Prescriber Update

Vol. 44 No. 2 June 2023

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

Contents

MEDSAFE
New Zealand Medicines and Medical Devices Safety Authority

Te Kāwanatanga o Aotearoa
New Zealand Government

MANATŪ HAUORA
MINISTRY OF HEALTH

Antipsychotic-induced constipation – high impact for patients

Key messages

- Constipation is a common side effect of all antipsychotics.
- Untreated or delayed diagnosis of antipsychotic-induced constipation may lead to serious complications such as ileus and intestinal obstruction.
- Clozapine treatment has a high risk of constipation and related complications, which can be fatal.
- Prescribers and others involved in patient care:
  - should regularly ask patients about bowel movements
  - remind patients to monitor their bowel movements frequently
  - inform patients to seek immediate medical attention if constipation occurs.

Antipsychotics are a class of medicines that are indicated for the treatment of schizophrenia and related disorders.[1]

Constipation is a common side effect of all antipsychotics that can occur at any stage of treatment.[1]

Regular monitoring of bowel movements is essential throughout antipsychotic treatment. Constipation is a risk factor for serious bowel-related complications if not detected and managed appropriately.[2,3]

Antipsychotics impact bowel motility

The neurotransmitters acetylcholine, serotonin and histamine play a role in promoting intestinal peristalsis, a mechanism required to push intestinal content through the colon to the rectum.[3]

Antipsychotics can inhibit the action of one or more of these neurotransmitters, resulting in prolonged gastrointestinal transit time, which contributes to constipation.[3]

The risk of constipation differs between antipsychotics, due to varying affinity with different neurotransmitter receptor types.[2,3]

Serious bowel-related adverse events with some antipsychotics

Untreated or delayed diagnosis of antipsychotic-induced constipation may increase the risk of ileus and/or intestinal obstruction.[2,3]

Complications of an intestinal obstruction can include intestinal ischaemia, intestinal necrosis and intestinal perforation. If these complications occur, patients require hospital admission and may need surgery.[5]

Serious bowel-related adverse events can occur at any time during treatment with antipsychotics, although the risk is higher with clozapine.[2,4] On rare occasions these events have proved fatal.[4]

Risk factors for developing antipsychotic-induced constipation

Some patients may have risk factors for developing constipation with antipsychotics, including concomitant medicine use, lifestyle factors, co-morbidities and antipsychotic dose.

Constipation is an adverse reaction of many medicines, including opioids or medicines with anticholinergic properties.[3] Be cautious about concomitant prescribing, especially for patients already taking clozapine.[3,4]

Lifestyle and dietary factors can contribute to constipation in people with schizophrenia. This includes poor dietary habits, limited fluid intake and low physical activity.[2,3]

Patients who are elderly, have a history of colonic disease or a history of lower abdominal surgery may be at a higher risk of constipation.[3,4]

The risk of antipsychotic-induced constipation may be dose related.[3]

Early detection and management are vital

The most commonly reported signs and symptoms associated with severe constipation include moderate to severe abdominal pain, abdominal distension, vomiting, paradoxical 'overflow' diarrhoea, reduced appetite and nausea. However, many patients with schizophrenia have abnormally high pain tolerance, and may not report symptoms associated with constipation.[6]

Members of the treating team should regularly ask patients about their bowel movements. Remind patients to monitor their bowel movements frequently. Whānau and caregivers could also be asked to help monitor the patient.[3,4]

Prescribers should advise patients to seek immediate medical attention when constipation occurs.[3,4]

Close monitoring of the patient's bowel movements is essential throughout treatment with clozapine. It is vital that constipation is recognised early and treated appropriately. As described above, complications can occur with delayed diagnosis.[4]

Management of antipsychotic-induced constipation may include non-pharmacological and/or pharmacological treatments.[3] With clozapine, prophylactic use of laxatives may be required. Follow local clinical guidelines.[4]

New Zealand case reports

The Centre for Adverse Reaction reporting (CARM) has received numerous reports of bowel-related adverse events with antipsychotics. Most of them are associated with clozapine (Table 1).

Table 1: Clozapine and significant gastrointestinal events reported to the Centre for Adverse Reactions Monitoring (CARM), by reported reaction term, as of 22 March 2023

Reaction term	Number of reports*
Constipation	95
Intestinal obstruction	32
Megacolon acquired	10
Ileus	9
Bowel motility disorder	8
Intestinal perforation, intestinal ischaemia, ileus paralytic, faecal impaction	4 (each)
Colitis	3
Gastrointestinal haemorrhage, peritonitis	2 (each)
Colitis ischaemic, small intestine obstruction, intestinal necrosis	1 (each)

* An individual report can have multiple reaction terms and may be represented in more than one of the reaction term counts.

Source: Centre for Adverse Reactions Monitoring

As of 22 March 2023, the bowel-related adverse events reported with other antipsychotics were:

- **constipation:** risperidone (2 reports); amisulpride, flupentixol, chlorpromazine, quetiapine, haloperidol (1 report each)
- **bowel motility disorder**: olanzapine (1)
- **colitis**: risperidone (1).

More information

For more information about antipsychotics, see the data sheet and consumer medicines information(CMI): Search for a data sheet or CMI.

For further information about clozapine:

- *Prescriber Update* June 2015: Clozapine – Close Monitoring Required
- *Prescriber Update* June 2011: Clozapine: Impacts on the colon
- Medsafe June 2020: Clozapine – Alert Communication: Important updates to clozapine data sheets and monitoring during COVID-19 pandemic

References

1. New Zealand Formulary (NZF). 2022. *NZF v130: Antipyschotic drugs* 01 Apr 2023. URL: nzf.org.nz/nzf_2098 (accessed 4 April 2023).
2. De Hert M, Hudyana H, Dockx L, et al. 2011. Second-generation antipsychotics and constipation: a review of the literature. *European Psychiatry* 26(1): 34-44. DOI: 10.1016/j.eurpsy.2010.03.003 (accessed 4 April 2023).
3. Xu Y, Amdanee N and Zhang X. 2021. Antipsychotic-induced constipation: a review of the pathogenesis, clinical diagnosis, and treatment. *CNS Drugs* 35(12): 1265–74. DOI: 10.1007/s40263-021-00859-0 (accessed 4 April 2023).
4. Viatris Ltd. 2023. *Clozaril New Zealand Data Sheet.* 13 March 2023. URL: medsafe.govt.nz/profs/Datasheet/c/Clozariltab.pdf (accessed 4 April 2023).
5. Smith DA, Kashyap S, Nehring SM. 2022. Bowel obstruction. In: *Statpearls [Internet]*. URL: ncbi.nlm.nih.gov/books/NBK441975/ (accessed 5 April 2023).
6. Medsafe. 2015. Clozapine – Close monitoring required. *Prescriber Update* 36(2): 18-21. URL: medsafe.govt.nz/profs/puarticles/June2015/June2015Clozapine.htm (accessed 21 April 2023).

