Prescriber Update

Vol. 46 No. 2 June 2025

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

Spotlight on Contrave (naltrexone + bupropion)

Key messages

- Contrave contains naltrexone and bupropion and is indicated for weight management in adults.
- Significant safety issues associated with Contrave that require careful management include psychiatric symptoms, seizures, cardiovascular effects, concomitant use with opioids, serotonin syndrome and drug-drug interactions.

This article on Contrave continues the spotlight series where Medsafe reviews the safety information on a specific medicine. Contrave is a fixed dose combination product containing naltrexone (an opioid receptor antagonist) and bupropion (a moderately weak inhibitor of neuronal reuptake of dopamine and noradrenaline).[1]

When used individually, naltrexone is approved for treatment of opioid and alcohol dependence and bupropion as an aid in smoking cessation.[2,3] There is evidence that naltrexone and bupropion individually supress hunger. Using them together may have a synergistic effect.[4]

What is Contrave (naltrexone + bupropion) indicated for?

Contrave is indicated, as an adjunct to a reduced-calorie diet and increased physical activity, for the management of weight in adults with an initial body mass index (BMI) of:

- ≥30 kg/m^2 (obese) or
- 27 to 29 kg/m^2 (overweight) in the presence of one or more weight-related comorbidities (eg, type 2 diabetes, dyslipidaemia or controlled hypertension).[1]

Considerations for use[1]

The following section describes some significant safety issues associated with Contrave. This is not a comprehensive description of all safety information – refer to the data sheet for full prescribing information.

Psychiatric symptoms

Suicidal events and panic attacks have been reported with the use of Contrave.

Counsel patients and their caregivers about the need to monitor for any clinical worsening, suicidal behavioural or thoughts and unusual changes in behaviour. Immediate medical attention should be sought if they occur.

Use Contrave with caution in patients with a history of mania. Activation of mania and hypomania has been reported in patients with mood disorders treated with other similar products.

Contrave is contraindicated in patients with a history of bipolar disorder. It is also contraindicated in patients with a current or previous diagnosis of bulimia or anorexia nervosa.

Seizures

There is a risk of seizures from the bupropion component. Use Contrave with caution in patients with risk factors for seizures, such as those taking concomitant medicines that can lower the seizure threshold or with a history of head trauma. Patients who experience a seizure while taking Contrave should discontinue treatment.

Contrave is contraindicated in patients with a history of or current seizure disorder or a known central nervous system tumour. It is also contraindicated in patients undergoing acute alcohol or benzodiazepine withdrawal.

Cardiovascular effects

Patients may develop elevated blood pressure or heart rate with Contrave. Hypertensive crisis has also been reported during the initial titration phase.

Check the patient's blood pressure and pulse prior to starting therapy and monitor this at regular intervals. Discontinue Contrave if there are clinically relevant and sustained increases in blood pressure or heart rate.

Use Contrave with caution in patients with controlled hypertension. Contrave is contraindicated in patients with uncontrolled hypertension.

Use with opioids

Serious life-threatening reactions have been observed with co-administration of Contrave and opioids. Contrave must not be used in patients currently dependent on opioids (including on opioid analgesics, opioid substitution therapy or in acute opioid withdrawal). To prevent withdrawal symptoms, wait at least 7 to 10 days after ceasing the opioid and use Contrave with caution. If opioid therapy is required later, stop Contrave treatment.

The effectiveness of opioid-containing medicines (eg, opioid based analgesics, anti-diarrhoeal, and cough suppressants) may be reduced with Contrave. For example, insufficient intra-/post-operative opioid analgesia during treatment with Contrave has been reported.

Patients requiring intermittent treatment with opioids (eg, due to a planned surgery) should stop Contrave for a minimum of 3 days before starting opioid treatment. The opioid dose should not be increased above the standard dose.

Serotonin syndrome

Serotonin syndrome has been reported when the bupropion component was co-administered with serotonergic medicines (eg, selective serotonin reuptake inhibitors, serotonin and noradrenaline reuptake inhibitors and opioids).

Contrave is contraindicated in patients taking concomitant monoamine oxidase inhibitors.

