# Prescriber Update

Vol. 41 No. 3 September 2020

www.medsafe.govt.nz ISSN 1179-075X (online)

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NEW ZEALAND MEDICINES AND MEDICAL DEVICES SAFETY AUTHORITY
A BUSINESS UNIT OF THE MINISTRY OF HEALTH
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# Spotlight on Maviret – De-liver-ing treatment in patients with hepatitis C

**Key messages**

- Maviret is a combination of two direct-acting antivirals (glecaprevir + pibrentasvir) and is used for the treatment of chronic hepatitis C.
- Glecaprevir and pibrentasvir are metabolised in the liver. Therefore, patients with impaired liver function will be exposed to increased levels of these antivirals, increasing the risk of adverse reactions.
- Assess the severity of liver disease before starting treatment:
  - Maviret can be used in patients with mild liver impairment (Child-Pugh A)
  - Maviret is not recommended in patients with moderate liver impairment (Child-Pugh B) and is contraindicated in patients with severe liver impairment (Child-Pugh C).

The Spotlight series continues with this article on Maviret, a combination direct-acting antiviral (DAA) medicine used for the treatment of chronic hepatitis C.

## Background

In August 2019, the United States Food and Drug Administration (FDA) warned about the rare occurrence of serious liver injury with use of hepatitis C medicines, including Maviret, in some patients with advanced liver disease.[1] The hepatitis C medicines implicated are all direct-acting antivirals (DAAs) that include a protease inhibitor.

The Medicines Adverse Reactions Committee reviewed the risk of serious liver injury in patients taking Maviret to determine the impact for New Zealand prescribers and patients.[2,3] The review highlighted the importance of only prescribing Maviret in patients with mild liver impairment as recommended in the data sheet.

## What is Maviret?

Maviret is a combination of the DAAs glecaprevir and pibrentasvir. It is indicated for the treatment of chronic hepatitis C infection due to any of the hepatitis C virus (HCV) genotypes.

DAAs disrupt viral replication and infection by targeting specific viral proteins. More than one target can be attacked if different groups of DAAs are combined.[4] Maviret contains the protease inhibitor glecaprevir and the protein NS5A inhibitor pibrentasvir.

## Patients with liver impairment

Before starting treatment, check the patient's liver function.

The data sheet states that:[5]

- Maviret can be used in patients with mild liver impairment (Child-Pugh A)
- Maviret is not recommended for patients with moderate liver impairment (Child-Pugh B)
- Maviret is contraindicated in patients with severe liver impairment (Child-Pugh C).

These prescribing recommendations are based on the increased exposure to the two DAAs, especially glecaprevir, in patients with impaired liver function. The increased exposure increases the risk of adverse reactions.

In clinical studies using the standard dose of Maviret, the glecaprevir area under the curve (AUC) was 33 percent higher in patients with Child-Pugh A cirrhosis, 100 percent (two-fold) higher in patients with Child-Pugh B, and 11-fold higher in patients with Child-Pugh C compared to study participants without HCV and with normal hepatic function.[5] The pibrentasvir AUC was also increased in patients with Child-Pugh B or C, but not to the same extent as glecaprevir.[5]

Similarly, population pharmacokinetic analysis showed glecaprevir exposure was increased by two-fold in patients with HCV and compensated cirrhosis compared to patients with HCV and no cirrhosis, while pibrentasvir exposure was similar for both patient groups.[5]

## Reported cases of liver injury

### New Zealand

The Centre for Adverse Reactions Monitoring (CARM) has not received any reports of liver-related adverse reactions in association with Maviret.

### United States[1]

The FDA's warning was based on 63 reported cases of worsening liver function associated with DAA treatment (Maviret, Zepatier and Vosevi), sometimes leading to liver failure and death.

- In many of the reported liver failure cases, patients had signs and symptoms of moderate to severe liver impairment (Child-Pugh B or C) or other serious liver problems prior to starting treatment with one of the DAAs. These patients should not have been treated with these medicines.
- Some patients were incorrectly classified as being Child-Pugh A, despite having evidence of a previous decompensation event, portal hypertension or decreased platelets at baseline.
- Some patients had other significant pre-existing risk factors, such as alcohol abuse or concomitant illness or were taking medicines associated with serious liver problems.

