Prescriber Update

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Contents

MEDSAFE
New Zealand Medicines and Medical Devices Safety Authority

Te Kāwanatanga o Aotearoa
New Zealand Government

MANATŪ HAUORA
MINISTRY OF HEALTH

Spotlight on cold and flu medicines containing pseudoephedrine

Key messages

- Pseudoephedrine is included in some cold and flu medicines for its nasal decongestant effects.
- Pseudoephedrine must not be used in people with uncontrolled hypertension or severe coronary artery disease, concomitantly with monoamine oxidase inhibitors (MAOIs), or people with hypersensitivity to pseudoephedrine.
- Cold and flu medicines containing pseudoephedrine are pharmacist-only medicines, meaning they can only be purchased after a consultation with a pharmacist. The pharmacist will advise if the medicine is clinically appropriate and record the sale.

Recently, Medsafe approved cold and flu medicines containing pseudoephedrine under an expedited process. These medicines have not been available in New Zealand for a number of years. This article is a reminder on the use of cold and flu medicines containing pseudoephedrine and provides information on how patients may obtain them.

What is pseudoephedrine?

Pseudoephedrine is a sympathomimetic used as a nasal decongestant.[1, 2] It provides short-term symptomatic relief of runny noses and nasal congestion due to conditions such as colds and flu.

Combination products contain pseudoephedrine with either paracetamol or ibuprofen, which relieve other cold and flu symptoms such as headache, body aches and fever. Some combination products also contain a sedating antihistamine to relieve sneezing, itchy or watery eyes and assist rest.

Use of pseudoephedrine

Cold and flu medicines containing pseudoephedrine can be used in adults and children aged 12 years and over. Advise patients of the following.

- Do not use more than one cold and flu medicine to avoid accidental overdose.
- Do not use in children aged under 12 years.
- Follow the recommended dose on the pack and do not exceed this dose.

When should pseudoephedrine be avoided?

Pseudoephedrine may exacerbate some existing medical conditions or increase the risk of adverse effects. Therefore, there are situations where the use of pseudoephedrine must or should be avoided, as outlined below.

Pseudoephedrine is contraindicated and must not be used in patients:[1, 2]

- with uncontrolled hypertension or severe coronary artery disease
- taking monoamine oxidase inhibitors (MAOIs) or who have taken MAOIs within the previous 14 days
- with known hypersensitivity or idiosyncratic reaction to pseudoephedrine and any other ingredients in the medicine.

Use pseudoephedrine with caution in patients with hepatic or renal impairment, severe hepatic or renal dysfunction, controlled hypertension, hyperthyroidism, diabetes mellitus, coronary or ischaemic heart disease, glaucoma and enlarged prostate.[1, 2]

Note that combination products have additional contraindications and cautions because they contain other active ingredients. Check the data sheets for full information.

Additionally, pseudoephedrine is included on the World Anti-Doping Agency (WADA) in-competition prohibited list.[3] Athletes must stop taking pseudoephedrine at least 24 hours before competition.[4]

Other considerations for use

Other considerations for use of pseudoephedrine include the following.[1,2]

- **Effects on sleep**: Advise patients of sleeplessness if taken a few hours before going to bed. However, note that combination products containing a sedating antihistamine may cause drowsiness.
- **Ischaemic colitis** (reduced blood flow to the colon): Advise patients to discontinue use and seek medical advice if they develop sudden abdominal pain, rectal bleeding or other symptoms of ischaemic colitis.
- **Skin reactions:** Advise patients to discontinue use and seek medical advice if they develop a rash with or without fever or erythema (skin redness).
- **Posterior reversible encephalopathy (PRES) or reversible cerebral vasoconstriction (RCVS):** Advise patients to discontinue use and seek medical advice if they develop sudden onset of severe headache, nausea, vomiting and visual disturbances.
- **Ischaemic optic neuropathy**: Advise patients to discontinue use and seek medical attention if they experience a sudden loss of vision or decreased visual acuity, such as scotoma (a blind spot).

Check the data sheets for full information, particularly for combination products.

How can patients obtain these medicines?

Cold and flu medicines containing pseudoephedrine are classified as pharmacist-only medicines, meaning they can only be purchased after a consultation with a New Zealand-registered pharmacist. The pharmacist will advise if the medicine is clinically appropriate for the patient and the sale will be recorded.[5]

Where can I find more information?