Reporting anaphylaxis? It's all in the detail

Key messages

- Report all suspected or confirmed cases of medicine-induced anaphylaxis to the Centre for Adverse Reactions Monitoring (CARM).
- Please provide as much detail as possible about the event so that CARM can add an appropriate alert in the national Medical Warning System (MWS).
- The MWS alerts healthcare professionals to known risk factors that may be important when making clinical decisions about a patient. For known anaphylaxis, the MWS can support care of patients who cannot communicate their medicine allergy history.

Report all cases of anaphylaxis to CARM

Anaphylaxis is a life-threatening systemic hypersensitivity reaction that is usually rapid in onset and can be fatal.

Report all suspected or confirmed cases of medicine-induced anaphylaxis to the Centre for Adverse Reactions Monitoring (CARM). CARM can then add an appropriate alert on the national Medical Warning System (MWS) for the patient.

The national Medical Warning System[1]

The MWS is a national alert service linked to the patient's National Health Index (NHI) number. It alerts healthcare professionals to known risk factors that may be important when making clinical decisions about a patient. The MWS is particularly important for patients who are unable to communicate, are confused, unconscious or may have forgotten a previous event.

The MWS has 2 types of medicine alerts: Danger and Warning.

- A Danger alert reflects a contraindication to further use for the patient. Used, for example, when the patient has had an anaphylactic-type reaction or any other life-threatening reaction.
- A Warning alert indicates that the medicine has caused the patient significant morbidity and should be avoided.

Some hospitals have systems in place and designated staff who enter Warning alerts into the MWS. Only CARM can place a Danger alert.

Detailed anaphylaxis ADR reports are important

Detailed ADR reports help the medical assessors at CARM determine whether an alert needs to be created in the MWS, and if so, the type of alert.

Medsafe and CARM acknowledge that reporter time and resource constraints may limit the level of clinical detail provided in reports. In addition, some clinical information may not be available at the time of the report submission. As much information as is available at the time of the event is appreciated.

The following details, where available, can support CARM's causality assessment.

- The time to onset from administering the medicine to the anaphylaxis symptoms.
- Signs and symptoms. The Brighton Collaboration case definition for anaphylaxis can be a useful guide for symptom reporting.
- Tryptase and allergy test results.

Attaching a general practice note, emergency department or hospital summary and specialist clinical letter to the report can provide this useful clinical information.

Submitting follow-up information, as it becomes available, will further assist CARM's causality assessment. CARM will also update the MWS as appropriate, for example, if allergy testing identifies that the patient is not allergic to the medicine.

Follow-up information can be submitted by emailing carmnz@otago.ac.nz. Please include the report number if available.

Brighton Collaboration case definition for anaphylaxis

The Brighton Collaboration produce case definitions of various conditions including anaphylaxis to help with safety monitoring, primarily of vaccines. These case definitions are an aid to determining diagnostic certainty, with level 1 being the highest certainty and level 5 the lowest.[2]

The case definition does not determine causality[2] and is not a substitute for clinical assessment or a clinical specialist's assessment following formal allergy testing.

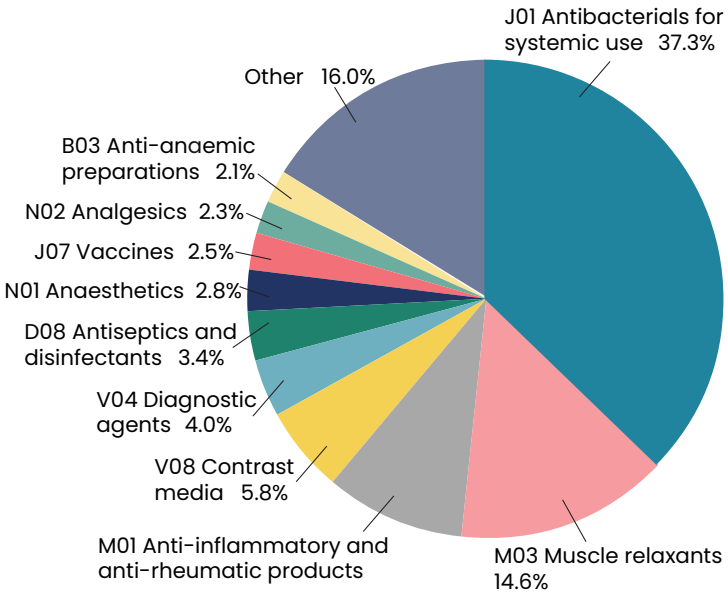
CARM use the Brighton Criteria when assessing reports of potential anaphylaxis.

Overview of anaphylaxis reports to CARM

From 1 January 2018 to 30 November 2022, CARM received a total of 720 case reports for 800 medicines suspected of causing immunoglobulin E (IgE)-mediated anaphylaxis. The majority of patients were women (63%), and most patients were reported to have recovered (87%).

The most frequently reported classes of medicines by Anatomical Therapeutic Chemical (ATC) code were systemic antibiotics, muscle relaxants, anti-inflammatories and anti-rheumatic products, and contrast media (Figure 1).

Figure 1: Top 10 classes of medicines, by ATC codes, associated with anaphylaxis in the CARM database, 1 January 2018 to 30 November 2022



The most frequently reported individual medicines were cefazolin (13.8%), rocuronium (10.1%), amoxicillin with clavulanic acid (7.5%), amoxicillin (3.6%), and diclofenac (3.3%).

For COVID-19 vaccines, there were 128 anaphylaxis reports meeting levels 1–3 of the Brighton Collaboration case definition, up to and including 30 November 2022.

