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Spotlight on tramadol, including updated advice for use in children

Key messages

- Tramadol is now contraindicated in children aged under 12 years and should be used with care in patients aged over 75 years.
- Patients who are CYP2D6 ultra-rapid metabolisers may be more sensitive to adverse reactions.

This article informs healthcare professionals of updated advice on the use of tramadol in children. It is also a reminder of tramadol's metabolism, use in patients aged over 75 years, and some serious adverse reactions.

What is tramadol?

Tramadol is a centrally-acting synthetic analgesic that exerts its effect by^{1,2}:

- binding to μ -opioid receptors
- inhibiting the reuptake of noradrenaline and serotonin.

Tramadol is used to relieve moderate to severe pain when paracetamol and/or a non-steroidal anti-inflammatory drug (NSAID) is not adequate^{1,2}.

The importance of CYP2D6

Tramadol is similar to codeine in that CYP2D6 is important for producing metabolites that have a greater affinity for the μ -opioid receptor than the parent drug³.

Tramadol's principal active metabolite is O-desmethytramadol (M1)¹. Animal models show M1 to be six-times more potent than tramadol in producing analgesia and 200 times more potent in μ -opioid binding¹.

Patients with a deficiency of CYP2D6 may have reduced benefit from tramadol³. On the other hand, patients who are ultra-rapid metabolisers may be more sensitive to adverse reactions, even at commonly prescribed doses³. The frequency of poor metaboliser and ultra-rapid metaboliser phenotypes varies between populations⁴.

Tramadol is contraindicated in children

Following review of their safety data, the companies have now contraindicated the use of tramadol in:

- children aged under 12 years
- children aged under 18 years for post-operative pain management following tonsillectomy and/or adenoidectomy.

The tramadol data sheets are in the process of being updated with these contraindications.

Use with caution in patients aged over 75 years

Serum concentrations of tramadol are slightly elevated, and the elimination half-life is slightly prolonged in patients aged over 75 years¹. Their tolerance of adverse reactions is expected to vary more widely. Therefore, use a lower maximum daily dose of 300 mg in these patients¹.

Serious adverse reactions

Tramadol is associated with adverse reactions seen for both opioid and antidepressant medicines². Tramadol should be administered cautiously in patients at risk of respiratory depression¹. Avoid concomitant use with benzodiazepines or other central nervous system (CNS) depressants unless there are no suitable alternative treatment options¹.

Tramadol may cause serotonin syndrome when taken alone or if the dose is increased, and more frequently when taken with another serotonergic medicine. Avoid concomitant use with selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants and mirtazapine. For more information about serotonin syndrome, see the September 2015 edition of *Prescriber Update* (medsafe.govt.nz/profs/PUArticles/Sep2015/InteractionsSerotoninSyndrome.htm).

Seizures have been reported in patients taking tramadol even at the recommended dose¹. Tramadol may also increase the seizure risk in patients taking other medicines that lower the seizure threshold¹. Avoid using tramadol in patients with epilepsy or those susceptible to seizures.

Please refer to the medicine data sheet for full prescribing information (search for data sheets at: medsafe.govt.nz/Medicines/infoSearch.asp).

Adverse reactions reported in New Zealand over the last five years

The Centre for Adverse Reactions Monitoring (CARM) has received 83 adverse reaction reports relating to tramadol from 1 January 2015 to 31 December 2019. The most frequently reported reactions were rashes (12), vomiting (10) and nausea (9).

Serotonin syndrome was reported in five cases (CARM IDs: 115985, 116267, 121427, 129817, 134414). Four of these cases reported a SSRI or SNRI as co-suspects. Convulsions were reported in five cases (CARM IDs: 121427, 124017, 129062, 129605, 133745).

Of the 83 reports, six were in children aged under 12 years and seven were in patients aged over 75 years.

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Ondansetron and oral cleft defects

Key messages

- Use of ondansetron during the first trimester of pregnancy is increasing.
- Epidemiological study data suggest a small increase in the risk of oral cleft defects (such as cleft lip or cleft palate) associated with first trimester exposure to ondansetron.
- With informed consent, ondansetron should only be used during the first trimester of pregnancy if the benefits of use clearly outweigh the risks of harm to the woman and fetus.

Ondansetron

Ondansetron is a selective serotonin (5-HT₃) receptor antagonist. The approved indications are the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and the prevention of post-operative nausea and vomiting. Ondansetron is also used off-label during early pregnancy¹.

New Zealand National Collections data show that first trimester use of ondansetron is increasing (Figure 1). The proportion of women who were dispensed ondansetron during the first trimester of pregnancy increased from 0.5 percent in 2009 to 9.6 percent in 2018.

Risk of cleft palate with ondansetron

Two recent epidemiological studies investigated the risk of orofacial cleft defects and other congenital malformations in infants who were exposed to ondansetron *in utero*, using data from large administrative claims databases in the United States^{2,3}.