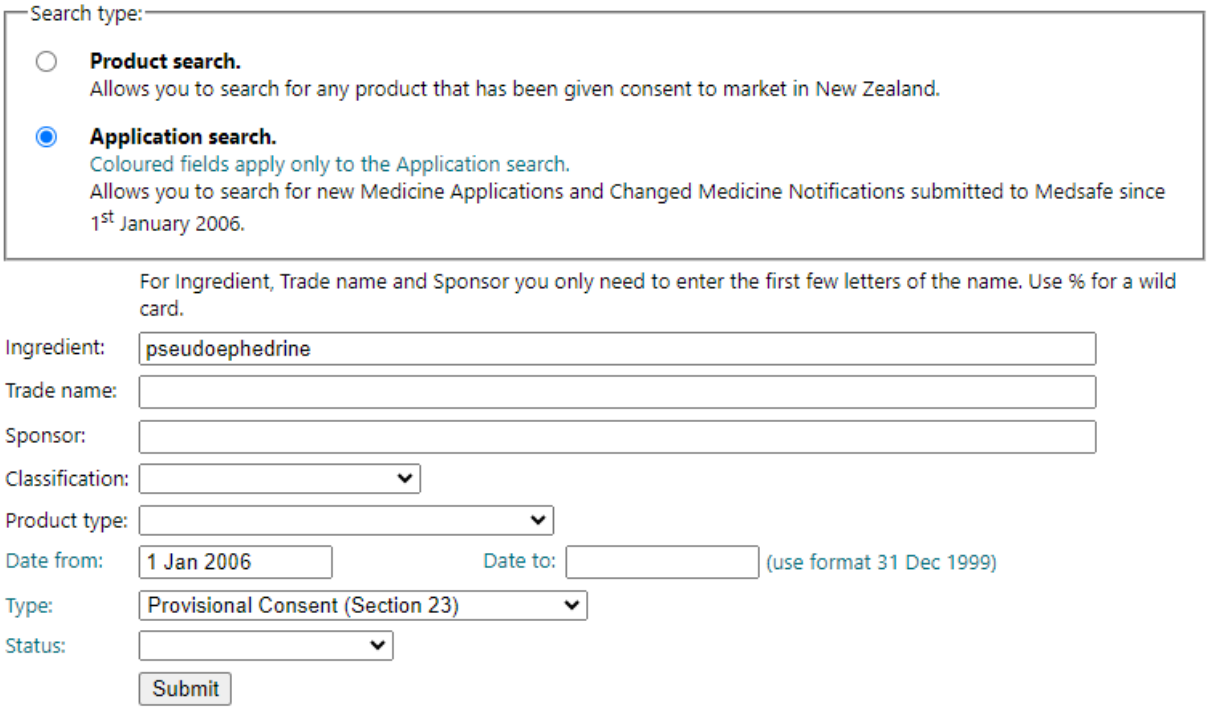
For full prescribing information, check the data sheets for each product.

To find approved pseudoephedrine products, use Medsafe's Product/Application Search.

1. Select 'Application search' for the Search type.
2. Enter 'pseudoephedrine' in the Ingredient field.
3. Select 'Provisional Consent (Section 23)' from the Type dropdown box.
4. Press Submit and the relevant products will be shown.

Figure 1 shows the Product/Application search webpage with relevant fields completed.

Figure 1: Screenshot of Medsafe's Product/Application Search webpage* to find approved pseudoephedrine-containing medicines



* URL: https://www.medsafe.govt.nz/regulatory/dbsearch.asp

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Medicines Monitoring: Calcium channel blockers and the possible risk of new-onset eczema

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
Calcium channel blockers	New-onset eczema	8 October 2024

- 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.

Summary of Bexsero adverse events following immunisation

Key messages

- Bexsero is a multicomponent recombinant meningococcal group B vaccine. It was added to the National Immunisation Schedule on 1 March 2023.
- Medsafe's review of adverse events following immunisation (AEFI) reported since Bexsero was added to the National Immunisation Schedule has not identified any new safety concerns.
- The most frequently reported AEFIs were injection site reactions (inflammation, erythema, pain) and pyrexia.

Meningococcal disease is caused by the bacterium *Neisseria meningitidis.* In 2022, over 80 percent of meningococcal disease cases in New Zealand were caused by group B bacteria.[1,2]

There are several vaccines available to protect against infection from different meningococcal groups. Bexsero is a multicomponent recombinant meningococcal group B vaccine. Bexsero was added to the New Zealand National Immunisation Schedule on 1 March 2023 for children at ages 3, 5 and 12 months, with a catch-up programme for those aged 12 to 59 months. It is also funded for eligible high-risk groups, including adolescents and young adults aged 13 to 25 years in communal living situations and those with certain medical conditions.[3]

This article provides a summary of the adverse events following immunisation (AEFI) reported with Bexsero in New Zealand between 1 March 2023 and 31 March 2024.

Bexsero indications and usage

Bexsero is indicated for active immunisation against invasive disease caused by *N. meningitidis* group B strains in individuals from 2 months of age and older. The use of this vaccine should be in accordance with official recommendations.[4]

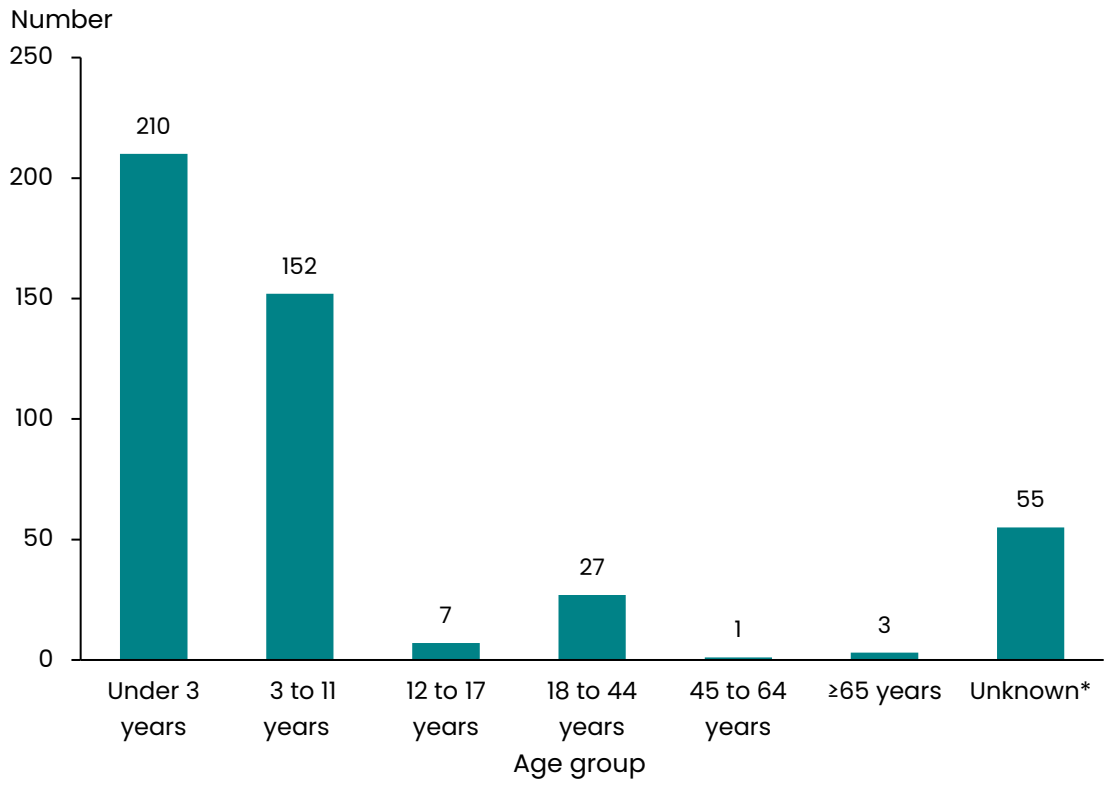
There were 9,910 doses of Bexsero administered between 1 March 2023 and 31 March 2024. In line with the National Immunisation Schedule, the majority of these (7,186 doses) were administered to children aged under 5 years.