Pharmacokinetic drug-drug interactions

Bupropion is an inhibitor of cytochrome P450 (CYP) 2D6. Medicines that are substrates of CYP2D6 may need a dose reduction, particularly if they have a narrow therapeutic index.

Bupropion is primarily metabolised by CYP2B6. Concomitant use with CYP2B6 inhibitors or inducers may increase or decrease bupropion levels respectively.[1]

Contrave can interact with a variety of other medicines. Refer to the data sheet for more information.

New Zealand case reports

Contrave was approved for use in New Zealand on 1 October 2020. As of 31 March 2025, there were 39 case reports where Contrave was reported to be the suspect medicine.

The most frequently reported reactions were nausea (7 reports), dizziness (6), tinnitus (4), urticaria (4), upper abdominal pain (3), headache (3), pruritus (3), tremor (3) and vomiting (3).

There were also two reports of seizures, one report of drug withdrawal syndrome associated with concomitant use of methadone, and one report of serotonin syndrome associated with concomitant use of a serotonergic medicine.

More information

- See the Contrave data sheet and consumer medicine information.
- New Zealand Formulary monograph for naltrexone + bupropion.
- Healthify has information for consumers about Contrave.

References

1. iNova Pharmaceuticals (New Zealand) Limited. 2025. *Contrave New Zealand Data Sheet* 29 April 2025. URL: www.medsafe.govt.nz/profs/datasheet/c/Contravetab.pdf (accessed 9 May 2025).
2. GlaxoSmithKline NZ Limited. 2024. *Zyban New Zealand Data Sheet* 22 March 2024 URL: www.medsafe.govt.nz/profs/datasheet/z/zybantab.pdf (accessed 8 April 2025).
3. Teva Pharma (New Zealand) Limited. 2019. *Naltraccord New Zealand Data Sheet* 28 February 2019. URL: www.medsafe.govt.nz/profs/datasheet/n/naltraccordtab.pdf (accessed 8 April 2025).
4. Schimiedel O and Proietto J. 2021. Naltexone/Bupropion (Contrave) for the treatment of obseity. In: *Research Review.* URL: www.researchreview.co.nz/getmedia/1f4d8209-5445-4b9b-9c88-b74b4a57f597/Product-Review-Contrave-for-Obesity-treatment.pdf.aspx?ext=.pdf (accessed 8 April 2025).

Glucagon-like peptide-1 receptor agonists: stay hydrated

Key messages

- Glucagon-like peptide-1 (GLP-1) receptor agonists are indicated for type 2 diabetes mellitus and weight management.
- Vomiting and diarrhoea are common adverse reactions associated with GLP-1 receptor agonists, which can lead to dehydration and renal impairment.

Glucagon-like peptide-1 (GLP-1) receptor agonists are indicated for type 2 diabetes mellitus and weight management. [1-5] These medicines mimic the hormone GLP-1,[1-5] and increase insulin secretion, suppress glucagon secretion and slow gastric emptying.[1] For the treatment of type 2 diabetes mellitus, GLP-1 receptor agonists may be used as monotherapy or in combination with other diabetes medicines.[1]

The GLP-1 receptor agonists currently approved in New Zealand are:

- dulaglutide (Trulicity)
- liraglutide (Saxenda, Victoza)
- semaglutide (Ozempic, Wegovy).

Gastrointestinal side effects are common

Gastrointestinal disorders are common, and usually non-serious, adverse reactions associated with GLP-1 receptor agonists.[1-5] However, nausea, vomiting and diarrhoea, especially at the initiation of treatment, can persist for several days. If the patient becomes dehydrated, they are at risk of an acute renal injury or worsening of chronic renal failure.[1,6]

Advise patients to stay well hydrated by drinking plenty of fluids (eg, water) and inform them of the potential risks associated with dehydration.[1,6] Also advise patients to seek medical attention if gastrointestinal symptoms are severe or persistent.[7]

Prescribers should consider delaying dose escalation or reducing to a lower maintenance dose if significant gastrointestinal symptoms occur in patients.[5] Also consider delaying administration if acute gastrointestinal illness is present on the day that the dose is due. Advise patients to follow their 'sick day management plan'.[8,9]

The data sheets contain information about dehydration and renal impairment.

