Prescriber Update

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Contents

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MINISTRY OF HEALTH

Spotlight on clonidine

Key messages

- Clonidine is indicated for hypertension, hypertensive crisis, prevention of migraine or recurrent vascular headaches, and menopausal flushing.
- Oral immediate release clonidine is not recommended for use in children – serious adverse reactions have been reported in this population group.
- Clonidine poisoning may occur in children due to exploratory ingestion. Remind patients and caregivers about the need to safely store and dispose of medicines so they remain out of sight and reach of children.

Adverse drug reactions have been reported in people using clonidine for off-label indications. This article is a reminder of the approved indications, noting that clonidine is not recommended for use in children. See the data sheets for full prescribing information.

Mechanism of action

Clonidine stimulates alpha-2 adrenoreceptors in the brain stem.[1,2] This results in reduced sympathetic outflow from the central nervous system and decreases in peripheral resistance, renal vascular resistance, heart rate and blood pressure.[1–3]

Indications and formulations

Clonidine containing medicines have several indications and formulations. Table 1 summarises the clonidine products that are approved and available in New Zealand.

Clonidine is not recommended for use in children[1-5]

Clonidine is not recommended for use in children due to the limited supporting efficacy and safety information from randomised control trials. Serious adverse reactions, including death, respiratory depression (slow, shallow breathing), bradycardia (low heart rate) and hypotension (low blood pressure), have been reported in children when clonidine has been used concomitantly with methylphenidate for an off-label purpose.

Table 1: Summary of clonidine products approved and available by product name, formulation and indication, as at 28 June 2023

Product	Formulation and strength	Indication
Catapres	Oral tablet 150mcg	Oral: treatment of hypertension (alone or concomitantly with other antihypertensive agents)
	Solution for injection 150mcg/mL	Parenteral: treatment of hypertensive crises
Catapres-TTS	Transdermal patch 2.5mg/3.5cm^2, 5mg/7.0cm^2, 7.5mg/10.5cm^2	Treatment of mild to moderate hypertension (alone or concomitantly with other antihypertensive agents)

Clonidine (Teva)	Oral tablet 25mcg	Prophylactic management of migraine or recurrent vascular headaches Management of vasomotor conditions commonly associated with menopause and characterised by flushing
Clonidine HCl injection	Solution for injection 150mcg/mL	Treatment of hypertensive crises
Clonidine Transdermal System USP	Transdermal patch 0.1mg/day, 0.2mg/day, 0.3mg/day	Treatment of mild to moderate hypertension (alone or concomitantly with other antihypertensive agents)

Sources:

Catapres, Catapres-TTS, Clonidine (Teva), Clonidine HCl Injection and Clonidine Transdermal System USP data sheets, available at: medsafe.govt.nz/Medicines/infoSearch.asp (accessed 17 July 2023).

Other considerations for use[1–5]

Clonidine can impair driving

Advise patients that they may experience dizziness, sedation and accommodation disorder (eg, blurry vision) during treatment with clonidine. Patients should not drive or operate machinery if they experience these effects.

Sudden discontinuation

Restlessness, palpitations, rapid rise in blood pressure, nervousness, tremor, headaches or nausea have been reported with sudden discontinuation of clonidine. Advise patients to speak to their healthcare provider before discontinuing treatment. Prescribers should gradually reduce the patient's dose over 2–4 days when discontinuing clonidine.

Adverse effects and overdose

The most frequently reported adverse effects include dry mouth, sedation, dizziness and orthostatic hypotension (dizziness when standing after sitting or lying down).[4,5] Transdermal application is also associated with skin reactions, including contact dermatitis (itchy rash), pruritis (itchy skin) and erythema (redness).[1,2]

There are an increasing number of international reports of clonidine overdose in children. These reports relate to accidental poisoning and dosing errors, many of which required medical intervention and/or hospitalisation.[6,7]

New Zealand data

Up to January 2023, the Centre for Adverse Reactions Monitoring (CARM) had received 127 suspected adverse reaction reports for clonidine, of which 11 were reported in children.

Of the 127 reports to CARM, the most frequently reported reaction terms were rash, dermatitis contact, depression, peripheral ischemia (impaired blood supply to the limbs) and nausea. Reports in children related to application site rash, somnolence (sleepiness), bradycardia and akathisia (a movement disorder that makes it hard to stay still).

From 1 January 2018 to 31 December 2022, the National Poisons Centre received 115 calls relating to clonidine exposure. Of these, 56 calls were related to exposure in a child aged 12 years or younger and in 21 of these calls, the child was exposed to clonidine by unintended exploratory access.

When prescribing or dispensing clonidine, remind patients about correct storage and disposal to ensure it remains out of sight and reach of children.

References

1. CARSL Consulting. 2019. Catapres-TTS New Zealand Data Sheet 1 February 2019. URL: www.medsafe.govt.nz/profs/Datasheet/c/CatapresTTS.pdf (accessed 22 June 2023).
2. Viatris New Zealand. 2022. Clonidine Transdermal System USP New Zealand Data Sheet 15 March 2022. URL: www.medsafe.govt.nz/profs/Datasheet/c/ClonidineTransdermalSystemUSP.pdf (accessed 23 June 2023).
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7. Osterhoudt K. 2023. Clonidine, xylazine, and related imidazole poisoning In: UpToDate 16 June 2023. URL: www.uptodate.com/contents/clonidine-and-related-imidazoline-poisoning (accessed 20 June 2023).

