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Contents

Celebrating 200 meetings of the Medicines Adverse Reactions Committee 71

Reminder: risk factors for ketoacidosis with SGLT-2 inhibitors 73

Medicine-induced interstitial lung disease 76

Medicines Monitoring: direct-acting oral anticoagulants and mood changes 79

Reminder: risk of hypophosphataemia with iron infusions 80

Quarterly summary of recent safety communications 82

Medicines that make you sweat: drug-induced hyperhidrosis 83

Summary of Shingrix adverse events following immunisation 85

Test your knowledge: the *Prescriber Update* quiz 2024 88

Aciclovir and valaciclovir: toxic in renal impairment 90

MARC's remarks: September 2024 meeting 91

Recent approvals: new active ingredients or new indications 92

Gathering knowledge from adverse reaction reports: December 2024 93

Recent data sheet updates: important new safety information 95

Quiz answers 97

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MANATŪ HAUORA
MINISTRY OF HEALTH

Celebrating 200 meetings of the Medicines Adverse Reactions Committee

The Medicines Adverse Reactions Committee (MARC) was established under the Medicines Act 1981 as an independent expert advisory committee to advise the Minister of Health, the Director-General of Health and Medsafe on the safety of approved medicines.

In celebration of the MARC's 200th meeting on 5 December 2024, Medsafe looks back at the history of the Committee.

Early beginnings before the Medicines Act 1981

The thalidomide tragedy that occurred in the early 1960s was the catalyst for the formation of national schemes for collecting information about adverse drug reactions (ADRs).[1] New Zealand's national surveillance scheme began in 1965, with the formation of the Centre for Adverse Reactions Monitoring (CARM) at the University of Otago and the Committee on Adverse Drug Reactions (CADR).[1–3]

CADR initially had seven members, with two representatives from the then Department of Health, the Royal Australasian College of Physicians and the Royal College of General Practitioners, and one representative from the Department of Pharmacology at University of Otago.[2]

From 1968, CADR's annual reports were published in the *New Zealand Medical Journal* and *New Zealand Dental Journal*.[4] Table 1 has excerpts from several of these reports.

Table 1: Excerpts from the third, seventh and eighth annual reports of the Committee on Adverse Drug Reactions

Third annual report (for the period April 1967 to March 1968)[a]
• 453 cases reported. The number of reactions to phenylbutazone and oxyphenbutazone has diminished sharply from previous years, probably due to decreased consumption. However, this has been accompanied by a precipitate increase in reactions to indomethacin.
Seventh annual report (for the period April 1971 to March 1972)[b]
• 963 cases reported. There was an intensive monitoring survey that occurred in hospitals in Dunedin during this period. Cases of thromboembolism considered to be associated with oral contraceptives continue to be reported, including 2 fatal cases of pulmonary embolism. Antibiotics were responsible for a high proportion of total number of reactions, with ampicillin most frequently reported.
Eighth annual report (for the period April 1972 and March 1973)[c]
• 601 cases reported. Anticonvulsants were again the group with the most commonly represented amongst the congenital abnormalities reported. A rather unexpected propensity to induce allergic reactions seems to be coming to light with beta-blockers in addition to their well-known capacity to precipitate asthma in susceptible subjects. Six cases of skin rash were reported including one of photodermatitis.

Sources:
New Zealand Committee on Adverse Drug Reactions. 1968. Third Annual Report. *New Zealand Medical Journal* 67(433): 635–9.
New Zealand Committee on Adverse Drug Reactions. 1972. Seventh Annual Report. *New Zealand Medical Journal* 76(486): 357–64.
New Zealand Committee on Adverse Drug Reactions. 1973. Eighth Annual Report. *New Zealand Medical Journal* 78(500): 309–16.

Following the introduction of the Medicines Act 1981, the CADR changed its name and some of its functions and became the MARC.

Ending the 20th century with their 100th meeting

The MARC held their 100th meeting on 25 November 1999. At that time, there were ten members on the MARC, and all were medical practitioners with various specialties.

By the 100th meeting, the MARC's functions were to advise on suspected ADR reports, review the scientific literature and respond to concerns from healthcare professionals.

Present day: a Committee that reflects the diverse health workforce of the 21st century

Today there are 13 members on the MARC. They are experts in various fields of clinical medicine, pharmacy, nursing, pharmacovigilance, epidemiology and biostatistics. There is also a layperson to represent consumer interests. See the Medsafe website for the Committee's composition and membership.

The MARC's functions include:

- providing advice on matters referred under section 36 of the Medicines Act 1981
- reviewing ADRs reported to CARM
- providing advice on medicine safety issues referred by Medsafe.

Over the years, the MARC has provided advice on many safety concerns with medicines. See the MARC meeting minutes and the reports presented to the MARC on the Medsafe website for more information.

Medsafe would like to thank all past and present members for their time and important contributions on the Committee.

References

1. Kunac DL, Harrison-Woolrych M and Tatley, MV. 2008. Pharmacovigilance in New Zealand: the role of the New Zealand Pharmacovigilance Centre in facilitating safer medicines use. New Zealand Medical Journal 121(1283): 76–89. URL: nzmj.org.nz/media/pages/journal/vol-121-no-1283/ed9e6a3f2a-1696470790/vol-121-no-1283.pdf (accessed 7 November 2024).
2. New Zealand Committee on Adverse Drug Reactions. 1965. Committee on Adverse Drug Reactions *New Zealand Medical Journal* 64(391): 163.
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4. New Zealand Committee on Adverse Drug Reactions. 1968. Third Annual Report. *New Zealand Medical Journal* 67(433): 635–9.

Reminder: risk factors for ketoacidosis with SGLT-2 inhibitors

Key messages

- Ketoacidosis is a serious adverse reaction associated with sodium-glucose co-transporter-2 (SGLT-2) inhibitor medicines.
- Patients taking SGLT-2 inhibitors are more likely to develop ketoacidosis when other risk factors are present, including acute illness, infections, surgery, pancreatic disorders, insulin dose reduction, insulin insufficiency, severe dehydration, reduced caloric intake, low carbohydrate diet, heavy alcohol use and a history of ketoacidosis.
- Inform patients about the signs, symptoms and risk factors for ketoacidosis and what to do if it occurs.

Ketoacidosis is a life-threatening condition that requires urgent hospitalisation.[1]

Ketoacidosis is a known adverse reaction of sodium-glucose co-transporter-2 (SGLT-2) inhibitor medicines, such as empagliflozin and dapagliflozin.[1]

This article is a reminder about ketoacidosis, in particular in patients being treated with SGLT-2 inhibitors. The article focuses on empagliflozin, the funded medicine in this class.

Ketoacidosis and SGLT-2 inhibitors

Mechanisms

SGLT-2 inhibitors predispose patients to ketoacidosis by multiple mechanisms that favour ketogenesis and lipolysis. These mechanisms include:[2]

- upregulation of glucagon
- glycosuria, which reduces blood glucose and allows for insulin dose reduction
- ketone reabsorption in the kidney
- osmotic diuresis.