## References


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# Allopurinol – Life-threatening interaction with azathioprine or mercaptopurine

**Key messages**

- Co-administration of allopurinol with azathioprine or mercaptopurine can lead to life-threatening bone marrow suppression.
- If concomitant use is unavoidable, reduce the dose of azathioprine or mercaptopurine to one-quarter of the recommended dose and monitor the patient's blood count.

## Background

Allopurinol is a xanthine oxidase inhibitor used to reduce hyperuricaemia of patients with gout.[1]

Azathioprine is an immunosuppressive agent. It is metabolised in the liver, initially to mercaptopurine, which in turn is converted into inactive products by xanthine oxidase.[2]

Mercaptopurine is a cytotoxic drug used in the treatment of leukaemia. It is converted to inactive products by xanthine oxidase.[3]

## The interaction and what to do about it

Inhibition of xanthine oxidase by allopurinol decreases the rate of conversion of azathioprine and mercaptopurine to inactive metabolites. The subsequent increased plasma concentrations of the active metabolites may lead to life-threatening leukopenia, thrombocytopenia or pancytopenia.[2]

Concomitant use of allopurinol and azathioprine or mercaptopurine is not recommended. However, if co-administration is necessary, reduce the dose of azathioprine or mercaptopurine to 25 percent of the recommended dose and closely monitor the patient's blood count.[2,4] For example, if a transplant patient taking a maintenance dose of azathioprine of 1–4 mg/kg bodyweight per day requires concomitant allopurinol, the azathioprine dose should be reduced to 0.25–1 mg/kg bodyweight per day.

## New Zealand case reports

Up to 30 June 2020, the Centre for Adverse Reactions Monitoring (CARM) had received 14 cases describing an interaction between allopurinol and azathioprine. In 13 of these cases, the patient experienced bone marrow suppression. Two recent cases reported pancytopenia (CARM IDs: 136060 and 136652). The majority of the 14 cases did not report that a dose reduction had occurred.

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# Gastrointestinal surgery – Consider possible effects on medicine pharmacokinetics

**Key messages**

- Gastrointestinal surgery can have complex effects on medicine pharmacokinetics:
  - absorption may decrease, resulting in reduced or lack of efficacy
  - significant weight loss, particularly after bariatric surgery, can affect first pass metabolism, volume of distribution and medicine clearance.
- It is difficult to predict for individual patients and medicines how the pharmacokinetics will change.
- For critical medicines, it may be prudent to change to non-oral versions if these are available before any significant surgery.

## Background

Bariatric surgery is becoming more common in New Zealand.[1] Both bariatric surgery and surgical management of intestinal disorders such as inflammatory bowel disease have the potential to significantly affect medicine pharmacokinetics, including absorption.

The potential effects of gastrointestinal surgery on medicine pharmacokinetics can be complex. Most often, absorption is decreased, resulting in decreased efficacy. Reduced medicine absorption can be easily overlooked as an explanation for lack of efficacy. However, there is minimal information on this issue in medicine data sheets and the scientific literature.[2–4]

## Bariatric surgery

Bariatric surgeries can be classified as restrictive, such as gastric banding and sleeve gastrectomy, malabsorptive or both, such as Roux-en-Y gastric bypass. Restrictive surgeries reduce the volume of food that can be consumed at one time. Malabsorptive procedures create a diversion around portions of the digestive tract.[3–5]

## Intestinal surgery

Surgical management of intestinal conditions can alter the gastrointestinal surface anatomy, physiology and length.[2] Any shortening of the intestine resulting from surgery has the potential to decrease medicine absorption. Compared to patients with a small intestinal stoma, colostomy patients are less likely to experience significant absorption problems with normal medicine doses and formulations.[2] Damage to the intestinal surface or blood flow may also affect medicine absorption.