Quarterly summary of recent safety communications

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

Date	Communication	Topic
10/08/2023	Dear Healthcare Professional Letter	Estradiol Transdermal Patches (Mylan) – Alternative Registered Carton (PDF, 3 pages, 506 KB)
07/08/2023	Consultation	Clozapine Survey 2023 (closes 6 October 2023)
04/07/2023	Dear Healthcare Professional Letter	Estradiol Transdermal Patches (Mylan) previously supplied under Section 29 (PDF, 3 pages, 180 KB)
19/06/2023	Monitoring	M² Update - Possible risk of seizures with clonidine
06/06/2023	Dear Healthcare Professional Letter	Fentanyl Sandoz Transdermal patch – Product Labelling and Data Sheet updates (PDF, 4 pages, 260 KB)
30/05/2023	Dear Healthcare Professional Letter	Sodium valproate (Epilim) use in people who can father children: important new safety information (PDF, 2 pages, 157 KB)
30/05/2023	Alert	Sodium valproate (Epilim) use in people who can father children: important new safety information

Reports of persisting serious adverse reactions to fluoroquinolones

Key messages

- Fluoroquinolones have been associated with prolonged, disabling and potentially irreversible serious adverse reactions.
- Tendonitis and tendon rupture may occur at sites other than the ankle.
- Peripheral neuropathy has also been reported in patients receiving fluoroquinolones.

The Centre for Adverse Reactions Monitoring (CARM) recently received a case of ciprofloxacin-induced tendonitis in the shoulders (CARM ID 148295). This presented as severe pain in the shoulders radiating to the wrist and hips starting within two weeks of taking ciprofloxacin. The reactions persisted and had not resolved at the time of reporting.

The report coincides with the European Medicines Agency publishing a reminder for healthcare professionals to only prescribe fluoroquinolones (for oral use, inhalation or injection) according to their approved uses, due to the risk of disabling, long-lasting and potentially irreversible adverse reactions.[1]

Fluoroquinolones

The fluoroquinolones currently available in New Zealand include ciprofloxacin, moxifloxacin and norfloxacin. As with all medicines, fluoroquinolones should be used in the approved indications as listed in the data sheets and after careful assessment of the benefits and risks for the individual patient.

Prolonged, disabling and potentially irreversible serious adverse reactions

Fluoroquinolones have been associated with prolonged, disabling and potentially irreversible serious adverse reactions involving different and sometimes multiple body systems, such as the musculoskeletal and nervous systems.[1–4]

Some of these very rare but serious reactions are described below. Inform patients about the risks associated with fluoroquinolones and advise them to tell their doctor straight away if symptoms develop.[1–4] Discontinuing fluoroquinolone treatment may reduce the risk of irreversible adverse reactions.[1]

Tendonitis and tendon rupture

Tendonitis (inflamed tendon) and tendon rupture (torn tendon) may occur at sites other than the ankle, as demonstrated by case described above. The Achilles tendon is most commonly affected, but any tendon can be involved.[2–4]

Time to onset has varied from within 48 hours after treatment initiation up to several months after discontinuation.[1–3] The risk is increased in older patients, patients with renal impairment or solid organ transplants, and during concurrent treatment with corticosteroids.[1–4]

The first signs of tendonitis include painful swelling and inflammation.[1–4]

Peripheral neuropathy

Sensory or sensorimotor polyneuropathy (damage to nerves involved in sensation or sensation and movement) have been reported in patients receiving fluoroquinolones.[1–4] Symptoms of peripheral neuropathy include pain, burning, tingling, numbness, or weakness.[1–4]

Other

Very rare cases of prolonged, disabling and potentially irreversible muscle pain or weakness, joint pain or swelling, fatigue, depression, problems with memory, sleeping, vision, hearing, and altered taste and smell have also been reported.[1–4]

New Zealand case reports of tendon disorders and neuropathy

CARM continues to receive reports of reactions relating to the tendon and neuropathy with fluoroquinolones. The number of reports is shown in Table 1.

Table 1: Number of reports of reactions relating to the tendon and neuropathy with fluoroquinolones received by the Centre for Adverse Reactions Monitoring, 1 January 2015 to 30 June 2023

Reaction	Number of reports
Tendonitis	43
Tendon rupture	15
Tendon disorders	7
Paraesthesias and dysaesthesias	12
Peripheral neuropathy	2

Notes:

a An individual report can have multiple reactions and may be represented in more than one of the reaction counts.

Source: Centre for Adverse Reactions Monitoring

References

1. European Medicines Agency. 2023. Fluoroquinolone antibiotics: reminder of measures to reduce the risk of long-lasting, disabling and potentially irreversible side effects 12 May 2023. URL: www.ema.europa.eu/en/news/fluoroquinolone-antibiotics-reminder-measures-reduce-risk-long-lasting-disabling-potentially (accessed 28 July 2023).
2. Viatris Ltd. 2022. Cipflox New Zealand Data Sheet 16 June 2022. URL: www.medsafe.govt.nz/profs/Datasheet/c/Cipfloxtabinf.pdf (accessed 26 July 2023).
3. Bayer New Zealand Limited. Avelox New Zealand Data Sheet 1 October 2019. URL: www.medsafe.govt.nz/profs/Datasheet/a/AveloxtabIVinf.pdf (accessed 26 July 2023).
4. Teva Pharma (New Zealand) Limited. Arrow – Norfloxacin New Zealand Data Sheet 9 November 2020. URL: www.medsafe.govt.nz/profs/Datasheet/a/ArrowNorfloxacintab.pdf (accessed 26 July 2023).

