Prescriber Update

Vol. 45 No. 3 September 2024

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

Contents

MEDSAFE
New Zealand Medicines and Medical Devices Safety Authority

Te Kāwanatanga o Aotearoa
New Zealand Government

MANATŪ HAUORA
MINISTRY OF HEALTH

Drug-induced tendinopathy

Key messages

- Fluoroquinolones, long-term glucocorticoids, statins and aromatase inhibitors are the most common medicine classes associated with tendinopathy.
- Progressive tendon degeneration without inflammation is a typical sign of drug-induced tendinopathy.
- Although the Achilles tendon is most commonly affected, drug-induced tendinopathy can occur in any tendon.

Tendonitis and tendon rupture have recently been associated with aromatase inhibitors, along with tenosynovitis. This article reviews tendon disorders with the most common classes of medicines.

Terminology of tendon disorders

Tendon disorders include tendonitis (tendon inflammation), tendon rupture (tendon tears) and tenosynovitis (inflammation of the tendon sheath).[1] The term tendonitis is often used to describe a broad range of tendon conditions. However, where inflammation is minimal or absent, tendinopathy may be more accurate.[2]

Inside a tendon

Tenoblasts and tenocytes make up 90% of cells in the tendon.[2] Together, they generate collagen and elastin fibres, as well as extracellular matrix components.[2] Chondrocytes make up the remaining 10% of tendon cells and these are found at entheses (tendon-bone junctions).[3]

Classic drug-induced tendinopathy shows signs of progressive tendon degeneration without inflammation.[3]

Medicines associated with tendinopathy

Drug-induced tendinopathy is most commonly associated with fluoroquinolones, long-term treatment with glucocorticoids, statins and aromatase inhibitors.[3] Table 1 summarises characteristics of drug-induced tendinopathy with these medicine classes.

Fluoroquinolones

Tendinopathy can occur with any fluoroquinolone (eg, ciprofloxacin, moxifloxacin, norfloxacin) and at any dose and route of administration.[3] It is usually an acute event occurring as early as within 48 hours but has been reported to occur up to several months after discontinuation of treatment.[4–6] Tendinopathy with fluoroquinolones may be prolonged, disabling and irreversible.[4–6]

Discontinue fluoroquinolone treatment at the first sign of tendonitis (eg, pain, swelling, inflammation) and use alternative treatment.[4–6] Advise patients to rest the affected limb and avoid inappropriate physical exercise.[5]

Long-term glucocorticoids

Tendinopathy usually occurs after at least three months of treatment with an oral or inhaled glucocorticoid.[3] Patients with autoimmune connective tissue disorders (eg, rheumatoid arthritis, systemic lupus erythematosus) treated with long-term oral glucocorticoids are particularly at risk.[2,3]

Statins[3]

Statin-induced tendinopathy can occur at any dose and about 8 to 10 months after exposure. Discontinue statin treatment if tendinopathy is suspected. Tendinopathy may recur if statin treatment is restarted.

Aromatase inhibitors

Tenosynovitis, particularly of the hands and wrists, has been linked with aromatase inhibitors (eg, anastrozole, letrozole, exemestane).[3] The onset time is reported to range from 2 weeks to 19 months.[2] More recently, cases of tendonitis and tendon rupture have also been reported in association with aromatase inhibitors.[1]

Closely monitor patients with tendon disorders and initiate appropriate measures such as immobilisation of the affected limb.[7,8]

Medsafe has requested the data sheets for aromatase inhibitors be updated to include more information on tendon disorders.

Table 1: Characteristics of drug-induced tendinopathy associated with the four main medicine classes

Medicine class	Route and dose	Time to onset	Type and site
Fluoroquinolones[a,b]	any	within 48 hours	Achilles tendon in 90% of cases, of which 40% of cases lead to tendon rupture
Glucocorticoids[b]	oral, inhaled	≥3 months	Achilles tendon and other large lower limb tendons, leading to rupture several years after starting a glucocorticoid
Statins[b]	any dose	8-10 months	Achilles tendon in just over 50% of cases, of which, one-third result in tendon rupture
Aromatase inhibitors[b–d]	unknown	2 weeks to 19 months	Tenosynovitis of the hands and wrists, tendonitis, tendon rupture (rare)

Sources:

a. Medicine data sheets, available at: www.medsafe.govt.nz/Medicines/infoSearch.asp
b. Bolon B. 2017. Mini-review: Toxic tendinopathy. *Toxicology Pathology* 45(7): 834-7. DOI: 10.1177/0192623317711614 (accessed 18 June 2024).
c. Health Canada. 2023. *Summary Safety Review – Third Generation Aromatase Inhibitors (anastrozole, exemestane, letrozole) – Assessing the Potential Risk of Tendon Disorders* 17 January 2023. URL: dhpp.hpfb-dgpsa.ca/review-documents/resource/SSR00289 (accessed 18 June 2024).
d. Kirchgesner T, et al. 2014. Drug-induced tendinopathy: From physiology to clinical applications. *Joint Bone Spine* 81(6): 485-92. DOI: https://doi.org/10.1016/j.jbspin.2014.03.022 (accessed 18 June 2024).