Overview of Bexsero AEFI reports

Between 1 March 2023 and 31 March 2024, Medsafe and the Centre for Adverse Reactions Monitoring (CARM) received 455 AEFI reports where Bexsero was reported to be the suspect medicine. Of these, 134 were considered serious by the reporter. In the majority of cases the reporter also indicated that the person had received other vaccines at the same time.

In line with the recommended immunisation schedule for Bexsero, the majority of reports were for children aged under 3 years (Figure 1). There were also three reports for adults aged 65 years and older. No additional safety concerns were identified from these reports in older adults.

Figure 1: Number of Bexsero adverse event reports by age group, 1 March 2023 to 31 March 2024

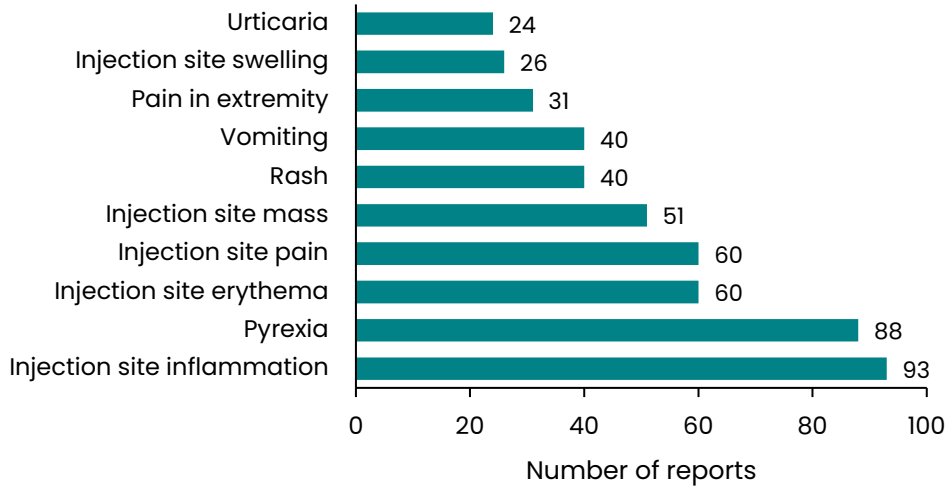


* There were 55 reports where age was unknown or not reported
Source: New Zealand Pharmacovigilance Database

Frequently reported AEFIs

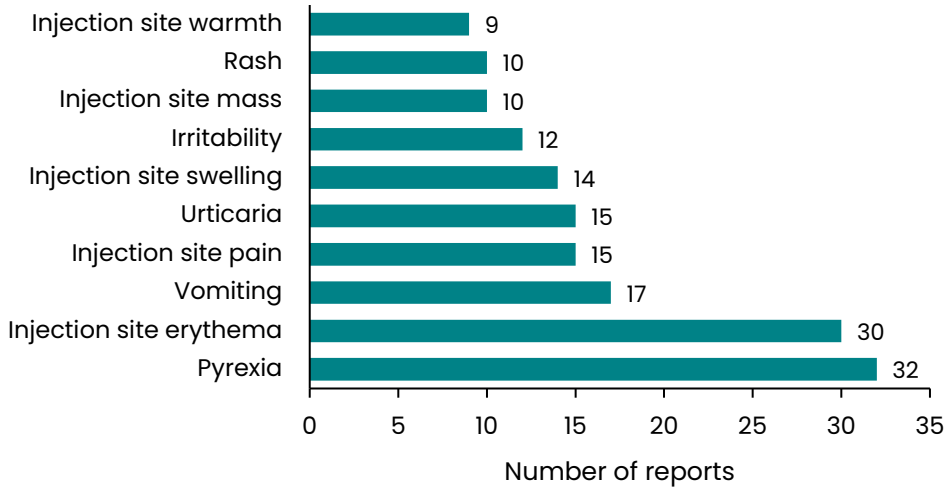
For all reports, the most frequently reported AEFIs were injection site inflammation, pyrexia (fever), injection site erythema (redness) and injection site pain (Figure 2). For serious reports, pyrexia, injection site erythema and vomiting were the most frequently reported AEFIs (Figure 3). All of these AEFIs are listed in the Bexsero data sheet.[4]