More information

- *Prescriber Update* June 2020: Alerting the Medical Warning System can save lives!
- The Brighton Collaboration case definition for anaphylaxis
- Report a suspected adverse reaction to CARM

References

1. Medsafe. 2020. Alerting the Medical Warning System can save lives! *Prescriber Update* 42(2): 29-30. URL: medsafe.govt.nz/profs/PUArticles/June2020/Medical-Warning-System.html (accessed 19 April 2023).
2. Gold MS, Amarasinghe A, Greenhawt M, et al. 2023. Anaphylaxis: Revision of the Brighton collaboration case definition. *Vaccine* 41(15): 2605-14. URL: sciencedirect.com/science/article/pii/S0264410X22014256 (accessed 11 April 2023).

Reminder: ACE inhibitor-induced angioedema can be fatal

Key messages

- Angioedema is a potentially serious adverse effect of angiotensin converting enzyme (ACE) inhibitors, which can be fatal. It can occur at any time during treatment.
- When prescribing ACE inhibitors, ask patients if they have used these medicines before and if they experienced any adverse reactions. Specifically ask about swelling.
- Do not restart any ACE inhibitor in patients with a history of ACE inhibitor-induced angioedema.

The Centre for Adverse Reactions Monitoring (CARM) recently received a report of fatal angioedema with an ACE inhibitor. The patient had experienced minor tongue swelling with an ACE inhibitor previously. A different ACE inhibitor was started at a later date, and the patient developed angioedema with a fatal outcome.

Medsafe is reminding health professionals about the risk of angioedema with ACE inhibitors and the importance of taking an adverse reaction and allergy history before starting any medicine.

ACE inhibitors

Angiotensin-converting enzyme inhibitors (ACE inhibitors) inhibit the conversion of angiotensin I to angiotensin II.[1] They have many indications, such as treatment of hypertension, myocardial infarction, heart failure and diabetic nephropathy.

ACE inhibitors approved in New Zealand include captopril, cilazapril, enalapril, lisinopril, perindopril, quinapril and ramipril.

ACE inhibitor-induced angioedema

Angioedema is a sudden localised swelling of the skin or mucous membranes without itching or urticaria. ACE inhibitor-induced angioedema often manifests as swelling of the face, lips or tongue. Rarely, airway involvement causes asphyxiation which can be fatal. Gastrointestinal symptoms associated with visceral angioedema can also occur.[2]

Angioedema is thought to occur in around 0.1% to 0.7% of patients who take an ACE inhibitor.[2] Onset is usually during the first weeks or months of therapy, but it can occur years into treatment.[3] Angioedema has also been reported with angiotensin II receptor blockers (ARBs; eg, candesartan, losartan), but the risk is thought to be lower than with ACE inhibitors.[4]

Management

If a patient taking an ACE inhibitor presents with signs of angioedema, consider ACE inhibitors as the cause and stop the medicine.

Clinical management of ACE-induced angioedema includes supportive care and monitoring, and airway management if the mouth or throat is involved.[2] Some patients experience repeated episodes even after stopping the ACE inhibitor. Counsel patients to seek immediate medical attention if angioedema recurs.

If ACE inhibitors are continued after an initial episode of angioedema, further episodes may occur that are more severe and life-threatening. ACE inhibitors are contraindicated in patients with a history of ACE inhibitor-induced angioedema. If clinically indicated, switch the patient to an alternative therapy as per local guidelines.[2,4]

Advice to health professionals

Before prescribing an ACE inhibitor, ask patients if they have taken these medicines before and if they had any adverse reactions. Specifically ask about swelling.

Inform patients who are starting ACE inhibitors about the symptoms of angioedema and advise them to seek urgent medical attention if these occur.

ACE inhibitors should not be prescribed to patients with a history of ACE inhibitor-induced angioedema. Educate patients who have experienced ACE inhibitor-induced angioedema about the need to avoid all ACE inhibitors in the future.[2,4]

Please report cases of ACE inhibitor-induced angiodema to CARM, so an appropriate alert can be added to the national Medical Warning System.

New Zealand case reports

As of 22 March 2023, CARM had received 479 reports of angioedema where the causal medicine was an ACE inhibitor, including 3 fatal reports.

More information

- *Prescriber Update* March 2021: Vildagliptin and ACE inhibitors – increased risk of angioedema
- bpac^{nz} March 2021: Prescribing ACE inhibitors: time to reconsider old habits
- Search for a data sheet
- *Prescriber Update* June 2020: Alerting the Medical Warning System can save lives!

References

1. New Zealand Formulary (NZF). 2023. *NZF v131: Angiotensin-converting enzyme inhibitors* 1 May 2023. URL: nzf.org.nz/nzf_1242 (accessed 3 May 2023).
2. Guyer A and Banerji A. 2023. ACE inhibitor-induced angioedema. In: *UpToDate* 10 March 2023. URL: uptodate.com/contents/ace-inhibitor-induced-angioedema (accessed 16 March 2023).
3. Makani H, Messerli FH, Romero J, et al. 2012. Meta-analysis of randomized trials of angioedema as an adverse event of renin–angiotensin system inhibitors. *The American Journal of Cardiology* 110(3): 383-91. DOI: 10.1016/j.amjcard.2012.03.034 (accessed 16 March 2023).
4. bpac^{nz}. 2021. *Prescribing ACE inhibitors: time to reconsider old habits* updated 25 November 2022. URL: bpac.org.nz/2021/ace.aspx (accessed 16 March 2023).

Quarterly summary of recent safety communications

The table below is a summary of recent safety communications for health care professionals and consumers. Click on a specific topic to go to the communication.

