Prescriber Update

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Contents

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Te Kāwanatanga o Aotearoa
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MINISTRY OF HEALTH

Spotlight on weekly methotrexate

Key messages

- Weekly methotrexate is indicated in adults for severe, recalcitrant disabling psoriasis and severe, recalcitrant active rheumatoid arthritis that are not responsive to other forms of therapy.
- Mistaken daily use may cause serious and sometimes life-threatening or fatal toxicity in many organ systems.
- When used for psoriasis and rheumatoid arthritis, check that patients, families and/or caregivers:
  - understand that methotrexate is taken **once weekly**, on the same day each week
  - are aware of the signs and symptoms of methotrexate toxicity and advise them to seek medical advice immediately if they occur.

This article reviews the safety profile of weekly methotrexate, an immunosuppressant used to treat psoriasis and rheumatoid arthritis.[1]

Methotrexate safety profile[1]

Methotrexate may cause significant adverse drug reactions and toxicity in many organ systems (Table 1).

For psoriasis and rheumatoid arthritis, the importance of once weekly dosing should be emphasised. Mistaken daily use increases the risk of life-threatening or fatal toxicity. The risk is higher at doses greater than 20mg per week.

Table 1: Adverse drug reactions and toxicity associated with methotrexate*

Organ system	Examples of adverse reactions/toxicity
Blood and lymphatic	Anaemia, pancytopenia, leucopoenia, neutropenia, thrombocytopenia, bleeding
Immune	Infections, including fatal sepsis
Gastrointestinal	Vomiting, diarrhoea, stomatitis, gingivitis, enteritis, hepatotoxicity, hepatic failure
Pulmonary	Interstitial pneumonitis, pleural effusion, fibrosis
Skin and subcutaneous disorders	Stevens-Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme, photosensitivity, increased risk of skin cancer
Renal	Severe nephropathy, renal failure
Reproductive	Defective oogenesis or spermatogenesis, congenital malformations, intrauterine growth restriction, spontaneous abortion

* Not an exhaustive list. Refer to methotrexate data sheets for known side effects.
Source: Rex Medical Ltd. 2024. *Trexate New Zealand Data Sheet* 27 September 2024. URL: www.medsafe.govt.nz/profs/Datasheet/t/trexatetab.pdf (accessed 15 January 2025).

Prescribing considerations

Methotrexate should only be prescribed by physicians with expertise in the use of methotrexate and a full understanding of the risks of methotrexate therapy.[1]

Other considerations are outlined below. Refer to the data sheets for full prescribing information.

Before beginning treatment[1]

Perform a full blood count, liver and renal function tests, and take a chest x-ray. Evaluate for personal and family history of liver disease, personal history of alcohol use or gastrointestinal ulcerative conditions.

If clinically indicated, screen for tuberculosis, hepatitis B and C, and perform a pregnancy test.

Monitor during treatment

Monitor blood count, liver and renal function throughout treatment.[1]

More frequent monitoring may be required during the initial phase of treatment, when the dose is increased, during episodes of changes to renal function, use of interacting medicines or in at-risk patients, such as the elderly.[1]

Folic acid or folinic acid may be used with methotrexate to reduce the risk of gastrointestinal side effects.[1]

Advise patients, family and/or caregivers to seek medical advice immediately if signs or symptoms of methotrexate toxicity occur, including sore throat, bruising, mouth ulcers, nausea, vomiting, abdominal discomfort, dark urine, shortness of breath or cough.[1]

Monitor patients regularly for treatment response and toxicity and manage accordingly.[1]

Importance of once weekly dosing

When methotrexate is taken as a single dose once weekly, ensure that patients, family and/or caregivers understand the correct number of tablets to take and what day of the week to take them.[1] Inform patients of what to do if they have missed a dose.[2]

Patients of childbearing potential[1]

Methotrexate is teratogenic and is contraindicated in pregnancy.

If either partner is receiving methotrexate, pregnancy should be avoided and effective contraception used during treatment and after discontinuation (for at least 3 months after treatment for males and at least 6 months for females).