Figure 2: All reports: Ten most frequently reported adverse event terms for Bexsero, 1 March 2023 to 31 March 2024



Source: New Zealand Pharmacovigilance Database

Figure 3: Serious reports: Ten most frequently reported event terms for Bexsero, 1 March 2023 to 31 March 2024



Source: New Zealand Pharmacovigilance Database

Adverse events of special interest

A review of serious reports identified 12 cases of seizures (including six cases of febrile convulsion) and five case of hypotonic-hyporesponsive episodes (HHE). Seizures, including febrile seizures, are listed in the Bexsero data sheet with a reporting frequency of 'uncommon' (≥1/1,000 to <1/100) and HHE is listed as a post-marketing adverse reaction.[4] As with all vaccines, anaphylaxis is a potential risk with Bexsero. To date, no cases of anaphylaxis following Bexsero vaccination have been reported in New Zealand.

Summary and more information

Overall, Bexsero AEFIs reported in New Zealand are consistent with the known safety profile of the vaccine and are listed in the data sheet. The majority of reported AEFIs were for local and systemic reactions typically associated with immunisation. Medsafe's review of these AEFI reports did not identify any new safety concerns.

The following links contain additional information about Bexsero and adverse events following immunisation.

- Bexsero data sheet
- Immunisation Advisory Centre: Bexsero
- Healthify: Bexsero
- Medsafe: Febrile seizures in children

References

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MARC's remarks: March 2024 meeting

The Medicines Adverse Reaction Committee (MARC) convened for their 197th meeting on 14 March 2024.

The Committee discussed the risk of renal tubular acidosis (RTA) and severe hypokalaemia with **ibuprofen**. They noted that hypokalaemic RTA appears to be specific to ibuprofen rather than a class effect of non-steroidal anti-inflammatory medicines (NSAIDs). The Committee agreed that the risk of hypokalaemic RTA with ibuprofen is dose dependent. The Committee recommended updates to the ibuprofen data sheets to state that the risk is increased with higher doses of ibuprofen and following acute overdose, however, it may also occur within the recommended dose range. The Committee also recommended that the data sheets include signs and symptoms of RTA to prompt healthcare professionals to consider this diagnosis in patients with unexplained hypokalaemia.

The Committee reviewed information on co-ingestion of **serotonin and noradrenaline re-uptake inhibitors (SNRIs)/selective serotonin re-uptake inhibitors (SSRIs)** with **alcohol** in overdose and suicide. The Committee discussed the synergistic pharmacodynamic mechanism between alcohol and medicines that cause CNS depression and stated that this combination is not advisable. They agreed that venlafaxine toxicity is different to that of SSRIs due to venlafaxine's potential for cardiac complications or seizures.

The Committee recommended that all SSRI data sheets contain consistent information about use with alcohol. The Committee noted that the venlafaxine data sheet was recently updated regarding this topic, so no further updates were required.

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

Medicine-induced hyponatraemia: increased risks in older people

Key messages

- Hyponatraemia (low serum sodium levels) is a common electrolyte disturbance in older people.
- Medicine use is a common cause of hyponatraemia.
- Due to a combination of risk factors, older people are more susceptible to hyponatraemia. Use medicines that may cause hyponatraemia with caution in older people.

The Centre for Adverse Reactions Monitoring (CARM)/Medsafe recently received a report where an older person experienced severe hyponatraemia shortly after starting a selective serotonin reuptake inhibitor (SSRI). The person was also taking furosemide (report ID 153509).

This article is a reminder about medicine-induced hyponatremia and risks in older people.

Hyponatraemia may be asymptomatic

Hyponatraemia (low levels of serum sodium) is a common electrolyte disturbance, especially in older people. It is defined as a serum sodium concentration of less than 135 mmol/L.[1]

Hyponatraemia signs and symptoms range from mild and nonspecific (such as weakness or nausea) to severe and life-threatening (such as seizures or coma).[2] Hyponatraemia may also be asymptomatic.[3]

In older people, hyponatraemia can be associated with cognitive impairment, gait disturbances and falls and fractures.[2]

How ageing contributes to an increased risk of hyponatraemia

Age-related decline in renal function, urinary concentrating ability and changes to homeostatic mechanisms can contribute to the development of hyponatraemia.[3] However, there are usually multiple factors implicated in the development of hyponatraemia in older people.[3]

- **Comorbidities:** Many conditions that are known to cause hyponatraemia are prevalent in the older population including congestive heart failure, chronic kidney disease, neurological disease, diabetes, hypothyroidism and malignancy.[2,3]
- **Medicines:** Medicines that cause hyponatraemia are often prescribed to older people, such as diuretics, selective serotonin reuptake inhibitors (SSRIs), antipsychotics and carbamazepine.[2,3]

- **Polypharmacy:** Use of higher doses or multiple medicines increases the risk of medicine-induced hyponatraemia.[3]

Other risk factors in older people include female gender, low body mass and low baseline serum sodium.[3]

New Zealand reports

Between 2000 and 2023 Medsafe and CARM received 288 reports of hyponatraemia, of which, 208 reports were in people aged over 65 years.

Table 1 outlines the most frequently reported suspect medicines (by medicine class) for the hyponatraemia reports in people aged over 65 years.