Date	Communication	Topic
09/05/2023	Monitoring	Interleukin inhibitors and the possible risk of pancreatitis
27/04/2023	Information leaflet	Risks of opioid medicines (Te Reo version) (PDF, 2 pages, 235 KB)
26/04/2023	Information leaflet	Stopping antidepressants: be cautious and go slow (PDF, 2 pages, 294 KB)
26/04/2023	Monitoring	Review of pholcodine-containing medicines – Provide your feedback by 8 May 2023
12/04/2023	Alert	Topiramate use in pregnancy: further restrictions for safety
06/04/2023	Dear Healthcare Professional Letter	Topamax (topiramate): Pregnancy-related safety update (PDF, 4 pages, 232 KB)
27/03/2023	Monitoring	Update – Abnormal uterine bleeding and oral anticoagulants (blood thinners)
20/03/2023	Alert	New legislation about medicines that can impair driving
02/03/2023	Monitoring	Reports of pericarditis following mpox vaccination
23/02/2023	Dear Healthcare Professional Letter	Lagevrio (molnupiravir) 200 mg capsules - Extension to shelf life of stock in market (PDF, 2 pages, 223 KB)
22/02/2023	Information leaflet	Nhan Sam Tuyet Lien Truy Phong Hoan capsules – information for patients in: English, Samoan and Tongan (PDF, 1 page, 570 KB each)
06/02/2023	Dear Healthcare Professional Letter	Dexmedetomidine: Increased risk of mortality in intensive care unit (ICU) patients ≤63.7 years (PDF, 3 pages, 835 KB)
24/01/2023	Dear Healthcare Professional Letter	Shelf life extension of Paxlovid (nirmatrelvir 150 mg/ritonavir 100 mg) film coated tablets (PDF, 3 pages, 193 KB)

Ocular nonsteroidal anti-inflammatory drugs (NSAIDs) and corneal melting

Key messages

- Corneal melting is a serious ophthalmological condition that can lead to corneal perforation and vision loss.
- Use of ocular nonsteroidal anti-inflammatory drugs has been associated with serious corneal adverse events, including signs/symptoms suggestive of corneal melting.
- Patients with signs/symptoms suggestive of corneal melting should discontinue treatment and seek immediate medical advice.

Ocular nonsteroidal anti-inflammatory drugs (NSAIDs) are prescription medicines used for the prophylaxis and treatment of ocular inflammation and/or pain associated with ocular conditions, often in the post-operative setting.[1] This article is a reminder that serious corneal adverse events can occur with these medicines.

What is corneal melting?

Corneal melting is a serious ophthalmological condition that begins with a defect in the corneal epithelium. If the defect is not corrected, the collagen in the corneal stroma breaks down, leading to corneal thinning. In some cases, corneal melting progresses to corneal perforation and vision loss.[2]

Various conditions can cause corneal melting, including eye infections, sterile inflammation, certain medical conditions (such as rheumatoid arthritis), and surgical or chemical injury to the cornea.[3]

Use of ocular NSAIDs has recently been linked to corneal melting. However, the mechanism behind this association is unknown.[2]

NSAID-induced corneal melting

Consider the possibility of corneal melting in patients using ocular NSAIDs who complain of blurred/distorted vision, worsening eye pain, eye irritation and hypersensitivity and/or ocular discharge. Check these patients for corneal damage.[4,5]

Risk factors

Certain situations may increase the risk for NSAID-induced corneal melting, including (list not exhaustive):

- frequent application and/or prolonged treatment duration[4]
- concomitant use of corticosteroids[4]
- concomitant conditions such as acute eye infections, rheumatoid arthritis, diabetes mellitus, ocular surface disease[4–6]
- recent complicated ocular surgery or patients with repeat ocular surgeries within a short period of time.[4,5]

Associated corneal disorders

Corneal disorders associated with corneal melting have been reported with ocular NSAID use. The Voltaren Ophtha and/or Acular Eye Drops data sheets include information about the following:

- punctate keratitis[4] (damage to the cells on the surface of the cornea)

- ulcerative keratitis[4,5] (corneal ulcer)
- corneal perforation[4,5]
- corneal thinning[4,5]
- corneal epithelial defect[4] or breakdown[5]
- corneal opacity.[4]

Management

Advise patients to seek urgent medical attention if they experience signs/symptoms suggestive of corneal melting. Early diagnosis and treatment are critical to prevent further corneal damage.[7]

Patients with evidence of corneal epithelial breakdown should immediately discontinue ocular NSAID treatment and be closely monitored.[4,5]

Due to the risk of corneal perforation and vision loss, patients with corneal melting are usually managed in a specialist setting. Management of corneal melting may involve medical and/or surgical intervention.[8]

New Zealand information

More than 11,000 people per year are dispensed an ocular NSAID.[9] Up to 22 March 2023, the Centre for Adverse Reactions Monitoring (CARM) had not received any case reports suggestive of corneal melting with ocular NSAIDs.

- See the ocular NSAID data sheets for information about known corneal effects. Search for a data sheet.
- As with any medicine, please report suspected adverse events with ocular NSAIDs to CARM.

References

1. New Zealand Formulary. 2023. *NZF v130: Ocular peri-operative drugs* 1 April 2023. URL: nzf.org.nz/nzf_6020 (accessed 11 April 2023).
2. Rigas B, Huang W and Honkanen R. 2020. NSAID-induced corneal melt: Clinical importance, pathogenesis, and risk mitigation. *Survey of Ophthalmology* 65(1): 1-11. DOI: doi.org/10.1016/j.survophthal.2019.07.001 (accessed 28 March 2023).
3. Hossain P. 2012. The corneal melting point. *Eye (Lond)* 26(8): 1029-30. DOI: 10.1038/eye.2012.136 (accessed 28 March 2023).
4. Novartis New Zealand Limited. 2022. *Voltaren Ophtha New Zealand Data Sheet* 2 November 2022. URL: medsafe.govt.nz/profs/Datasheet/v/voltarenophtha.pdf (accessed 28 March 2023).
5. Allergan New Zealand. 2018. *Acular Eye Drops New Zealand Data Sheet* May 2018. URL: medsafe.govt.nz/profs/datasheet/a/aculareyedrops.pdf (accessed 28 March 2023).
6. Sule A, Balakrishnan C, Gaitonde S, et al. 2002. Rheumatoid corneal melt. *Rheumatology* 41(6): 705-06. DOI: 10.1093/rheumatology/41.6.705 (accessed 29 March 2023).
7. Medsinge A, Gajdosova E, Moore W, et al. 2016. Management of inflammatory corneal melt leading to central perforation in children: a retrospective study and review of literature. *Eye (Lond)* 30(4): 593-601. DOI: 10.1038/eye.2015.278 (accessed 12 April 2023).
8. Dana R. 2023. Ocular manifestations of rheumatoid arthritis. In: *UpToDate* 7 March 2023. URL: uptodate.com/contents/ocular-manifestations-of-rheumatoid-arthritis (accessed 28 March 2023).
9. Te Whatu Ora. 2022. *Pharmaceutical Data Web Tool* 7 November 2022. URL: tewhatuora.shinyapps.io/pharmaceutical-data-web-tool/ (accessed 12 April 2023).