Make sure that patients understand the need to plan any pregnancies.

Methotrexate is also contraindicated in breastfeeding.

New Zealand case reports

From 1 January 2014 to 31 December 2024, there were 101 case reports for methotrexate where the reported indication was for psoriasis or arthritis conditions. Of these 101 reports, 89 were reported as serious. Where demographic information was reported, the majority of reports were in older adults (median age 66 years), European/Other ethnicity (71 reports) and women (71 reports).

The most frequently reported adverse reactions were nausea (12 reports), pancytopenia (10), pneumonitis (10), mouth ulceration (7), interstitial lung disease (6), malaise (5), thrombocytopenia (5), headache (4), hepatic enzyme increased (4), neutropenia (4) and sepsis (4).

More information

- See the methotrexate data sheets and consumer medicine information (CMI): Search for a data sheet or CMI.
- Healthify has information for consumers about methotrexate: Methotrexate tablets for inflammatory conditions.
- Medsafe has published a *Prescriber Update* article about interactions with low-dose methotrexate.
- Refer to local clinical guidelines for information on methotrexate prescribing and monitoring.

References

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Medicines Monitoring: Anti-CD20 monoclonal antibodies and pyoderma gangrenosum

WE NEED YOUR HELP!

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

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

- M² (Medicines Monitoring) is a Medsafe scheme designed to collect more information on potential safety signals for specific medicines.
- Please send your report to CARM/Medsafe (as for any suspected adverse reaction). This can be done even if the reaction happened some time ago. Please include as much information as possible as this helps the medical assessors at CARM to investigate whether the medicine caused the reaction.
- For further information about M², see the Medsafe website.

* The appearance of a possible safety issue in this scheme does not mean Medsafe and CARM have concluded that this medicine causes the reaction.

Factors contributing to colchicine toxicity

Key messages

- Colchicine has a narrow therapeutic index and the separation between therapeutic and toxic doses is not well defined. Colchicine toxicity has a high mortality rate.
- Renal and hepatic impairment, older age and certain medicines can increase colchicine plasma levels, resulting in toxic effects. Consider these factors when initiating and continuing patients on colchicine.
- Early symptoms of colchicine toxicity include burning and rawness in the mouth and throat, followed by severe nausea, vomiting, abdominal pain and haemorrhagic diarrhoea.
- Educate patients on the early symptoms of colchicine toxicity. Advise them to stop colchicine immediately and seek medical advice if symptoms occur.
- Educate patients on safe storage and disposal to prevent paediatric exposure, which can be fatal.

At their December 2024 meeting, the Medicines Adverse Reactions Committee discussed two case reports of colchicine toxicity. As a result, the Committee recommended reminding prescribers about the importance of pre-existing comorbidities and concomitant medicines when prescribing colchicine.

This article highlights factors that can increase colchicine plasma levels and lead to toxicity and describes the symptoms of colchicine toxicity.

Signs and symptoms of colchicine toxicity

Colchicine has a narrow therapeutic index and the separation between therapeutic and toxic doses is not well defined.[1] Colchicine toxicity has a high mortality rate.

There is a latent period of 2 to 12 hours between colchicine overdose and the onset of gastrointestinal symptoms. The first signs of toxicity may be a feeling of burning and rawness in the mouth and throat and difficulty in swallowing, followed by severe nausea, vomiting, abdominal pain and haemorrhagic diarrhoea.[2] Cardiotoxicity (increased troponin) may also develop at any time after ingestion and has a poor prognosis.

Multisystem failure generally occurs 24 to 72 hours after overdose. This generally includes central nervous system toxicity, bone marrow depression, hepatocellular and renal damage and respiratory distress. Death may occur as a result of respiratory depression, dysrhythmia, cardiovascular collapse or sepsis.[2]

There is no specific antidote for colchicine toxicity.[2] National Poisons Centre advice is that management of acute ingestions is directed towards limiting absorption via activated charcoal and whole bowel irrigation, if possible, within 2 hours of ingestion. Beyond this, treatment is supportive. Recombinant granulocyte-stimulating factor (G-CSF) may reduce the risk of severe sepsis in cases of colchicine-induced neutropenia.[3] For advice on the management of colchicine overdose, contact the National Poisons Centre on 0800 POISON (0800 764 766).