Other

Drug-induced tendinopathy has also been reported after exposure to several other medicines, but the evidence is less consistent.[2] These include anabolic steroids, isotretinoin and antiretroviral agents (especially protease inhibitors).[3]

Risk factors

Risk factors for drug-induced tendinopathy include:[3]

- advanced age (because of deterioration in tenocytes)
- obesity and physical exertion (because of high loads and sudden shifts in axial stress)
- pre-existing disease such as autoimmune connective tissue disorders and renal failure
- treatment with two or more medicines known to induce tendinopathy.

New Zealand case reports

From 1 January 2014 to 30 June 2024, Medsafe and the Centre for Adverse Reactions Monitoring (CARM) received 103 case reports of tendon disorders with medicines (excluding vaccines). The top four suspect medicines in these reports were ciprofloxacin (n=73), norfloxacin (n=9), zoledronic acid (n=5) and prednisone (n=3).

In these 103 cases, the median age was 65 years and the median time to onset was nine days (range 1 day to 561 days).

Further information

- Third generation aromatase inhibitors and tendon disorders: meeting minutes and report (Medicines Adverse Reactions Committee, 7 December 2023 meeting).
- Reports of persisting serious adverse reactions to fluoroquinolones (*Prescriber Update*, September 2023).

References

1. Health Canada. 2023. *Summary Safety Review – Third Generation Aromatase Inhibitors (anastrozole, exemestane, letrozole) – Assessing the Potential Risk of Tendon Disorders* 17 January 2023. URL: dhpp.hpfb-dgpsa.ca/review-documents/resource/SSR00289 (accessed 18 June 2024).
2. Kirchgesner T, et al. 2014. Drug-induced tendinopathy: From physiology to clinical applications. *Joint Bone Spine* 81(6): 485-92. DOI: https://doi.org/10.1016/j.jbspin.2014.03.022 (accessed 18 June 2024).
3. Bolon B. 2017. Mini-review: Toxic tendinopathy. *Toxicology Pathology* 45(7): 834-7. DOI: 10.1177/0192623317711614 (accessed 18 June 2024).
4. Viatris Ltd. 2022. *Cipflox New Zealand Data Sheet* 16 June 2022. URL: www.medsafe.govt.nz/profs/Datasheet/c/Cipfloxtabinf.pdf (accessed 10 July 2024).
5. Bayer New Zealand Limited. 2021. *Avelox New Zealand Data Sheet* 14 October 2021. URL: www.medsafe.govt.nz/profs/Datasheet/a/AveloxtablVinf.pdf (accessed 10 July 2024).
6. Teva Pharma (New Zealand) Limited. 2020. *Arrow – Norfloxacin New Zealand Data Sheet* 9 November 2020. URL: www.medsafe.govt.nz/profs/Datasheet/a/ArrowNorfloxacintab.pdf (accessed 10 July 2024).
7. Douglas Pharmaceutical Ltd. 2024. *Letara New Zealand Data Sheet* 19 February 2024. URL: www.medsafe.govt.nz/profs/Datasheet/l/Letaratab.pdf (accessed 16 July 2024).
8. Viatris Ltd. 2024. *Letrole New Zealand Data Sheet* 15 January 2024. URL: www.medsafe.govt.nz/profs/Datasheet/l/letroletab.pdf (accessed 16 July 2024).

Medicines Monitoring: Direct-acting oral anticoagulants; Calcium channel blockers

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
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.

MARC's remarks: June 2024 meeting

The Medicines Adverse Reaction Committee (MARC) convened for their 198th meeting on 13 June 2024.

The Committee discussed the risk of symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) with **systemic antibiotics** and **systemic antifungals**. They noted that SDRIFE is associated with many medicines, particularly beta lactam antibiotics and antifungals, and SDRIFE is listed as an adverse reaction in the amoxicillin + clavulanic acid data sheets. The Committee commented that SDRIFE is usually self-limiting and the sequelae are rare, and acknowledged the recent Prescriber Update article about SDRIFE (December 2023). They agreed that the skin reaction warnings in the medicine data sheets are adequate, and no further actions are needed.

The Committee noted a Medsafe review of **Bexsero** vaccine adverse reaction reports and agreed with Medsafe's conclusion that these reports do not raise any new safety concerns. The Committee also acknowledged the *Prescriber Update* article: Summary of Bexsero adverse events following immunisation (June 2024), which was based on this review.

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

Reminder: angiotensin converting enzyme inhibitors and angiotensin receptor blockers are contraindicated in pregnancy

Key messages

- Angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) are contraindicated in pregnancy. Use of these medicines in pregnancy is associated with fetal and neonatal toxicity.
- If a patient is planning pregnancy or becomes pregnant, discontinue the ACEi/ARB and swap to an alternative antihypertensive medicine.

Background

The Centre for Adverse Reactions Monitoring (CARM) received a suspected adverse reaction report for losartan and empagliflozin (co-suspect medicines) in a fetus exposed to these medicines *in utero* (report ID 145301). The reported reactions were fetal distress syndrome, fetal disorder and Potter's syndrome (a rare condition associated with decreased amniotic fluid and kidney failure in the fetus[1]). There is limited data on the safety of empagliflozin during pregnancy. For information on management of diabetes during pregnancy refer to local clinical guidelines.

This article is a reminder that ACEi/ARBs are contraindicated in pregnancy.