## Effects on pharmacokinetics

### Absorption

Although medicines can be absorbed throughout the entire gastrointestinal tract, most absorption occurs in the upper small intestine due to the large surface area, relatively high blood flow and optimal pH for drug absorption. Absorption in the large intestine is generally confined to slow-release formulations of medicines and medicines where the primary effect is in the large intestine.[2]

Release (disintegration of the tablet or capsule) and dissolution of the active ingredient are the first steps of the absorption process. Although few medicines are absorbed from the

stomach, disintegration of the tablet or capsule usually starts in the stomach. A reduction in the stomach surface area with resulting shorter gastric transit time and reduced acid secretion can have important effects on the dissolution of the active ingredients of medicines.[4] Lower gastric volumes likely reduce absorption due to the decrease in solvent volume available to dissolve the medicine.[3] Enteric-coated medicines may require the acidic environment of the stomach to dissolve the coating before the active ingredient can be absorbed in the intestine.[4,5] Reduction in food intake will reduce the absorption of medicines that require food to increase their bioavailability, such as rivaroxaban.[5]

Surgical procedures that rearrange gut anatomy or shorten the small intestine may reduce the absorption of lipophilic medicines that require the presence of bile salts. Altered exposure to bile salts in the small intestine may also affect the enterohepatic cycle, which is important for medicines such as digoxin.[4]

In summary, absorption of medicines can be affected by:[2–5]

- change in gastric motility
- decreased gastric volume
- decreased food content
- decreased acid in the stomach
- decreased surface area/length of the small intestine
- bypass of bile secretions (malabsorptive bariatric surgery)
- disruption of the enterohepatic cycle
- bypass of carrier/uptake/transporter proteins (malabsorptive bariatric surgery)
- integrity of the mucosa.

**Additional effects due to weight loss**

When significant weight loss is intended or a consequence of surgery, there can be additional pharmacokinetic effects. Many patients experience hypoalbuminemia after bariatric surgery,[6] which may affect highly protein bound medicines. Clearance of medicines also tends to change with significant weight loss.[5]

In summary, additional pharmacokinetic effects may include:[3,5]

- changes in first pass metabolism (possible decrease after malabsorptive surgery and possible increase after weight loss)
- changes in volume of distribution due to loss of fatty tissue following weight loss
- changes to the clearance of medicines due to weight loss
- decrease in plasma albumin concentrations.

## Strategies for medicine management

Since changes in medicine pharmacokinetics are difficult to predict, an individualised approach is needed. It should also be noted that that changes to medicine absorption may be temporary or permanent and may develop over time post-surgery.[3] See Table 1 for suggested medicine management strategies.

Pharmacists or medicines information services can provide advice on the pharmacokinetics of medicines and alternative formulations for individual patients.[2]

**Table 1: Suggested strategies for management of medicines following gastrointestinal surgery[a–c]**

| |
|---|
| Switch critical medicines to non-oral forms, eg, an oral contraceptive can be changed to an implant or IUD. |
| Switch critical medicines to those which can be closely monitored for efficacy or safety, eg, if anticoagulation is needed warfarin may be preferable to dabigatran or rivaroxaban. |
| Switch to a liquid dose form or dissolvable or crushable tablets if no non-oral form is available. Check the osmolarity, excipients and medicine volume required of the oral form as some hyperosmolar products (particularly those containing sorbitol as a sweetener) can cause osmotic diarrhoea. |
| Dose by weight, particularly if significant weight loss is anticipated. |
| Avoid using extended release formulations or enteric coated medicines. |
| Use medicines with low first-pass metabolism if possible. |
| Consider increasing the dose if efficacy is reduced. |

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# Avoid switching brands of topiramate

Medsafe is reminding healthcare professionals that some medicines need to be prescribed by brand.[1] This reminder follows a recent report to the Centre for Adverse Reactions Monitoring (CARM ID: 136121) of a patient who experienced pre-seizure symptoms after changing brands of topiramate.

Changing brands of topiramate should be avoided if possible. Medsafe recommends prescribers follow the UK Medicines and Healthcare products Regulatory Agency's (MHRA) advice on switching brands of antiepileptic medicines.[2] Brand switches for topiramate must be carefully considered, taking into account factors such as seizure frequency and treatment history.[2]

Checking with patients which brand of topiramate they are taking and prescribing by brand will help to ensure patients receive the brand they are stabilised on.