Patient comorbidities and concomitant medicines contribute to colchicine toxicity

Renal impairment[2]

As 10-20% of the colchicine dose is excreted in urine, renal impairment can significantly reduce the clearance and prolong the half-life of colchicine.

If the patient's creatinine clearance is:

- ≤50 mL/min – reduce the colchicine dose by half
- ≤10 mL/min – colchicine is contraindicated.

Hepatic impairment[2]

Colchicine is metabolised by the liver. In patients with hepatic impairment, consider reducing the individual or total daily dose or increasing the interval between doses.

Colchicine is contraindicated in patients with severe hepatic impairment.

Elderly patients

Elderly patients are more likely to have age-related renal impairment and be taking multiple medicines that may interact with colchicine (see below).[2,4] Consider alternative therapy in elderly patients who are small and slight (less than 50 kg) or who have renal or hepatic impairment.[2]

Drug-drug interactions

Colchicine is a substrate of the efflux transporter P-glycoprotein (P-pg) and is metabolised by cytochrome P450 3A4 (CYP 3A4). If colchicine is administered with medicines that inhibit P-gp or CYP 3A4, increased colchicine plasma concentrations are likely.[2]

Some medicines that can interact with colchicine include:[5]

- azole antifungals: itraconazole, fluconazole and ketoconazole
- macrolide antibiotics: clarithromycin, roxithromycin and erythromycin
- calcium channel blockers: diltiazem and verapamil
- amiodarone
- ciclosporin.

Colchicine is contraindicated in patients with impaired renal or hepatic function and who are taking a P-gp or strong CYP 3A4 inhibitor.[2]

In patients with normal renal and hepatic function who are taking a P-gp or strong CYP 3A4 inhibitor, adjust the colchicine dose as appropriate and monitor for an increase in colchicine adverse effects.[5]

The leukopenic and thrombocytopenic effects of colchicine may be intensified by concomitant or recent use of medicines that cause blood dyscrasias or bone marrow suppression (such as anti-inflammatory medicines, angiotensin-converting enzyme inhibitors, carbamazepine, clozapine, methotrexate, tricyclic antidepressants). Colchicine may also increase the risk of bleeding in patients taking medicines that impair blood clotting or cause haemorrhage, such as anticoagulants.[2]

Prescribing considerations

Check the patient's renal and hepatic function, age and concomitant medicines when initiating and continuing colchicine treatment.

Educate patients on the symptoms of early colchicine toxicity. Advise them to stop colchicine immediately and seek medical advice if they experience gastrointestinal side effects.[2,6] Postpone further treatment for at least 3 days if gastrointestinal symptoms occur.[2]

Counsel patients on when and how to take colchicine, as lack of understanding can be a risk factor for toxicity (eg, using for non-gout related acute pain, taking more colchicine than prescribed). Also counsel patients with small children on safe storage and disposal.[7] Ingestion of any colchicine is dangerous to a toddler. Consider monthly dispensing, if appropriate.

More information

For healthcare professionals

- Refer to the colchicine data sheet
- Previous *Prescriber Update* articles about colchicine and the safe storage of medicines:
  - Keeping patients informed about colchicine use (December 2014)
  - Spotlight on colchicine (March 2018)
  - Colchicine: Beware of toxicity and interactions (March 2011)
  - Colchicine: painful insights from recent poisoning data in New Zealand (June 2021)
  - Medicine safety reminder: avoid unintentional poisoning in the home (March 2024).

For consumers

- Consumer information leaflet on medicines for gout. Also available in te reo Māori and Samoan.