Risk factors

Type 2 diabetes mellitus (T2DM) itself is a risk for ketoacidosis (diabetic ketoacidosis). However, there have also been reports of ketoacidosis in nondiabetic patients taking empagliflozin.[1]

Patients taking SGLT-2 inhibitors may also have other factors that predispose them to ketoacidosis, as shown in Table 1.

Table 1: Risk factors for ketoacidosis in patients taking SGLT-2 inhibitors

Acute illness or infection
Surgery
Pancreatic disorders leading to insulin deficiency
Inappropriate insulin dose reduction (including via insulin pump failure)
Severe dehydration
Malnourished/Reduced caloric intake
Low carbohydrate or ketogenic diet
Heavy alcohol use
History of ketoacidosis

Sources:
Boehringer Ingelheim (NZ) Limited. 2024. *Jardiance New Zealand Data Sheet* 21 March 2024 URL: medsafe.govt.nz/profs/Datasheet/j/jardiancetab.pdf (accessed 1 October 2024).

Musso G, Saba F, Cassader M, et al. 2020. Diabetic ketoacidosis with SGLT2 inhibitors. *British Medical Journal* 371: m4147. DOI: 10.1136/bmj/m4147 (accessed 1 October 2024).

Chow E, Clement S, Garg R. 2023. Euglycemic diabetic ketoacidosis in the era of SGLT-2 inhibitors. *BMJ Open Diabetes Research & Care* 11(5): e003666. DOI: 10.1136/ bmjdrc-2023-003666 (accessed 1 October 2024).

Prescribing considerations

Use caution when prescribing SGLT-2 inhibitors to patients with risk factors that may predispose them to ketoacidosis.[1]

Inform patients taking SGLT-2 inhibitors about ketoacidosis risk factors, signs and symptoms. Blood glucose levels may be normal or only mildly elevated. Symptoms may be non-specific and include nausea, vomiting, malaise, anorexia, abdominal pain, excessive thirst, shortness of breath, dizziness or confusion. Advise patients to seek medical attention immediately if they experience ketoacidosis symptoms, irrespective of blood glucose levels.[1–3]

Consider monitoring ketones and temporarily discontinuing SGLT-2 inhibitors in clinical situations known to predispose patients to ketoacidosis.[1,3] Refer to local clinical guidelines for further advice, including management before surgery/procedures and during acute illness.

Ketoacidosis may be prolonged in patients with T2DM, despite stopping SGLT-2 inhibitors.[4]

New Zealand case reports: empagliflozin

Between January 2021 and 15 September 2024, there were 87 case reports of ketoacidosis in people who were taking empagliflozin.

All cases were reported as serious. The median onset time was 59 days (range 1 to 703 days). Table 2 shows the demographic distribution of the case reports.

Table 2: Gender, age and ethnicity distibution of case reports of ketoacidosis* with empagliflozin, 1 January 2021 to 15 September 2024

Demographic	Number (n=87)
Gender	
Male	46
Female	40
Not reported	1
Age (years)	
18-44	13
45-64	33
65-74	12
75 and older	8
Not reported or unknown	21
Ethnicity	
Māori	7
Pacific Peoples	3
Asian	2
European/Other	23
Not reported or unknown	52

* Includes MedDRA preferred terms: diabetic ketoacidosis (61), ketoacidosis (14), euglycaemic diabetic ketoacidosis (7), ketosis (3), blood ketone body increased (1), blood ketone body present (1).

Source: Suspected adverse reactions reported to the New Zealand Pharmacovigilance Database (accessed 15 September 2024).

In some cases, the reporter also included information to show that the patient had other risk factors, including:

- acute infection
- dietary changes
- dehydration
- weight loss
- insulin dose reduction or omission
- surgery/procedure
- high alcohol intake.

Further information

Previous *Prescriber Update* articles

- Reminder: Flozins and the risk of diabetic ketoacidosis and Fournier's gangrene (December 2022)
- Spotlight on empagliflozin (December 2020)

Resources

- Medsafe: Data sheet and consumer medicine information search
- New Zealand Society for the Study of Diabetes: Type 2 Diabetes Management Guidance
- bpac^{nz}: Type 2 diabetes management toolbox: from lifestyle to insulin
- Healthify:
  - Empagliflozin
  - Jardiamet - empagliflozin + metformin
  - Diabetes – type 2 sick day plan

References

1. Boehringer Ingelheim (NZ) Limited. 2024. *Jardiance New Zealand Data Sheet* 21 March 2024 URL: medsafe.govt.nz/profs/Datasheet/j/jardiancetab.pdf (accessed 1 October 2024).
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4. Health Canada. 2024. *Summary Safety Review – Sodium-glucose-co-transporter-2 (SGLT2) inhibitors (canagliflozin, dapagliflozin, empagliflozin) – Assessing the potential risks of prolonged or incident diabetic ketoacidosis despite stopping treatment in adult patients with type 2 diabetes* 10 October 2024. URL: dhpp.hpfb-dgpsa.ca/review-documents/resource/SSR1724175682293 (accessed 4 October 2024).

Medicine-induced interstitial lung disease

Key messages

- Interstitial lung disease (ILD) describes a broad spectrum of disorders that cause damage to the lungs. The damage may be irreversible and ILD can be fatal.
- Many medicines are associated with ILD. Due to the potential for serious outcomes, early recognition of ILD and withdrawal of the medicine is vital. Monitor respiratory function and symptoms throughout treatment with medicines known to cause ILD.
- Inform patients taking medicines associated with ILD about this risk. Advise them to seek medical attention early if they develop cough, chest pain, shortness of breath, fever or chills.

At their September 2024 meeting, the Medicines Adverse Reactions Committee discussed a case report of non-specified lung injury with methotrexate (report ID NZ-Medsafe-157198). The Committee recommended that Medsafe reminds prescribers that medicines can cause interstitial lung disease.

Many medicines can cause ILD

ILD is an umbrella term encompassing a broad spectrum of disorders that cause inflammation or fibrosis (scarring) of the pulmonary interstitium (lung tissue). This damage impairs gas exchange in the lungs and can lead to respiratory failure and death.[1]

ILD is the most common type of pulmonary toxicity associated with medicines.[2] Examples of medicines associated with ILD include nitrofurantoin, methotrexate, amiodarone, leflunomide, cytotoxic medicines and some biological agents (Table 1). However, hundreds of medicines have been reported to cause ILD.