Recent data sheet updates: important new safety information

Table 1 below provides a list of data sheets recently updated with important new safety information. Note that this is not a comprehensive list of all recently updated data sheets, nor does it describe all changes to a particular data sheet.

Table 1: Recently updated data sheets (by active ingredient): important new safety information

Active ingredient(s)	Medicine	Data sheet updates	
		Section	Summary of new safety information
Atezolizumab	Tecentriq	4.2	Dose modifications: recommendations for patients with immune-mediated myelitis, immune-mediated facial paresis, haemophagocytic lymphohistiocytosis (HLH)
		4.4	Warnings and precautions: immune-mediated myelitis, immune-mediated facial paresis, HLH
		4.8	Undesirable effects: immune-mediated myelitis, immune-mediated facial paresis, HLH, dry mouth
Carboplatin	Carboplatin Accord	4.9	Overdose: no known antidotes, overdose enhances expected toxic effects, may result in death
Carboplatin	Carboplatin DBL	4.6	Fertility: continue to use contraception for 7 months after treatment for females and for 4 months after treatment for males. Breastfeeding: discontinue breastfeeding during treatment and 1 month after treatment, or discontinue treatment
Dulaglutide	Trulicity	4.8	Undesirable effects: constipation, flatulence, abdominal distension, gastroesophageal reflux disease, eructation
Esketamine	Spravato	4.4	Warnings and precautions: hepatotoxicity with chronic ketamine use
Etanercept	Enbrel	4.4	Warnings and precautions: uveitis
		4.6	Pregnancy: contraception recommendations for females of childbearing potential. Lactation: live vaccine administration in breastfed infants
Etopophos	Etopophos	4.4	Warnings and precautions: secondary leukaemia, tumour lysis syndrome
		4.5	Interactions: medicines with similar myelosuppressive effects (additive effect)
		4.8	Undesirable effects: severe myelosuppression, other toxicities, infertility
Ezetimibe + simvastatin	Zimybe	4.8	Undesirable effects: vision blurred, visual impairment, lichenoid drug eruptions, muscle rupture, gynaecomastia
Fludarabine	Fludara Oral	4.6	Fertility, pregnancy and lactation: strengthens warnings for females; males to use effective contraception during treatment and for 95 days after treatment

Active ingredient(s)	Medicine	Data sheet updates Section	Summary of new safety information
Levothyroxine	Synthroid	4.3	Contraindications: acute myocarditis, acute pancarditis
		4.4	Warnings and precautions: biotin interference with thyroid immunoassays
		4.5	Interactions: St John's wort, biotin
Loperamide	Diamide	4.8	Undesirable effects: acute pancreatitis
Rosuvastatin	Crestor	4.4	Warnings and precautions: myasthenia gravis, ocular myasthenia
		4.6	Pregnancy and lactation: elaborates on pregnancy and lactation warnings, lactation data added
		4.8	Undesirable effects: ocular myasthenia, myasthenia gravis, lichenoid drug eruption
Topiramate*	Topamax	4.4	Warnings and precautions: strengthens warnings in women of childbearing potential
		4.6	Pregnancy: monotherapy is preferred for antiepileptic drugs (AEDs) in general. With topiramate, increased risk of neurodevelopmental disorders in infants exposed in utero

* See the Medsafe alert communication: Topiramate use in pregnancy: further restrictions for safety

More information

To find out if sponsors have made any changes to their data sheets, see Section 10 'Date of revision of the text' (at the end of each data sheet).

- Search for a data sheet

Sodium-glucose co-transporter 2 (SGLT2) inhibitors and potential risk for polycythaemia

Key messages

- Polycythaemia (erythrocytosis) refers to increased haemoglobin and/or haematocrit in the blood, due to an abnormally high concentration of red blood cells (erythrocytes).
- Elevated haematocrit levels have been reported with sodium-glucose co-transporter 2 (SGLT2) inhibitor medicines.
- Consider SGLT2 inhibitors as a potential cause for polycythaemia, where no other causes are identified.

The Centre for Adverse Reactions Monitoring (CARM) has received a case report of polycythaemia with empagliflozin (CARM ID 142929).

This article highlights information about the potential risk of polycythaemia with sodium-glucose co-transporter 2 (SGLT2) inhibitor medicines.

What is polycythaemia?[1,2]

Polycythaemia (erythrocytosis) is an elevation of haemoglobin and/or haematocrit levels above the normal range due to an abnormally high concentration of red blood cells (erythrocytes).

Depending on the cause, polycythaemia is subclassified into relative or absolute polycythaemia.

Relative polycythaemia refers to plasma volume depletion (ie, haemoconcentration without an increase in erythrocyte mass), most commonly caused by diuretics, vomiting or diarrhoea.

Absolute polycythaemia refers to increased erythrocyte mass and is categorised into primary or secondary. Mutations in erythrocyte progenitor cells cause primary polycythaemia and elevated serum erythropoietin levels cause secondary polycythaemia. Polycythaemia vera is a type of primary polycythaemia associated with a Janus Kinase-2 (JAK2) mutation. Elevated erythropoietin in secondary polycythaemia may be due to hypoxia, erythropoietin-producing solid tumours or some medicines, such as erythropoietin or testosterone.

Some types of polycythaemias, particularly polycythaemia vera, are associated with an increased risk of thrombosis.

SGLT2 inhibitors may increase haematocrit by stimulating erythropoiesis

In type 2 diabetes, increased glucose uptake via the SGLT2 in the kidney causes metabolic stress. Damage to erythropoietin-secreting cells in the kidney may occur, subsequently reducing serum erythropoietin levels.[3]

SGLT2 inhibitors may help alleviate this metabolic stress in the kidneys through inhibition of SGLT2. As a result, the kidneys may increase secretion of erythropoietin, stimulating red blood cell production (erythropoiesis).[3]

SGLT2 inhibitors are thought to increase haematocrit levels secondary to increasing erythropoietin levels.[3] In clinical trials, participants taking empagliflozin or dapagliflozin were reported to have increased haematocrit levels from baseline compared to the placebo group.[4,5]

Identifying the underlying cause of polycythaemia is important

Diagnosing the specific cause of polycythaemia is needed for appropriate management.[1,2] In some cases, specialist input may be needed.[2] Follow local guidelines.