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Quarterly summary of recent safety communications

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

Date	Communication	Topic
27/02/2025	Monitoring	Update – Reports of pericarditis following mpox vaccination
12/02/2025	Dear Healthcare Professional Letter	Konakion MM (phytomenadione) Paediatric 2mg/0.2mL solution for injection: Temporary supply of overseas product (PDF, 2 pages, 284 KB)
28/01/2025	Dear Healthcare Professional Letter	Imbruvica: Newly identified risk of hepatotoxicity (including hepatic failure) in warnings and precautions section of the Imbruvica NZ data sheet and consumer medicine information (PDF, 4 pages, 296 KB)
16/01/2025	Monitoring	Anti-CD20 monoclonal antibodies (rituximab, ocrelizumab, obinutuzumab, ofatumumab) and the possible risk of pyoderma gangrenosum

MARC's remarks: December 2024 meeting

The Medicines Adverse Reaction Committee (MARC) convened for their 200th meeting on 5 December 2024.

The Committee discussed the risk of cutaneous vasculitis with **direct-acting oral anticoagulants (DOACs)**. The Committee noted that the cause of this condition can be difficult to identify and may be due to medicines or an autoimmune reaction. On review of the data presented, the Committee concluded that there is a risk of cutaneous vasculitis with DOACs and recommended data sheet updates for approved DOACs.

The Committee reviewed the Risk Management Plan (RMP) for **Jynneos (vaccina vaccine)**. They noted that myo-/pericarditis is an important potential risk in the RMP, but there is no information on myo-/pericarditis in the data sheet. The Committee considered that it would be helpful for healthcare professionals to know about this potential risk and recommended that the data sheet be updated with this information. They also recommended that Medsafe update the currently published monitoring communication on reports of pericarditis following mpox vaccination.

At the meeting, the Committee further discussed **clozapine** blood monitoring requirements following on from the report presented at the September 2024 MARC meeting. The Committee agreed that changes to the blood monitoring requirements for clozapine are needed. They recommended that Medsafe should further review possible options for changes and seek additional expert advice.

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

Medroxyprogesterone acetate and meningioma

Key messages

- Meningioma is a newly identified, very rare, side effect of medroxyprogesterone acetate.
- Discontinue treatment with medroxyprogesterone acetate if meningioma occurs.

What are meningiomas?

Meningiomas are tumours of the meninges, the membrane surrounding the brain and spinal cord. Meningiomas are often benign and asymptomatic but may cause neurological symptoms through compression of adjacent tissues.[1]

Meningiomas are more common in women and the incidence increases with age.[1]

Hormonal factors, including progesterone, may influence the development of meningioma. This hypothesis is supported by a higher frequency of meningioma in females than males and the presence of hormone receptors on meningiomas.[1,2]

Meningioma with medroxyprogesterone depot

Medroxyprogesterone acetate is a synthetic progestogen. Medroxyprogesterone depot injection (Depo-Provera) is indicated for suppression of ovulation and treatment of endometriosis. It also has oncological indications.[3] Medroxyprogesterone tablets (Provera) are indicated for treatment of dysfunctional uterine bleeding, endometriosis, menopausal hormone therapy and diagnosis of amenorrhea.[4]

A case-control study using French health system data found that prolonged exposure to injectable medroxyprogesterone acetate was associated with an increased risk of intracranial meningioma requiring surgery. The absolute risk remained low. Note that this result was based on a small number of exposed cases and should therefore be interpreted with caution.[5] However, meningiomas have been associated with other progesterones, such as cyproterone (see below).

The Depo-Provera and Provera tablet data sheets have been updated to warn that meningioma has been reported with long-term use of medroxyprogesterone and to discontinue the medicine if meningioma occurs. Use caution when prescribing this medicine to people with a history of meningioma.[3]

Are oral contraceptives associated with meningioma?