Antidepressant withdrawal: taper antidepressants slowly

Key messages

- Withdrawal symptoms can occur when stopping antidepressants. These can be severe in some people.
- Slowly tapering antidepressants reduces the risk of withdrawal symptoms developing.
- Patients should be provided with information on antidepressant withdrawal and monitored for withdrawal symptoms.

This article reminds prescribers about the risk of antidepressant withdrawal (also known as discontinuation syndrome).[1] It is important to inform patients about this risk, and some resources are highlighted below.

What is antidepressant withdrawal?

Antidepressant withdrawal comprises one or more adverse effects that can occur when people discontinue antidepressants. In some people, withdrawal symptoms can be severe and protracted.[2]

Symptoms of antidepressant withdrawal

Antidepressant withdrawal can be associated with a wide range of symptoms. Table 1 provides some examples (list not exhaustive).

Table 1: Symptoms of antidepressant withdrawal

Most common	Common	Less common
Dizziness	Sleep difficulties	Suicidal thoughts
Fatigue	Anxiety	Sexual dysfunction
Headache	Irritability	Cognitive dysfunction
Nausea	Tremor	Loss of coordination

Source: Hirsch M and Birnbaum RJ. 2022. Discontinuing antidepressant medications in adults. In: *UpToDate* 21 October 2022. URL: uptodate.com/contents/discontinuing-antidepressant-medications-in-adults (accessed 21 June 2023).

Risk factors for antidepressant withdrawal

Antidepressant withdrawal can happen any time an antidepressant is reduced or stopped, but is more likely when:[2]

- antidepressants are stopped abruptly
- antidepressants are tapered too quickly
- someone has been taking a high dose of antidepressants
- someone has been on antidepressants for a long time.

All antidepressants can cause withdrawal symptoms, but some are associated with a higher risk (eg, venlafaxine and paroxetine).[3]

Dose tapering

To reduce the risk of antidepressant withdrawal, slowly taper the patient's dose before stopping it completely.[2] Provide the patient with information on antidepressant withdrawal (see below) and monitor them for withdrawal symptoms.

Refer to the sponsor's data sheet and local clinical guidelines for further information on stopping antidepressants.

Patient information

- Advise patients to speak to their healthcare provider if they are thinking about stopping or reducing their antidepressant, or if they are having withdrawal symptoms.
- For more information on a specific antidepressant, patients can refer to the sponsor's consumer medicine information (CMI): Search for a CMI.
- A Medsafe information leaflet is also available: Stopping antidepressants: be cautious and go slow.
- See also the Healthify information: Antidepressants.

References

1. Davies J and Read J. 2019. A systematic review into the incidence, severity and duration of antidepressant withdrawal effects: Are guidelines evidence-based? *Addictive Behaviors* 97: 111-21. DOI: https://doi.org/10.1016/j.addbeh.2018.08.027 (accessed 21 June 2023).
2. Hirsch M and Birnbaum RJ. 2022. Discontinuing antidepressant medications in adults. In: *UpToDate* 21 October 2022. URL: www.uptodate.com/contents/discontinuing-antidepressant-medications-in-adults (accessed 21 June 2023).
3. Royal College of Psychiatrists. 2020. *Stopping antidepressants* November 2020. URL: www.rcpsych.ac.uk/mental-health/treatments-and-wellbeing/stopping-antidepressants (accessed: 21 June 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. Click on the medicine name to view the sponsor's 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
Amoxicillin	Alphamox (capsules) Alphamox (suspension)	4.4	Warnings and precautions: drug-induced enterocolitis syndrome (DIES), Kounis syndrome; contains maltodextrin and sorbitol as excipients (suspension only)
		4.8	Undesirable effects: DIES, Kounis syndrome, linear IgA disease
Carbamazepine	Tegretol	4.1	Indications: Should not be used for status epilepticus
		4.4	Warnings and precautions: type I (immediate) hypersensitivity reactions; contains propylene glycol as an excipient
		4.5	Interactions: removal of loratadine
		4.6	Pregnancy: risk of neurodevelopmental disorders; take folic acid supplementation 4 weeks prior to and continue for 12 weeks after conception
Citalopram	Cipramil	4.8	Undesirable effects: hyperprolactinaemia
Fluconazole	Canesoral	4.5	Interactions: everolimus, ivacaftor
Fluconazole + Clotrimoxazole	Canesoral Duo	4.6	Pregnancy: continue contraceptive measures throughout treatment and for approximately 1 week after the final dose
		4.8	Undesirable effects: drug reaction with eosinophilia and systemic symptoms (DRESS)
Gabapentin	Neurontin	4.4	Warnings and precautions: withdrawal symptoms; women of childbearing potential must use contraception during treatment
		4.6	Pregnancy: inclusion of observational study data; neonatal withdrawal syndrome in newborns exposed in utero
Ibuprofen + paracetamol	Mersynofen	4.4	Warning and precautions: Kounis syndrome
		4.8	Undesirable effects: Kounis syndrome, fixed drug eruptions (FDE)
Iodised oil	Lipiodol Ultra Fluid	4.3	Contraindications: hysterosalpingography in patients with known or suspected reproductive tract neoplasia