Hypertension in pregnancy

Uncontrolled hypertension in pregnancy may progress to pre-eclampsia and has been linked to adverse maternal and fetal outcomes.[2,3]

Antihypertensives are recommended in all pregnant people with severe hypertension to acutely lower blood pressure. They should also be considered in pregnant people with gestational hypertension, especially with other risk factors for pre-eclampsia and/or co-morbidities.[2]

Risks associated with ACEi and ARBs

ACEi (enalpril, lisinopril, perindopril, quinapril, ramipril) and ARBs (candesartan, losartan) are first-line treatments for hypertension in adults. However, they are contraindicated in pregnancy.[3,4]

Use of these medicines in pregnancy has been associated with fetal and neonatal toxicity, including skull defects, oligohydramnios (decreased amniotic fluid volume), hypotension, hyperkalaemia, renal failure and fetal death.[3,5]

When prescribing ACEi and ARBs to patients of childbearing potential

- Exclude pregnancy prior to treatment initiation and ask the patient if they are planning to become pregnant.
- Inform patients that ACEi/ARBs may be harmful to the baby if taken during pregnancy, and to seek medical advice if they become pregnant.
- If your patient is planning to become pregnant, consider switching them to an alternative antihypertensive before conception.

- If a patient becomes pregnant during ACEi/ARB treatment, discontinue the medicine and replace it with another antihypertensive if clinically indicated.

Further information

For information about the management of hypertension in pregnancy, refer to local clinical guidelines.

The following links provide additional information about hypertension and medicines.

- Te Whatu Ora - Health New Zealand: Diagnosis and Treatment of Hypertension and Pre-eclampsia in Pregnancy in Aotearoa New Zealand
- bpac^{NZ}: Hypertension in adults: the silent killer
- Medsafe: Data sheets and Consumer Medicines Information search

References

1. Kaneshiro NK, Dugdale DC and Conaway B. 2023. Potter syndrome. In: *Mount Sinai Health Library* URL: www.mountsinai.org/health-library/diseases-conditions/potter-syndrome (accessed 26 July 2024).
2. Te Whatu Ora – Health New Zealand. 2022. *Diagnosis and Treatment of Hypertension and Pre-eclampsia in Pregnancy in Aotearoa New Zealand* October 2022. URL: www.tewhatuora.govt.nz/assets/Publications/Evidence-Statements-Hypertension-and-Pre-Eclampsia.pdf (accessed 5 July 2024).
3. New Zealand Formulary (NZF). 2024. NZF v.145: *Drugs affecting the renin-angiotensin system* 1 July 2024. URL: nzf.org.nz/nzf_1240 (accessed 5 July 2024).
4. bpac^{NZ}. 2024. *Hypertension in adults: the silent killer* 23 May 2024. URL: bpac.org.nz/2023/hypertension.aspx (accessed 5 July 2024).
5. Servier Laboratories Ltd. 2023. *Coversyl New Zealand Data Sheet* 16 February 2023. URL: www.medsafe.govt.nz/profs/Datasheet/c/Coversyltab.pdf (accessed 5 July 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
02/09/2024	Dear Healthcare Professional Letter	Copaxone (Glatiramer acetate) 20 mg/mL and 40 mg/mL – Long term anaphylactic reactions (PDF, 3 pages, 406 KB)
22/08/2024	Consultation	Proposed updates to the Guideline on the Regulation of Therapeutic Products in New Zealand: Clinical Trials
8/08/2024	Monitoring	M² Direct-acting oral anticoagulants and potential for patients to experience mood changes
09/07/2024	Monitoring	M² Update - DPP-4 inhibitors and the possible risk of ileus
22/05/2024	Dear Healthcare Professional Letter	ClopineCENTRAL - update related to recent migration to ClopineCENTRAL 2.0 (PDF, 2 pages, 442 KB)

Acid-base imbalances with medicines: hyperchloremic acidosis

Key messages

- Hyperchloremic acidosis is a type of metabolic acidosis associated with a normal anion gap.
- Some medicines can affect the mechanisms of acid-base homeostasis in the kidneys, which may lead to hyperchloremic acidosis.

The Centre for Adverse Reactions Monitoring (CARM) and Medsafe recently received a report of hyperchloremic acidosis with topiramate. The person had been taking topiramate for a number of years before the reaction occurred (report ID 155109).

This article is a reminder about hyperchloremic acidosis with topiramate, plus other medicines that may cause this side effect.

Background

Metabolic acidosis occurs when either an increase in the production of acids or a loss of bicarbonate from the body overwhelms the mechanisms of acid-base homeostasis, or when renal acidification mechanisms are compromised.[1]

Metabolic acidosis is further classified into two groups based on the presence of unmeasured anions (anion gap).[1]

- **High anion gap metabolic acidosis** is associated with acid accumulation from increased acid production or acid ingestion. Causes include lactic acidosis, ketoacidosis and renal failure.[1]
- **Normal anion gap metabolic acidosis** (also called hyperchloremic acidosis) is associated with bicarbonate loss from the gastrointestinal tract or impaired excretion of hydrogen ions or bicarbonate absorption from the kidneys (renal tubular acidosis). Causes include diarrhoea and adrenal insufficiency.[1]

As well as physiological processes, medicines can impact the acid-base balance in the body and may contribute to metabolic acidosis by different mechanisms.[1]

Topiramate lowers serum bicarbonate levels

Topiramate may cause a renal tubular, hyperchloremic acidosis in some individuals due to inhibition of carbonic anhydrase in the kidneys, affecting bicarbonate reabsorption.[2]

A decrease in serum bicarbonate level usually occurs early in treatment but may happen any time during treatment. Decreases are usually mild to moderate. However, decreases in serum bicarbonate to levels below 10 mmol/L have been reported[2] (the adult reference range[3] is 22–29 mmol/L).