### References


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# Quarterly summary of recent safety communications

The table below is a summary of recent safety communications to health care professionals and consumers, published on the Medsafe website (**medsafe.govt.nz**).

| Date | Communication | Topic |
|---|---|---|
| 31/07/2020 | Monitoring | Rocuronium bromide solution for injection 10mg/mL, Hameln, and reports of lack of efficacy |
| 29/07/2020 | Committees | Medicines Classification Committee – Reclassification of Codeine |
| 23/07/2020 | Monitoring | Yes! Cassette Pregnancy Test Kit (also known as Smiths BioMed Rapid Pregnancy Test Kit) – Reports of false positives presenting as faint lines and inconclusive results |
| 16/06/2020 | Dear Healthcare Professional letter | Tramal (tramadol) data sheet safety update to precautions and contraindications (PDF, 2 pages, 597 KB) |
| 9/06/2020 | Alert | Important updates to clozapine data sheets and monitoring during Covid-19 pandemic |
| 28/05/2020 | Alert | Miracle Mineral Solution – dangerous and potentially life-threatening side effects |
| 27/05/2020 | Dear Healthcare Professional letter | Microlut Supply of Australian-labelled Microlut to New Zealand (PDF, 2 pages, 380 KB) |

# MARC's remarks: June 2020 meeting

See the Medsafe website for the MARC meeting minutes (**medsafe.govt.nz/profs/MARC/Minutes.asp**) and the reports presented to the MARC (**medsafe.govt.nz/committees/MARC/Reports.asp**).

The Medicines Adverse Reactions Committee (MARC) met on 11 June 2020 to discuss a number of medicine-related safety concerns.

The MARC discussed the possible association of **fluconazole** use in pregnancy, including single-dose treatment for vulvovaginal candidiasis, with spontaneous abortion and congenital malformations. The MARC recommended that the data sheets should be updated to include information on the effects of low-dose fluconazole treatment during pregnancy and that the pregnancy information should be harmonised across all data sheets.

The MARC discussed the use of **oral sedating antihistamines** in children for sedation. The MARC recommended that the indication for sedation of children be removed from over-the-counter medicines containing sedating antihistamines.

The MARC discussed the risk of serious liver injury in patients with advanced liver disease who are treated with hepatitis C medicines, including **Maviret**. The MARC recommended data sheet updates to strengthen the warning not to use Maviret in patients with advanced liver disease. For more information, see the Maviret article on page 45 of this edition of *Prescriber Update*.

The MARC discussed the available evidence relating to associations between **antiepileptic medicines** and neurodevelopmental disorders. The Committee recommended Medsafe writes to the sponsor about the possible association between lamotrigine and the development of autism spectrum disorder in children exposed *in utero* and whether this information should be included in the data sheet.

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Note that ACC, the Health Quality and Safety Commission, the Ministry of Health and Foetal Anti-Convulsant Syndrome New Zealand (FACS NZ) have released updated information resources about the benefits and risks of anti-seizure/mood stabilising medicines for people who could become pregnant. The resources can be downloaded or ordered from ACC (**acc.co.nz/for-providers/treatment-safety** – see the Fetal Anticonvulsant Syndrome section).

# Kounis syndrome – 'Allergic angina' associated with some medicines

**Key messages**

- Kounis syndrome is a hypersensitivity reaction affecting the coronary arteries.
- In Kounis syndrome. the release of inflammatory mediators in response to an allergic stimulus may result in coronary artery spasm, atheromatous plaque rupture and/or coronary stent thrombosis.
- Consider Kounis syndrome in a patient who develops angina symptoms shortly after starting a medicine.

### CARM case report

The Centre for Adverse Reactions Monitoring (CARM) recently received a report of coronary artery spasm associated with the use of amoxicillin/clavulanic acid injection in a 36-year-old male (CARM ID: 135996).

### What is Kounis syndrome?

'Allergic angina' may occur in the context of an acute hypersensitivity reaction, a phenomenon known as Kounis syndrome.[1] Kounis syndrome was first described in 1991[2] and although seemingly rare, it is increasingly recognised as an allergic reaction to medicines, foods and environmental allergens.[3]

The underlying mechanism for Kounis syndrome is mast cell activation and release of inflammatory mediators.[4] Three variants of Kounis syndrome have been identified.[1,4–6]

- Type I occurs in patients with structurally normal coronary arteries and no cardiovascular risk factors. The acute release of inflammatory mediators induces coronary vasospasm, which may or may not result in acute myocardial infarction.
- Type II Kounis syndrome occurs in patients with pre-existing coronary artery disease, in whom the acute release of inflammatory mediators induces coronary vasospasm that may lead to plaque rupture and myocardial infarction.
- Type III Kounis syndrome occurs in patients with a coronary artery stent, in whom the release of inflammatory mediators may result in stent thrombosis.