New Zealand case reports

Between May 2007 (when the first GLP-1 receptor agonist was approved in New Zealand) and 31 March 2025, there were 111 case reports where a GLP-1 receptor agonist was reported to be the suspect medicine. Of these 111 reports, 63 were for dulaglutide, 38 for liraglutide, 5 for semaglutide (not currently marketed) and 5 for exenatide (approval lapsed).

The most frequently reported reactions were nausea (29 reports), vomiting (24) and diarrhoea (20).

There were 11 reports of renal adverse drug reactions, 7 of which were for dulaglutide, 3 for liraglutide and 1 for exenatide.

Additional information

See the specific GLP-1 receptor agonist data sheets for more information.

References

1. Eli Lilly and Company (NZ) Limited. 2021. *Trulicity New Zealand Data Sheet* 29 January 2025. URL: www.medsafe.govt.nz/profs/Datasheet/t/trulicityinj.pdf (accessed 17 April 2025).
2. Novo Nordisk Pharmaceuticals. 2023. *Ozempic New Zealand Data Sheet* 15 November 2024. URL: www.medsafe.govt.nz/profs/Datasheet/o/Ozempicinj.pdf (accessed 17 April 2025).
3. Novo Nordisk Pharmaceuticals. 2016. *Saxenda New Zealand Data Sheet* 27 January 2025. URL: www.medsafe.govt.nz/profs/Datasheet/s/saxendainj.pdf (accessed 17 April 2025).
4. Novo Nordisk Pharmaceuticals. 2010. *Victoza New Zealand Data Sheet* 27 January 2025. URL: www.medsafe.govt.nz/profs/Datasheet/v/Victozainj.pdf (accessed 17 April 2025).
5. Novo Nordisk Pharmaceuticals. 2025. *Wegovy New Zealand Data Sheet* 20 March 2025. URL: www.medsafe.govt.nz/profs/Datasheet/w/wegovyinjection.pdf (accessed 17 April 2025).
6. Medicines and Healthcare products Regulatory Agency. 2024. GLP-1 receptor agonists: reminder of the potential side effects and to be aware of the potential for misuse. *MHRA Safety Update* 18(3): 1. URL: www.gov.uk/drug-safety-update/glp-1-receptor-agonists-reminder-of-the-potential-side-effects-and-to-be-aware-of-the-potential-for-misuse (accessed 17 April 2025).
7. Eli Lilly and Company (NZ) Limited. 2024. *Trulicity Consumer Medicine Information* May 2024. URL: www.medsafe.govt.nz/Consumers/CMI/t/trulicity.pdf (accessed 24 April 2025).
8. New Zealand Formulary (NZF). 2025. *NZF v155: Glucagon-like peptide 1 receptor agonists (diabetes mellitus)* 1 May 2025. URL: nzf.org.nz/nzf_70808 (accessed 7 May 2025).
9. Healthify. 2022. *Diabetes – type 2 sick day plan* updated 25 September 2024. URL: healthify.nz/health-a-z/d/diabetes-type-2-sick-day-plan (accessed 7 May 2025).

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
14/04/2025	Monitoring	Update – Direct acting oral anticoagulants and potential for patients to experience mood changes
09/04/2025	Alert	Use of carbamazepine during pregnancy: Growth risks for babies
01/04/2025	Dear Healthcare Professional Letter	Topamax (topiramate): New restrictions to prevent exposure during pregnancy (PDF, 4 pages, 143 KB)
01/04/2025	Alert	Ayurvedic medicines update
31/03/2025	Dear Healthcare Professional Letter	Venofer (iron sucrose) 20 mg/mL solution for injection – Interim packaging (PDF, 2 pages, 314 KB)

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 1 February 2025 to 24 April 2025.

Table 1: Recent approvals of medicines with new active ingredients

Medicine	New active ingredient	Dose form: strength(s)	Therapeutic area
Fenofibrate Viatris	Fenofibrate	Film coated tablet: 48mg, 145mg	Hypercholesterolaemia, dyslipidaemia, diabetic retinopathy
Omjjara	Momelotinib	Film coated tablet: 100mg, 150mg, 200mg	Myelofibrosis

New indications

Table 2 shows approved medicines with new indications for additional therapeutic areas gazetted during the period 1 February 2025 to 24 April 2025.