The topiramate data sheets recommend monitoring serum bicarbonate levels during topiramate treatment. Consider more frequent monitoring if people have underlying conditions that predispose them to metabolic acidosis (eg, diarrhoea, renal failure). If metabolic acidosis develops and persists, consider reducing the dose or discontinuing topiramate (using dose tapering).[2]

Chronic, untreated metabolic acidosis may increase the risk of nephrolithiasis (renal stone formation) or nephrocalcinosis (calcium deposits in the kidney) and reduce growth rates in children.[2]

Refer to the data sheets for further information.

Other medicines

Several other medicines have been reported to contribute to hyperchloremic acidosis due to direct or indirect effects on the reabsorption of bicarbonate or excretion of hydrogen in the kidneys.[1,4]

Examples include:

- other carbonic anhydrase inhibitors, such as acetazolamide and zonisamide[1,2]
- renin-angiotensin-aldosterone system inhibitors, such as angiotensin-converting enzyme inhibitors and aldosterone receptor blockers.[4]

References

1. Kraut JA, Madias NE. 2010. Metabolic acidosis: pathophysiology, diagnosis and management. *Nature Reviews Nephrology* 6(5): 274–85. DOI: 10.1038/nrneph.2010.33 (accessed 12 July 2024).
2. Janssen-Cilag (New Zealand) Ltd (2023). *Topamax New Zealand Data Sheet* 23 March 2023. URL: www.medsafe.govt.nz/profs/Datasheet/t/topamaxtabcap.pdf (acessed 24 July 2024).
3. Health New Zealand | Te Whatu Ora. 2023. *Laboratory Test Reference Guide: Bicarbonate*. URL: lab.waikatodhb.health.nz/test-guide/view/105/bicarbonate (accessed 26 July 2024).
4. Pham AQ, Xu LH, Moe OW. 2015. Drug-induced metabolic acidosis. *F1000Research* 4(F1000 Faculty Rev): 1460. DOI: 10.12688/f1000research.7006.1 (accessed 12 July 2024).

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 April 2024 to 18 July 2024.

Table 1: Recent approvals of medicines with new active ingredients

Medicine	New active ingredient	Dose form: strength(s)	Therapeutic area
Aquipta	Atogepant	Tablet: 10mg, 60mg	Migraine
Halaven	Eribulin	Solution for injection: 1mg/2mL	Breast cancer (locally advanced or metastatic) Liposarcoma (unresectable)
Sarclisa	Isatuximab	Concentrate for injection: 100mg/5mL, 500mg/25mL	Multiple myeloma
Tezspire	Tezepelumab	Solution for injection in pre-filled syringe or pen: 210mg	Asthma (severe)

New indications

There were no approved medicines with new indications for additional therapeutic areas gazetted during the period 19 April 2024 to 18 July 2024.

More information

See the Medsafe website for:

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

Medicines and food: interacting combinations

Key messages

- Certain foods may alter the pharmacokinetics and/or pharmacodynamics of a medicine. This interaction may be clinically relevant, resulting in decreased effectiveness of the medicine or increased risk of adverse reactions to the medicine.
- Consider potential food–medicine interactions when starting new medicines and counsel patients accordingly.
- Refer to the medicine data sheet and relevant interaction checkers for information on potential food-medicine interactions and applicable management.

This article highlights some foods and food groups that have the potential to interact with medicines. It is not a comprehensive list.

Pharmacokinetic interactions between medicines and foods

Some foods may affect the absorption, distribution, metabolism or excretion of a medicine.[1]

Fruit and fruit products

Fruit and their products contain diverse chemical compounds, some of which affect the metabolism and elimination of orally administered medicines. For example, naringin (a flavonoid) and bergamottin and 6′,7′-dihydroxybergamottin (furanocoumarins) inhibit the cytochrome P450 isoenzyme, CYP3A4.

Other chemical compounds in fruit inhibit organic anion-transporting polypeptides (membrane transporter proteins) and P-glycoprotein (efflux transporter).[2]

Grapefruit juice inhibits intestinal CYP3A4, and so is expected to increase the exposure of medicines metabolised by this enzyme, such as statins and calcium channel blockers.[2] An interaction with grapefruit juice is particularly relevant for medicines that have a narrow therapeutic index (eg, ciclosporin) or with poor oral bioavailability (eg, felodipine).[1]

Other fruits reported to interact with some medicines include orange, pomelo and cranberry.[2]

Food rich in divalent ions

Food rich in divalent ions (eg, calcium and magnesium), such as milk, cheese and yoghurt, may form chelate complexes with certain medicines. These complexes may then decrease the absorption and bioavailability of the medicine.[3]

Because they form these chelate complexes, fluoroquinolones (eg, oral ciprofloxacin) should not be taken concurrently with dairy products or mineral fortified drinks (eg, milk, yoghurt, calcium fortified orange juice). However, if these products are ingredients of meal, they will not significantly affect ciprofloxacin absorption.[4]

Dairy products may also affect oral iron[5] and tetracycline[3] absorption.