Methenamine	Hiprex		Newly published data sheet
Mesalazine	Asacol Pentasa	4.4	Warnings and precautions: discolouration of urine after contact with sodium hypochlorite (bleach); drug reaction with eosinophilia and systemic symptoms (DRESS)
		4.8	Undesirable effects: DRESS
Methylphenidate	Concerta	4.8	Undesirable effects: gynaecomastia
Omeprazole	Losec	4.4	Warnings and precautions: renal impairment, including acute tubulointerstitial nephritis (TIN)
		4.8	Undesirable effects: TIN
Oxycodone	OxyNorm	4.2	Dose and method of administration: treatment goals and discontinuation
		4.4	Warnings and precautions: opioid use disorder
		4.8	Undesirable effects: drug dependence, opioid tolerance and opioid withdrawal syndrome
		4.9	Overdose: toxic leukoencephalopathy
Rivaroxaban	Xarelto	4.4	Warnings and precautions: anticoagulant-related nephropathy
		4.8	Undesirable effects: as per 4.4
Valproic acid (sodium valproate)	Epilim*	4.4	Warnings and precautions: risk of neurodevelopmental disorders including autism spectrum disorders after paternal exposure to valproate
		4.6	Pregnancy: as per 4.4
Vitamins (A, C, D, E and B complex)	Cernevit	4.3	Contraindications: hypersensitivity to peanut protein
		4.4	Warnings and precautions: cross□allergic reactions between soybean and peanut proteins

* See the Alert communication: Sodium valproate (Epilim) use in people who can father children: important new safety information

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

Vanishing bile duct syndrome – a complication of drug-induced liver injury

Key messages

- Vanishing bile duct syndrome (VBDS) can occur as a complication of drug-induced liver injury. It is characterised by progressive destruction and disappearance of the bile ducts in the liver.
- Patients with VBDS may present with symptoms of cholestasis, which can occur one to six months after starting the offending medicine. There is no standardised treatment. However, symptoms may resolve following the withdrawal of the offending medicine.
- Antibiotics are the medicine class most frequently associated with VBDS.

What is vanishing bile duct syndrome (VBDS)?

Bile ducts transport bile from the liver and gallbladder to the small intestine, where the bile helps to break down the fats from food.

VBDS is characterised by progressive destruction and disappearance of the bile ducts (ductopenia) in the liver, which slows or stops the flow of bile (cholestasis).[1] VBDS can be diagnosed with a liver biopsy.[2] VBDS may lead to a blockage of the bile duct system (biliary obstruction) and permanent liver damage.[2]

The mechanism behind VBDS is unknown but it can be caused by immune-mediated disorders, cancers, infections and medicines. One suggested mechanism is T-cell-mediated immune dysfunction leading to biliary apoptosis (programmed cell death).[2]

VBDS is a complication of drug-induced liver injury

Vanishing bile duct syndrome is a rare but serious complication of drug-induced liver injury.[3]

Antibiotics are most frequently associated with VBDS, although several drug classes and medicines have been implicated. Table 1 lists the most frequently reported medicine classes and medicines associated with VBDS.[3]

Signs and symptoms of VBDS have been reported one to six months after starting the offending medicine.[2] Some patients may be asymptomatic and VBDS is initially identified based on laboratory abnormalities. Other patients may have symptoms of cholestasis, such as persistent pruritus (itching), fatigue and jaundice (yellowing of the skin). Additionally, patients with chronic cholestasis may have skin xanthomas (fatty skin lesions), dyslipidaemia (abnormal fat levels in the blood), and fat-soluble vitamin deficiencies (low levels of vitamins A, D, E and K).[2]

Patients with VBDS have laboratory test results that are generally consistent with cholestasis (ie, abnormal liver function tests, including elevated serum alkaline phosphatase, total bilirubin and gamma-glutamyl transpeptidase).[2]

Table 1: Medicine class and medicines most frequently reported to cause vanishing bile duct syndrome

Medicine class	Medicines
Penicillins	Amoxicillin, amoxicillin + clavulanic acid
Fluoroquinolones	Ciprofloxacin, moxifloxacin
Sulphonamides	Co-trimoxazole (trimethoprim + sulfamethoxazole)
Macrolides	Azithromycin
Antivirals	Nevirapine
Anticonvulsants	Carbamazepine, lamotrigine
Rheumatologic agents	Allopurinol
Antineoplastic agents	Temozolomide
Non-steroidal anti-inflammatories	Ibuprofen

Note:

List not exhaustive. Table is adapted from the source below to show the most frequently reported medicines that were also approved and available in New Zealand on 3 July 2023.

Source:

Adapted from: National Institute of Diabetes and Digestive Kidney Diseases. 2012. Vanishing bile duct syndrome. In: *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury* updated 11 December 2019. URL: www.ncbi.nlm.nih.gov/books/NBK548715/ (accessed 30 June 2023).