Table 1: Examples of medicines associated with ILD (list not exhaustive)

Medicine	Comments
Nitrofurantoin	Irreversible interstitial pneumonitis and/or pulmonary fibrosis can occur with long-term therapy. Treatment should not be prescribed beyond six months unless the benefits outweigh the risks. Acute or subacute pulmonary reactions can also occur with short courses.
Methotrexate	Acute or chronic interstitial pneumonitis and pulmonary fibrosis may occur and progress rapidly.
Amiodarone	Pulmonary fibrosis and/or pneumonitis have been reported. This is usually reversible following early withdrawal of amiodarone therapy.
Leflunomide	ILD has been reported.
Cytotoxic medicines	Many cytotoxic medicines are associated with ILD, including bleomycin, mitomycin, gemcitabine, oxaliplatin, melphalan, busulfan, carmustine, bortezomib, docetaxel and cyclophosphamide.
Biological medicines	ILD has been reported with biological medicines, including immune checkpoint inhibitors, TNF-alpha inhibitors and monoclonal antibodies.
Other antineoplastic medicines	Pneumonitis and/or ILD has been reported with protein and tyrosine kinase inhibitors (eg, alectinib, dasatinib, everolimus) and poly (ADP-ribose) polymerase inhibitors (eg, niraparib, olaparib).

Sources:

Schwaiblmair M, Behr W, Haeckel T, et al. 2012. Drug induced interstitial lung disease. *Open Respiratory Medical Journal* 6: 63-74. DOI: 10.2174/1874306401206010063 (accessed 11 October 2024).

Medicine data sheets, available at: medsafe.govt.nz/Medicines/infoSearch.asp (accessed 14 October 2024).

New Zealand Formulary (NZF). 2024. *NZF v148: Cytotoxic drugs* 1 October 2024. URL: nzf.org.nz/nzf_4381 (accessed 14 October 2024).

Monitor for medicine-induced ILD

The presenting symptoms of ILD are non-specific and include cough, dyspnoea and fatigue. ILD diagnosis is based on clinical features and radiological and histological findings. Where appropriate, consider medicines as part of differential diagnosis of new or worsening respiratory symptoms.[1]

Risk factors for medicine-induced ILD include:[1]

- age (children and elderly patients are at an increased risk of drug toxicity)
- underlying lung disease
- co-administration with other medicines associated with ILD (drug interactions).

When treating patients with medicines known to cause ILD, monitor respiratory function and symptoms throughout treatment. Delayed recognition of ILD increases the risk of irreversible lung damage and death. Refer to medicine data sheets and local guidelines for specific monitoring requirements.

Treatment of medicine-induced ILD often involves prompt withdrawal of the medicine and treatment with corticosteroids. Early recognition and treatment may improve the prognosis.[1]

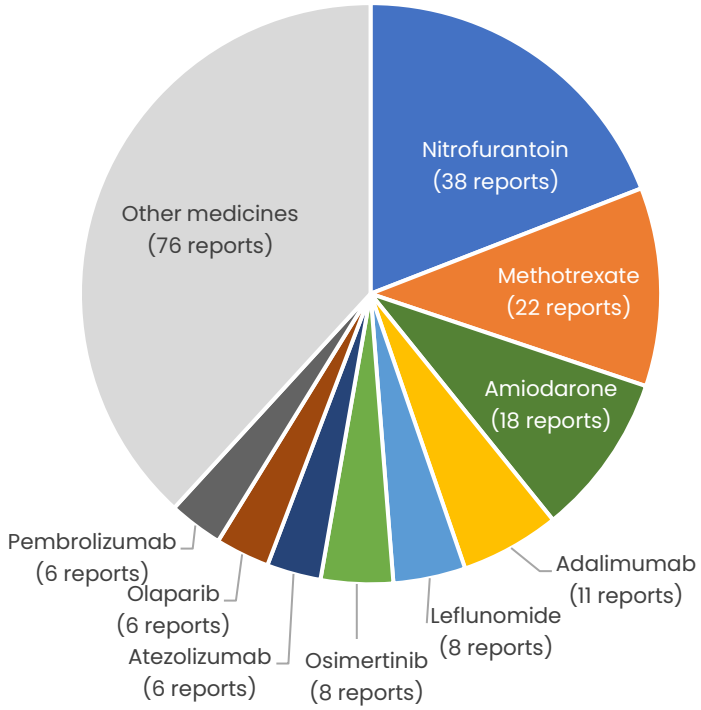
Inform patients about the risk of ILD

Patients who are taking medicines associated with ILD should be aware of this risk. Advise them to seek prompt medical attention if they develop cough, chest pain, shortness of breath, fever or chills. Inform patients that early treatment of ILD is important to reduce the chance of irreversible lung damage.

New Zealand case reports

There were 173 cases of ILD reported with a medicine between 1 January 2014 and 30 September 2024, of which 30 had a fatal outcome. Nitrofurantoin, methotrexate and amiodarone were the most frequently reported medicines (Figure 1).

Figure 1: Number of interstital lung disease reports[a,b] by medicine, 1 January 2014 to 30 September 2024



Notes:

a. Medicines (excluding vaccines) in the New Zealand Pharmacovigilance Database as suspected of causing interstitial lung disease (as indicated by Preferred Terms within the Standardised MedDRA Query 'interstitial lung disease') from 1 January 2014 to 30 September 2024.

b. The sum of the ILD reports by medicine (199) is greater than the number of reports (173) because a single case report can have more than one suspect medicine.

Source: Reports of suspected adverse reactions to the New Zealand Pharmacovigilance database (accessed 7 October 2024)

More information

For more information on individual medicines and ILD, refer to the data sheet.

- Search for a data sheet

See also previous *Prescriber Update* articles about medicine-induced ILD.

- Medicine-induced lung disease (June 2016)
- Nitrofurantoin – do the benefits outweigh the risks long-term? (June 2012)
- Amiodarone pulmonary toxicity – early recognition is vital (December 2013)

References

1. Wijsenbeek M, Suzuki A and Maher TM. 2022. Interstitial lung diseases. *The Lancet* 400(10354): 769-86. DOI: 10.1016/S0140-6736(22)01052-2 (accessed 11 October 2024).
2. Schwaiblmair M, Behr W, Haeckel T, et al. 2012. Drug induced interstitial lung disease. *Open Respiratory Medical Journal* 6: 63-74. DOI: 10.2174/1874306401206010063 (accessed 11 October 2024).

Medicines Monitoring: direct-acting oral anticoagulants and mood changes

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
Direct-acting oral anticoagulants	Mood changes	February 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.

Reminder: risk of hypophosphataemia with iron infusions

Key messages

- Hypophosphataemia is a known adverse reaction of iron infusions, especially ferric carboxymaltose.
- Hypophosphataemia can be severe and prolonged. In some patients, it can cause complications such as osteomalacia and fractures.
- Consider if a patient is at risk of hypophosphataemia when prescribing parenteral iron.

Parenteral iron is used to treat and/or prevent iron deficiency when oral iron preparations are unsuitable or have been unsuccessful.[1] The following parenteral iron preparations are currently approved and funded for use in the community:[2,3]

- ferric carboxymaltose (Ferinject)
- iron polymaltose (Ferrosig).