Pharmacodynamic interactions between medicines and food

Consuming certain foods may have an additive, synergistic or antagonistic effect with a medicine.[3]

Food rich in tyramine

Some foods are high in tyramine, such as mature cheese, pickled herring, broad bean pods, meat extracts (eg, Bovril) and yeast extract (eg, Marmite and Vegemite).

Tyramine is a trace monoamine with sympathomimetic properties. In comparison to the monoamine neurotransmitters (noradrenaline, adrenaline, dopamine and serotonin), tyramine levels are relatively low in the body. However, ingestion of dietary tyramine can displace the monoamine neurotransmitters, particularly noradrenaline, from pre-synaptic storage vesicles, releasing them into the circulation. Increased noradrenaline causes vasoconstriction, increased heart rate and a rise in blood pressure.[6]

The monoamine oxidase (MAO) enzyme metabolises monoamines. In normal circumstances, the A form of this enzyme (MAO-A) metabolises circulating noradrenaline so that it does not accumulate to dangerous levels. MAO-A also metabolises tyramine before it can release noradrenaline into the circulation. However, MAO inhibitor (MAOI) medicines significantly reduce the body's capacity to metabolise tyramine. Patients taking MAOIs who eat a high-tyramine meal may be at risk of hypertensive crisis (severely elevated blood pressure).[7]

Irreversible and non-selective MAOIs, such as tranylcypromine, have the greatest risk of serious interactions, and patients taking these medicines should completely avoid tyramine-rich food.[8] In contrast, patients taking reversible MAOIs, such as moclobemide or linezolid, should avoid consuming large amounts of tyramine-rich food.[9,10]

Diet rich in Vitamin K

Vitamin K-rich food includes broccoli, brussels sprouts, green leafy vegetables and liver.

Warfarin blocks production of vitamin K-dependent blood clotting factors to produce an anticoagulant effect. Sudden changes in diet that significantly increase or decrease the intake of Vitamin K-rich foods may affect control of anticoagulation. Inform patients taking warfarin to seek medical advice making any major changes to their diet.[11]

Further information

For information on potential food–medicine interactions and their management (eg, avoiding concurrent use or separating intake), refer to:

- section 4.5 of the medicine data sheets
- the New Zealand Formulary interaction checker (based on Stockley's Interaction Alerts).

See also previous *Prescriber Update* articles on food and medicine interactions.

- Can I have a drink with that? (alcohol)
- Liquorice – All sorts of side effects and interactions (liquorice)
- Fruit interactions with common medicines (fruit and fruit products)
- Warfarin: eat, drink and be wary (interactions with warfarin)

Refer patients to the Medicines and diet section of Healthify for more information.

References

1. Petric Z, Žuntar I, Putnik P, et al. 2020. Food-drug interactions with fruit juices. *Foods* 10(1): 33. DOI: 10.3390/foods10010033 (accessed 17 July 2024).
2. Preston CL, Jones S and Sandhu H. 2014. How fruit juice interacts with common medicines. *Pharmaceutical Journal* 293(7831): 369-72. URL: pharmaceutical-journal.com/article/ld/how-fruit-juice-interacts-with-common-medicines (accessed 17 July 2024).
3. Bushra R, Aslam N and Khan AY. 2011. Food-drug interactions. *Oman Medical Journal* 26(2): 77-83. DOI: 10.5001/omj.2011.21 (accessed 17 July 2024).
4. Viatris Ltd. 2022. *Cipflox New Zealand Data Sheet* 16 June 2022. URL: www.medsafe.govt.nz/profs/datasheet/c/cipfloxtabinf.pdf (accessed 17 July 2024).
5. Viatris Ltd. 2023. *Ferodan New Zealand Data Sheet* 13 September 2023. URL: www.medsafe.govt.nz/profs/datasheet/f/ferodansol.pdf (accessed 17 July 2024).
6. Burns C and Kidron A. 2024. Biochemistry, Tyramine. In: *StatPearls [Internet]* updated 10 October 2022. URL: pubmed.ncbi.nlm.nih.gov/33085344/ (accessed 17 July 2024).
7. Stahl SM and Felker A. 2008. Monoamine oxidase inhibitors: a modern guide to an unrequited class of antidepressants. *CNS Spectrums* 13(10): 855-70. DOI: 10.1017/s1092852900016965 (accessed 17 July 2024).
8. Boucher & Muir (NZ) Ltd t/a Mercury Pharma (NZ). 2022. *Parnate New Zealand Data Sheet* 29 November 2022. URL: www.medsafe.govt.nz/profs/datasheet/p/Parnatetab.pdf (accessed 17 July 2024).
9. Viatris Ltd. 2023. *Aurorix New Zealand Data Sheet* 24 May 2023. URL: www.medsafe.govt.nz/profs/datasheet/a/aurorixtab.pdf (accessed 17 July 2024).
10. Pfizer New Zealand Limited. 2023. *Zyvox New Zealand Data Sheet* 18 September 2023. URL: www.medsafe.govt.nz/profs/datasheet/z/Zyvoxinjtabsusp.pdf (accessed 17 July 2024).
11. GlaxoSmithKline NZ Limited. 2023. *Marevan New Zealand Data Sheet* 14 March 2023. URL: www.medsafe.govt.nz/profs/datasheet/m/Marevantab.pdf (accessed 17 July 2024).