Management

Due to its rarity, there is no standardised treatment for VBDS.[1] Management can involve supportive measures and monitoring for signs of disease progression and complications of chronic cholestasis. Specialist input may be required.[2]

VBDS may improve by treating the underlying cause or withdrawing the offending medicine.[1]

References

1. Izzo P, Gallo G, Codacci Pisanelli M, et al. 2022. Vanishing bile duct syndrome in an adult patient: Case report and review of the literature. *Journal of Clinical Medicine* 11(12): 3253. URL: www.mdpi.com/2077-0383/11/12/3253 (accessed 29 June 2023).
2. Reau N. 2023. Hepatic ductopenia and vanishing bile duct syndrome in adults. In: *UpToDate* 22 February 2023. URL: www.uptodate.com/contents/hepatic-ductopenia-and-vanishing-bile-duct-syndrome-in-adults (accessed 29 June 2023).
3. National Institute of Diabetes and Digestive Kidney Diseases. 2012. Vanishing bile duct syndrome. In: *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury* updated 11 December 2019. URL: www.ncbi.nlm.nih.gov/books/NBK548715/ (accessed 30 June 2023).

MARC's remarks: June 2023 meeting

The Medicines Adverse Reactions Committee (MARC) convened on 8 June 2023.

The Committee reviewed the efficacy of **molnupiravir (Lagevrio)** and agreed that molnupiravir appears to be less effective than nirmatrelvir/ritonavir (Paxlovid) against the current variants of concern of COVID-19. However, there are some benefits in reducing symptom severity, reducing viral load and accelerating recovery time. The Committee acknowledged that molnupiravir may be appropriate in cases where alternative COVID-19 therapeutics are not suitable or available. The Committee agreed that the available evidence on the efficacy of molnupiravir supports its current indication.

The Committee reviewed the safety and efficacy of **pholcodine.** A recent study found that exposure to this medicine increases the risk of perioperative anaphylaxis with neuromuscular blocking agents (NMBA) used in surgery.[1] Overall, the Committee considered there was evidence of an association between previous pholcodine use and an increased risk of anaphylaxis from NMBA administration. Whilst the risk of anaphylaxis may be small, it can be a serious and life-threatening event. The Committee agreed that the risk minimisation measures proposed by the company were not sufficient to manage this risk and recommended to the Minister's delegate that the consent for pholcodine be revoked under Section 35 of the Medicines Act 1981 due to safety concerns. The available efficacy data was considered limited.

The Committee reviewed the Risk Management Plan for **Epidyolex**, an oral **cannabidiol** medicine indicated for certain severe types of epilepsy. The Committee noted the risk of hepatotoxicity with this medicine but considered that the sponsor's ongoing monitoring and risk minimisation measures were appropriate. The Committee were satisfied with the Epidyolex Risk Management Plan.

Medsafe updated the Committee on the signal evaluation of pericarditis following **mpox vaccination.** The Committee noted Medsafe's plan to continue monitoring this safety concern.

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

Reference

1. Mertes PM, Petitpain N, Tacquard C, et al. 2023. Pholcodine exposure increases the risk of perioperative anaphylaxis to neuromuscular blocking agents: the ALPHO case-control study. *British Journal of Anaesthesia* 131(1): 150–8. DOI: https://doi.org/10.1016/j.bja.2023.02.026.

Clozapine survey

Medsafe welcomes participants to take part in a survey about clozapine.

The aim of the survey is to gain important insights into experiences of:

- people who take clozapine (whānau, family and/or caregivers may answer on their behalf if required)
- healthcare professionals who support people who take clozapine.

The survey is open to people living in New Zealand and will be available until 6 October 2023.

To learn more about the survey and to take part, please click on the link below:

- Clozapine survey

Please share this link with other people who may wish to participate in the survey.

If you have any questions, please contact us at: medsafeadrquery@health.govt.nz

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.

Recent approvals: new active ingredients or new indications

New active ingredients

Table 1 shows recent approval of medicines with new active ingredients, gazetted during the period 7 April 2023 to 13 July 2023.

Table 1: Recent approvals of medicines with new active ingredients

Medicine	New active ingredient	Dose form: strength(s)	Therapeutic area
Adcetris	Brentuximab vedotin	Powder for injection: 50mg	Hodgkin lymphoma, peripheral T-cell lymphoma, cutaneous T-cell lymphoma
Libtayo[a]	Cemiplimab	Concentrate for infusion: 350mg/7mL	Metastatic or locally advanced cutaneous squamous cell carcinoma
Ryzodeg 70/30[b]	Insulin degludec	FlexTouch solution for injection: 70U/mL Penfill solution for injection: 70U/mL	Diabetes mellitus (for patients aged 6 years and older)
Brukinsa[a]	Zanubrutinib	Capsule: 80mg	Waldenström's macroglobulinaemia, mantle cell lymphoma
Jivi	Damoctocog alfa pegol	Powder for injection: 250IU, 500IU, 1000IU, 2000IU, 3000IU	Haemophilia A (congenital factor VIII deficiency)
Rybrevant[a]	Amivantamab	Concentrate for infusion: 350mg/7mL	Locally advanced or metastatic non-small cell lung cancer
Jemperli[a]	Dostarlimab	Solution for infusion: 500mg/10mL	Recurrent or advanced mismatch repair deficient endometrial cancer

a. Provisional consent
b. Ryzodeg 70/30 also contains 30 U/mL insulin aspart as an active ingredient

New indications

There were no approved medicines with new indications for additional therapeutic areas gazetted during the period 7 April 2023 to 13 July 2023.