Parenteral iron use, particularly ferric carboxymaltose, is increasing in New Zealand.[4] This article is a reminder that hypophosphataemia can occur following iron infusions.

Risk of hypophosphataemia

Hypophosphataemia is a known adverse reaction associated with the use of ferric carboxymaltose and iron polymaltose,[5,6] although the risk is highest with ferric carboxymaltose.[7] In clinical trials with ferric carboxymaltose, hypophosphataemia was a common finding on laboratory testing.[5]

Mechanism

The proposed mechanism for treatment-related hypophosphataemia is an increase in fibroblast growth factor-23 (FGF23), which ultimately leads to excessive renal excretion of phosphate and low serum phosphate.[7,8]

Severity

Most cases of treatment-related hypophosphataemia are transient and asymptomatic.[5] However, severe and prolonged hypophosphataemia and complications of hypophosphataemia (such as osteomalacia [softening of the bones] and fractures) can also occur, particularly in patients with risk factors.[5,7,8]

Risk factors

Table 1 lists risk factors for treatment-related hypophosphataemia. Patients requiring repeated iron infusions are most at risk of hypophosphataemia and its related complications.[7]

Table 1: Risk factors for the development of hypophosphataemia with iron infusions

Treatment with ferric carboxymaltose
Recurrent or ongoing blood loss (eg, abnormal uterine bleeding, hereditary haemorrhagic telangiectasia, gastrointestinal bleeding)
Malabsorptive disorders (eg, bariatric surgery, inflammatory bowel disease, coeliac disease)
Normal renal function
Severe iron deficiency
Low body weight
Low baseline serum phosphate
High serum parathyroid hormone (PTH)

Source: Table adapted from Van Doren L, Steinheiser M, Boykin K, et al. 2024. Expert consensus guidelines: Intravenous iron uses, formulations, administration, and management of reactions. *American Journal of Hematology* 99(7): 1338–48. DOI: 10.1002/ajh.27220 (accessed 16 October 2024).

New Zealand case reports

There were 45 case reports of hypophosphataemia following parenteral iron infusions reported during the period 1 January 2016 to 30 September 2024.

Of the 45 reports:

- 39 were in females
- 44 were associated with ferric carboxymaltose
- 40 were serious.

There were no reports of osteomalacia or fracture with these medicines.

Prescribing considerations

When prescribing parenteral iron:[5,7]

- consider the side effect profile of different iron preparations and patient risk factors for hypophosphataemia
- inform patients about the risk of hypophosphataemia and symptoms to look out for (eg, bone pain, arthralgia, fatigue)
- monitor phosphate levels in patients at increased risk of hypophosphataemia or related complications
- re-evaluate treatment if hypophosphataemia occurs.

Further information

- For more information about parental iron preparations, see the data sheet and consumer medicines information (CMI): Search for a data sheet or CMI.
- Refer to local clinical guidelines for the management of hypophosphataemia or iron deficiency.

References

1. New Zealand Formulary (NZF). 2024. NZF v148: Parenteral iron 1 October 2024. URL: nzf.org.nz/nzf_4931 (accessed 31 October 2024).
2. Pharmac. 2024. *Community Schedule* 1 November 2024. URL: schedule.pharmac.govt.nz/ScheduleOnline.php (accessed 30 October 2024).
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8. Schaefer B, Tobiasch M, Wagner S, et al. 2022. Hypophosphatemia after intravenous iron therapy: Comprehensive review of clinical findings and recommendations for management. *Bone* 154: 116202. DOI: 10.1016/j.bone.2021.116202 (accessed 16 October 2024).

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
01/11/2024	Dear Healthcare Professional Letter	Noriday tablets (Norethisterone 0.35mg, 3 x 28 tablet blister pack) – supply of UK pack (PDF, 1 page, 147 KB)
30/10/2024	Dear Healthcare Professional Letter	Safety information for isotretinoin prescribers (PDF, 2 pages, 165 KB)
28/10/2024	Dear Healthcare Professional Letter	Ferinject (ferric carboxymaltose) 50 mg/mL solution for injection - Interim packaging (PDF, 2 pages, 189 KB)
16/10/2024	Monitoring	Update - Calcium channel blockers and the possible risk of new-onset eczema
25/09/2024	Dear Healthcare Professional Letter	Lyllana (estradiol) transdermal patches (PDF, 2 pages, 164 KB)
22/09/2024	Notice	Nitrous oxide advisory
16/09/2024	Dear Healthcare Professional Letter	Versacloz (clozapine) 50mg/mL oral suspension syringe change (PDF, 1 page, 351 KB)

Medicines that make you sweat: drug-induced hyperhidrosis

Key messages

- Drug-induced hyperhidrosis refers to excessive and uncontrollable sweating caused by a medicine.
- Medicines commonly associated with hyperhidrosis include acetylcholinesterase inhibitors, opioids, serotonin and noradrenaline reuptake inhibitors, selective serotonin reuptake inhibitors and tricyclic antidepressants.
- Hyperhidrosis may lead to social embarrassment, decreased self-confidence and emotional distress. Consider lowering the dose or changing the medicine to manage the condition.

Two cases of drug-induced hyperhidrosis were recently reported to the New Zealand Pharmacovigilance database. The suspect medicines were methylphenidate and entacapone (report IDs: 155330 and 153818, respectively). Sweating/hyperhidrosis is a known adverse reaction of these medicines and is listed in the respective data sheets.

This article provides an overview of drug-induced hyperhidrosis, associated medicines and mechanisms.

Drug-induced hyperhidrosis

Hyperhidrosis refers to excessive and uncontrollable sweating.[1] Hyperhidrosis can be classified as primary and of unknown cause (idiopathic), or secondary due to an underlying medical condition, medicines or other causes.[2]

Drug-induced hyperhidrosis is the most common cause of secondary hyperhidrosis. It can affect any part of the body and may be unilateral, asymmetrical or generalised. Untreated hyperhidrosis can lead to skin infections, social embarrassment, decreased self-confidence and emotional distress.[3]

Mechanism

The thermoregulatory pathway maintains body temperature, and involves the hypothalamus, spinal thermoregulatory centres, sympathetic ganglia and the eccrine-neuroeffector junction. Acetylcholine is an important mediator in the regulation of body temperature and sweating. Medicines that act on these pathways and increase acetylcholine transmission may increase sweating.[3,4]

Table 1 provides examples of medicines that can cause hyperhidrosis and the proposed mechanisms.