Table 1: Hyponatraemia reports in people aged over 65 years: Most frequently reported suspect medicines, by class, 1 January 2000 to 31 December 2023

Medicine class	Suspect medicine	Number of reports
Diuretics	Bendroflumethiazide	35
	Chlortalidone	8
Proton pump inhibitor	Omeprazole	22
Antidepressants	Citalopram	19
	Fluoxetine	14
	Paroxetine	9
	Escitalopram	6
	Venlafaxine	7
Antiepileptic	Carbamazepine	8
Angiotensin II receptor inhibitors	Cilazapril	6
Antibiotics	Trimethoprim	6
Other	Colecalciferol	12

Source: New Zealand Pharmacovigilance Database

Prescribing considerations

Many medicines can cause hyponatraemia. Check the medicine data sheet for further information. When prescribing to older people, consider the following for medicines that are known to cause hyponatraemia.

- Use with caution.[3]
- If using a combination of medicines that cause hyponatraemia, consider lower doses or use alternative treatment options.[3]
- Most cases of medicine-induced hyponatremia occur within the first few weeks. However, hyponatraemia may also occur later in treatment if other risk factors for hyponatraemia develop or during concurrent illness.[3]
- Check plasma sodium levels before and shortly after starting treatment.[3] Continue to monitor plasma sodium levels closely throughout treatment as clinically indicated.
- If medicine-induced hyponatraemia occurs, manage the patient's sodium levels and stop the suspected medicine if clinically indicated.[3,4]

Further information

- The ionic truth about hyponatraemia – *Prescriber Update* June 2016
- For information on the management of hyponatremia, refer to local clinical guidelines.

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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
17/05/2024	Dear Healthcare Professional Letter	Phenergan (promethazine): Restriction of oral formulation use in children less than 6 years of age (PDF, 4 pages, 88KB)
13/05/2024	Alert	Promethazine (oral): Do not use in children under 6 years of age due to the risk of psychiatric and central nervous system side effects
02/05/2024	Dear Healthcare Professional Letter	Paracetamol Kabi – shortage of 1000mg/100mL solution for injection vial and temporary supply of UK-labelled product (PDF, 2 pages, 115 KB)
24/04/2024	Dear Healthcare Professional Letter	Oramorph – Supply of provisionally approved Oramorph 10mg/5mL to address supply shortage of morphine hydrochloride oral solution (PDF, 1 page, 242 KB)
08/04/2024	Alert	Do not use NaturaCoco Moisturising Cream or Dok Apo Moisturiser Soothing Cream
08/04/2024	Monitoring	M^2 Calcium channel blockers and the possible risk of new-onset eczema
05/03/2024	Dear Healthcare Professional Letter	Dexmedetomidine Viatris 200mcg/2mL concentrate for infusion – labelling exemption to allow supply of Dexmedetomidine Mylan from Australia (PDF, 1 page, 204 KB)
05/03/2024	Dear Healthcare Professional Letter	Rocuronium bromide (Hameln) – supply of Croatian/Slovenian-labelled Rocuronium bromide (Hameln) solution for injection 10mg/mL (PDF, 3 pages, 427 KB)
February 2024	Dear Healthcare Professional Letter	Coversyl – Changes to 4mg tablet appearance and changes to packaging (PDF, 4 pages, 457 KB)

Potassium in dietary supplements may lead to hyperkalaemia

Key messages

- Some medicines can cause hyperkalaemia. A high intake of potassium, for example, in some dietary supplements, may also increase the risk of experiencing hyperkalaemia.
- In patients with hyperkalaemia or signs and symptoms suggestive of hyperkalaemia, remember to ask about dietary supplement use.

The Centre for Adverse Reactions Monitoring (CARM)/Medsafe recently received a report of an elderly person with chronic kidney disease who experienced hyperkalaemia (report ID 153740). The person was taking a potassium-containing supplement marketed for joint health. The product was thought to be a contributing factor to the hyperkalaemia. This is the fourth CARM report where a dietary or herbal supplement was reported to have caused hyperkalaemia.

Hyperkalaemia

Hyperkalaemia is defined as a serum potassium level greater than 5.3 mmol/L. It is more common in older people and those with renal impairment.[1]

Hyperkalaemia is often asymptomatic. When there are signs and symptoms, these may include:[1]

- nausea and vomiting
- muscle pain and weakness
- paraesthesia
- flaccid paralysis
- ECG changes, palpitations and arrythmias.

Severe hyperkalaemia (≥7.0 mmol/L or ≥5.4 mmol/L with ECG changes or symptoms) is life-threatening.[1]

Medicines and supplements may contribute to hyperkalaemia

A wide range of medicines can cause hyperkalaemia through a variety of mechanisms, for example, by inhibition of the renin-angiotensin system or interference with potassium renal excretion. Hyperkalaemia-inducing medicines include angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), non-steroidal anti-inflammatory drugs (NSAIDs), spironolactone, potassium supplements, beta blockers, digoxin and trimethoprim.[2]

Some herbal ingredients in supplements contain potassium, including (but not limited to) stinging nettle, evening primrose, turmeric, dandelion. Other supplements may contain potassium as an ingredient or excipient, for example, glucosamine sulfate–potassium chloride complex.[1,3]

New Zealand reports

Between 1986 and 2023, Medsafe and CARM received 84 reports of hyperkalaemia. The most frequently reported suspect medicines include ACE inhibitors (21 reports), trimethoprim or cotrimoxazole (17 reports), NSAIDs (9 reports), spironolactone (6 reports) and ARBs (6 reports).

Prescribing considerations

Remind patients who are at risk of hyperkalaemia to carefully read the ingredients list and seek medical advice before taking potassium-containing supplements.

If hyperkalaemia occurs, consider whether a medicine or supplement could be a contributing factor and discontinue the suspect medicine or supplement if appropriate.[1]

For information on the management of hyperkalaemia, refer to local clinical guidelines.