More information

See the Medsafe website for:

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

Infusion-related reactions – not all allergy related

Key messages

- Infusion-related reactions may be allergic or pseudo-allergic.
- Overlapping clinical presentations may make distinguishing between these different infusion-related reactions challenging.
- If signs and symptoms of anaphylaxis are present, immediately discontinue the infusion and initiate appropriate management.

The Centre for Adverse Reactions Monitoring (CARM) received a report of a vancomycin infusion-related reaction where the patient developed redness and itch (ID 145998). Previously called 'Red Man Syndrome', the clinical presentation of severe vancomycin infusion reaction may mimic that of anaphylaxis.[1]

This article highlights examples of medicines that may cause infusion-related reactions.

What are infusion-related reactions?

Infusion-related reactions are potentially serious adverse events associated with parenteral administration of medicines and may have different underlying causes.[2]

Infusion-related reactions may be allergic or pseudo-allergic.

- **Allergic** type or hypersensitivity reactions can be classified into types I to IV, depending on the mechanism. Anaphylaxis is the most severe presentation of an immunoglobulin E (IgE)-mediated (type I) medicine reaction.[2]
- **Pseudo-allergic** type or nonimmune hypersensitivity reactions are rare, unpredictable reactions to a medicine. The mechanisms underlying most pseudo-allergic reactions are not known. With vancomycin infusion reaction, mast cells are activated independent of IgE and the clinical presentation can mimic an IgE-mediated allergic reaction.[2]

It may be difficult to distinguish clinically between allergic and pseudo-allergic reactions. However, both types of reaction can be potentially life threatening. If signs and symptoms of anaphylaxis are present, immediately discontinue the infusion and initiate appropriate management.[2]

Administer medicines with potential for infusion-related reactions in a suitable environment with adequately trained personnel and resuscitation equipment.

Examples of medicines associated with infusion-related reactions

Vancomycin, intravenous iron and monoclonal antibodies are examples of medicines associated with infusion-related reactions (not an exhaustive list).

Vancomycin

Rapid administration of vancomycin may cause vancomycin infusion reaction, a pseudo-allergic reaction.[2]

To minimise the risk of vancomycin infusion reaction, administer vancomycin at a rate of 500mg/hour or slower, and at an appropriate dilution.[3]

Symptoms of vancomycin infusion reaction may include hypotension (low blood pressure), flushing, erythema (skin redness), urticaria (skin welts), pruritis (itchiness), or pain and muscle spasm of the chest and back. Stopping the infusion usually stops the symptoms. Rule out other causes such as anaphylaxis.[1,3]

Depending on the severity of the vancomycin infusion reaction, it may be possible to restart the infusion at a reduced rate after the symptoms have resolved. Monitor the patient closely for further reactions.[1,3]

Intravenous iron

For intravenous administration of iron polymaltose, use a slow infusion rate initially and observe the patient. Increase the rate if the infusion is well tolerated. The approximate infusion time is 5 hours.[4]

Ferric carboxymaltose can be administered via slow intravenous undiluted injection or as a diluted infusion. For 500mg–1,000mg doses, the minimum infusion time should be 15 minutes.[5]

Monitor patients during and after iron administration. If an infusion-related reaction occurs, stop the infusion and take appropriate action.[6]

Mild infusion-related reactions with intravenous iron may include symptoms such as itching, flushing, sensation of heat, slight chest tightness, hypertension or back/joint pains. The reaction may be related to the rate of the infusion, rather than an allergic reaction.[6] Following resolution of mild symptoms, restart the infusion at a slower rate if clinically appropriate.[6]

Rarely, serious allergic reactions, including anaphylaxis, can occur with intravenous iron.

Monoclonal antibodies

Infusion-related reactions can occur with monoclonal antibodies, with potential to cause a wide spectrum of symptoms.[7]

Rituximab is a monoclonal antibody associated with a high incidence of pseudo-allergic infusion reactions. To reduce this risk, premedicate the patient and administer the first rituximab dose at a slower rate (refer to the data sheet and/or clinical guidelines for premedication recommendations). Patients who have elevated white blood cells are more likely to have severe infusion-related reactions.[7,8]

Symptoms of rituximab infusion reactions may include fever, chills, rigors, hypotension, urticaria and angioedema and features of cytokine release syndrome. Symptoms are usually reversible with interruption of the infusion. Decision for retreatment depends on the severity and nature of the reaction.[7,8]

Anaphylactic reactions have been reported with rituximab and must be differentiated from other types of infusion reactions.[7]

Further information

Refer to the relevant data sheet for further information about administration and infusion-related reactions.

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Restrictions on the supply, prescribing and administration of controlled drugs

Key messages

- Due to their potential for harm, there are additional restrictions on the supply, prescribing and administration of certain controlled drugs.
- Unless covered by an exemption or a blanket approval, supplying, prescribing or administering a controlled drug requires individual approval from the Minister of Health.
- Importing controlled drugs into New Zealand requires a Licence to Import Controlled Drugs for each consignment of controlled drug(s).
- The Medicines Control branch of Medsafe administers the ministerial approval and importation of controlled drugs processes.
- The Medicinal Cannabis Agency administers ministerial approval for medicinal cannabis products.