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

Medicine (active ingredient)	Dose form: strength(s)	New therapeutic area
Keytruda (pembrolizumab)	Concentrate for infusion: 25mg/mL	Malignant pleural mesothelioma
Kisqali (ribociclib)	Film coated tablet: 200mg	Early breast cancer
Saizen (somatropin)	Solution for injection: 5.83mg/mL, 8mg/mL	Growth disturbance in short children born small for gestational age

More information

See the Medsafe website for:

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

Short-term nitrofurantoin use can cause hepatic reactions

Key messages

- Hepatic reactions can occur with both short-term and long-term nitrofurantoin use.
- Use nitrofurantoin with caution in patients with hepatic dysfunction.
- Nitrofurantoin is contraindicated in patients with previous history of nitrofurantoin-related hepatotoxicity.

Hepatic reactions are well-known adverse reactions associated with long-term use of nitrofurantoin. However, they have also been reported with short-term use. The New Zealand nitrofurantoin data sheets are being updated to reflect this risk.

Nitrofurantoin is a bactericidal antibiotic indicated for the treatment and prophylaxis of urinary tract infections. There are two products approved in New Zealand: Nifuran (immediate release tablets) and Macrobid (modified release capsules). Refer to the nitrofurantoin data sheets for full prescribing information.

Serious hepatic reactions[1]

Nitrofurantoin can cause serious hepatic reactions, such as hepatitis, cholestatic jaundice, chronic active hepatitis, autoimmune hepatitis and hepatic necrosis, with some cases being fatal.

These reactions can occur with both short-term and long-term use. Cholestatic jaundice is typically associated with short-term use, while chronic active hepatitis, which can progress to hepatic necrosis, is generally linked to long-term use.

Nitrofurantoin is contraindicated in those who have previously experienced hepatic adverse reactions to nitrofurantoin. It may be used with caution in patients with known hepatic dysfunction. Consider regular monitoring of liver function, especially for patients on long-term therapy. Discontinue nitrofurantoin if signs and symptoms of hepatotoxicity occur.

Educate patients and caregivers about the signs and symptoms of hepatic dysfunction, such as yellowing of the skin or eyes, upper right abdominal pain, dark urine and pale or grey-coloured stools, itching or joint pain and swelling, and advise them to seek immediate medical advice if they occur.

New Zealand case reports

From 1 January 2010 to 31 March 2025, there were 25 cases of hepatobiliary disorders reported in association with nitrofurantoin. The reported adverse reactions included hepatitis (11 reports), jaundice (6), hepatic cirrhosis (4), cholestatic hepatitis (3), hepatic necrosis (1) and autoimmune hepatitis (1). In 15 of the 25 cases, the hepatic reactions occurred within 7 days of starting treatment.

Reference

1. Te Arai BioFarma Limited. 2025. *Macrobid New Zealand Data Sheet* 23 March 2025. URL: www.medsafe.govt.nz/profs/Datasheet/m/macrobidcap.pdf (accessed 10 April 2025).

MARC's remarks: March 2025 meeting

The Medicines Adverse Reaction Committee (MARC) convened for their 201st meeting on 13 March 2025.

The Committee discussed the safety of **fluoroquinolone antibiotics** and recommended data sheet updates to reflect the current knowledge of the medicines' safety profile. This includes updating the warning about disabling and potentially persistent adverse reactions to state that these may be potentially irreversible. The Committee also recommended updating the indications to include a risk-benefit statement for fluoroquinolone use.

The Committee discussed the risk of **topical corticosteroid** withdrawal reactions and recommended data sheet updates for potent and very potent topical corticosteroids. The indications section should state that the medicine is indicated for short-term use only (up to four continuous weeks) and the overdose section should describe the risk of topical steroid withdrawal. The Committee also recommended that the package labelling of topical corticosteroids should state their potency, for example, mild, moderate, potent or very potent.