Table 1: Drug classes/medicines associated with hyperhidrosis and mechanism (list not exhaustive)

Drug class[a,b]	Examples[c]	Mechanism[a,b]
Acetylcholinesterase inhibitors	Galantamine Rivastigmine	Cholinesterase inhibition leading to increased levels of acetylcholine
Opioids	Codeine Fentanyl Morphine Oxycodone Tramadol	Release of histamine and subsequently acetylcholine
Selective serotonin reuptake inhibitors	Citalopram Escitalopram Fluoxetine Paroxetine	Serotonergic effect on hypothalamus or spinal cord
Serotonin and noradrenaline reuptake inhibitors	Venlafaxine	Serotonergic effect on hypothalamus or spinal cord
Tricyclic antidepressants	Amitriptyline Clomipramine Dosulepin Imipramine	Noradrenaline reuptake inhibition and stimulation of peripheral adrenergic receptors.
Medicines that affect endocrine function • Glucocorticoid steroids • Thyroid medicines	Dexamethasone Hydrocortisone Prednisone Levothyroxine	Release of various hormones that influence regulatory feedback loops

Sources:

a. Cheshire WP and Fealey RD. 2008. Drug-induced hyperhidrosis and hypohidrosis: incidence, prevention and management. *Drug Safety* 31(2): 109-26. DOI: 10.2165/00002018-200831020-00002 (accessed 18 September 2024).
b. Ting SO and Oakley A. 2020. Drug-induced hyperhidrosis. In: *DermNet* April 2020. URL: dermnetnz.org/topics/drug-induced-hyperhidrosis (accessed 18 September 2024).
c. Sweating/hyperhidrosis is listed in the data sheets, available at: medsafe.govt.nz/Medicines/infoSearch.asp

Management

If a patient's medicine is suspected to cause hyperhidrosis, consider reducing the dose or changing to an extended-release formulation. Pharmacological and non-pharmacological measures (eg, topical antiperspirants) may help to reduce symptom severity.[3]

If the hyperhidrosis is severe and outweighs the medicine's therapeutic benefit, discontinue the medicine and swap to an alternative medicine less likely to cause sweating.[2,3]

New Zealand case reports

There were 376 cases of hyperhidrosis with medicines (excluding vaccines) reported during the period 1 January 2010 to 30 September 2024. The top five most frequently reported medicines were:

- venlafaxine (49 reports)
- iohexol (13)
- tramadol (12)
- varenicline (9)
- zoledronic acid (9).

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Summary of Shingrix adverse events following immunisation

Key messages

- Shingrix vaccine is used to prevent shingles and post-herpetic neuralgia. It has been the funded shingles vaccine since 1 December 2022.
- Local injection site reactions (inflammation, pain, redness) and general systemic reactions (headache, tiredness, fever) were the main adverse events following immunisation reported with Shingrix.

This article provides a summary of adverse events following immunisation (AEFI) reported with Shingrix to the New Zealand Pharmacovigilance Database from 1 December 2022 to 31 August 2024.

What is Shingrix?

Shingrix is a recombinant varicella zoster vaccine used to prevent shingles (herpes zoster) and post-herpetic neuralgia. Two doses are needed: an initial dose followed by a second dose two to six months later.[1]

Unlike Zostavax, Shingrix is not a live vaccine and may be given to immunocompromised people because there is no risk of shingles from vaccine strains.

Vaccine efficacy (prevention of disease) in clinical trials was more than 90% in healthy people, and slightly lower in immunocompromised people (67–87%).[1] Therefore, some vaccinated people may still get shingles.

On 1 December 2022, Shingrix replaced Zostavax as the funded shingles vaccine for people aged 65 years. Funding was widened on 1 July 2024 to include some immunocompromised people aged 18 years or older.[2]

What is shingles?

Shingles is a blistering and painful rash caused by reactivation of the varicella zoster virus in a person who has previously had varicella disease (usually chickenpox during childhood).[3,4] It occurs when a person's immune response is impaired and unable to suppress the virus.[3]

Shingles is more common in adults, especially older people.[4] The lifetime risk of shingles is about 1 in 3 and increases to 1 in 2 in people aged over 85 years.[3]

A common complication of shingles is post-herpetic neuralgia (PHN), which is chronic skin pain in an area previously affected by shingles. PHN can last for several months or longer and be severe or debilitating.[3,4]

How many doses of Shingrix have been administered?

There were 76,646 doses of Shingrix administered from 1 December 2022 to 31 August 2024. Most (73,391 doses) were administered to patients aged 65 years or older, which is consistent with funding in this age group.

New Zealand case reports

Between 1 December 2022 and 31 August 2024, there were 296 case reports where Shingrix was reported as the suspect medicine. Of these, 106 cases were considered serious by the reporter.

Age was reported for 250 cases, and most people were aged 65 years or older (228 cases; median age for all cases: 65 years).

Most frequently reported AEFI terms

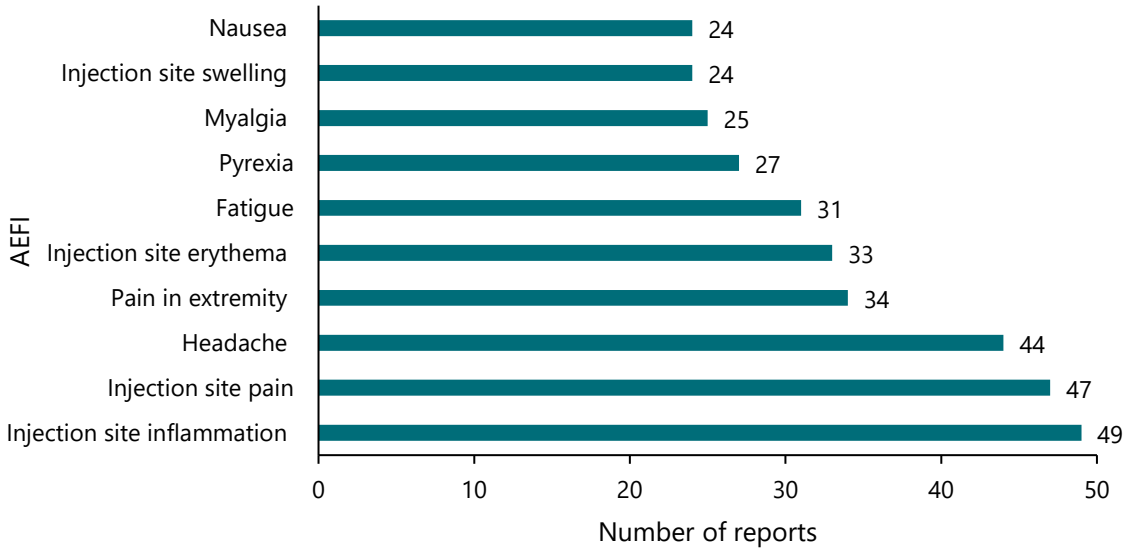
In all 296 cases, the most frequently reported AEFI terms were injection site inflammation, injection site pain, headache, pain in extremity and injection site erythema (Figure 1).

In the 106 serious cases, the most frequently reported AEFI terms were injection site erythema, headache, herpes zoster, vaccination failure and pain in extremity (Figure 2).