Gathering knowledge from adverse reaction reports: September 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: 154140 **Age:** 46 years **Gender:** Male **Medicine(s):** Cyproterone acetate **Reaction(s):** Meningioma	A meningioma was discovered in a patient who was on long-term treatment with cyproterone acetate. The meningioma was removed and cyproterone stopped.
	The Siterone data sheet warns that meningiomas have been reported with prolonged (years) use of cyproterone acetate at doses of 25mg per day and above. Discontinue cyproterone acetate in patients diagnosed with meningioma. See also the September 2020 *Prescriber Update* article: Cyproterone acetate and the risk of meningioma.
Report ID: 154277 **Age:** 52 years **Gender:** Male **Medicine(s):** Nadolol **Reaction(s):** Asthma	After starting nadolol, the patient's asthma symptoms worsened.
	Bronchial asthma or other obstructive lung disorders are listed as a contraindication in the Nadolol BNM data sheet.
Report ID: 156370 **Age:** 37 years **Gender:** Female **Medicine(s):** Sodium valproate **Reaction(s):** Polycystic ovarian syndrome	The patient was diagnosed with polycystic ovarian syndrome (PCOS) while taking sodium valproate.
	PCOS is listed as a rare ADR in the Epilim data sheet. Increased weight is common with valproate and may be a risk factor for PCOS.
Report ID: 156487 **Age:** 34 years **Gender:** Female **Medicine(s):** Pseudoephedrine **Reaction(s):** Abdominal pain, diarrhoea, rectal haemorrhage, muscle spasms, ischaemic colitis	A day after starting pseudoephedrine, the patient developed abdominal pain, diarrhoea, cramps and rectal bleeding, likely due to ischaemic colitis. Pseudoephedrine was stopped and the patient was recovering.
	Ischaemic colitis is listed as a very rare ADR in the Sudafed data sheet. Advise patients to discontinue pseudoephedrine and seek medical advice if sudden abdominal pain, rectal bleeding or other symptoms of ischaemic colitis 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).

Medicines may cause or exacerbate myasthenia gravis

Key messages

- Some medicines, such as immune checkpoint inhibitors and statins, can cause autoimmune reactions that may induce or exacerbate myasthenia gravis (MG). Other medicines, such as aminoglycosides, antimuscarinics, neuromuscular blockers and benzodiazepines, affect neuromuscular transmission and may exacerbate MG.
- MG was recently identified as a rare adverse effect associated with statins. Medsafe has requested the NZ sponsors of these medicine to update their data sheets with this association.
- Advise patients taking medicines with a known MG association to be alert for new or worsening MG symptoms, and to seek medical advice if these occur. Symptoms include drooping eyelids, double vision, problems with chewing or swallowing, speech disturbance, limb weakness and shortness of breath.

Myasthenia gravis

Myasthenia gravis (MG) is a neuromuscular transmission disorder. It is caused by autoantibodies blocking or destroying nicotinic acetylcholine receptors (AChR) or other proteins at the neuromuscular junction of skeletal muscles.[1,2]

MG is characterised by fluctuating weakness of the voluntary muscles that control eye movements, facial expression, speaking, swallowing, limb movement and breathing. Symptoms include drooping eyelids, double vision, problems with chewing or swallowing, speech disturbance, limb weakness and shortness of breath.[3] Generalised MG involves multiple groups of muscles and ocular MG only affects the eye muscles.[1]

People of any age can be affected, but MG typically starts in women aged under 40 years and men aged over 60 years.[3]

Numerous factors may cause or exacerbate MG, including medicines (described below), stress, tiredness, infections, excess physical activity, warm weather, surgery and changes in immunomodulatory treatments.[3,4]

Diagnosis and treatment

MG is typically diagnosed with a detailed neurological examination, laboratory and/or electrodiagnostic testing. Approximately 85% of patients with generalised MG have AchR antibodies, and approximately 40% who are seronegative for AChR antibodies are positive for muscle-specific tyrosine kinase (MuSK) antibodies.[1]

Treatment aims to reduce the symptoms and may include:[5,6]

- avoiding triggers
- anticholinesterases to improve strength
- immunosuppressants or immunomodulatory treatment to suppress the autoimmune reaction
- surgery to remove the thymus gland (thymectomy).

Medicine-related myasthenia gravis

Many medicines are associated with MG. Immune checkpoint inhibitors, tyrosine kinase inhibitors and statins may cause new-onset (*de novo*) MG or exacerbate existing MG by causing an autoimmune reaction at the neuromuscular junction.[1,2,7]

Other medicines, such as aminoglycosides, antimuscarinics, neuromuscular blockers and benzodiazepines, affect neuromuscular transmission and may exacerbate or unmask MG symptoms.[1,7]

Table 1 lists examples of medicines, by class, that may cause or exacerbate MG as listed in the respective data sheets. Note that the list is not exhaustive.

Table 1: Examples of medicines, by class, that may cause or exacerbate myasthenia gravis (list not exhaustive)

Class	Examples*	Class	Examples*
Immune checkpoint inhibitors	Atezolizumab Durvalumab Ipilimumab Nivolumab Pembrolizumab	Neuromuscular blockers	Botulinum toxin type A Atracurium Mivacurium Rocuronium Vecuronium Suxamethonium
Statins	Atorvastatin Pravastatin Rosuvastatin Simvastatin	Benzodiazepines	Clonazepam Diazepam Lorazepam Temazepam
Tyrosine kinase inhibitors	Lenvatinib	Beta-blockers	Propranolol Nadolol
Aminoglycosides	Gentamycin Amikacin Tobramycin	Fluoroquinolones	Norfloxacin Ciprofloxacin Moxifloxacin
Antimuscarinics	Atropine (systemic) Hyoscine (scopolamine) Propantheline	Macrolides	Azithromycin Clarithromycin Erythromycin Roxithromycin

* Refer to the respective data sheets for information about myasthenia gravis. Data sheets are available at: www.medsafe.govt.nz/Medicines/infoSearch.asp

Patients with pre-existing MG

Some medicines may exacerbate MG and so are not recommended or should be used with caution in patients with pre-existing MG.