Labelling requirements for medicines

New labelling requirements for the potassium content in oral medicines came into effect on 1 March 2024. If the total potassium content of the maximum recommended daily dose is greater than 39 mg (1 mmol) elemental potassium, the medicine packaging must state the quantity of potassium contained in each dosage unit.[4] However, this requirement does not apply to dietary supplements, as they are not subject to the Medicines Regulations 1984.

Medicine data sheets and Consumer Medicine Information (CMI) also list excipients.

Further information

- Medsafe patient leaflet on new labelling requirements for excipients
- *Prescriber Update* September 2015: Medicines and hyperkalaemia
- United States National Kidney Foundation: Herbal supplements and kidney disease
- Search for a data sheet or CMI

References

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4. Medsafe. 2023. *Label Statements Database* Edition 2.02 August 2023: Potassium salts. URL: www.medsafe.govt.nz/regulatory/labelling.asp (accessed 8 April 2024).

Recent approvals: new active ingredients or new indications

New active ingredients

Table 1 shows recent approvals of medicines with new active ingredients gazetted during the period 2 February 2024 to 18 April 2024.

Table 1: Recent approvals of medicines with new active ingredients

Medicine	New active ingredient	Dose form: strength(s)	Therapeutic area
Zolgensma	Onasemnogene abeparvovec	Solution for infusion: 20TVG/mL 5.5mL vial, 8.3mL vial	Paediatric patients with spinal muscular atrophy
Scemblix	Asciminib	Film-coated tablet: 20mg, 40mg	Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase
Columvi*	Glofitamab	Concentrate for infusion: 10mg/10mL, 2.5mg/2.5mL	Adult patients with relapsed or refractory diffuse large B-cell lymphoma
Arexvy	Recombinant respiratory syncytial virus (RSV) pre-fusion F protein	Suspension for injection: 120mcg	Prevention of lower respiratory tract disease caused by RSV-A and RSV-B subtypes in adults aged ≥60 years

* Provisional consent

New indications

Table 2 shows approved medicines with new indications for additional therapeutic areas gazetted during the period 2 February 2024 to 18 April 2024.

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	Human epidermal growth factor receptor 2 (HER2)-positive gastric or gastroesophageal junction adenocarcinoma

More information

See the Medsafe website for:

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

Dexamethasone: a highly potent and long-acting steroid

Key messages

- Dexamethasone is a highly potent and long-acting glucocorticoid. The risk of adverse effects is higher with dexamethasone than with other less-potent steroids.
- Serious adverse effects include adrenal suppression, severe psychiatric reactions, osteonecrosis, and increased susceptibility to infections.
- Prescribe dexamethasone at the lowest effective dose for the shortest possible duration. Withdrawal of dexamethasone should be gradual to reduce the risk of acute adrenal insufficiency.

This article is a reminder about the potential for serious adverse effects with dexamethasone.

Indications

Dexamethasone is a highly potent and long-acting corticosteroid with high glucocorticoid activity and minimal mineralocorticoid activity. Dexamethasone is approximately six times more potent than prednisone.[1]

Systemic dexamethasone is indicated for replacement therapy in adrenal insufficiency and to treat variety of severe autoimmune, inflammatory and allergic disorders.[2,3] In addition, the tablets are indicated for treatment of severe COVID-19 disease and the solution for injection for the treatment of shock.[2,3] Topical and intravitreal presentations are also available for the treatment of certain eye disorders.[4,5]

Serious adverse effects

Some of the more serious adverse effects from systemic administration of dexamethasone are described below. See the data sheets for more information.

Adrenal insufficiency[2,3]

Adrenal suppression may occur with the use of all glucocorticoids. Symptoms of adrenal suppression are non-specific and can include malaise, muscle weakness, mental changes, desquamation of the skin, nausea and vomiting, hypoglycaemia and dehydration.

The degree and duration of adrenal suppression is variable among patients and depends on the dose, frequency, and duration of therapy. Adrenal insufficiency may persist for several months after treatment discontinuation.

Abrupt withdrawal of glucocorticoids may result in life-threatening acute adrenal sufficiency.

Neuropsychiatric

Neuropsychiatric disturbances, including mood disturbances, insomnia, personality changes, irritability, anxiety, mania, depression, and suicidal ideation typically occur within a few days or weeks of starting treatment.[2,3]

Insomnia is considered to be a significant predictor for the onset of affective disorders including major depression,[6] anxiety and psychotic disorders.[7,8]

Individuals with an existing or previous history of severe affective disorders may be at greater risk of neuropsychiatric adverse reactions.[2,3]

Musculoskeletal

Musculoskeletal complications include osteonecrosis, myopathy, osteoporosis and fractures.[2,3]

Approximately 30 to 50 percent of long-term glucocorticoid users develop secondary osteoporosis. Osteonecrosis can occur independently of osteoporosis, affecting 9 to 40 percent of patients on prolonged therapy or with short-term high doses.[9,10]

In infancy, childhood and adolescence, long-term treatment with glucocorticoids can cause growth retardation, which may be irreversible.[2,3]

Immunosuppression[2,3]

Suppression of the inflammatory response and immune function increases susceptibility to and the severity of infections. The typical signs and symptoms of serious infections may be masked. Latent infections, such as latent tuberculosis, can reactivate.

Live vaccines are contraindicated in individuals on high-dose corticosteroids.

New Zealand reports

Between January 1993 and March 2024, Medsafe and the Centre for Adverse Reactions Monitoring (CARM) received 87 reports where the suspect medicine was reported as dexamethasone (excluding combination products).

