

# Unapproved medicines and unapproved uses of medicines: keeping prescribers and patients safe

## Firstly, what is an approved medicine?

An approved medicine is a medicine which has been through a regulatory process in New Zealand and can be considered safe to prescribe, under the conditions set out in the Medicine Data Sheet. The prescriber must still consider both the benefits and risks of using the medicine, before it is prescribed.

In New Zealand, medicines are approved by the Minister of Health, under advisement from the Medicines and Medical Devices Safety Authority (Medsafe). Medsafe's regulatory approval process ensures that both prescribers and patients have access to safe, quality medicines and medical devices. For a medicine to be approved for sale, distribution and marketing in New Zealand, the company that markets the medicine must apply for consent in accordance with the Medicines Act 1981. When a medicine is approved, it is only approved for the specific indications, doses and routes of administration that were applied for. If the medicine is a prescription medicine or a restricted medicine the company must submit a Medicine Data Sheet that outlines the use of the medicine for prescribers. Any changes to the datasheet, such as a new indication or dose, must be applied for and approved.

The Medicines Adverse Reaction Committee (MARC) works with Medsafe to advise the Minister of Health on the safety of approved medicines, specifically the risk-benefit profile of new medicines. The Centre for Adverse Reactions Monitoring (CARM) collects reports of suspected adverse reactions to medicines and informs Medsafe of potential safety issues with approved medicines.

If a significant safety or quality issue is identified, a warning or recall is requested by Medsafe, and in extreme cases, the Minister of Health can withdraw consent for the approval of the medicine.

## Australia New Zealand Therapeutic Products Agency

In 2011 it was announced that regulatory agencies Medsafe and the Australian Therapeutic Goods Administration (TGA) were to be superseded by the Australia New Zealand Therapeutic Products Agency (ANZTPA), by mid-2016. Medicines and medical devices in Australia and New Zealand will then be regulated and monitored through a single approval and reporting process.

During the lead-in period, Medsafe and the TGA will be publishing recalls and warnings for therapeutic products in a joint database, and establishing a joint protocol for approval of medicines. An online database for patients to search for information on adverse medicine reactions is already available.



For further information see: [www.anztpa.org](http://www.anztpa.org)

The screenshot shows the ANZTPA website interface. At the top, there are navigation tabs: Home, About ANZTPA, Newsroom, Consultations, Projects, Medicinal Information, and Contact Us. Below the navigation is a search bar. The main content area is titled "Transition to the Australia New Zealand Therapeutic Products Agency (ANZTPA)". It features a "Featured" section with a link to "Total TGA and Medsafe project: Trans-Tasman Early Warning System of Safety Concerns with Medicines and Medical Devices". There is also a "Search adverse events" section with a "Search" button and a "Report an adverse event" section with a "Report" button. The footer contains the ANZTPA logo and contact information.

## Commonly used medicines which are unapproved in New Zealand

- Melatonin is used for various sleep disturbances such as insomnia and some parasomnias. It is only approved for short-term treatment of insomnia in people aged over 55 years (Circadin 2 mg tablets). Other melatonin products in New Zealand, e.g. 3 mg capsules and 1 mg and 3 mg tablets, are not approved.
- Indometacin (indomethacin) is a NSAID used for pain in inflammatory conditions such as rheumatic disease. This medicine was previously approved in New Zealand, but is now no longer approved because the approved product is no longer available and the product supplied is different.
- Ethambutol is used in the long-term management of tuberculosis, which is prevalent in some parts of New Zealand. This medicine is fully subsidised on the Pharmaceutical Schedule, but is not an approved medicine.
- Liothyronine is a synthetic thyroid hormone, unapproved in New Zealand, which is sometimes used in patients with hypothyroidism.
- Thiamine injection is used for the management of Wernicke's encephalopathy in patients going through acute alcohol withdrawal. It is an unapproved medicine in New Zealand, although oral thiamine is approved.

