sometimes justified to prescribe a licensed drug for an unlicensed indication. Examples include the prescribing of generic formulations (for which indications are not described), the use of well-established drugs for proven but unlicensed indications, the use of drugs for conditions for which there are no other treatments (even in the absence of strong evidence and the use of drugs in individuals not covered by licensed indications (eg. children).
- In all cases the evidence must be carefully considered and the benefit:risk ratio assessed before a drug is prescribed for an unlicensed indication
- Patients and their carers should be properly informed if a doctor prescribes a licensed drug for an unlicensed indication.