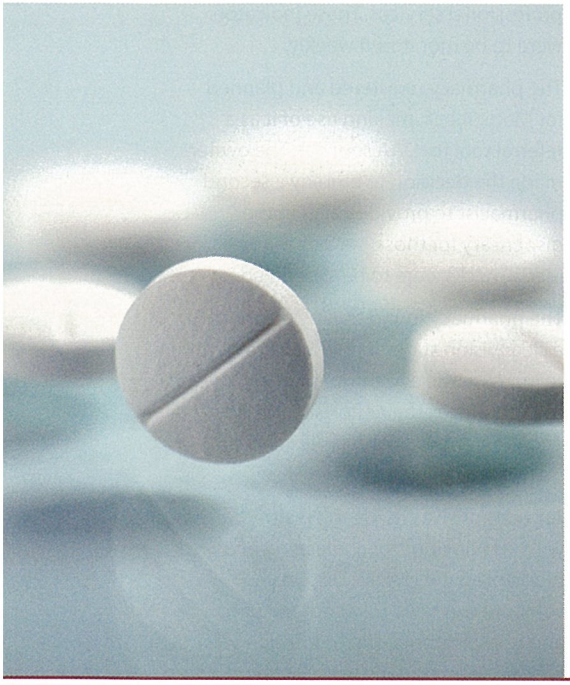

Guidelines for off-label medicines use

BY DR LAETITIA HATTINGH, MPS

The off-label prescribing and dispensing of medicine is the use of a registered medicine in a manner that is different from that approved by the Therapeutic Goods Administration (TGA).

Information about off-label or unregistered use of a medicine is therefore not included in the product information (PI) which has a summary of the scientific information relevant to the safe and effective use of a registered medicine.[1] Examples of off-label use include the use of a medicine:[2]

- For a different clinical indication,
- In unapproved subpopulations (for example: patient age range e.g. paediatric or geriatric patients, and pregnant women), and
- By varying the dosage or the method of administration.

There are various explanations as to why pharmaceutical companies may choose not to submit an application for a new indication after a product has registration with the TGA. One reason is that there may be little motivation to undertake studies for registering the medicine for a new or an uncommon indication considering the financial costs involved with the clinical trials and TGA registration processes.

Off-label use of medicines is legal and allows prescribers to use their professional clinical judgement to prescribe medicines outside the TGA approved conditions. Indeed, off-label use of medicines is common practice with research indicating rates of up to 40% in adults and up to 90% in pediatric patients.[3] The high percentage of off-label medicine use in pediatric patients is due to the fact that most medicines are registered on the basis of pre-marketing clinical trials involving adults.[4]

Clinical evidence

Clinical trials are usually carried out in restricted groups of patients and trials often exclude people who are older and in general poor health. It is therefore often only after a medicine has been registered and is being used by large numbers of patients that new indications are revealed. Knowledge about a medicine's benefits and side-effects subsequently increases over time as new evidence becomes available after the medicine has been registered. Prescribers' freedom to prescribe medicines off-label allows adopting of new practices based on the new evidence. Off-label prescribing encourages innovation in clinical practice.

However, as independent health professionals pharmacists should take appropriate precautionary measures before dispensing a medicine for off-label use. Pharmacists should be familiar with the clinical evidence to support off-label use when dispensing off-label medicine. The evidence to support off-label medicine use could be high-quality or in some cases there may be little evidence but a need to innovate. For example, when there are no alternatives and the potential benefits outweighs the risks.

Gazarian et al. defined three broad categories of off-label use, namely[3]:

- Use justified by high-quality evidence,
- Use within the context of a formal research proposal, and
- Exceptional use, justified by individual clinical circumstances.

These categories could be used to guide decisions about the appropriateness of off-label medicine use. It is also important to collaborate with the prescriber in order to establish the reason for the off-label prescribing. This information is required to be able to determine whether there is appropriate evidence to support the off-label use. Additionally, the dispensing process should involve checking whether there is not another registered medicine that could be used.