## What is an unapproved medicine?


An unapproved medicine is a medicine for which consent, or provisional consent, has not been given by the Minister of Health for sale, distribution or marketing in New Zealand, i.e. it has not been through the Medsafe regulatory process, approval has lapsed, the application was withdrawn or the product available is different in some way to the product that was approved. Unapproved medicines may still be prescribed to patients.

Section 25 of the Medicines Act allows an authorised prescriber to "procure the sale or supply of any medicine" for a patient in their care. This means that prescribers may prescribe any medicine to a patient (within their scope of practice), regardless of whether it is approved or unapproved in New Zealand. However, the prescriber must always provide an adequate professional and ethical standard of care, which includes gaining informed consent from the patient for use of the unapproved medicine.

Section 29 of the Medicines Act allows the sale or supply of unapproved medicines. The person or company who supplies the medicine must notify the Director-General of Health of the supply (via Medsafe), and record the name of the prescribing medical practitioner, the patient for whom the medicine was prescribed and the name and place of supply.

There are many medicines which are commonly used, and approved for use, in other countries, but which are not currently approved in New Zealand. This does not necessarily mean that they are unsafe to use. It is more likely that no application has been made for approval in New Zealand. Medsafe cannot vouch for the quality, safety and efficacy of unapproved medicines and may not be in a position to monitor and advise on their safety. Responsibility lies with the practitioner who prescribes an unapproved medicine. The practitioner must consider the evidence and clinical experience of the use of the unapproved medicine and weigh up the risks and benefits.

N.B. The original source, quality, safety and efficacy of medicines purchased online cannot be verified or guaranteed. When obtaining "unapproved medicines" it is recommended that a New Zealand supply chain be used.

 For further information see: "Medsafe warns of dangers of purchasing medicines online", Medsafe, 2011. Available from: [www.medsafe.govt.nz/hot/media/2011/DangersOfPurchasingMedicinesOnline.asp](http://www.medsafe.govt.nz/hot/media/2011/DangersOfPurchasingMedicinesOnline.asp)

## What is an unapproved use of a medicine?

If an approved medicine is prescribed outside of the approved indications, dose range or route of administration, this is an unapproved use of a medicine, also known as “off-label” use.

The Medicines Act allows the practitioner to determine the dose and route of a medicine which is prescribed and the indication for which it is prescribed for, but the prescriber must take responsibility for the safety of this if it is an unapproved use.

Approved medicines which are prescribed for an unapproved indication, dose or route can be supplied as usual, i.e. it is not necessary for Section 29 notification to occur if a practitioner prescribes “off-label”.

## Why consider prescribing a medicine in an unapproved way?

There are many reasons why a prescriber may consider an unapproved use of a medicine, ranging from following established treatment guidance to implementing new evidence that has emerged from the literature. In some cases, the prescriber may not even be aware that a medicine is being prescribed in an unapproved way, as it is used so commonly, e.g. the use of tricyclic antidepressants for neuropathic pain, omeprazole for reflux in infants (unapproved in children aged < 1 year) or nifedipine for the treatment of Raynaud’s phenomenon.

### Prescribing medicines in children

Many of the medicines administered to children are used off-label. This is because trials have not usually been conducted in this patient group and, therefore, the company marketing the medicine has not applied for use to be approved for this age-group. This is also why it is common for a medicine to be contraindicated for use in pregnant women.

An example of off-label prescribing in children is azithromycin, which is recommended for prophylaxis and treatment of pertussis in children. Although azithromycin is an approved medicine, pertussis is currently an unapproved indication for use.

It can be difficult for a practitioner to weigh up the risks and benefits of using a particular medicine in a child, when there is limited or conflicting evidence of effectiveness or safety. For example, selective serotonin reuptake inhibitors (SSRIs) are considered the first-line pharmacological treatment for depression, and the only pharmacological option considered

## Check the Medicine Data Sheet or New Zealand Formulary before prescribing

Indications for medicines may differ with new formulations or generic versions, and for different agents within the same class of medicine. For example, the indications for SSRIs vary. Depression is the only consistent indication for all members of the group, while indications for obsessive compulsive, panic, social anxiety and post traumatic stress disorders are specific to individual types of SSRI. Paroxetine has the longest list of indications, ranging from depression to social phobia. All SSRI data sheets caution against the use of these medicines in children aged under 18 years.