Note that this article describes restrictions on the supply, prescribing and administration of controlled drugs, but is not about prescribing periods.

The legislation

Controlled drugs are classified under the Misuse of Drugs Act 1975. The supply, prescribing and administration of controlled drugs are more restricted than for other medicines, reflecting the need to restrict access to, and minimise the misuse of, controlled drugs.[1] Controlled drugs are classified into three schedules based on the risk of harm the medicine poses to individuals or to society by their misuse.[2]

Ministerial approvals and exemptions

Regulation 22(1) of the Misuse of Drugs Regulations 1977 (the Regulations) sets out further controls around the supply, prescribing and administration of certain controlled drugs. For these controlled drugs, anyone wishing to undertake these activities requires approval from the Minister of Health (see Table 1). There are some exemptions to this requirement, as defined in Regulation 22(2) (Table 2).

To confirm the classification of a medicine, refer to the Medsafe Classification Database.

Table 1. Classes of controlled drugs, with examples, that require ministerial approval[a] to supply, prescribe and administer

Controlled drug classes[b] that require ministerial approval	Examples
Class A	Carfentanil Lysergic acid (essential precursor for manufacture of LSD) Lysergide (N,N-diethyllysergamide or lysergic acid diethylamide) Psilocybine
Class B1 or Class B2	GHB (gamma-hydroxybutyrate) MDMA (2-methylamino-1-(3,4-methylenedioxyphenyl) propane)
Class C1	Cannabis plant

a. Some exemptions apply. See Table 2.

b. Controlled drug classes are described in Schedules 1 to 3 of the Misuse of Drugs Act 1975.

Source: *Misuse of Drugs Regulations 1977*. URL: www.legislation.govt.nz/regulation/public/1977/0037/latest/DLM54840.html (accessed 21 July 2023).

Table 2. Controlled drugs that are exempt from requiring ministerial approval to supply, prescribe and administer

Controlled drug (Class)	Description and conditions
Cocaine (A)	Cocaine, or anything to which any of clauses 2 to 5 of Schedule 1 of the Misuse of Drugs Act 1975 for the time being applies in relation to cocaine
Morphine or opium (B1)	Morphine or opium, or anything to which any of clauses 2 to 5 of Schedule 2 of the Misuse of Drugs Act 1975 for the time being applies in relation to morphine or opium
Medicinal cannabis	Any of the following that have been assessed as complying with the minimum quality standard, and specified in a medicinal cannabis licence accordingly, under the Misuse of Drugs (Medicinal Cannabis) Regulations 2019: • A consignment of starting material for export • A cannabis-based ingredient • A medicinal cannabis product
Fentanyl (B1)	

Source: *Misuse of Drugs Regulations 1977*. URL: www.legislation.govt.nz/regulation/public/1977/0037/latest/DLM54840.html (accessed 21 July 2023).

Blanket approvals

Ministerial approvals (often referred to as 'blanket' approvals) have been granted for the supply, prescribing and administration of certain controlled drugs in defined circumstances (see Table 3).[3] These blanket approvals are published in the New Zealand Gazette and define circumstances under which the blanket approvals apply.

Table 3. Blanket approvals granted for certain controlled drugs in defined circumstances

Click on the controlled drug to view the Gazette notice and the approved defined circumstances for prescribing, supplying and administering

Controlled drug with blanket approval (Class)
Dexamfetamine (B1)
Ephedrine (B2)
Lisdexamfetamine (B2)
Methylphenidate (B2)
Pseudoephedrine (B2)
Sativex (B1)

Source: Medsafe. 2023. *Restrictions on the Supply, Prescribing or Administration of Medicines under the Medicines Act 1981 and Misuse of Drugs Regulations 1977*. URL: www.medsafe.govt.nz/profs/riss/restrict.asp (accessed 21 July 2023).

Applying for ministerial approval

For all circumstances that are not covered by the exemptions or 'blanket' approvals, individual ministerial approval is required to supply, prescribe and administer controlled drugs listed in Table 1.

To prescribe a controlled drug listed in Table 1, a prescriber is required to provide evidence to support their decision to prescribe a particular controlled drug requiring ministerial approval. This evidence must be included as part of the application and should demonstrate the clinical reasoning for prescribing. Ministerial approvals are granted for a specific application and to a defined patient, or patient group.

Examples where individual ministerial approval is required:

- to investigate the efficacy of MDMA as part of a clinical trial
- to prescribe methylphenidate for an indication not specified in the 'blanket' approval for methylphenidate.

The Medicines Control branch of Medsafe administers the ministerial approval process. For information about the process for seeking approval, email: medicinescontrol@health.govt.nz

Guidance for supply chain licence holders

Controlled drugs that require ministerial approval must be authorised on a licence before the licence holder can undertake any activities.

Guidance for pharmacies

A pharmacy can only supply a controlled drug that requires ministerial approval in accordance with a valid ministerial approval (either a 'blanket' approval or an individual approval). It is the responsibility of the prescriber to specify the approval number and expiry date on prescriptions for individual approvals.