The acute coronary syndrome typically begins within one hour of exposure to the offending allergen, although longer onset times have been reported.[5]

### Which medicines are associated with Kounis syndrome?

To date, Kounis syndrome has been associated with a variety of medicines including beta-lactam antibiotics,[7] non-steroidal anti-inflammatory drugs,[8] intravenous iron preparations[9] and rocuronium.[10] Currently in New Zealand, Kounis syndrome is listed in the data sheets for diclofenac,[11,12] carboplatin,[13,14] clopidogrel[15] and Mersyndol (paracetamol + codeine + doxylamine).[16]

### How is Kounis syndrome treated?

Management of Kounis syndrome involves removing the offending allergen, managing the acute coronary vasospasm, and treating the allergic response.[6] Careful selection and use of medicines are needed when managing the acute condition to avoid further histamine release or exacerbation of coronary vasospasm.[17]

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# Cyproterone acetate and the risk of meningioma

**Key messages**

- Meningiomas are the most common primary intracranial tumours.
- Exposure to cyproterone acetate is associated with meningioma.
- The risk of meningioma with cyproterone acetate increases as the cumulative dose rises.
- Cyproterone acetate treatment must be stopped if a patient is diagnosed with meningioma.

## What is a meningioma?

Meningiomas are the most common primary intracranial tumours.[1] Although the majority of meningiomas are benign, they are associated with morbidity and decreased quality of life.[1]

Meningiomas can be slow growing and are often asymptomatic.[2] However, typical symptoms of meningioma include:[1]

- headache due to increased intracranial pressure
- focal neurological (including cranial nerve) deficits (eg, visual changes, loss of hearing or smell)
- generalised and/or partial seizures
- personality changes
- confusion
- altered level of consciousness.

The incidence of meningioma increases with age, with a median age at diagnosis of 65 years.[2] Meningiomas are more common in women.[1] Hormonal factors may have a role in the development of meningioma.[2]

## Cyproterone acetate and reminders for health care professionals

Exposure to cyproterone acetate may increase the risk of meningioma.[3,4] Cyproterone acetate is a synthetic progestogen with anti-androgenic activity.[4]

Cyproterone acetate (as 50 or 100 mg tablets) is indicated:[5]

- in men as an antiandrogen treatment in inoperable carcinoma of the prostate and for the reduction of drive in sexual deviations (pathologically altered or increased sexuality)
- in women for severe signs of androgenisation (eg, very severe hirsutism, severe androgenetic alopecia, often attended by severe forms of acne and/or seborrhoea).

Low-dose cyproterone acetate (2 mg), combined with an ethinylestradiol can also be used in women for the treatment of signs of androgenisation including hirsutism.[6]

A recent cohort study in France has demonstrated a dose-dependent association between cyproterone acetate and the risk of meningioma, and the risk increases as the cumulative dose rises.[4]

Health care professionals are reminded that:[5]

- the occurrence of meningiomas (single and multiple) is associated with the use of cyproterone acetate, primarily at doses of 25 mg/day and above

- use of cyproterone acetate is contraindicated in patients with a meningioma or a history of meningioma
- if a patient treated with cyproterone acetate is diagnosed with meningioma, treatment must be permanently stopped.

### New Zealand case reports

Up to 31 March 2020, the Centre for Adverse Reactions Monitoring (CARM) has received two reports of meningioma associated with cyproterone acetate (CARM IDs: 77874 and 100772). Both patients were women who had been treated with cyproterone acetate for more than 10 years. One report stated the dose as 50 mg (CARM ID: 77874). The other report did not include the dose.

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# DRESS syndrome – Monitor for long-term sequelae

**Key messages**

- Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is associated with long-term autoimmune sequelae.
- Patients require careful monitoring for autoimmune disease following recovery from DRESS syndrome.