There are also some anomalies between similar medicines, e.g. metoprolol succinate is indicated as an adjunct treatment in heart failure, but metoprolol tartrate is not.

for younger people. However, SSRIs are unapproved for use in people aged under 18 years, and are associated with potentially serious adverse effects.

### Indication creep

Once a medicine has been approved in New Zealand, its use is often expanded across a broader range of conditions. However, the efficacy and safety of such use may not always be established. For example, quetiapine is indicated for the treatment of schizophrenia and related psychoses, but it is increasingly being prescribed for unapproved indications such as sedation in people with dementia, and for anxiety and insomnia. This is a worrying trend given that a larger population is being exposed to the potential serious adverse effects associated with quetiapine and other atypical antipsychotics, e.g. type 2 diabetes, sudden cardiac death and increased mortality in older people.\*

Another concerning example of indication creep is oxycodone, which is approved for moderate to severe pain, including cancer pain, but appears to be frequently prescribed inappropriately in place of a weaker opioid.

### Data sheets not updated

Sometimes medicines are prescribed off-label because

\* McKean A, Monasterio E. Off-label use of atypical antipsychotics: cause for concern? *CNS Drugs* 2012;26(5):383-90.

evidence suggests that a non-indicated dose or route of administration is recommended, but the medicine supplier has, for whatever reason, not sought regulatory approval to update the data sheet. For example, low dose bendrofluzide has only recently been officially incorporated into the product datasheet despite guidelines for hypertension recommending low doses for many years.

### **How do you prescribe an unapproved medicine or an approved medicine for an unapproved indication?**

The decision to prescribe an unapproved medicine, or to prescribe off-label, is at the discretion of the practitioner, based on their clinical experience and judgement, and in consultation with the patient.

The Health and Disability Commissioner's Code of Consumer Rights covers the obligation for a practitioner to obtain informed consent from the patient, before prescribing an unapproved medicine.

### **Increased professional responsibility and liability**

If a patient experiences an adverse event while taking an unapproved medicine, or a medicine prescribed for an unapproved use, the responsibility, and liability, rests with the prescriber. Therefore, it is recommended that a decision to prescribe an unapproved medicine is documented in the patient's notes, including the rationale for the prescription, and that the decision was discussed with the patient. In general, it is recommended that prescribers obtain written consent from the patient when prescribing an unapproved medicine. It is acknowledged, however, that when off-label use of a medicine is so common that it is regarded as usual practice, obtaining consent may not be considered necessary, and this is at the clinician's discretion.

### **What should you tell the patient?**

The patient should be fully informed that the medicine they are being prescribed is unapproved, or that the medicine is approved, but is being prescribed for a condition, at a dose, or via a route, that is unapproved.

The expected benefits, risks, adverse effects and cost should be discussed, along with other treatment options. Any warnings or contraindications associated with the medicine should be explained.

If the medicine is considered to be experimental, e.g. there is minimal or conflicting evidence to support its use, it is rarely

used or it is part of a clinical trial, the prescriber must obtain written consent from the patient. A plan for monitoring treatment and adverse effects should be put in place.

If a patient is prescribed an unapproved medicine, the prescriber must advise them that the details about the supply of medicine (Section 29), including their name, will be recorded by the supplier and may also be sent to Medsafe.

### **What if the patient asks for a medicine they used overseas?**


Patients who have immigrated to New Zealand or have spent time overseas may request that their doctor prescribes them a medicine that they have been using, which is not approved in New Zealand. Such medicines can be imported for use, but it is the obligation of the practitioner to consider approved, and subsidised, alternatives and be adequately informed about the medicine, e.g. researching the literature, consulting with colleagues, before assisting the patient to obtain it. Practitioners should have a plan in place to monitor the effect of the medicine.