There were 17 serious cases reporting both vaccination failure and herpes zoster infection, all of which had very limited information. Seven cases reported a time to onset of vaccination failure that was at least 1 year after Shingrix vaccination. As noted above, no vaccine is 100% effective.

Overall, the majority of the AEFIs reported were local administration site reactions and general systemic reactions that are known to occur with immunisation.

Figure 1: All cases – Ten most frequently reported AEFI terms[a] for Shingrix, 1 December 2022 to 31 August 2024

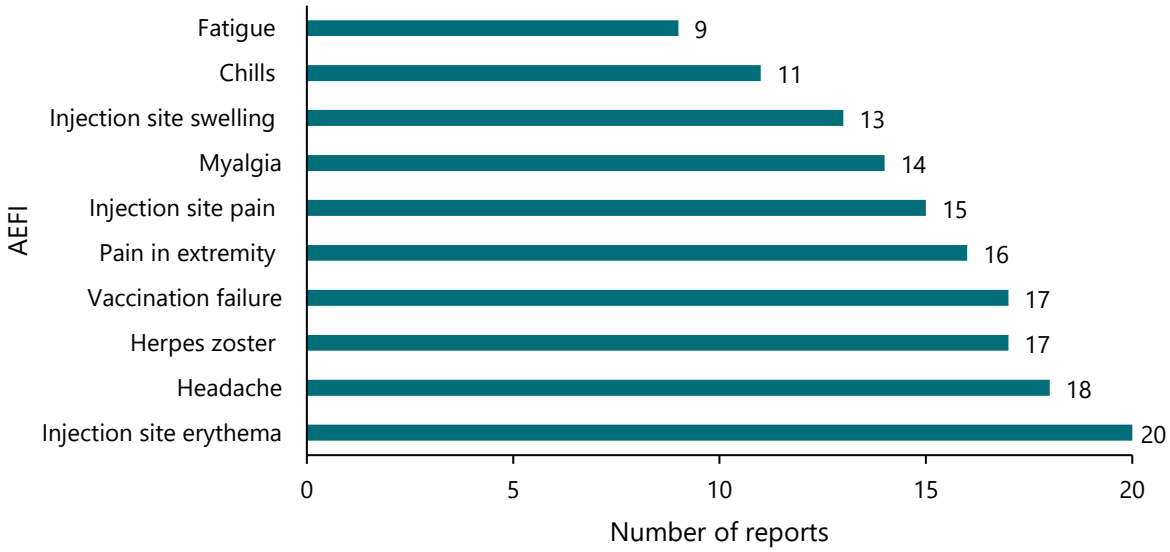


Notes

a. A case may contain more than one AEFI term. Therefore the number of cases does not equal the number of AEFIs.

Source: Suspected adverse reactions reported to the New Zealand Pharmacovigilance Database (accessed 7 October 2024).

Figure 2: Serious cases – Ten most frequently reported AEFI terms[a,b] for Shingrix, 1 December 2022 to 31 August 2024



Notes

a. A case may contain more than one AEFI term. Therefore the number of cases does not equal the number of AEFIs.

b. 17 cases reporting both vaccination failure and herpes zoster infection. The reports had very limited information, which was insufficient for medical assessment.

Source: Suspected adverse reactions reported to the New Zealand Pharmacovigilance Database (accessed 7 October 2024).

Additional information

More information on Shingrix is available from the following links:

- Shingrix data sheet
- Immunisation Advisory Centre: Shingrix
- Healthify: Shingrix vaccine

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Test your knowledge: the *Prescriber Update* quiz 2024

Have you been reading *Prescriber Update* in 2024?

Have you kept up to date with emerging safety signals?

Test your knowledge with the end-of-year *Prescriber Update* quiz.

Answers to the quiz are on page 97 and the Medsafe website.

1. Pseudoephedrine must not be used in patients:
   a. with uncontrolled hypertension or severe coronary artery disease
   b. taking monoamine oxidase inhibitors (MAOIs) or who have taken MAOIs within the previous 14 days
   c. with known hypersensitivity or idiosyncratic reaction to pseudoephedrine and any other ingredients in the medicine
   d. all of the above

2. Drug-induced tendinopathy is most commonly associated with which four classes of medicines?

3. Which of the following statements is false?
   a. Sodium-glucose co-transporter-2 (SGLT-2) inhibitors predispose patients to ketoacidosis by multiple mechanisms that favour ketogenesis and lipolysis.
   b. Some risk factors for ketoacidosis include acute infection, surgery, pancreatic disorders, high carbohydrate diet, heavy alcohol use, severe dehydration.
   c. Monitor ketones and temporarily discontinue SGLT-2 inhibitors in clinical situations known to predispose patients to ketoacidosis.
   d. Patients with ketoacidosis secondary to SGLT-2 inhibitors may have normal blood glucose levels.

4. Approximately what percentage of long-term glucocorticoid users develop secondary osteoporosis?
   a. 30 to 50 percent
   b. 20 to 40 percent
   c. 10 to 20 percent
   d. 5 to 10 percent

5. Antihistamines and leukotriene receptor antagonists are associated with psychiatric side effects. List three other medicine classes (excluding psychotropics) that can cause psychiatric side effects.

6. Topiramate inhibits which enzyme in the kidneys, thereby lowering serum bicarbonate levels?

7. Plasma levels of certain antiepileptic medicines (AEM) may decrease during pregnancy. Which of the following are possible pharmacokinetic mechanisms for the decreases?
   a. altered protein binding, decreased hepatic metabolism, increased renal clearance, increased gastrointestinal absorption
   b. increased gastrointestinal absorption, altered protein binding, enhanced hepatic metabolism, decreased renal clearance
   c. enhanced hepatic metabolism, increased renal clearance, reduced gastrointestinal absorption, altered protein binding
   d. reduced renal clearance, reduced gastrointestinal absorption, altered protein binding, reduced hepatic metabolism

8. True or false: Bioequivalence studies are designed to investigate switchability.

9. A principal histological feature of _____ is the accumulation of phospholipids and the inducing medicine/metabolite in affected cells.

10. The risk of hypophosphataemia with parenteral iron infusions is highest with [iron polymaltose / ferric carboxymaltose].

Bonus question
In which year was the 100th Medicines Adverse Reactions Committee (MARC) meeting held?
   a. 1981
   b. 1999
   c. 2010
   d. 2024

Aciclovir and valaciclovir: toxic in renal impairment

Key messages

- Aciclovir can accumulate in patients with renal impairment. Therefore, a dose adjustment is needed in these patients to reduce the risk of risk of neurotoxicity.
- Monitor patients closely for signs of neurotoxicity, which may include confusion, agitation, hallucinations or seizures.

This article is a reminder about using aciclovir, and its prodrug valaciclovir, in patients with renal impairment.