### DRESS syndrome is a type of SCAR

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a type of severe cutaneous adverse reaction (SCAR).[1] It is characterised by a rash, haematologic abnormalities (eosinophilia, atypical lymphocytosis), lymphadenopathy and internal organ involvement, typically 2–8 weeks after exposure to the offending drug.[1,2]

DRESS symptoms, diagnosis and commonly associated medicines have been described in previous issues of *Prescriber Update*.[3,4]

### Long-term autoimmune sequelae

Patients are at risk of long-term autoimmune sequelae following recovery from DRESS syndrome.[5,6] Retrospective cohort studies have reported autoimmune sequelae such as Graves' disease, Hashimoto's thyroiditis, type 1 diabetes mellitus, systemic lupus erythematosus, alopecia areata and autoimmune haemolytic anaemia in patients who have recovered from DRESS syndrome.[5,6]

The pathogenic mechanism leading to the development of autoimmune disease months to years after the acute drug reaction is not well understood.[5,6] Reactivation of human herpes viruses (HHVs) in DRESS syndrome may play a role in the development of autoimmune sequelae.[2]

### Long-term monitoring required following DRESS syndrome

Patients with DRESS syndrome require careful long-term follow-up for symptoms and signs of autoimmune disease.[6]

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## WE NEED YOUR HELP!

MEDICINES MONITORING

Please send your reports to CARM (**nzphvc.otago.ac.nz/reporting/**) for the potential safety issues* listed in the table below.

| Medicine(s) | Potential safety issue | Active monitoring ends |
|---|---|---|
| Fluoxetine and levothyroxine | Interaction | 30 November 2020 |

- M² (Medicines Monitoring) is a Medsafe scheme designed to collect more information on potential safety signals for specific medicines.
- Please send your report to CARM (as for any suspected adverse reaction). This can be done even if the reaction happened some time ago. Please include as much information as possible as this helps the medical assessors at CARM to investigate whether the medicine caused the reaction.

For further information about M², see the Medsafe website (**medsafe.govt.nz/profs/M2MedicinesMonitoring.asp**).

* The appearance of a possible safety issue in this scheme does not mean Medsafe and CARM have concluded that this medicine causes the reaction.

# Gathering knowledge from adverse reaction reports: September 2020

Adverse reaction reporting is an important component of medicine safety monitoring. Case reports can highlight significant safety issues concerning therapeutic products and their use.

The table below presents a selection of recent informative cases from the Centre for Adverse Reactions Monitoring (CARM) database.

| Case details[a,b] | Reaction description and data sheet information[b,c] |
|---|---|
| **CARM ID:** 135306<br>**Age:** 87<br>**Gender:** Female<br>**Medicine(s):** Carbamazepine, rivaroxaban<br>**Reaction(s):** Drug ineffective, drug interaction | An 87-year-old patient already taking carbamazepine was prescribed rivaroxaban. While taking rivaroxaban, the patient developed pulmonary emboli. |
| | The interaction between carbamazepine and rivaroxaban is described in both the Tegretol (**medsafe.govt.nz/profs/Datasheet/t/Tegretoltabsyrup.pdf**) and Xarelto (**medsafe.govt.nz/profs/Datasheet/x/Xareltotab.pdf**) data sheets. Carbamazepine is a potent CYP3A4 inducer and CYP3A4 is one of the main pathways by which rivaroxaban is cleared. Therefore, co-administration may lead to reduced levels of rivaroxaban. |
| **CARM ID:** 135633<br>**Age:** 42<br>**Gender:** Female<br>**Medicine(s):** Amphotericin B, gabapentin, methadone<br>**Reaction(s):** Cardiac arrest, hyperkalaemia | Following treatment with amphotericin B, the patient experienced hyperkalaemia with subsequent fatal cardiac arrest. |
| | The AmBisome data sheet states that hyperkalaemia has been reported with an incidence of less than 1 percent, and there have been post-marketing reports of cardiac arrest (**medsafe.govt.nz/profs/Datasheet/a/AmBisomeinj.pdf**). |
| **CARM ID:** 136715<br>**Age:** 8<br>**Gender:** Female<br>**Medicine(s):** Oxybutynin<br>**Reaction(s):** Anxiety, fear, hallucination, psychotic disorder, sleep disorder | Shortly after starting oxybutynin, the patient developed anxiety and fear, which then progressed to hallucinations. She was unable to sleep due to the severity of the hallucinations. The symptoms resolved once the medicine was stopped. |
| | The Warnings and precautions section of the Apo-oxybutynin data sheet states that anticholinergic CNS effects (eg, hallucinations, agitation, confusion and somnolence) have been reported (**medsafe.govt.nz/profs/Datasheet/a/Apooxybutynintabsyrup.pdf**). Monitoring is recommended, especially in first few months after initiating therapy or increasing the dose. Anxiety and hallucinations are listed as Undesirable effects. |