N.B. Section 29 notification is not required if a medical practitioner imports a medicine to treat a patient. If the medicine is supplied from one medical practitioner to another, the supplying practitioner is encouraged to notify Medsafe. If a Pharmacist imports the medicine for the medical practitioner, they must notify Medsafe of the supply using the Section 29 reporting mechanism.

### **Are only approved medicines subsidised?**


In New Zealand, the Pharmaceutical Management Agency (PHARMAC) is responsible for deciding which medicines are subsidised for use in New Zealand. The New Zealand Pharmaceutical Schedule indicates to prescribers which medicines are subsidised (either fully or partly), including any criteria for subsidy, e.g. Special Authority.

Although most medicines on the Pharmaceutical Schedule are approved medicines, and it is PHARMAC's preference to subsidise approved medicines where possible, this is not a criterion for subsidy. The decision to subsidise a medicine is based on the pharmaceutical needs of patients in New Zealand, and is dependent on the available funding. All patients who meet the criteria for subsidy (as per the Schedule), have equal access to the funding for a medicine, should a practitioner decide to prescribe it. PHARMAC is not responsible for the safety or quality of the medicines listed on the Pharmaceutical Schedule, nor for the supply or use of the medicine in accordance with the Medicines Act.

Unapproved medicines are identified in the Pharmaceutical Schedule with this symbol:  Where an approved medicine is subsidised for an unapproved use, this is also clearly indicated in the Schedule.


 The New Zealand Formulary also contains information about the approval and subsidy status of medicines.


#### Resources

 For further information about regulatory processes, refer to Medsafe: [www.medsafe.govt.nz](http://www.medsafe.govt.nz)

For information on unapproved medicines, see: [www.medsafe.govt.nz/profs/unapp.asp](http://www.medsafe.govt.nz/profs/unapp.asp)

For Medicine data sheets see: [www.medsafe.govt.nz/profs/Datasheet/dsform.asp](http://www.medsafe.govt.nz/profs/Datasheet/dsform.asp)


 Comprehensive information on both approved and unapproved medicines is available from the New Zealand Formulary: [www.nzf.org.nz](http://www.nzf.org.nz)

 To review the Medicines Act 1981, see: [www.legislation.govt.nz/act/public/1981/0118/latest/DLM53790.html](http://www.legislation.govt.nz/act/public/1981/0118/latest/DLM53790.html)

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## A cautionary tale

Dabigatran is a recently approved medicine in New Zealand. The indications for dabigatran are for prevention of stroke and systemic embolism in people with non-valvular atrial fibrillation and for venous thromboembolism prophylaxis after major orthopaedic surgery. Some practitioners in New Zealand have been prescribing dabigatran for unapproved indications, such as in patients with mechanical heart valves, despite there being no evidence supporting this use. Medsafe, the United States Food and Drug Administration and the European Medicines Agency and have now stated that dabigatran is contraindicated in people with mechanical heart valves. So far several cases have been reported to CARM of patients with mechanical valves experiencing adverse reactions to dabigatran, such as developing thrombosis on the prosthetic valve. This is a clear example of an inappropriate use of a medicine for an unapproved indication.

 For further information see: "Dabigatran revisited", BPJ 50 (Feb, 2013).

## Benzbromarone is an unapproved, but subsidised medicine

Benzbromarone has been used for the treatment of gout in other countries for many years, but drug companies have not currently applied for this medicine to be approved for sale, distribution or marketing in New Zealand. However, patients with gout in New Zealand have already been using this medicine, based on adequate evidence of effectiveness and safety from international studies, experience of clinical use and expert clinical opinion.

Benzbromarone was initially funded by PHARMAC for some patients under one or more of its exceptions schemes, which allow funding of a medicine for named

patients in specified circumstances. However, following positive reviews of benzbromarone by PHARMAC's advisory committees, and in the absence of availability of an approved version, PHARMAC has decided to fund an unapproved version of benzbromarone for the treatment of gout. Benzbromarone is to be listed on the Pharmaceutical Schedule from 1 April, 2013, fully subsidised, for all patients who meet the Special Authority criteria.

 For further information see Page 12