An association between use of combined or progestogen-only oral contraceptives and meningioma has not been established.[2]

Long-term treatment with high cumulative doses of cyproterone has been associated with a significantly increased risk of meningioma.[2] The relevance to low doses of cyproterone contained in some oral contraceptives is uncertain. However, the ethinylestradiol + cyproterone (Ginet) data sheet contraindicates use in people with current or past meningioma and warns that treatment should be stopped if meningioma is diagnosed.[6]

More information

- See also a previous *Prescriber Update* article: Cyproterone acetate and the risk of meningioma (September 2020)
- Search for a data sheet

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Sickle-cell crisis with pegfilgrastim and filgrastim

Key messages

- Sickle cell disease (SCD) is a group of inherited red blood cell disorders.
- Patients with SCD can experience sickle cell crisis, which is characterised by episodes of severe acute pain.
- Sickle cell crisis (including fatal cases) has been reported in patients with SCD who received pegfilgrastim and/or filgrastim.

A case of sickle cell crisis in a patient taking pegfilgrastim was reported to the New Zealand Pharmacovigilance database. To date, this is the first report received for sickle cell crisis reported with any medicine in New Zealand.

Sickle cell disease

Sickle cell disease (SCD) refers to a group of inherited red blood cell (RBC) disorders. Genetic mutations change the haemoglobin structure, which causes abnormal, crescent-shaped (sickle) red blood cells and leads to vaso-occlusive crisis, anaemia and organ damage. SCD is a multisystem disease associated with episodes of acute illness and progressive organ damage.[1,2]

There are several genotypes associated with SCD, the most common genotype is homozygous haemoglobin SS (HbSS) which causes sickle cell anaemia. The prevalence of SCD is high among the people of sub-Saharan Africa, South Asia, the Middle East, and the Mediterranean.[2]

Sickle cell crisis

Patients with SCD can experience episodes of acute pain commonly referred to as sickle cell pain crises (SCC) or vaso-occlusive crises (VOCs). SCC/VOCs are the primary presenting cause of hospitalisation and morbidity associated with SCD.[3]

Most episodes of SCC do not have an identifiable cause. Some triggers include hypoxia, infections, fever, dehydration, exposure to cold/weather changes and stress.[2,3] These triggers cause haemoglobin polymerisation (the process by which haemoglobin molecules stick together to form fibres) resulting in rigid, sickle-shaped red blood cells. The blood cells do not easily flow through the circulation and cause small vessel occlusion, pain, local hypoxia and inflammation.[2]

Pain can occur in any region but frequently affects the extremities, back and chest areas.[2] Clinical consequences of SCC/VOCs include acute chest syndrome, hepatic and renal injury, cerebrovascular accident (stroke) and multiorgan failure resulting in death.[3]

Pegfilgrastim and filgrastim and SCC

SCC (in some cases fatal) has been reported in patients with SCD treated with pegfilgrastim/filgrastim.[4,5]

Leukocytosis (high leukocyte count) has been observed in patients taking pegfilgrastim.[4,5] In patients with SCD, leukocytosis in the absence of infection is a predictor of poor clinical outcomes.[6] Therefore, clinicians should exercise caution when administering pegfilgrastim/filgrastim to patients with SCD.[4,5]

Refer to the appropriate guidelines and/or specialist advice for management of SCC in patients with SCD.

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Gathering knowledge from adverse reaction reports: March 2025

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

The table below presents a selection of recent informative cases reported to the New Zealand Pharmacovigilance Database.