Importation of controlled drugs

If a particular controlled drug substance or dosage form is not available from the local supply chain, the controlled drug may need to be imported from overseas. Each consignment of controlled drug(s) imported into New Zealand requires a new 'Licence to Import Controlled Drugs'. Importation also needs to comply with international obligations (eg, The International Narcotics Control Board requirements). For controlled drugs which require ministerial approval, ministerial approval must be granted before a Licence to Import Controlled Drugs can be issued. Refer to Table 4 for a list of entities and individuals who may import controlled drugs.

Table 4. Entities and individuals who may import controlled drugs

Prescribers to whom ministerial approval was granted
Pharmacies in response to a valid prescription
A holder of a Licence to Deal in Controlled Drugs

Sources:

Misuse of Drugs Act 1975. URL: www.legislation.govt.nz/act/public/1975/0116/latest/DLM436101.html (accessed 21 July 2023).

Misuse of Drugs Regulations 1977. URL: www.legislation.govt.nz/regulation/public/1977/0037/latest/DLM54840.html (accessed 21 July 2023).

To apply for a Licence to Import Controlled Drugs, an application form needs to be completed and submitted to the Medicines Control branch of Medsafe. Please email Medicines Control for the application form, and for any queries relating to importation of controlled drugs or ministerial approvals: medicinescontrol@health.govt.nz

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Gathering knowledge from adverse reaction reports: September 2023

Adverse reaction reporting is an important part of medicine safety monitoring. Case reports can highlight significant safety issues with medicines and how they are used.

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: 146140 **Age:** 51 years **Gender:** Male **Medicine(s):** Empagliflozin **Reaction(s):** Necrotising fasciitis (Fournier's gangrene)	While taking empagliflozin, the patient experienced progressive worsening of a sore in the anogenital area. He became critically unwell with Fournier's gangrene, which required extensive tissue debridement.
	There is a warning for necrotising fasciitis in the Jardiance data sheet. Patients treated with Jardiance who present with pain or tenderness, erythema, swelling in the genital or perineal area, fever or malaise should be evaluated for necrotising fasciitis. Urogenital infection may precede necrotising fasciitis. If necrotising fasciitis is suspected, discontinue Jardiance and promptly treat the patient (including broad-spectrum antibiotics and surgical debridement if necessary). See the Medsafe consumer leaflet, available in English, Te Reo and Samoan (PDFs, 2 pages, approx. 200 KB). See also the previous *Prescriber Update* articles: • Reminder: Flozins and the risks of diabetic ketoacidosis and Fournier's gangrene • Empagliflozin: advise patients on the risk of ketoacidosis and Fournier's gangrene.
CARM ID: 147682 **Age:** 10 years **Gender:** Male **Medicine(s):** Amoxicillin **Reaction(s):** Tooth discolouration	Following treatment with amoxicillin suspension, the child experienced front teeth discolouration.
	Superficial tooth discolouration is listed as a rare post-marketing adverse reaction in the Alphamox data sheet. Good oral hygiene may help to prevent tooth discolouration, as it can be removed by brushing.
CARM ID: 147125 **Age:** 64 years **Gender:** Female **Medicine(s):** Dulaglutide **Reaction(s):** Pancreatitis necrotising	The patient stopped taking dulaglutide as it made her feel unwell. She restarted treatment, and again felt unwell. This progressed to sudden onset abdominal pain, with very high lipase levels. She was diagnosed with acute necrotising pancreatitis.
	There is a warning for acute pancreatitis in the Trulicity data sheet. If acute pancreatitis is suspected, discontinue treatment until evaluation is complete. If confirmed, permanently discontinue Trulicity.

Case details[a,b]	Reaction description and data sheet information[b,c]
CARM ID: 146827 **Age:** 11 years **Gender:** Male **Medicine(s):** Cetirizine **Reaction(s):** Seizure	The child experienced a seizure following treatment with cetirizine. He had a history of seizures.
	The Zista data sheet states to use cetirizine with caution in epileptic patients and those at risk of convulsions. Convulsions are listed as a rare adverse reaction.
CARM ID: 146559 **Age:** 57 years **Gender:** Male **Medicine(s):** Adalimumab **Reaction(s):** Systemic lupus erythematous (SLE), rheumatoid arthritis, C-reactive protein increased, rash	Soon after starting adalimumab, the patient experienced a rash that spread to his limbs. His arthritis progressively worsened, with an increase in C-reactive protein. The reporter suspected a lupus-like reaction to adalimumab.
	SLE is listed as an uncommon adverse reaction in the Amgevita data sheet.
CARM ID: 147860 **Age:** 63 years **Gender:** Male **Medicine(s):** Liraglutide **Reaction(s):** Diarrhoea, anuria, acute kidney injury	The patient experienced severe diarrhoea soon after starting liraglutide therapy. He became anuric and went into renal failure.
	Gastrointestinal disorders, including diarrhoea, are commonly reported adverse reactions with Victoza therapy. They may occur more frequently at the beginning of therapy and diminish with a few days or weeks of continued treatment. Signs and symptoms of dehydration, including renal impairment and acute renal failure, have been reported. Advise patients of the potential risk of dehydration due to gastrointestinal side effects and to take precautions to avoid fluid depletion.

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 exactly.

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).

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