SGLT2 inhibitors may increase a patient's haematocrit and/or haemoglobin levels. In some patients, these elevations may be above normal levels.[6] Cases of polycythaemia associated with SGLT2 inhibitor use have been reported in the literature.[7]

Consider SGLT2 inhibitors as a potential cause for secondary polycythaemia.[6]

More information

For more information, see the empagliflozin and dapagliflozin data sheets and consumer medicines information (CMI).

- Search for a data sheet or CMI

References

1. Tefferi A. 2022. Diagnostic approach to the patient with erythrocytosis/polycythemia. In: *UpToDate* 21 November 2022. URL: uptodate.com/contents/diagnostic-approach-to-the-patient-with-erythrocytosis-polycythemia (accessed 5 April 2023).
2. Mithoowani S, Laureano M, Crowther MA, et al. 2020. Investigation and management of erythrocytosis. *Canadian Medical Journal* 192(32): E913-18. DOI: 10.1503/cmaj.191587 (accessed 13 April 2023).

3. Sano M and Goto S. 2019. Possible mechanism of hematocrit elevation by sodium glucose cotransporter 2 Inhibitors and associated beneficial renal and cardiovascular effects. *Circulation* 139(17): 1985-87. DOI: 10.1161/circulationaha.118.038881 (accessed 5 April 2023).
4. Boehringer Ingelheim (N.Z) Limited. 2022. *Jardiance New Zealand Data Sheet* 29 August 2022. URL: medsafe.govt.nz/profs/Datasheet/j/jardiancetab.pdf (accessed 5 April 2023).
5. AstraZeneca Limited. 2022. *Forxiga New Zealand Data Sheet* 18 July 2022. URL: medsafe.govt.nz/profs/Datasheet/f/forxigatab.pdf (accessed 5 April 2023).
6. Gangat N, Szuber N, Alkhateeb H, et al. 2021. JAK2 wild-type erythrocytosis associated with sodium-glucose cotransporter 2 inhibitor therapy. *Blood* 138(26): 2886–9. DOI: doi.org/10.1182/blood.2021013996 (accessed 5 April 2023).
7. Chin-Yee B, Solh Z and Hsia C. 2020. Erythrocytosis induced by sodium-glucose cotransporter-2 inhibitors. *Canadian Medical Journal* 192(42): E1271. DOI: 10.1503/cmaj.76686 (accessed 29 April 2023).

MARC's remarks: March 2023 meeting

The Medicines Adverse Reactions Committee (MARC) convened on 9 March 2023.

The Committee reviewed the association between pancreatitis and the **interleukin-6 (IL-6) inhibitor**, **tocilizumab**. The Committee considered there was evidence to suggest an association between pancreatitis and tocilizumab and that there may be biological plausibility for other IL-6 inhibitors to also cause pancreatitis. The Committee recommended data sheet updates to include the risk of pancreatitis with IL-6 inhibitors. Medsafe has published a monitoring communication to collect more information on the possible risk with other IL inhibitors.

The risk of pre-eclampsia with **probiotic supplements** used in pregnancy was discussed. The Committee considered the current evidence did not support a plausible causal relationship between probiotic supplementation and an increased risk of pre-eclampsia.

The Committee considered whether **vaping** increases the risk of thromboembolism, particularly in women taking **hormonal therapy (combined oral contraceptives and hormone replacement therapy)**. The Committee noted that smoking further increases the risk of thromboembolism in women taking hormonal therapy, but the effects of vaping are unknown. The Committee agreed that there is currently no evidence that vaping increases the risk of thromboembolism, but any potential association will become clearer with time. The Committee considered that it is important for healthcare professionals to state the vaping status of the patient when submitting adverse drug reaction reports to the Centre for Adverse Reactions Monitoring (CARM).

See the Medsafe website for the MARC meeting minutes and the reports presented to the MARC.

Autoimmune complications of immunotherapy

Key messages

- Immune checkpoint inhibitors (ICIs) are a type of immunotherapy used to treat several cancers. ICIs inhibit receptor systems known as immune checkpoints, allowing the host's T-cells to attack cancer cells.
- Immune-related adverse events (irAEs) are a type of autoimmune side effect. IrAEs can occur at any time during treatment with ICIs, and even months after stopping treatment.
- Early identification and management of irAEs is essential for the safe use of ICIs.

The Centre for Adverse Reactions Monitoring (CARM) received a case report (CARM ID 143560) of a patient diagnosed with type 1 diabetes mellitus following treatment with pembrolizumab. This article is a reminder of immune-related adverse events associated with immune checkpoint inhibitors.

Immune checkpoint inhibitors

Normally, the immune system uses a combination of co-inhibitory and co-stimulatory receptors and their ligands, known as immune checkpoints, to protect the body from infection, autoimmune disorders and allergies. However, by developing mechanisms to avoid them, cancer cells can evade these immune checkpoints and grow uncontrollably.[1]

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that target and inhibit immune checkpoints. This inhibition stimulates the host's immune system to recognise and attack cancer cells.[1] ICIs are indicated for the treatment of several advanced or metastatic cancers, and include pembrolizumab (Keytruda), durvalumab (Imfinzi), atezolizumab (Tecentriq), nivolumab (Opdivo) and ipilimumab (Yervoy).

Two key immune checkpoints targeted by immune checkpoint inhibitors are the cytotoxic T-lymphocyte antigen-4 (CTLA-4) receptor and the programmed death-1 (PD-1) receptor plus its ligand PD-L1.[2] These immune checkpoints are self-recognition signal receptor systems that allow the body's immune system to distinguish between its own cells and foreign pathogens. Cancer cells can exploit these immune checkpoints to reduce T-cell activity and thus weaken the immune system's response to the cancer.