The Committee discussed the risk of Parkinson's disease with **stimulant medicines** (eg, methylphenidate, dexamfetamine, lisdexamfetamine) used for the treatment of attention deficit hyperactivity disorder. The Committee considered that the available evidence is insufficient to support an association and did not recommend any regulatory action.

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

Medicines Monitoring: Anti-CD20 monoclonal antibodies and pyoderma gangrenosum

MEDICINES MONITORING

WE NEED YOUR HELP!

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

Medicine(s)	Potential safety issue	Active monitoring ends
Anti-CD20 monoclonal antibodies	Pyoderma gangrenosum	16 July 2025

- 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/Medsafe (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.

Vitamin B6 (pyridoxine) and peripheral neuropathy

Key messages

- Peripheral neuropathy is a known side effect of vitamin B6.
- Vitamin B6 is commonly present in dietary supplements such as vitamin B complexes and multivitamin and mineral preparations, often in combination with magnesium or zinc. Vitamin B6 is also an ingredient in some medicines.
- In patients with signs and symptoms of peripheral neuropathy, remember to ask about supplement use.

The New Zealand Pharmacovigilance database recently received a case report where the person experienced symptoms of peripheral neuropathy in association with a vitamin B6-containing dietary supplement (report ID 161190).

The Australian Therapeutic Goods Administration has also received a number of reports of peripheral neuropathy linked to vitamin B6 exposure and has taken regulatory action.[1]

Vitamin B6

Vitamin B6 (pyridoxine) is a water-soluble vitamin found in food. It may also be an ingredient in dietary supplements and some medicines.[1]

Vitamin B6 is commonly present in multivitamin and mineral preparations that are intended for purposes other than B vitamin supplementation, such as zinc and magnesium supplements.[1] Advise patients to check labels of any supplements they are taking.

The recommended daily intake of vitamin B6 ranges from 0.5 to 1.7 mg/day, depending on age and gender.[2]

Peripheral neuropathy

Peripheral neuropathy can be caused by genetic factors, infections, metabolic disorders, exposure to toxins and the presence of underlying medical conditions.[3]

Depending on the nerves affected, patients with peripheral neuropathy may present with a wide spectrum of symptoms, including paraesthesia (burning, tingling, pricking sensations), hyperaesthesia, weakness, atrophies, reduced or diminished reflexes and pain.[3]

Long-term use of high doses of vitamin B6 is associated with severe peripheral neuropathy.[4] However, cases have also been reported in patients taking lower doses for a prolonged period.[1,3,5] Prescribers should be aware that vitamin B6 is contained in many different supplements and the patient may not be aware that they are taking it.[1,6]

New Zealand case reports

From 1 January 2010 to 28 February 2025 there were six cases reported in New Zealand where the suspect medicine was a pyridoxine-containing product and the patient's symptoms were suggestive of peripheral neuropathy (report IDs: 108875, 146625, 147097, 147746, 157407, 161190). In five of these reports, the suspect product was a dietary supplement that contained vitamin B6/pyridoxine.

Considerations for healthcare professionals

In patients presenting with signs and symptoms of peripheral neuropathy, consider vitamin B6 supplementation as a possible cause, and ask about dietary supplement use.

For information on the management of peripheral neuropathy, refer to local guidelines.

References

1. Therapeutic Goods Administration. 2022. *Peripheral neuropathy with supplementary vitamin B6 (pyridoxine)* 4 October 2022. URL: www.tga.gov.au/news/safety-updates/peripheral-neuropathy-supplementary-vitamin-b6-pyridoxine (accessed 28 April 2025).
2. National Health and Medical Research Council, Australian Government Department of Health and Ageing, New Zealand Ministry of Health. 2017. *Nutrient Reference Values for Australia and New Zealand Including Recommended Dietary Intakes* version 1.2 updated September 2017. URL: www.nhmrc.gov.au/about-us/publications/nutrient-reference-values-australia-and-new-zealand-including-recommended-dietary-intakes (accessed 10 April 2025).
3. Muhamad R, Akrivaki A, Papagiannopoulou G, et al. 2023. The role of vitamin B6 in peripheral neuropathy: a systematic review. *Nutrients* 15(13): 2823. DOI: 10.3390/nu15132823 (accessed 10 April 2025).
4. Multichem NZ Ltd. 2021. *Pyridoxine Multichem New Zealand Data Sheet* 11 November 2021. URL: www.medsafe.govt.nz/profs/Datasheet/a/Apopyridoxinetab.pdf (accessed 30 April 2025).
5. van Hunsel F, van de Koppel S, van Puijenbroek E, et al. 2018. Vitamin B6 in health supplements and neuropathy: case series assessment of spontaneously reported cases. *Drug Safety* 41(9): 859-69. DOI: 10.1007/s40264-018-0664-0 (accessed 14 April 2025).
6. Therapeutic Goods Administration. 2022. *Health supplements containing vitamin B6 can cause peripheral neuropathy* 10 November 2022. URL: www.tga.gov.au/news/safety-alerts/health-supplements-containing-vitamin-b6-can-cause-peripheral-neuropathy (accessed 8 May 2025).