Case details[a,b]	Reaction description and data sheet information[b,c]
Report ID: 157971 **Age:** 38 years **Gender:** Male **Medicine(s):** Hydrocortisone + natamycin + neomycin **Reaction(s):** Penile ulceration	The patient developed penile ulcers after using Pimafucort cream. Pimafucort was withdrawn and the event resolved.
	Pimafucort should only be used for specific conditions when a combination of a corticosteroid, antimycotic and antibiotic is clinically indicated. It should not be applied to the genital area, including the foreskin, due to the risk of local skin reactions, such as rash or ulcerations. These reactions may be related to the neomycin component.
Report ID: 158368 **Age:** 40 years **Gender:** Female **Medicine(s):** Pregabalin **Reaction(s):** Amenorrhoea, weight increased, luteinising hormone (LH) increased, follicle stimulating hormone (FSH) increased	After starting pregabalin, the patient developed amenorrhea and weight gain. Pregabalin was discontinued and her periods resumed and hormone levels normalised.
	There is a warning for weight gain in the Lyrica data sheet. Amenorrhoea is listed as a rare ADR.
Report ID: 158607 **Age:** 6 years **Gender:** Female **Medicine(s):** Elexacaftor + tezacaftor + ivacaftor **Reaction(s):** Liver function tests (LFTs) increased, transaminases increased	After starting Trikafta, the child developed mildly elevated LFTs (increased transaminases). Three months later LFTs had markedly increased, and the medicine was stopped. Once LFTs had improved, Trikafta was restarted at a lower dose. LFTs immediately increased and the medicine was stopped again.
	There is a warning for elevated transaminases in the Trikafta data sheet. Transaminase and bilirubin levels should be monitored before and during treatment, and the data sheet provides advice on when to interrupt and/or resume treatment.
Report ID: 158657 **Age:** 15 years **Gender:** Male **Medicine(s):** Fluoxetine **Reaction(s):** Gynaecomastia	A year after starting fluoxetine, the patient developed gynaecomastia.
	Gynaecomastia is listed as a very rare ADR in the Arrow-Fluoxetine data sheet.

Continues

Case details[a,b]	Reaction description and data sheet information[b,c]
Report ID: 159035 **Age:** 38 years **Gender:** Female **Medicine(s):** Liraglutide **Reaction(s):** Acute cholecystitis necrotic	Four months after starting liraglutide, the patient developed acute gangrenous cholecystitis.
	The Saxenda data sheet has a warning for cholelithiasis and cholecystitis. Substantial or rapid weight loss can increase the risk of acute gallbladder disease. Inform patients about cholelithiasis and cholecystitis symptoms.
Report ID: 159549 **Age:** 7 years **Gender:** Male **Medicine(s):** Montelukast **Reaction(s):** Suicidal ideation	Three months after starting montelukast, the child developed suicidal ideation. The symptoms persisted after stopping the medicine.
	There is a warning for neuropsychiatric events in the Montelukast Viatris data sheet. Symptoms usually resolve after stopping treatment but have persisted in some cases. Before starting treatment with montelukast, prescribers should discuss the risks of neuropsychiatric events with patients and/or caregivers. Advise them to be alert for possible changes in mood and behaviour and to notify their doctor if these occur. See also the March 2024 *Prescriber Update* article: Unexplained mood and behavioural changes – could it be a side effect?

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 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 18 October 2024 to 31 January 2025.

Table 1: Recent approvals of medicines with new active ingredients

Medicine	New active ingredient	Dose form: strength(s)	Therapeutic area
Dayvigo	Lemborexant	Film coated tablet: 5mg, 10mg	Insomnia
Tevimbra	Tislelizumab	Concentrate for injection: 100mg/10mL	Oesophageal squamous cell carcinoma; Non-small cell lung cancer
Vyalev	Foscarbidopa + Foslevodopa	Solution for infusion: 12mg/mL + 240mg/mL	Parkinson's disease
Winlevi	Clascoterone	Topical cream: 1% w/w	Acne vulgaris

New indications

Table 2 shows approved medicines with new indications for additional therapeutic areas gazetted during the period 18 October 2024 to 31 January 2025.

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

Medicine (active ingredient)	Dose form: strength(s)	New therapeutic area
Cosentyx (secukinumab)	Solution for injection: 75mg/0.5mL 150mg/mL 300mg/2mL Powder for injection: 150mg	Hidradenitis suppurativa (acne inversa)
Enhertu (trastuzumab deruxtecan)	Powder for infusion: 100mg	Non-small cell lung cancer
Keytruda (pembrolizumab)	Concentrate for infusion: 25mg/mL	Biliary tract carcinoma; Merkel cell carcinoma
Skyrizi (risankizumab)	Concentrate for infusion: 600mg/10mL (vial) Solution for injection: 75mg/0.83mL (syringe) 150mg/mL (pen or syringe) 180 mg/1.2mL (cartridge) 360mg/2.4mL (cartridge)	Ulcerative colitis