Pharmacists should consult evidence based medicine information resources to guide decision-making such as the *Australian Medicines Handbook* (AMH) or the *Therapeutic Guidelines*. The AMH signposts the off-label indications by the designation 'accepted indication'.[5]

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Informed consent

It is best for a patient or carer to know that a medicine is being prescribed and dispensed for off-label use and the reasoning behind the decision. Patients or carers may want the level of supporting evidence to be disclosed and indeed have a right to receive relevant information in order to make an informed decision. It is also important to explain that information about the indication will not be covered in the Consumer Medicines Information (CMI) leaflet as CMIs only cover the registered indications and other details from the approved PI.

Clinical judgement

Off-label use of medicines is widespread and often is clinically appropriate. However, it is a grey area with little guidance for prescribers and dispensers.[6] Pharmacists need to be aware of the risks involved as it challenges claims and expectations that medicine safety and efficacy have been fully evaluated. It raises particular concerns when medicines have high potential for toxicity.

Pharmacists should use their independent clinical judgement, based on the relevant information and evidence, to determine whether the off-label medicine will be safe and appropriate for the patient.

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Cochrane on zinc supplementation

Zinc supplements reduce diarrhoea and other infections in malnourished children, and may prevent death, according to a study published in *The Cochrane Library*. The study is the first Cochrane systematic review to focus on zinc as a means to prevent childhood death, including deaths caused by diarrhoea – one of the biggest killers of under-fives.

Zinc is a micronutrient with important roles in growth and in the immune, nervous and reproductive systems. The human body cannot make it, so it has to come from our diet. It is estimated that more than one in six people globally are deficient in zinc and that around one in every 58 deaths in children under five is related to zinc deficiency. Zinc deficiency is common in Southeast Asia, sub-Saharan Africa and parts of Latin America.

The authors were interested in whether zinc supplements could reduce childhood death and disease, and help support growth. They reviewed data from 80 trials involving 205,401 children aged six months to 12 years, mostly in low and middle income countries. Overall, they concluded that zinc supplementation could benefit children as part of wider programs to address public health and nutrition challenges in these countries.

Senior researcher Professor Zulfiqar Bhutta from the Center of Excellence in Women and Child Health, Aga Khan University, Karachi, Pakistan, and Sick Kids Center for Global Child Health, Toronto, Canada said: 'We should remember that supplements are not a substitute for a well-balanced diet. However, in countries where zinc deficiency is common, supplements may help to reduce child deaths and related diseases in the short-term.'

Dabigatran in stroke prevention

Details of a 6,000 patient study of dabigatran etexilate were announced last month at the European Stroke Conference, Nice, France.

The RE-SPECT ESUS study will investigate the blood thinner dabigatran etexilate for the prevention of recurrent stroke in patients who have already suffered an embolic stroke of undetermined source (ESUS). Such a stroke occurs when a blood clot (embolus) forms somewhere in the body and travels through the bloodstream to the brain.

Boehringer Ingelheim will investigate dabigatran etexilate in the hope that even more patients at risk of stroke can benefit from the treatment.

According to the company dabigatran etexilate has been shown to successfully prevent strokes in patients with atrial fibrillation. Effective antithrombotic therapy with dabigatran etexilate may also reduce the risk of recurrent stroke in patients who have suffered an ESUS.

Professor Hans-Christoph Diener, Chairman of the Department of Neurology at the University of Duisburg-Essen in Germany and lead investigator of the study said: 'The results obtained from the RE-SPECT ESUS study will help to address current gaps in knowledge, supporting physician choice of appropriate therapy and improving patient care.'

The study will examine the efficacy and safety of dabigatran etexilate 150 mg or 110 mg twice daily versus acetylsalicylic acid 100mg once daily for secondary stroke prevention, with patients being followed for up to three years.