| | |
|---|---|
| **CARM ID:** 136785<br>**Age:** Unknown<br>**Gender:** Male<br>**Medicine(s):** Cetirizine<br>**Reaction(s):** Rebound effect | The patient experienced severe itch and hives upon discontinuation of cetirizine. |
| | Rebound pruritus is described in the Warnings and precautions section of the Zista data sheet (**medsafe.govt.nz/profs/Datasheet/z/zistatab.pdf**). Pruritus and/or urticaria may occur when cetirizine is stopped, even if those symptoms were not present before treatment initiation. In some cases, the symptoms may be intense and may require treatment to be restarted. The symptoms should resolve when the treatment is restarted. |
| **CARM ID:** 136860<br>**Age:** 5<br>**Gender:** Male<br>**Medicine(s):** Topiramate<br>**Reaction(s):** Dyspnoea, metabolic acidosis | While gradually increasing the topiramate dose, the patient experienced heavy breathing. Although clinically well, the patient's venous blood gas results showed compensated metabolic acidosis. |
| | Metabolic acidosis is described in the Topamax (**medsafe.govt.nz/profs/Datasheet/t/topamaxtabcap.pdf**) and Topiramate Actavis (**medsafe.govt.nz/profs/Datasheet/t/topiramateactavistab.pdf**) data sheets. Topiramate inhibits renal carbonic anhydrase resulting in decreased serum bicarbonate levels. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing topiramate (using dose tapering). |

Notes:

a. Only the medicines suspected to have caused the reaction are listed in the table.

b. The reactions listed in the 'Case details' column are coded according to the Medical Dictionary for Regulatory Activities (MedDRA), an internationally used set of standardised terms relating to medical conditions, medicines and medical devices. The reactions listed in the 'Reaction description' column are based on what was reported to CARM, and do not always match the MedDRA term.

c. If the suspect medicine's brand name is not described in the report to CARM, only the data sheet for the funded medicine is included in the table.

Information about suspected adverse reactions reported to CARM is available on the Medsafe website using the Suspected Medicines Adverse Reaction Search (SMARS) (**www.medsafe.govt.nz/Projects/B1/ADRSearch.asp**).

By selecting the ingredient of a medicine, you can find out:

- the number of reports and suspected adverse reactions for that ingredient. The suspected reactions are grouped by body system or organs (Summary report)
- single case reports, listing the medicines involved that contain the ingredient and the suspected adverse reactions (Detail report).

# Recent approvals: New active ingredients or new indications

For the period 16 April 2020 to 15 July 2020.

### Recent approvals of medicines with new active ingredients

| Trade Name (active ingredient) | Dose form and strength(s) | Therapeutic area |
|---|---|---|
| Inovelon (rufinamide) | Tablet<br>100 mg<br>200 mg<br>400 mg | Epilepsy |
| Nerlynx (neratinib) | Tablet<br>40 mg | Breast cancer |
| Rozlytrek (entrectinib) | Capsule<br>100 mg<br>200 mg | Neurotrophic tyrosine receptor kinase (NTRK) fusion-positive locally advanced or metastatic solid tumours<br>Non-small cell lung cancer |
| Takhzyro (lanadelumab) | Solution for injection<br>300 mg/2 mL | Hereditary angioedema (C1-esterase-inhibitor deficiency or dysfunction) |
| UroFos (fosfomycin) | Oral granules<br>3 g | Urinary tract infection |
| Zavicefta (avibactam; ceftazidime) | Powder for infusion<br>2000 mg/500 mg | Infection |

### Recent approvals of medicines with new indications

There were no recent approvals of medicines with new indications for the period 16 April 2020 to 15 July 2020.