Gathering knowledge from adverse reaction reports: June 2025

Adverse drug reaction (ADR) reporting is an important component 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 reported to the New Zealand Pharmacovigilance Database.

Case details[a,b]	Reaction description and data sheet information[b,c]
Report ID: 154372 **Age:** 71 years **Gender:** Male **Medicine(s):** Zoledronic acid **Reaction(s):** Hypophosphataemia	Following a zoledronic acid infusion, the patient developed hypophosphataemia.
	There is a warning about hypophosphataemia in the Aclasta data sheet.
Report ID: 160125 **Age:** not reported **Gender:** Male **Medicine(s):** Omeprazole **Reaction(s):** Anger, mood changes	After starting omeprazole for the first time, the patient experienced mood changes.
	The Omeprazole Actavis data sheet lists agitation, aggression, confusion, depression and hallucinations as rare ADRs. See also the March 2024 *Prescriber Update* article: Unexplained mood and behavioural changes – could it be a side effect?
Report ID: 160432 **Age:** 56 years **Gender:** Male **Medicine(s):** Chlorpromazine **Reaction(s):** Cholestatic hepatitis	Ten days after completing a course of chlorpromazine, the person experienced reduced appetite, right upper quadrant abdominal discomfort, constipation, jaundice, fevers and night sweats. He was diagnosed with acute cholestatic hepatitis.
	The Largactil data sheet has a warning about severe liver toxicity, which can be fatal. Advise patients or caregivers to immediately seek medical attention for signs and symptoms of liver injury.
Report ID: 160509 **Age:** 94 years **Gender:** Male **Medicine(s):** Testosterone **Reaction(s):** Pulmonary oil microembolism, disorientation, unresponsive to stimuli, syncope, cyanosis, chest pain, cough	Immediately after receiving a testosterone injection, the patient experienced symptoms suggestive of a pulmonary oil microembolism.
	The Reandron data sheet states that pulmonary microembolism of oily solutions can in rare cases lead to signs and symptoms such as cough, dyspnoea, malaise, hyperhidrosis, chest pain, dizziness, paraesthesia or syncope. These reactions may occur during or immediately after the injections and are reversible.

Continues

Case details[a,b]	Reaction description and data sheet information[b,c]
Report ID: 161091 **Age:** 31 years **Gender:** Female **Medicine(s):** Rivaroxaban **Reaction(s):** Vaginal haemorrhage	One day after starting rivaroxaban, the person developed uncontrollable vaginal bleeding.
	Urogenital tract haemorrhage (including haematuria and menorrhagia) is listed in the Xarelto data sheet.

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, and do not always match the MedDRA term exactly.
c. If the suspect medicine's brand name is not described in the ADR report, only the data sheet for the funded medicine is included in the table.

Information about reported suspected adverse reactions is available on the Medsafe website using the Suspected Medicines Adverse Reaction Search (SMARS).

By selecting the ingredient of a medicine or vaccine, 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 and/or vaccines involved that contain the ingredient and the suspected adverse reactions (Detail report).

Hyperkalaemia or BRASH syndrome?