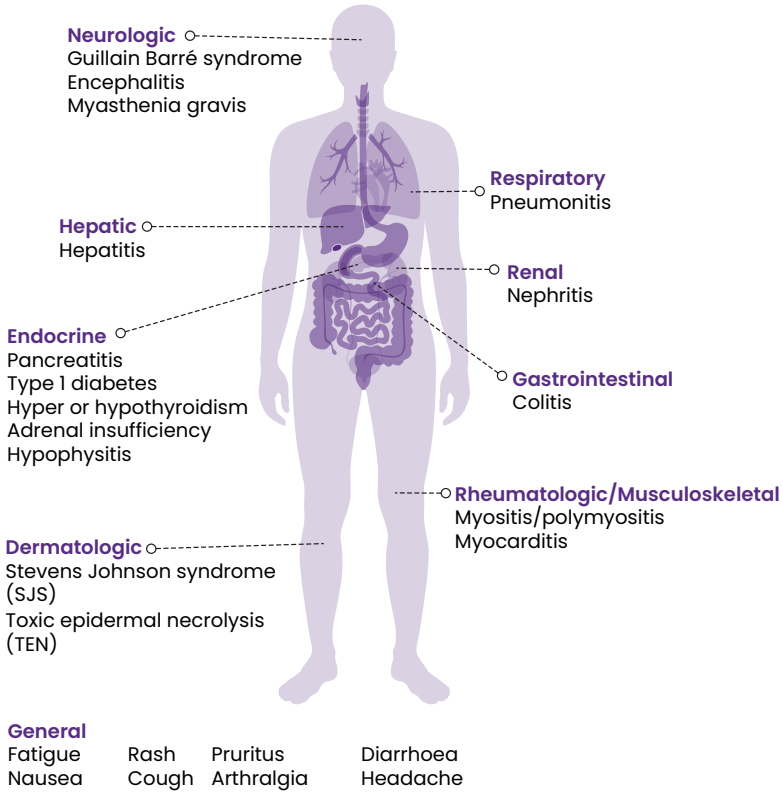
Immune-related adverse events (irAEs)

By targeting the self-recognition signal receptor systems, immune checkpoint inhibitors remove one of the immune system's safeguards. They increase T-cell activity against cancer cells, but ICIs may also increase the risk of T-cell attack on healthy cells, leading to immune-related adverse effects irAEs.[2]

Immune-related adverse effects associated with ICIs vary in severity and may affect different organ systems (Figure 1).

- Common irAEs include fatigue, rash, itching, diarrhoea and nausea.[2]
- Less common but potentially more serious irAEs can affect the lungs, liver, endocrine system (such as the thyroid and adrenal glands) and gastrointestinal system. These irAEs may include respiratory disorders, hepatitis, thyroiditis, colitis and pancreatitis.[2]
- Rare irAEs include neurological and blood disorders, and autoimmune conditions such as rheumatoid arthritis, type 1 diabetes and adrenal insufficiency.[2]

Figure 1: The spectrum of immune-related adverse events* by affected body system



* Not a complete list. Refer to the data sheets for more information.

Sources: Keytruda, Imfinzi, Tecentriq, Opdivo and Yervoy data sheets, available at: medsafe.govt.nz/Medicines/infoSearch.asp (accessed 4 May 2023).

Monitoring for irAEs

Immune-related adverse events can occur during treatment with ICIs but may also occur after treatment stops. Clinicians should consider the possibility of irAEs in ICI-treated patients with any unexplained illness.[1] The specific symptoms and signs of irAEs may indicate which organ system is affected, such as shortness of breath (respiratory), low libido (endocrine) or joint pain (musculoskeletal).[2] Patients may also have abnormal blood test results, such as abnormal liver function tests, low cortisol levels or abnormal thyroid function tests.[2]

Rapid identification of irAEs can improve patient outcomes.[2] Based on the severity of the irAE, withhold immune checkpoint inhibitor therapy and consider administering corticosteroids.[3–7]

Refer to the data sheets for further guidance.

- Search for a data sheet

References

1. bpac^{NZ}. 2018. *Immune checkpoint inhibitors: a new cancer treatment*. URL: bpac.org.nz/2018/checkpoint.aspx (accessed 16 October 2022).
2. Pastow M and Johnson DB. 2023. Toxicities associated with checkpoint inhibitor immunotherapy. In: *UpToDate* 28 March 2023. URL: uptodate.com/contents/toxicities-associated-with-immune-checkpoint-inhibitors (accessed 19 April 2023).
3. Merck Sharp & Dohme (New Zealand) Limited. 2022. *Keytruda New Zealand Data Sheet* 1 February 2023. URL: medsafe.govt.nz/profs/datasheet/k/Keytruda.pdf (accessed 19 April 2023).
4. AstraZeneca Limited. 2023. *Imfinzi New Zealand Data Sheet* 21 March 2023. URL: medsafe.govt.nz/profs/datasheet/i/imfinziinf.pdf (accessed 19 April 2023).

5. Roche Products (New Zealand) Limited. 2023. *Tecentriq New Zealand Data Sheet* 2 March 2023. URL: medsafe.govt.nz/profs/Datasheet/t/Tecentriqinf.pdf (accessed 4 May 2023).
6. Bristol-Myers Squibb (NZ) Limited. 2022. *Opdivo New Zealand Data Sheet* 2 September 2022. URL: medsafe.govt.nz/profs/Datasheet/o/opdivoinf.pdf (accessed 4 May 2023).
7. Bristol-Myers Squibb (NZ) Limited. 2022. *Yervoy New Zealand Data Sheet* 3 August 2022. URL: medsafe.govt.nz/profs/datasheet/y/yervoyinj.pdf (accessed 19 April 2023).

Recent approvals: new active ingredients or new indications

Table 1 shows recent approval of medicines with new active ingredients and Table 2 shows approved medicines with new indications for additional therapeutic areas. These medicines were gazetted during the period 21 December 2022 to 6 April 2023.