Of the 87 reports, there were:

- 14 reports of osteonecrosis, with 3 of those occurring in children aged under 18 years
- 8 reports of psychiatric disorders, including confusional state, mania, abnormal behaviour, aggression, anxiety, delusion, disorientation and insomnia.

Prescribing considerations

When prescribing dexamethasone:

- use the lowest effective dose for the shortest possible period to manage the patient's condition
- consider risk factors that might make the patient more susceptible to adverse effects (eg, age, physical and psychiatric comorbidities)
- regularly monitor the patient for adverse effects
- avoid long-term use in children due to the risk of growth retardation
- ensure gradual withdrawal to reduce the risk of acute adrenal insufficiency.

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Gathering knowledge from adverse reaction reports: June 2024

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 from the Centre for Adverse Reactions Monitoring (CARM)/Medsafe database.

Case details[a,b]	Reaction description and data sheet information[b,c]
Report ID: 152982 **Age:** 74 years **Gender:** Female **Medicine(s):** Nitrofurantoin **Reaction(s):** Hepatitis, abdominal pain	Following a course of nitrofurantoin a week earlier, the patient experienced abdominal pain. Her liver function tests (LFTs) were abnormal, and she was diagnosed with hepatitis. Nitrofurantoin was discontinued and her LFTs slowly improved.
	Hepatic reactions, including hepatitis, are listed as rare ADRs in the Nifuran and Macrobid data sheets.
Report ID: 153407 **Age:** 53 years **Gender:** Female **Medicine(s):** Naltrexone + bupropion **Reaction(s):** Tinnitus	The patient developed severe tinnitus while taking Contrave.
	Tinnitus is listed as a common ADR in the Contrave data sheet.
Report ID: 153807 **Age:** 42 years **Gender:** Male **Medicine(s):** Amoxicillin, ibuprofen **Reaction(s):** Acute interstitial nephritis	Soon after starting treatment with amoxicillin, plus intermittent ibuprofen, the person developed severe renal impairment. Renal biopsy identified acute interstitial nephritis.
	Interstitial nephritis and tubulointerstitial nephritis are listed as very rare ADRs in the Alphamox and Brufen data sheets, respectively.

Continues

Case details[a,b]	Reaction description and data sheet information[b,c]
Report ID: 154727 **Age:** 65 years **Gender:** Female **Medicine(s):** Clopidogrel **Reaction(s):** Polyarthritis	After taking clopidogrel for a few weeks, the patient developed pain and swelling in her finger that then progressed to other joints. Clopidogrel was withdrawn and the symptoms resolved.
	Arthritis is listed as a very rare ADR in the Arrow-Clopid data sheet.
Report ID: 155052 **Age:** 9 years **Gender:** Male **Medicine(s):** Methylphenidate **Reaction(s):** Aggression	Within an hour of starting methylphenidate at a low dose, the child became severely agitated and aggressive.
	There is a warning about aggression, anxiety and agitation in the Rubifen data sheet. Monitor patients beginning treatment with methylphenidate tablets for the appearance or worsening of aggressive behaviour, marked anxiety or agitation.

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).

A reminder: generic medicines, bioequivalence and switchability

Key messages

- Generic medicines approved in New Zealand are bioequivalent to the respective innovator or 'brand name' medicine.
- This means that for almost all medicines, patients should experience the same safety and efficacy when starting the medicine, regardless of brand.
- However, bioequivalence does not directly measure 'switchability'. Extra care is needed for certain medicines when switching patients to a different brand.
- Eltroxin is the funded levothyroxine brand, and the manufacturer has reformulated the medicine. While most patients will not experience any issues with the change, prescribers should carefully monitor patients when changing them to the new formulation.

Generic medicines and bioequivalence

Generic medicines are required to be the same as innovator or 'brand-name' medicines in dosage, safety, effectiveness, strength, stability and quality, as well as in the way they are made.[1]

During the pre-market approval process, Medsafe assesses evidence provided by sponsors to show that their generic medicine is bioequivalent to the innovator. Bioequivalence studies are small clinical trials that generally involve single doses given to healthy volunteers. Medicines are bioequivalent if the rate and extent of absorption of the active ingredient into the bloodstream (bioavailability) meet internationally agreed criteria for similarity.[2–4]

Bioequivalence means a patient can expect to experience the same safety and efficacy when starting on either an approved generic or the innovator (brand name) medicine. Bioequivalence is not required to be checked between generics. However, because the difference between generics and the innovator is so small, patients would not normally experience any difference in efficacy or safety.

Bioequivalence and switchability

An innovator medicine can generally be substituted with an approved generic and vice versa because of the comparable bioavailability demonstrated through bioequivalence studies. However, these studies are not designed to investigate patients' suitability to change from one brand to another during their treatment ('switchability').

For most medicines, patients can switch between approved brands during treatment without issue. However, switching between different brands should ideally be avoided for some specific medicines. A medicine's switchability may be affected by its therapeutic index or pharmacokinetics, or the patient population. For example, medicines with a narrow therapeutic index are often carefully titrated to a safe and effective dose for individual patients, and small changes can have a clinically meaningful impact on efficacy. In some patients or for certain medicines, formulation or significant manufacturing changes can affect the patient's response, despite the demonstration of bioequivalence between the old and new medicine.

Other non-pharmacological factors may influence a patient's experience when changing medicine brands. These could include preconceptions of generic medicines or concerns about change in general, resulting in the patient experiencing and reporting real side effects, as commonly seen in patients taking placebos in clinical trials. However, there are also other reasons that patients may feel a difference in effect between brands (eg, infection), and it can be difficult to determine the cause of an adverse event seemingly linked to a brand switch.