Key messages

- Patients with BRASH syndrome may present with a range of symptoms from asymptomatic bradycardia to multiorgan failure. The main differential diagnosis to consider is isolated hyperkalaemia.
- BRASH syndrome involves the synergistic effects of atrioventricular (AV) node blockers with hyperkalaemia, causing profound bradycardia.
- Triggers include hypovolaemia due to illness and starting or increasing the dose of medicines such as AV blockers. Medicines that cause acute kidney injury, hyperkalaemia or reduced cardiac output may also contribute to the development of BRASH syndrome.

The New Zealand Pharmacovigilance database recently received a case report of BRASH syndrome in a patient taking propranolol and diltiazem. As this was the first report of BRASH syndrome, we have included this article to explain the symptoms and encourage reporting of any further cases.

What is BRASH syndrome?[1]

BRASH syndrome is an increasingly recognised clinical entity. The acronym describes the signs of this syndrome: bradycardia, renal failure, atrioventricular (AV) nodal blockade, shock and hyperkalaemia.

In BRASH syndrome, the synergistic effects of AV node blockers with hyperkalaemia result in profound bradycardia that is greater than expected from either factor alone. A reduced cardiac output leads to worsening renal dysfunction that exacerbates the hyperkalaemia, creating a vicious cycle that can progress to multiorgan failure.

Triggers include hypovolaemia due to illness and starting or increasing the dose of medicines such as AV blockers. Older people with underlying cardiac or renal impairment, especially those taking multiple AV blockers, are at greater risk.

Clinical presentation and evaluation

Patients with BRASH syndrome may present with a range of symptoms from asymptomatic bradycardia to multiorgan failure. The main differential diagnosis to consider is isolated hyperkalaemia.

In patients with isolated hyperkalaemia, bradycardia generally results from severe hyperkalaemia. However in BRASH syndrome, bradycardia often occurs with moderate hyperkalaemia. In addition, an electrocardiogram (ECG) may show bradycardia without other features of hyperkalaemia.

Similarly, in patients experiencing BRASH syndrome, the bradycardia is not explained by supratherapeutic levels of AV node blockers. Patients are generally taking their medicines at the correct dose.

Healthcare professionals should consider BRASH syndrome in patients taking AV blocking medicines who present with signs of bradycardia and/or hyperkalaemia, even if they seem relatively well.

Which medicines are associated with BRASH syndrome?

Calcium channel blockers and beta-blockers depress AV node conduction and are most often associated with BRASH syndrome. Renally-cleared beta-blockers may increase the risk, as accumulation can occur as renal function worsens.[1]

Other medicines that are associated with precipitating factors such as acute kidney injury, hyperkalaemia or reduced cardiac output may also contribute to the development of BRASH syndrome. Examples include angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), spironolactone, digoxin and amiodarone.[1,2]

References

1. Farkas JD, Long B, Koyfman A, et al. 2020. BRASH syndrome: bradycardia, renal Failure, AV blockade, shock, and hyperkalemia. *Journal of Emergency Medicine* 59(2): 216-23. DOI: 10.1016/j.jemermed.2020.05.001 (accessed 28 March 2025).
2. Shah P, Gozun M, Keitoku K, et al. 2022. Clinical characteristics of BRASH syndrome: systematic scoping review. *European Journal of Internal Medicine* 103: 57-61. DOI: 10.1016/j.ejim.2022.06.002 (accessed 28 March 2025).

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.

To find out if sponsors have made any changes to their data sheets, refer to:

- section 10 'Date of revision of the text' at the end of each data sheet. Search for a data sheet
- the New/updates to data sheets and CMIs page on the Medsafe website.

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

Click on the specific medicine to open the data sheet.

