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# Ongoing challenges of off-label prescribing

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## SUMMARY

Off-label prescribing refers to prescribing that is not concordant with the indications, doses, routes of administration or patient groups included in the Australian approved product information.

Off-label prescribing is common, especially for vulnerable patient groups who tend to be excluded from clinical trials, such as children and pregnant women.

There may be increased risk of prescriber liability if the patient experiences an adverse event following off-label prescription, particularly when supporting evidence or guidelines are lacking. There may be additional costs to the patient if the medicine is not subsidised for the off-label indication.

Prescribers should ensure patients are aware when a medicine is being prescribed off label, and informed of potential benefits and harms.

Alternative pathways for approval of new indications, doses and patient groups may reduce the need for off-label prescribing.

## Introduction

Off-label prescribing is common in all healthcare settings.[1-3] It is particularly common among vulnerable patient groups, including children, pregnant women, people with mental health disorders and older people.[4] Prescribers need to be aware of clinical, safety, ethical, legal and financial issues associated with off-label prescribing to ensure the quality use of medicines.

## What is off-label prescribing?

The 'label', a term used by the US Food and Drug Administration, is synonymous with the Australian approved product information (PI). The PI shows that a medicine has been registered (approved) in Australia by the Therapeutic Goods Administration (TGA). Off-label prescribing refers to prescribing that is not concordant with the indications, doses, routes of administration or patient groups included in the approved PI. The PI can be accessed by anyone via the TGA's website.

## Why does off-label prescribing occur?

Off-label prescribing often occurs because certain patient groups (e.g. children, pregnant women) were excluded from preregistration clinical trials, so the approved PI does not include these groups, even if evidence later emerges indicating that the medicine is effective and safe for them.

Pharmaceutical companies cannot promote a medicine for a use that is not consistent with the approved PI; yet they may be unwilling to prepare submissions and pay the costs associated with seeking TGA approval for additional patient groups. They may also be unwilling to prepare submissions for approval of additional indications. This is particularly likely if the anticipated financial return does not offset the cost of regulatory approval (e.g. if the medicine is low cost, there are generic or biosimilar competitors, or the medicine will only be prescribed for a small number of people).[5]

An example of this is rituximab, which depletes B-lymphocytes and is prescribed off label for over 60 related conditions according to a 2013 survey.[6] Rituximab was first registered for B-cell lymphoma and lymphocytic leukaemia, and some years later for severe rheumatoid arthritis and various types of vasculitis. For multiple other conditions, off-label prescribing of rituximab was experimental and required individual patient approvals via hospital drug committees. The use of rituximab for some of these off-label indications is now evidence-based and incorporated into treatment guidelines and hospital and state formularies; however, many of these indications have not been approved by the TGA. Applications for approval of additional indications are increasingly unlikely because biosimilar brands of rituximab are available and rituximab is an unrestricted benefit on the Pharmaceutical Benefits Scheme (PBS).

Off-label prescribing in primary care sometimes follows initiation of a medicine for an off-label indication in hospital. For example, off-label prescribing of quetiapine occurs in hospital for insomnia or agitation associated with delirium or dementia.[7,8] General practitioners may feel pressured to continue to prescribe quetiapine after a patient is discharged from hospital.


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Pressure to prescribe a medicine for an off-label indication may also be driven by social media, influential articles in the medical literature,[9] approval in other countries, or word of mouth among patients and prescribers. For example, semaglutide, a glucagon-like peptide-1 (GLP-1) analogue that is approved in Australia for type 2 diabetes, has been discussed in the medical literature as a treatment option for the management of obesity,[10,11] and has been approved for this indication in some countries. Consumer pressure to prescribe semaglutide has been intense because of its promotion on social media and consumer-directed websites.

## What are the risks associated with off-label prescribing?

The evidence supporting off-label use of a medicine has generally been less thoroughly scrutinised than for TGA-approved uses, and the balance of benefits and harms may not be as well known.[12] There may be increased risk of prescriber liability and patient complaint if a patient experiences an adverse event caused by a medicine prescribed off label. For example, semaglutide has been rarely linked with acute pancreatitis, a potentially serious condition. Pregabalin has been widely prescribed off label for non-neuropathic chronic pain states (e.g. low back pain), with potential for adverse outcomes including dependence, mood disorders, suicidality, and sedation especially when used in combination with other sedating drugs.[13] The less evidence supporting the prescribing decision, the greater the risk. For example, there is good evidence that pregabalin is not effective in sciatica, so this weakens the rationale for off-label prescribing for this condition.[14] If the off-label indication is supported in trusted resources such as the *Australian Medicines Handbook*,[15] *Therapeutic Guidelines*,[16] or state-based formularies for public hospitals, then patients and prescribers have not only guidance, but also some level of protection should the decision to prescribe be challenged.