More information

See the Medsafe website for:

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

Immune effector cell-associated neurotoxicity syndrome (ICANS)

Key messages

- Immune effector cell-associated neurotoxicity syndrome (ICANS) may occur following the use of any immunotherapy that activates or engages T-cells and/or other immune effector cells.
- Neurologic symptoms include difficulty with language or speech, altered level of consciousness and cognitive impairment.
- Management of ICANS is mostly supportive and may include corticosteroids, depending on severity.

The Columvi (glofitamab) data sheet was recently updated with information on the risk of immune effector cell-associated neurotoxicity syndrome (ICANS). This article provides an overview of ICANS.

What is ICANS?

Immune effector cell-associated neurotoxicity syndrome (ICANS) is a disorder involving the central nervous system occurring a median of 4–5 days following the use of any immunotherapy that activates or engages T-cells and/or other immune effector cells.[1-3]

The underlying mechanism of ICANS is not fully understood. However, cytokines, myeloid cells, T-cells and disruption of the blood brain barrier may all play a role.[4]

ICANS frequently occurs concurrently with or shortly after cytokine release syndrome (CRS), but can also occur on its own.[4,5]

Risk factors for ICANS include high disease burden, older age and patients with high-grade CRS. The risk also differs depending on each specific immunotherapy product.[2,5]

Signs and symptoms of ICANS

Signs and symptoms of ICANS are initially vague and can be variable.[5] They can be progressive and include aphasia (difficulty with language or speech), altered level of consciousness, cognitive impairment, motor weakness, seizures and cerebral oedema.[1]

Non-neurologic symptoms may also be present including hepatic failure, severe hypertension, infection and electrolyte abnormalities.[1]

The features of ICANS overlap with other encephalopathies. However, on examination, a key characteristic of ICANS is an alert patient who is mute.[1,5]

Immunotherapies associated with ICANS

Chimeric antigen receptor (CAR) T-cell therapies are most commonly associated with ICANS. The incidence of ICANS appears to be highest for CD19-targeting CAR T-cell therapies, particularly those that have CD28-containing CAR T-cell constructs (eg, axicabtagene ciloleucel, brexucabtagene autoleucel).[2,3]

T-cell engaging therapies are also associated with ICANS, but the frequency and pattern is less well characterised than with CD19-targeting CAR T-cell therapies. T-cell engaging therapies include CD3 bispecific medicines (eg, blinatumomab, epcoritamab, glofitamab).[3]

Management of ICANS

Management of ICANS depends on severity. Supportive care and corticosteroids are the mainstays of treatment.[5]

ICANS is usually self-limiting with symptoms lasting between 5 and 17 days. In very rare cases, malignant cerebral oedema may develop, which may be fatal.[6]

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Recent data sheet updates: important new safety information

Table 1 below provides a list of data sheets recently updated with important new safety information. Note that this is not a comprehensive list of all recently updated data sheets, nor does it describe all changes to a particular data sheet.