Aciclovir and valaciclovir

Aciclovir and valaciclovir are antiviral medicines used to prevent and/or treat viral infections, including herpes simplex, varicella zoster and cytomegalovirus (CMV).[1] Aciclovir is available in intravenous (IV) and oral formulations, while valaciclovir is available only in oral form.

Oral aciclovir has low bioavailability. Valaciclovir is a prodrug of aciclovir designed to increase bioavailability. IV aciclovir has the greatest bioavailability and is recommended for treatment of severe infections.[1,2]

Neurotoxicity with renal impairment

Aciclovir is eliminated by renal clearance, involving both glomerular filtration and tubular secretion. Aciclovir can therefore accumulate in patients with renal impairment.[1,3,4]

High blood levels of aciclovir can result neurotoxicity.[1]

Aciclovir readily crosses the blood-brain barrier. In patients with renal impairment, the medicine levels can increase and cause neurotoxicity.[1] Symptoms may include lethargy, confusion, hallucinations, agitation, seizures and coma, and are generally reversible upon discontinuation of treatment.[1,3,4]

Prescribing considerations

Assess the patient's renal function before prescribing aciclovir or valaciclovir. Reduce the dose and/or frequency according to the level of impairment. Refer to the recommendations in the respective data sheets.

- Search for a data sheet

During treatment, ensure adequate hydration and monitor patients for neurological adverse effects.[3,4]

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MARC's remarks: September 2024 meeting

The Medicines Adverse Reaction Committee (MARC) convened for their 199th meeting on 12 September 2024.

The Committee discussed the blood monitoring requirements of **clozapine** to manage the risk of clozapine-induced neutropenia and agranulocytosis. The Committee commented on difficulties the blood monitoring can cause, and wondered if they are a barrier to clozapine use. The Committee agreed that further expert advice was needed before proposing any changes to monitoring.

The Committee reviewed the recent study by Meng et al,[1] showing an association between **benzodiazepines** and the risk of miscarriage. They considered the findings from this study to be sufficient to require action. The Committee recommended updates to the relevant data sheets to include information on the risk of miscarriage when used in pregnancy and to communicate risks to women who are planning pregnancy.

The Committee discussed the risk of pyoderma gangrenosum (PG) from **anti-CD20 antibodies (rituximab, obinutuzumab, ocrelizumab and ofatumumab)**. They considered that the current evidence of an association between anti-C20 antibodies and PG is weak given the small number of cases reported and confounding by underlying autoimmune disease. The Committee recommended that Medsafe issue a monitoring communication to gather more information on a possible association.

Medsafe presented a summary of New Zealand case reports of ketoacidosis with **empagliflozin**. The Committee noted Medsafe's ongoing efforts to raise awareness of this adverse reaction. See also the article about risk factors for ketoacidosis with SGLT-2 inhibitors on page 73 of this edition of *Prescriber Update*.

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

Reference

1. Meng L-C, Lin C-W, Chuang H-M, et al. 2024. Benzodiazepine use during pregnancy and risk of miscarriage. *JAMA Psychiatry* 81(4): 366–73. DOI: 10.1001/jamapsychiatry.2023.4912.

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 19 July 2024 to 17 October 2024.

Table 1: Recent approvals of medicines with new active ingredients

Medicine	New active ingredient	Dose form: strength(s)	Therapeutic area
Jynneos[a]	Vaccinia vaccine	Suspension for injection: 0.5mL	Prevention of mpox disease in adults
Topamine[a]	Silver diamine fluoride	Topical solution: 38%	Dental caries, dentinal hypersensitivity

a. Provisional consent

New indications

Table 2 shows approved medicines with new indications for additional therapeutic areas gazetted during the period 19 July 2024 to 17 October 2024.

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

Medicine (active ingredient)	Dose form: strength(s)	New therapeutic area
Fasenra (benralizumab)	Solution for injection in prefilled syringe or pen: 30mg/mL	Eosinophilic granulomatosis with polyangiitis (EGPA) – adult patients
Vabysmo (faricimab)	Solution for intravitreal injection: 120mg/mL	Macular oedema secondary to retinal vein occlusion (RVO)
Nubeqa (darolutamide)	Film coated tablet: 300 mg	Metastatic hormone sensitive prostate cancer (mHSPC)
Enhertu (trastuzumab deruxtecan)	Powder for infusion: 100mg	HER2-low breast cancer
Keytruda (pembrolizumab)	Concentrate for infusion: 25mg/mL	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.

Gathering knowledge from adverse reaction reports: December 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 reported to the New Zealand Pharmacovigilance Database.

Case details[a,b]	Reaction description and data sheet information[b,c]
Report ID: 155224 **Age:** 54 years **Gender:** Female **Medicine(s):** Promethazine **Reaction(s):** Restless legs syndrome, dyskinesia	About an hour or so after taking a dose of promethazine, the patient developed extreme restless legs and involuntary jerky movements.
	Restlessness and extrapyramidal symptoms are listed in the Allersoothe data sheet.
Report ID: 155264 **Age:** Not reported **Gender:** Female **Medicine(s):** Liraglutide **Reaction(s):** Pancreatitis	The person developed pancreatitis after starting liraglutide.
	There is a warning about acute pancreatitis in the Victoza data sheet. Prescribers should inform patients about the characteristic symptoms of pancreatitis. If suspected, liraglutide should be discontinued. If pancreatitis is confirmed, liraglutide should not be restarted.
Report ID: 156555 **Age:** 13 years **Gender:** Male **Medicine(s):** Sumatriptan **Reaction(s):** Angioedema, oropharyngeal discomfort, pruritus	A patient with a history of hypersensitivity to sulfamethoxazole + trimethoprim developed facial angioedema, pruritis and oropharyngeal discomfort within 30 minutes of taking sumatriptan.
	The Sumagran data sheet states that patients with known hypersensitivity to sulphonamides may exhibit an allergic reaction following administration of sumatriptan. Evidence of cross sensitivity is limited; however, prescribers should exercise caution before using sumatriptan in these patients. Sumatriptan should not be used in children as the safety and effectiveness has not been established.

Continues

Case details[a,b]	Reaction description and data sheet information[b,c]
Report ID: 157552 **Age:** 57 years **Gender:** Female **Medicine(s):** Sertraline **Reaction(s):** Microscopic colitis	Some weeks after starting oral sertraline, the patient developed symptoms of microscopic colitis with frequent loose bowel motions, urgency and some cramping abdominal pains. Biopsy confirmed microscopic lymphocytic colitis and sertraline was withdrawn.
	Microscopic colitis is listed in the Setrona data sheet. See also the December 2022 *Prescriber Update* article, Microscopic colitis - could it be caused by a medicine?
Report ID: 157692 **Age:** Not reported **Gender:** Female **Medicine(s):** Misoprostol **Reaction(s):** Bronchospasm	Within 2 hours of taking misoprostol, the asthmatic patient developed severe bronchospasm.
	The Cytotec data sheet states that bronchospasm may occur with some prostaglandins and prostaglandin analogues. This should be considered in patients with a history of asthma.
Report ID: 158113 **Age:** 55 years **Gender:** Female **Medicine(s):** Ropinirole **Reaction(s):** Impulse control disorder	During treatment with ropinirole, the patient experienced impulse control disorder, with symptoms of overeating, overspending and heightened, unwanted sexual arousal.
	The Ropin data sheet states that patients should be regularly monitored for the development of impulse control disorders. Inform patients and carers of the symptoms, including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating. Consider dose reduction/tapered discontinuation if such symptoms develop.