Table 1: Recent approvals of medicines with new active ingredients

Medicine	New active ingredient[a]	Dose form: strength(s)	Therapeutic area
Comirnaty Original/ Omicron BA.1[b]	Riltozinameran	Suspension for injection: 15mcg + 15 mcg/0.3mL	COVID-19 prevention
Comirnaty Original/ Omicron BA.4-5[b]	Famtozinameran	Suspension for injection: 15mcg + 15 mcg/0.3mL	COVID-19 prevention
Diacomit	Stiripentol	Capsule: 250mg, 500 mg Powder for oral suspension: 250mg, 500mg	Severe myoclonic epilepsy in infancy (Dravet syndrome)
Leqvio	Inclisiran	Solution for injection: 284mg/1.5mL	Cardiovascular disease
Orkambi	Lumacaftor	Tablet: 100mg + 125mg, 200mg + 125mg Granules: 100mg + 125mg, 150mg + 188mg	Cystic fibrosis
Ozempic	Semaglutide	Solution for injection: 1.5mL, 3mL	Type 2 diabetes
Qinlock	Ripretinib	Tablet: 50mg	Gastrointestinal stromal tumours
Vazkepa	Icosapent	Capsule: 998mg	Cardiovascular disease
Yondelis	Trabectedin	Powder for infusion: 0.25mg, 1 mg	Liposarcoma or leiomyosarcoma

a. The medicine may also contain other active ingredients
b. Provisional approval

Table 2: Approved medicines with new indications for additional therapeutic areas

Medicine (active ingredient)	Dose form and strength(s)	New therapeutic area
Cosentyx (secukinumab)	Solution for injection: 75mg/0.5mL, 150mg/mL, 300mg/2mL Powder for injection: 150mg	Juvenile idiopathic arthritis
Nucala (mepolizumab)	Powder for injection: 100 mg/mL Solution for injection (pre-filled pen and pre-filled syringe): 100 mg/mL	Chronic rhinosinusitis with nasal polyps, hypereosinophilic syndrome

See the Medsafe website for:

- more information about these medicines
- data sheets of currently marketed medicines
- Gazette notices for approved medicine applications.

We need your help!

Please send your reports to CARM for the potential safety issues* listed in the table below.

Medicine(s)	Potential safety issue	Active monitoring ends
Interleukin inhibitors	Pancreatitis	1 November 2023

- 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.

* 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: June 2023

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: 145519 **Age**: 68 **Gender**: Male **Medicine(s)**: Mesalazine **Reaction(s)**: Myocarditis, dyspnoea, malaise, cough	Soon after starting treatment with mesalazine, the patient experienced a dry cough, chest discomfort and shortness of breath. He was diagnosed with myocarditis, likely due to mesalazine.
	Myocarditis is listed as a rare adverse drug reaction in the Asacol and Pentasa data sheets. The Ascaol data sheet also includes a warning for cardiac hypersensitivity reactions, including myocarditis.
CARM ID: 145611 **Age**: 7 **Gender**: Male **Medicine(s)**: Cyclopentolate **Reaction(s)**: Seizure	A child with a history of epilepsy had a seizure following administration of cyclopentolate eye drops.
	The Cyclogyl data sheet states that seizures and acute psychosis induced by cyclopentolate are especially prominent in children. Cyclopentolate should be used with caution in children with known epilepsy.
CARM ID: 145769 **Age**: 13 months **Gender**: Female **Medicine(s)**: Paracetamol **Reaction(s)**: Medication error	Due to a medication error, the child received a supratherapeutic dose of paracetamol.
	To avoid medication errors with paracetamol, prescribe precisely and dispense diligently. Do not rely on colour and flavour because they can change. See the September 2019 *Prescriber Update* article: Paracetamol - Dangerous when not used correctly.
CARM ID: 145939 **Age**: 66 **Gender**: Male **Medicine(s)**: Vildagliptin **Reaction(s)**: Pemphigoid, histology	The patient experienced bullous pemphigoid during treatment with vildagliptin.
	The Galvus data sheet lists bullous pemphigoid as a postmarketing adverse drug reaction of unknown frequency. See also the March 2019 *Prescriber Update* article: Bullous pemphigoid - A blistering problem.

Case details[a,b]	Reaction description and data sheet information[b,c]
CARM ID: 146727 **Age**: 77 **Gender**: Female **Medicine(s)**: Simvastatin, Rosuvastatin **Reaction(s)**: Myocardial infarction, rhabdomyolysis, multiple organ dysfunction syndrome	A few weeks after starting rosuvastatin, the patient experienced cough, back pain, reduced urine output, and lower limb weakness. She was diagnosed with statin-induced rhabdomyolysis.
	The Rosuvastatin Viatris data sheet includes a warning about the effects of HMG-CoA reductase inhibitors on skeletal muscle (eg, myalgia, myopathy and, rarely, rhabdomyolysis). Rosuvastatin should be prescribed with caution in patients with pre-disposing factors for myopathy, such as renal impairment and older age. Advise patients to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

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).

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).

Medsafe
New Zealand Medicines and Medical Devices Safety Authority
A business unit of Manatū Hauora | the Ministry of Health

Editor
Vikki Cheer
Medsafe, PO Box 5013, Wellington 6140, New Zealand
Email: medsafeadrquery@health.govt.nz

Editorial Team
Lizzie Collings, Advisor Pharmacovigilance
Maria Storey, Team Leader Pharmacovigilance
Nevin Zhong, Senior Advisor Pharmacovigilance
Dr Rooman Javed, Senior Medical Advisor
Sou Mieng Tran, Advisor Pharmacovigilance
Dr Susan Kenyon, PhD, Manager Clinical Risk
Tegan Coventry, Senior Advisor Pharmacovigilance

Acknowledgements
Dr Jennifer Lee and Dr Alveera Hynes, New Zealand Pharmacovigilance Centre
Dr Lisa Dawson, Whangarei Hospital
Reviewers do not write the articles and are not responsible for the final content. Medsafe retains editorial oversight of all content.
Medsafe also acknowledges the contribution of the New Zealand Pharmacovigilance Centre in providing data and analysis for articles.

Medical Advisors
Dr Karin van Bart, Medical Advisor
Dr Tracey O'Flynn, Medical Advisor

Group Manager Chris James

Prescriber Update is published and distributed by Medsafe in the interests of safer, more effective use of medicines and medical devices. While the information and advice included in this publication are believed to be correct, no liability is accepted for any incorrect statement or advice. No person proposing to prescribe a medicine to any other person should rely on the advice given in this publication without first exercising his or her professional judgement as to the appropriateness of administering that medicine to another person.

Prescriber Update is available at
medsafe.govt.nz/publications/prescriber-update.asp

Data sheets, consumer medicine information, media releases, medicine classification issues and adverse reaction forms are available at **medsafe.govt.nz**

Published with the permission of the Director-General of Health.

This work is licensed under the Creative Commons Attribution 4.0 International licence. In essence, you are free to: share, ie, copy and redistribute the material in any medium or format; adapt, ie, remix, transform and build upon the material. You must give appropriate credit, provide a link to the licence and indicate if changes were made.