Refer to the data sheets and clinical guidelines before prescribing medicines that can cause autoimmune reactions or affect neuromuscular transmission to patients with pre-existing MG. Seek specialist advice as appropriate.

Patients with suspected medicine-related MG

Refer to the data sheet and consider stopping the medicine if clinically appropriate. Follow local clinical guidelines for MG diagnosis and treatment.

Statins and MG

Myasthenia gravis was recently identified as an adverse effect associated with statins.[3] Medsafe has requested the NZ sponsors of these medicines to update their data sheets to reflect this association.

In a few cases, statins were reported to induce or exacerbate MG or ocular myasthenia, including reports of recurrence when the same or a different statin was administered. The statin should be discontinued if these conditions occur.[8–11]

Advise patients who are taking statins to be alert for any new symptoms that could be MG, or for worsening symptoms of pre-existing MG, and to seek medical advice if these occur.[3]

NZ case reports

As of 30 June 2024, Medsafe and the Centre for Adverse Reactions Monitoring (CARM) had received 5 reports of myasthenia gravis:

- 3 reports where pembrolizumab was the suspect medicine (NZ-Medsafe: 155420, 156395, 156552)
- 2 reports where atorvastatin was the suspect medicine (NZ-Medsafe: 156410, 156483).

References

1. Sheikh S, Alvi U, Soliven B, et al. 2021. Drugs that induce or cause deterioration of myasthenia gravis: an update. *Journal of Clinical Medicine* 10(7): 1537. DOI: 10.3390/jcm10071537 (accessed 19 June 2024).
2. Gras-Champel V, Masmoudi I, Batteux B, et al. 2020. Statin-associated myasthenia: A case report and literature review. *Therapie* 75(3): 301-9. DOI: 10.1016/j.therap.2019.07.004 (accessed 20 June 2024).
3. Medicines and Healthcare products Regulatory Agency. 2023. *Statins: very infrequent reports of myasthenia gravis* 26 September 2023. URL: www.gov.uk/drug-safety-update/statins-very-infrequent-reports-of-myasthenia-gravis (accessed 19 June 2024).
4. Shah A. 2023. *Myasthenia gravis* updated 5 December 2023. URL: emedicine.medscape.com/article/1171206-overview (accessed 20 June 2024).
5. National Health Service (UK). 2023. *Myasthenia gravis* 13 September 2023. URL: www.nhs.uk/conditions/myasthenia-gravis/ (accessed 24 June 2024).
6. New Zealand Formulary (NZF). 2024. *NZF v144: Drugs that enhance neuromuscular transmission* 1 June 2024. URL: nzf.org.nz/nzf_5702 (accessed 24 June 2024).
7. Narayansaswami P, Sanders D, Wolfe G, et al. 2021. International consensus guidance for management of myasthenia gravis. *Neurology* 96(3): 114-22. DOI: 10.1212/WNL.0000000000011124 (accessed 19 June 2024).
8. A. Menarini New Zealand Pty Ltd. 2024. *Crestor New Zealand Data Sheet* 8 May 2024. URL: www.medsafe.govt.nz/profs/Datasheet/c/Crestortab.pdf (accessed 4 July 2024).

9. Viatris Ltd. 2024. *Lorstat New Zealand Data Sheet* 21 June 2024. URL: www.medsafe.govt.nz/profs/Datasheet/l/lorstattab.pdf (accessed 19 August 2024).
10. Clinect NZ Pty Ltd. 2024. *Pravastatin New Zealand Data Sheet* 9 April 2024. URL: www.medsafe.govt.nz/profs/Datasheet/p/pravastatintab.pdf (accessed 4 July 2024).
11. Viatris Ltd. 2023. *Simvastatin Viatris New Zealand Data Sheet* 16 November 2023. URL: www.medsafe.govt.nz/profs/Datasheet/s/simvastatinmylantab.pdf (accessed 4 July 2024).

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
Acetylcysteine • DBL Acetylcysteine	4.4	Patients with asthma or history of bronchospasm; Patients with a history of oesophageal varices and peptic ulcer
Allergens and grass pollen extract • Oralair	4.4	Severe allergic reactions; Previous systemic allergic reaction to allergen immunotherapy; Asthma; Cardiovascular diseases; Beta-adrenergic blockers; MAOIs, tricyclic antidepressants and COMT inhibitors; Mild to moderate local allergic reactions; Autoimmune diseases in remission; Lactose
Amphotericin B • AmBisome	4.2	Dose updates for Systemic mycoses (including mucormycosis, cryptococcal meningitis) and Empirical treatment of presumed fungal infection of febrile neutropenic patients
Anastrozole • Aremed[b]	4.4	Tenosynovitis, tendonitis, tendon rupture
Atazanavir • Atazanavir Viatris	4.5	Apalutamide; Other lipid-modifying agents; Antiplatelets; Antineoplastics; Gonadotropin-releasing hormone antagonist receptor antagonists; Kinase inhibitors; Dexamethasone and other corticosteroids
Bupropion • Zyban	4.4	Brugada syndrome
	4.8	Alopecia
Busulfan • Myleran	4.5	Deferasirox; Paracetamol
Cyclizine • Cyclizine lactate (injection) • Nausicalm (tablet)	4.2	Use in hepatic impairment
	4.4	General warnings; Nervous system
	4.6	Use in breastfeeding women is not recommended