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).

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
Amoxicillin + clavulanic acid • Augmentin	4.8	Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE)[b]
Baclofen • Lioresal Intrathecal	4.4	Withdrawal effects: tachycardia
	4.8	Hypersensitivity
	4.9	Overdose symptoms: tachycardia, tinnitus
Bumetanide • Burinex	4.4, 4.8	Toxic epidermal necrolysis (TEN) and Stevens Johnson Syndrome (SJS)
Busulfan • Myleran	4.2	Should only be used and administered by specialist clinicians experienced in cancer chemotherapy
Cefalexin • Cefalexin Sandoz	4.8	SDRIFE[b]
Clarithromycin • Klacid	4.5	Interactions with hydroxychloroquine/chloroquine, corticosteroids, ivabradine
Eptifibatide • Eptifibatide Viatris	4.3	Do not use to treat patients with concomitant or planned administration of a thrombolytic agent (high risk of bleeding)
Flucloxacillin • Flucil	4.5	Interactions with methotrexate, warfarin, posaconazole and voriconazole
	4.8	SDRIFE[b]
Gadobutrol • Gadovist	4.8	Acute respiratory distress syndrome (ARDS); Pulmonary oedema
Glofitamab • Columvi	4.2, 4.4, 4.7, 4.8	Immune effector cell-associated neurotoxicity syndrome (ICANS)
Hydroxychloroquine • Plaquenil	4.4	Reactivation of infections: herpes zoster, tuberculosis, hepatitis B
Infliximab • Remicade	4.2	Consider delaying treatment if the patient has a planned surgical procedure
	4.8	Post-procedural complications (infectious and non-infectious); Paradoxical drug-induced immune disorder (eg, new onset psoriasis)
Lamotrigine • Lamictal	4.2, 4.4, 4.5	Interaction with oestrogen-containing therapies, including hormone replacement therapies
	4.8	Pseudolymphoma

Continues

Active ingredient(s) • Medicine(s)	Data sheet updates Section[a]	 Summary of new safety information
Lidocaine • Xylocaine	4.4	Kounis syndrome
Lithium • Lithium carbonate • Priadel	4.3	Contraindicated in Brugada syndrome or family history of Brugada syndrome
	4.4	Bariatric surgery: dose reductions and monitoring; Brugada syndrome: unmasking or aggravation; QT prolongation: avoid in patients with congenital long QT syndrome, use with caution in patients with risk factors or concomitant use with medicines that prolong the QT interval
	4.8	Brugada syndrome; Drug reaction with eosinophilia and systemic symptoms (DRESS); Cardiomyopathy; Cutaneous ulcers; Lichenoid drug reactions; Parathyroid adenoma; Parathyroid hyperplasia; Myoclonus; Encephalopathy; Peripheral neuropathy; Delirium; Rhabdomyolysis; Nephrotic syndrome
Morphine sulfate • Sevredol	4.4, 4.8	Acute generalised exanthematous pustulosis (AGEP)
Nirmatrelvir + ritonavir • Paxlovid	4.6	Discontinue breastfeeding during treatment and for 48 hours after completing treatment
Remdesivir • Veklury	4.2	Removal of renal testing requirement; No dose adjustment in renal or hepatic impairment
	4.6	Pregnancy: do not use during first trimester, use in second or third trimesters only if benefits outweigh risks.
Ropivacaine + fentanyl • Naropin with Fentanyl	4.4	Horner's syndrome
	4.6	Foetal bradycardia
	4.8	Anaphylactic shock
Valaciclovir • Vaclovir	4.8	Headache; Aggressive behaviour; Delirium
Valproic acid (sodium valproate) • Epilim	4.8	Hyperpigmentation
Venetoclax • Venclexta	4.2, 4.8, 5.1	New dose regimen and safety information for Venclexta in combination with ibrutinib
Vortioxetine • Brintellix	4.4	Sexual dysfunction

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; 4.7: Effects on ability to drive and use machines; 4.8: Undesirable effects; 4.9: Overdose; 5.1: Pharmacodynamic properties.

b. See the December 2023 *Prescriber Update* article about SDRIFE.

Quiz answers

1. d. Pseudoephedrine must not be used in patients with uncontrolled hypertension or severe coronary artery disease, taking monoamine oxidase inhibitors (MAOIs) or who have taken MAOIs within the previous 14 days, or with known hypersensitivity or idiosyncratic reaction to pseudoephedrine and any other ingredients in the medicine. (June 2024)
2. Drug-induced tendinopathy is most commonly associated with fluoroquinolones, long-term glucocorticoids, statins and aromatase inhibitors. (September 2024)
3. b. Acute infection, surgery, pancreatic disorders, heavy alcohol use and severe dehydration are true risk factors for ketoacidosis, but a high carbohydrate diet is false. A low carbohydrate diet is a risk factor for ketoacidosis. (December 2024)
4. a. Approximately 30 to 50 percent of long-term glucocorticoid users develop secondary osteoporosis. (June 2024)
5. Along with antihistamines and leukotriene receptor antagonists, medicine classes that can cause psychiatric side effects include: ACE inhibitors, antivirals, antibiotics, anticholinergics, beta-blockers, calcium channel blockers, cardiac glucosides, combined oral contraceptives, corticosteroids, proton pump inhibitors, other (isotretinoin, tacrolimus). (March 2024)
6. Topiramate inhibits carbonic anhydrase in the kidneys, affecting bicarbonate reabsorption. (September 2024)
7. c. Possible pharmacokinetic mechanisms for decreases in plasma AEM levels in pregnancy are enhanced hepatic metabolism, increased renal clearance, reduced gastrointestinal absorption, altered protein binding. (March 2024)
8. False. Bioequivalence studies are not designed to investigate patients' suitability to change from one brand to another during their treatment ('switchability'). (June 2024)
9. A principal histological feature of drug-induced phospholipidosis is the accumulation of phospholipids and the inducing medicine/metabolite in affected cells. (March 2024)
10. The risk of hypophosphataemia with parenteral iron infusions is highest with ferric carboxymaltose. (December 2024)

Bonus question

b. The 100th MARC meeting was held on 25 November 1999. (December 2024)

Medsafe

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