To find out if sponsors have made any changes to their data sheets, 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
Aflibercept • Eylea	4.8	Scleritis
Alectinib • Alecensa	4.6	Increase in contraception requirements for female patients of childbearing potential from 1 week post last dose to 5 weeks post last dose
Baclofen • Pacifen	4.4	Encephalopathy
	4.8	Encephalopathy; Hypersensitivity; Alopecia; Sexual dysfunction; Swelling face; Peripheral oedema
Carbamazepine • Tegretol	4.3, 4.4	Contraindicated in neonates below 4 weeks of age due to the propylene glycol (PG) content and the immaturity of both metabolic and renal clearance of PG in this population
	4.6	Additional information added to Pregnancy risk summary: Microcephaly; Small for gestational age (SGA); Neurodevelopmental disorders (Autism spectrum disorder, Intellectual disability, ADHD)
Celecoxib • Celebrex (Aspen)	4.4, 4.8	Skin: Fixed drug eruptions (FDE) and generalised bullous fixed drug eruptions (GBFDE)
Chlorhexidine • Chlorhexidine Acetate • Chlorhexidine Acetate with Cetrimide	4.4	Preoperative skin preparation: Eye contact must be avoided. Permanent corneal injury has been reported
	4.8	Fatal anaphylactic reaction; Corneal erosion; Corneal epithelium defect/Corneal injury; Visual impairment
Colecalciferol • Vit.D3	4.3	Additional contraindications: Nephrolithiasis; Pregnancy; Lactation; Children under 18 years of age
	4.4	Use with caution in patients with arteriosclerosis, cardiac function impairment, sarcoidosis, other granulomatous diseases. New sections: Monitoring; Renal impairment; Hepatic impairment; Long-term administration
	4.5	New interactions: Calcium, Phosphate; Digoxin; Corticosteroids; Rifampicin; Isoniazid; Antifungals; Actinomycin; Different vitamin D analogues
	4.6	Do not use during pregnancy or while breastfeeding
	4.9	Updated overdose symptoms; toxicity in paediatric population

Continues

Active ingredient(s): • Medicine(s)	Data sheet updates Section[a]	Summary of new safety information
Diclofenac • Voltaren Rapid Extra Strength	4.8	Kounis syndrome
Hydrocortisone + natamycin + neomycin • Pimafucort[b]	4.2	Only use when a combination of a corticosteroid, antimycotic and antibiotic is indicated. Do not apply to genital areas.
	4.4	Local skin reactions
Isotretinoin • Oratane	4.3	Contraindicated during breastfeeding; Concomitant use with tetracyclines is contraindicated due to the risk of benign intracranial hypertension
	4.4	Paediatric use: Not recommended for children aged under 12 years; use with caution in those aged 12 to 17 years Skin and subcutaneous disorders: Use sunscreen with SPF50 Musculoskeletal and connective tissue disorders: Sacroiliitis
	4.8	Sacroiliitis; Urethritis
Leflunomide • Arava	4.4	Skin reactions: Impaired wound healing after surgery that may require treatment interruption and a washout procedure
Meropenem • Meropenem-AFT	4.4	Rhabdomyolysis; Neurological sequelae; Skin and subcutaneous tissue disorders
	4.8	Acute generalised exanthematous pustulosis (AGEP); Rhabdomyolysis; Kounis syndrome
Midazolam • Midazolam-Baxter	4.1, 4.2	Now indicated only for the intravenous and intramuscular routes of administration
	4.4	Paediatric use: Safety and effectiveness in children below the age of 8 years have not been established.
	4.6	Increased risk of miscarriage when used during pregnancy
Propofol • Diprivan	4.8	Hepatitis; Acute hepatic failure
Testosterone • Testogel	4.4	Inadvertent testosterone transfer: Skin to skin transfer – pregnant women and children; Precautions for the patient and to improve partner safety
	4.8	Anxiety; Decreased libido; Emotional lability; Prostate abnormalities; Benign prostate hyperplasia; Prostatomegaly prostatic disorder; Spermatogenesis and semen disorders; Oligospermia; Testicular atrophy; Azoospermia

a. Data sheet sections listed in the table are: 4.1: Therapeutic indications; 4.2: Dose and method of administration; 4.3: Contraindications; 4.4: Special warnings and precautions for use; 4.5: Interaction with other medicines and other forms of interaction; 4.6: Fertility, pregnancy and lactation; 4.8: Undesirable effects; 4.9: Overdose.

b. See also the Gathering Knowledge article on page 12 for a case of genital ulceration following use of Pimafucort.

Medsafe

New Zealand Medicines and Medical Devices Safety Authority
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Editor

Vikki Cheer
Email: medsafeadrquery@health.govt.nz

Editorial Team

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Tegan Coventry, Senior Advisor Pharmacovigilance

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Medical Advisor

Dr Karin van Bart, Senior Medical Advisor

Group Manager

Chris James

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