Active ingredient(s): • Medicine(s)	Data sheet updates Section[a]	Summary of new safety information
Adalimumab • Humira	4.8	Autoimmune hepatitis
Dorzolamide + Timolol • Dortimopt	4.8	Atrioventricular block; Cardiac failure; Tachycardia; Hypertension; Dysgeusia
Dulaglutide[b] • Trulicity	4.4	Severe gastrointestinal disease: advise patients of the risk of dehydration and take precautions to avoid fluid depletion
Flucloxacillin • Staphlex	4.5	Interaction with voriconazole
Liraglutide[b] • Saxenda • Victoza	4.4	Risk of pulmonary aspiration in association with general anaesthesia or deep sedation due to delayed gastric emptying
Losartan • Losartan Actavis	4.4, 4.8	Intestinal angioedema
Macrogol + electrolytes • Plenvu	4.4, 4.8	Seizures; Oesophageal rupture (Boerhaave syndrome)
Metronidazole • Flagyl	4.3	Cockayne syndrome
	4.4	Posterior reversible encephalopathy syndrome (PRES); Inflammatory bowel disease (IBD)
	4.8	PRES; Severe irreversible hepatoxicity/acute liver failure in patients with Cockayne syndrome
Neisseria meningitidis Group A, C, W135, Y polysaccharide • MenQuadfi	4.2	May be given as a single booster dose to individuals who have previously been primed with meningococcal vaccine at least 3 years prior (changed from 4 years)
	4.5	May be given concomitantly with meningococcal B (MenB) vaccine
	4.8	Increased rate and intensity of systemic adverse reactions with concomitant MenB (clinical study in those aged 13–26 years)
Normal immunoglobulin • Privigen • Privigen NZ	4.4	Aseptic meningitis syndrome (AMS): new information about AMS symptoms and examination; monitor patients with recurrent AMS for the emergence or worsening of symptoms that may indicate progression to brain/cerebral oedema.

Continues

Active ingredient(s): • Medicine(s)	Data sheet updates	
	Section[a]	Summary of new safety information
Oxaliplatin • Oxaliplatin Accord • Oxaliplatin (Alchemy)	4.6	Use effective contraception before starting and during treatment, and for at least 9 months after the last dose for female patients of childbearing potential and for at least 6 months after the last dose for male patients with female partners of childbearing potential; Potential adverse effects on male fertility; Breastfeeding is contraindicated during treatment and for 3 months after the last dose.
Oxycodone • Oxycodone Sandoz	4.4	Hepatobiliary disorders (pancreatitis and diseases of the biliary tract)
	4.5	Interactions with selective serotonin re-uptake inhibitors (SSRI) or serotonin norepinephrine re-uptake inhibitors (SNRI)
Risedronate • Risedronate Sandoz	4.4	Bisphosphates may cause hypocalcaemia and/or hypophosphatemia due to effects on bone. Monitoring of calcium and phosphate may be needed throughout treatment, especially in individuals with risk factors.
Rivaroxaban • Xarelto	4.8	Splenic rupture (secondary to severe bleeding)
Tamoxifen • Tamoxifen Sandoz	4.4	QTc interval prolongation in patients with underlying risks and cardiac morbidities
Tigecycline • Tygacil	4.8	Fixed drug eruption
Zoledronic acid[c] • Aclasta	4.4	Bisphosphates may cause hypocalcaemia and/or hypophosphatemia due to effects on bone. Consider calcium and phosphate post each infusion and monitor for symptoms of hypocalcaemia and hypophosphatemia.

a. Data sheet sections listed in the table are: 4.2: Dose and method of administration; 4.3: Contraindications; 4.4: Special warnings and precautions for use; 4.5: Interaction with other medicines and other forms of interaction; 4.6: Fertility, pregnancy and lactation; 4.8: Undesirable effects.

b. See also the article on GLP-1 receptor agonists and renal adverse events on page 24.

c. See also the Gathering Knowledge article on page 31 for a case of hypophosphataemia following a zoledronic acid infusion.

Medsafe

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

Editor

Vikki Cheer
Email: medsafeadrquery@health.govt.nz

Editorial Team

Jo Prankerd, Senior Advisor Pharmacovigilance
Jessy Park, Advisor Pharmacovigilance
Lily Chan, Principal Technical Specialist Pharmacovigilance
Maria Storey, Team Leader Pharmacovigilance
Nevin Zhong, Senior Advisor Pharmacovigilance
Sou Mieng Tran, Senior Advisor Pharmacovigilance
Dr Susan Kenyon, PhD, Manager Clinical Risk
Tegan Coventry, Senior Advisor Pharmacovigilance

Acknowledgements

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

Medical Advisor

Dr Karin van Bart, Senior Medical Advisor

Group Manager

Chris James