Changes to the Pharmac-funded medicine supplier or supply chain issues may lead to an unavoidable brand change for the patient. If changing a difficult-to-switch medicine is necessary and/or a patient expresses concerns about a change, prescribers should take extra care, including counselling, monitoring and dose adjustment.

Anti-epileptic medicines

Anti-epileptic medicines (AEMs) as a medicine class can cause difficulties when switching patients between brands. Medsafe recommends that prescribers follow the UK Medicines and Healthcare products Regulatory Agency's (MHRA) advice regarding AEMs, which places them in three categories based on switchability.[5]

Category 3 medicines (eg, levetiracetam, gabapentin) generally have high bioavailability and a wide therapeutic index, meaning that switching is relatively straightforward. Whereas patients taking category 1 medicines (eg, phenytoin, phenobarbital) should remain on the same brand, as clinically relevant differences between brands can occur despite bioequivalence being shown.[5] Recent New Zealand experience supports this advice, with many patients experiencing difficulties when the funded lamotrigine brand (a category 2 AEM) was changed in 2019,[6] and when the formulation of the brand name phenytoin medicine Dilantin was altered.[7]

Levothyroxine and Eltroxin reformulation

Levothyroxine is another example where brand switching is not recommended if avoidable, with dose changes of the same brand also requiring careful monitoring and titration. This is largely due to the medicine's complex pharmacokinetic profile and narrow therapeutic index, meaning that slight differences in bioavailability and serum levels have clinically relevant impacts. This lack of switchability was highlighted in New Zealand in 2007 when the Eltroxin brand of levothyroxine was reformulated by the manufacturer. Despite bioequivalence being successfully demonstrated between the old and new formulations, many patients reported issues following the change.[8,9] Similar experiences were also reported in Denmark and France.[10]

Medsafe recently assessed and approved another minor formulation change for Eltroxin, which will be implemented from June 2024. While most patients will not experience any issues with the change, prescribers should carefully monitor patients when changing them to the new formulation.

For information about this change refer to:

- the manufacturer's Dear Healthcare Professional letter (PDF, 2 pages, 98 KB)
- Pharmac's information about the change
- the Eltroxin data sheet for dose titration and monitoring advice.

More information

Medsafe publishes copies of Dear Healthcare Professional letters sent to healthcare professionals by medicine manufacturers and sponsors. These may include information supply chain issues and brand substitutions.

Refer to the Pharmac website for:

- supply issues, discontinuations and brand changes
- the Community Schedule and the Hospital Medicines List
- consultations and decisions, including tender results.

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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, see Section 10 'Date of revision of the text' (at the end of each data sheet). Search for a data sheet

See also 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*	Summary of new safety information
Benzathine benzylpenicillin • Bicillin L-A	4.8	Kounis syndrome
Clindamycin • Dalacin C capsule	4.2	To avoid oesophageal irritation, take with a full glass of water and no less than 30 minutes before lying down
Docetaxel • DBL Docetaxel	4.6	Pregnancy: women of childbearing potential should use effective contraception during treatment and for at least 2 months after the last dose; male patients with female partners of childbearing potential should use effective contraception during treatment and for at least 4 months after the last dose
Etanercept • Enbrel	4.6	Live vaccines can be considered for infants 16 weeks after stopping breastfeeding
Ezetimibe • Ezetimibe Sandoz	4.3	Concomitant use is contraindicated with: fenofibrate in patients with gallbladder disease; a statin during pregnancy and lactation; a statin in patients with active liver disease or unexplained persistent elevations in serum transaminases
	4.8	Nausea, arthralgia, drug-induced liver injury, increased creatine phosphokinase (CPK), elevations of liver transaminases, severe cutaneous adverse reactions (SCAR), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS)
Infliximab • Remicade	4.8	Weight increased
Liraglutide • Victoza • Saxenda	4.8	Delayed gastric emptying, urinary tract infection, intestinal obstruction including ileus
Methylphenidate • Ritalin, Ritalin LA	4.4	Acute angle closure glaucoma, increased intraocular pressure and glaucoma
	4.8	Erectile dysfunction, increased intraocular pressure
Osimertibinib • Tagrisso	4.8	Skin hyperpigmentation
Pembrolizumab • Keytruda	4.4	Other immune-mediated adverse reactions: haemolytic anaemia, exocrine pancreatic insufficiency

Continues

Active ingredient(s): • Medicine(s)	Data sheet updates Section*	 Summary of new safety information
Pirfenidone • Esbriet	4.4	SCAR, including SJS, TEN and DRESS
	4.8	
Rifampicin + isoniazid • Rifinah	4.5	Rifampicin interaction with caspofungin
Ropivacaine • Naropin	4.4	Horner's syndrome
Secukinumab • Cosentyx	4.4	Hypersensitivity reactions: angioedema. Eczematous eruptions
	4.8	Dermatitis, dermatitis exfoliative generalised, angioedema
Silver sulfadiazine • Flamazine	4.4	SJS, TEN
	4.8	
Tacrolimus • Tacrolimus Sandoz	4.4	Thrombotic microangiopathy
	4.5	Increase tacrolimus blood levels: concomitant use with hepatitis C virus (HCV) protease inhibitors, letermovir or amiodarone may require decreased tacrolimus doses. Decrease tacrolimus blood levels: caspofungin
	4.8	Cytomegalovirus (CMV) infection, thrombotic microangiopathy

* 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

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