There may be additional costs to the patient when a medicine is prescribed and dispensed off label outside of a public hospital. New medicines that are under patent are expensive. Listing a medicine for subsidy by the PBS is necessary for most people to access treatment; however, with some exceptions, PBS subsidies only apply to TGA-registered indications, patient groups, doses and routes of administration.

For medicines that are listed on the PBS for specific approved indications, there may be increased costs to the health system if the medicine is prescribed and dispensed under the PBS for a non-approved off-label indication, a practice known as 'leakage'.[17] For example, it appears likely there has been extensive leakage through the PBS of semaglutide, which as noted above, is increasingly prescribed off label for people who are overweight.

Off-label use can also contribute to medicine shortages. There is currently a global shortage of semaglutide. The TGA has stated that the shortage is due to the manufacturer being unable to provide sufficient supplies to meet increasing demands caused mainly by off-label prescribing for weight loss.[18] While off-label use does not necessarily represent inappropriate use, the shortage has resulted in significant barriers to semaglutide access for people with insufficiently controlled type 2 diabetes. In September 2023, the TGA advised prescribers to avoid starting new patients on semaglutide and to consider switching existing patients to an alternative.[18]

## Practical considerations for prescribers

Patients need to be fully informed of the benefits and harms of any medicine their doctor recommends, and have the opportunity to provide informed consent prior to commencing therapy. This can be more challenging if off-label use is proposed, particularly if evidence is lacking for use of the medicine for a particular indication. The consumer medicines information (CMI) is helpful for patients regarding potential adverse effects and monitoring recommendations, but the absence of information about the off-label use needs to be part of the discussion.

It is recommended to document in the medical record the harms and benefits discussed with the patient, and their informed consent to treatment. This practice ought to be standard with any prescription, but is even more important if prescribing is off label.

The Council of Australian Therapeutic Advisory Groups and The Royal Australian and New Zealand College of Psychiatrists have published guidance for off-label prescribing.[12,19] Key recommendations from these organisations are summarised in Box 1.

## Reducing the need for off-label prescribing

The fact that off-label prescribing is so common suggests there is a deficit in our national medicines registration process. This deficit places undue responsibility on prescribers, especially those in paediatrics and primary care, as they must evaluate the evidence and cost–benefit to prescribe a medicine off label. It also disadvantages patients by limiting access to treatments and, in some cases, PBS subsidies.

There needs to be greater incentive for pharmaceutical companies to seek approval for new indications and patient groups. There also needs to be

## Box 1. Guidance for off-label prescribing[12,19]

1. Only consider off-label use of a medicine when medicines approved by the TGA are unavailable, ineffective, not tolerated or unsuitable.
2. Use high-quality evidence and treatment guidelines to determine appropriateness of off-label medicine use.
3. If off-label use of a medicine is not considered routine or is not supported by evidence or guidelines, consult a specialist or hospital Drug and Therapeutics Committee before prescribing.
4. If off-label use of a medicine could be considered experimental, approval from an ethics committee may be required.
5. Involve the patient (and their relative or carer if necessary) in shared decision making when recommending off-label use of a medicine. Ensure they understand the potential benefits and harms, and have provided consent.
6. Document the reason(s) for off-label treatment, and patient or carer informed consent in the medical record.
7. Ensure appropriate information is available at all steps of the medicines management pathway (prescribing, supply, administration and monitoring).
8. Monitor and document outcomes, effectiveness and adverse events associated with the medicine prescribed off label. An end point should be decided as part of the overall treatment plan to determine whether the treatment should continue or be ceased. The parameters for this should also be discussed with the patient, where possible, and documented.
9. Communicate the reason for off-label use, patient consent, duration of treatment and ongoing monitoring requirements to other prescribers involved in the patient's care and at transitions of care.
10. Consider prescriber liability and accountability.

alternative, accessible pathways that do not depend solely on pharmaceutical company support. For example, stakeholders such as professional societies and colleges, and consumer organisations, should be able to apply to the TGA to have new evidence-based and guideline-supported indications, doses or patient groups approved for a medicine. Such pathways would align with Australia's National Medicines Policy.[20] Where an application is not initiated by a pharmaceutical company, engagement with the industry would be important to ensure adequate supply of the medicine can be made available if the TGA approval is extended.

The rapid growth of digital health makes large-scale postmarketing medicine safety and effectiveness studies more feasible.[4,21] By addressing evidence gaps specific to vulnerable patient groups, such as children and pregnant women, these studies have potential to inform applications to update medicine approvals.

## Conclusion

Off-label prescribing is common. It may be unavoidable and appropriate in some clinical situations. Prescribers need to be aware of the safety, ethical and financial considerations associated with off-label prescribing. They should use shared decision making to ensure patients are aware that a medicine is being prescribed off label and informed of potential benefits and risks. Alternative pathways for approval of new indications, doses or patient groups may reduce the need for off-label prescribing. <

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