See the Medsafe website for more information about these medicines (**medsafe.govt.nz/regulatory/DbSearch.asp**). Data sheets of currently marketed medicines are also available (**medsafe.govt.nz/Medicines/infoSearch.asp**).

# Importing unapproved medicines for supply

**Key messages**

- Importing unapproved medicines risks supplying substandard or falsified medicines to patients.
- Some simple checks can help prevent patients from being supplied substandard or falsified medicines.
- Certificates of Analysis should be received and retained with every importation of medicine.
- Importers supplying unapproved medicines under section 29 of the Medicines Act 1981 must send details of the supply to Medsafe. This helps us to protect patients.
- Importers and prescribers of unapproved medicines are responsible for ensuring that they are appropriate in terms of quality, safety and efficacy.

## Importing medicines into New Zealand

The Medicines Act 1981 (the Act) places tight controls over the medicine supply chain through a system of licences to manufacture, sell, supply, pack, possess or administer medicines. These controls mean that prescribers and patients can be assured that approved medicines imported through the licensed supply chain are legitimate and have appropriate quality, safety and efficacy.

However, wholesalers, hospital and community pharmacies may import unapproved medicines for further supply in response to a prescription from a medical practitioner (section 29 of the Act).[1] Also, in some instances, authorised prescribers may directly import medicines for patients in their care (section 25 of the Act).[1] These less frequent importations of medicines are usually due to the lack of an approved product available in New Zealand.

## Risks of importing and supplying unapproved medicines

Unapproved medicines imported into New Zealand have not gone through the usual medicine approval process in New Zealand and may not meet internationally agreed standards for quality, safety and efficacy. The risk of inadvertently importing a falsified or substandard medicine is also increasing as global supply chains become more complex and e-commerce spreads.[2]

Importers and prescribers of unapproved medicines are responsible for ensuring that they are appropriate in terms of quality, safety and efficacy.

### How can importers reduce the risk of importing a falsified or substandard medicine?

Some simple checks can help, such as:

- check that the specification of these products meets international guidelines, for example, pharmacopoeia
- check whether a reputable overseas regulator has approved the products
- source the medicine from reputable, legitimate suppliers
- ask for information on the supply chain and storage conditions through the supply chain
- visually inspect the medicines received
- compare new stock to old stock for likeness and consistency of labelling

- check any patient information leaflets and product labelling for spelling and grammar
- have a documented procedure in place which describes how these checks are completed.

Any suspicion of counterfeit or poor-quality medicine should be immediately reported to Medsafe: **recalls@health.govt.nz**

### Legal requirements for import and supply of unapproved medicines

Importers of any medicine must meet their legal obligations specified under section 42 of the Act.[1] Anyone importing a medicine, including authorised prescribers and medical practitioners, must obtain details of the specifications for testing the quality of that medicine and a certificate of the results of testing for every batch of that medicine. These details are usually in the 'Certificates of Analysis' or 'COA', which importers can request from the exporter. Under the Act, officers can request a copy of the COAs at any time so importers should retain these in a safe place.

Importers supplying unapproved medicines under section 29 of the Act must provide information on the supply to Medsafe (the section 29 declaration/notification form is available at: **medsafe.govt.nz/regulatory/unapproved.asp**). International regulatory bodies will notify Medsafe of falsified or counterfeit medicines or medicines with a suspected quality issue. If these medicines have been imported into New Zealand, Medsafe can take action to protect patients.

### More information

- Supplying unapproved medicines – including the section 29 declaration/notification form (**medsafe.govt.nz/regulatory/unapproved.asp**)
- Use of unapproved medicines and unapproved use of medicines (**medsafe.govt.nz/profs/RIss/unapp.asp**)

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**Acknowledgement**
Dr Chris Cameron, Capital and Coast District Health Board
Bryan Simpson, New Zealand Formulary

Medsafe also acknowledges the contribution of the New Zealand Pharmacovigilance Centre in providing data and analysis for articles.

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