Continues overleaf

Active ingredient(s): • Medicine(s)	Data sheet updates Section[a]	 Summary of new safety information
Doxorubicin • Caelyx	4.4, 4.8	Interstitial lung disease
	4.6	Women of childbearing potential should avoid pregnancy, and use effective contraception during treatment and for 8 months after stopping; Men with female partners of childbearing potential should use effective contraception, and not father a child during treatment and for up to 6 months after stopping
Diazoxide • DBL Diazoxide	4.4, 4.8	Necrotising enterocolitis in neonates and infants
Digoxin • Lanoxin	4.5	Increase effects of digoxin: posaconazole, osimertinib; Decrease effects of digoxin: acarbose
Droperidol • Droleptan • Droperidol Panpharma	4.3	Pheochromocytoma
	4.4	Central nervous system; Cardiovascular (arrhythmia)
	4.5	Medicines that induce extrapyramidal symptoms; Medicines that induce electrolyte imbalance; CYP1A2 and CYP3A4 inhibitors
	4.7	Major influence on ability to drive or operate machinery; Wait at least 24 hours after last dose
	4.8	New table of adverse effects
Dulaglutide • Trulicity	4.4	Gastroparesis; Pulmonary aspiration
	4.8	Intestinal obstruction including ileus; Elevated liver enzymes
Epirubicin • Epirubicin Ebewe	4.4	Embryo-fetal toxicity
	4.6	Use contraception during treatment, and for at least 3.5 months after last dose for males and at least 6.5 months after last dose for females; Avoid breastfeeding during treatment and for at least 7 days after last dose
Etanercept • Enbrel	4.8	Glomerulonephritis
Montelukast • Montelukast Viatris	4.4	Neuropsychiatric events in adults, adolescents and children[c]
Nifedipine • Nyefax Retard	4.3	Patients with acute or unstable cardiovascular disease or significant gastrointestinal disease.
	4.8	Peripheral oedema; Pulmonary oedema; Intestinal ulcer; Intestinal obstruction; Bezoar; Dysphagia
Nintedanib • Ofev	4.4, 4.8	Posterior reversible encephalopathy syndrome (PRES)
Ondansetron (injection) • Ondansetron AFT • Ondansetron Kabi	4.2	Dose restrictions in elderly patients due to the risk of dose-dependent QT prolongation
	4.4, 4.8	Myocardial ischaemia
Ondansetron (tablets) • Onrex	4.4, 4.8	QT prolongation; Myocardial ischaemia
Pegaspargase • Oncaspar	4.4, 4.8	Veno-occlusive disease (VOD)
Pravastatin • Pravastatin Viatris	4.4	Contains lactose; Myasthenia gravis/Ocular myasthenia[d]
	4.5	Colchicine; Nicotinic acid; Rifampicin; Coumarin anticoagulant
	4.8	Myasthenia gravis; Ocular myasthenia; Fatal and non-fatal hepatic failure

Continues overleaf

Active ingredient(s): • Medicine(s)	Data sheet updates	
	Section[a]	Summary of new safety information
Sulfadiazine silver • Flamazine	4.4, 4.8	Stevens-Johnson syndrome (SJS); Toxic epidermal necrolysis (TEN)
Terlipressin • Glypressin	4.4	Cardiovascular and pulmonary disease; Renal impairment; Hepatic impairment; Respiratory events; Sepsis/septic shock; Skin necrosis (unrelated to the injection site)
	4.8	Sepsis/septic shock
Vinblastine • DBL Vinblastine	4.6	Women of childbearing potential: avoid pregnancy, use highly effective contraception during treatment and for 7 months after the last dose; Men with female partners of childbearing potential: use highly effective contraception during treatment and for at least 4 months after the last dose. Do not breastfeed during treatment and for 1 week following the last dose

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 machinery; 4.8: Undesirable effects

b. See the drug-induced tendinopathy article on page 51.

c. See the article about unexplained mood and behavioural changes in the March 2024 edition of *Prescriber Update.*

d. See the myasthenia gravis article on page 63.

Correction: Summary of Bexsero adverse events following immunisation

The June 2024 edition of *Prescriber Update* contained an article about adverse events following Bexsero immunisation. The doses of vaccine administered were incorrectly described and the article has been updated on the Medsafe website.

There were 364,796 doses of Bexsero administered between 1 March 2023 and 31 March 2024. In line with the National Immunisation Schedule, the majority of these (327,037 doses) were administered to children aged under 5 years.

Medsafe

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

Editor

Vikki Cheer
Email: medsafeadrquery@health.govt.nz

Editorial Team

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

Acknowledgements

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

Medical Advisors

Dr Karin van Bart, Medical Advisor
Dr Tina Ireland, Senior Medical Advisor

Group Manager

Chris James