The first was a retrospective cohort study of 1,816,414 pregnancies from 2000 to 2013, in which 88,467 (4.9 percent) pregnancies were associated with a prescription for ondansetron in the first trimester. Oral cleft defects occurred in 14.0 per 10,000 exposed infants compared to 11.1 per 10,000 unexposed infants (adjusted relative risk 1.24, 95% CI: 1.03–1.48)².

The second was a nested case-control study of 864,083 mother-child pairs registered from 2000 to 2014, in which 5,557 mother-child pairs were administered ondansetron in the first trimester. Ondansetron exposure was associated with a numerical increase in oral cleft defects, although this increase did not reach statistical significance (adjusted odds ratio 1.30, 95% CI: 0.75–2.25)³.

The Medicines Adverse Reactions Committee (MARC) discussed the risk of oral cleft defects associated with first-trimester exposure to ondansetron at the March 2020 meeting (see MARC's remarks on page 30). The Committee noted that although the effect sizes in the recently reported studies were small and there is some uncertainty in the data, the current evidence suggests a small increase in the risk of oral cleft defects associated with the use of ondansetron in the first trimester⁴.

Clinical implications

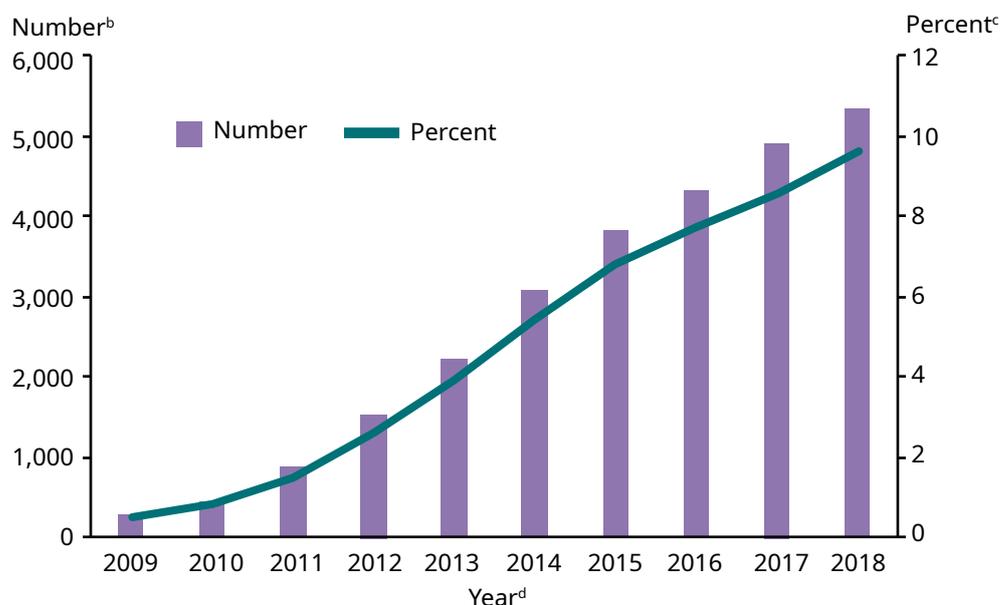
The recent studies suggest an approximate 25 percent increase in the risk of oral cleft defects with first trimester use of ondansetron, amounting to an additional 3 cases per 10,000 exposed pregnancies.

The data sheets of ondansetron-containing medicines are being updated with information on the increased risk of oral cleft defects associated with first trimester use.

In line with the Code of Health and Disability Services Consumers' Rights, authorised prescribers must advise the patient when the use of ondansetron in pregnancy is unapproved (off-label) and obtain informed consent^{5,6}.

The possible benefit of using ondansetron during the first trimester of pregnancy must be weighed against the risk of harm. As with all medicines, benefit-risk assessment needs an individualised approach⁷.

Figure 1: Use of ondansetron during the first trimester^a of pregnancy in New Zealand, public hospitalisations data, 2009–2018



Notes:

- First trimester calculated as the first 13 weeks of pregnancy.
- Number: number of women dispensed ondansetron during the first trimester of pregnancy. Only includes pregnancies that reached at least 20 weeks gestation.
- Percent: number of women dispensed ondansetron/total number of women who reached at least 20 weeks gestation.
- Year: based on the expected delivery date.

Source: National Collections, Ministry of Health. 2020.

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Alerting the Medical Warning System can save lives!

Key messages

- The Medical Warning System (MWS) is used to alert health care professionals in district health board secondary care that a particular patient has had a previous serious adverse drug reaction. This can save lives.
- It is important to inform the Centre for Adverse Reactions Monitoring of these life-threatening reactions as they can update the MWS for that patient.

Background

Recently the Centre for Adverse Reactions Monitoring (CARM) received a case report in which a patient died after treatment with an antibiotic. Investigation into the patient's history showed that earlier the patient had experienced an anaphylactic reaction to the same medicine at a different treatment centre. However, this information was not recorded in the Medical Warning System (MWS), and the anaphylactic reaction had not been reported to CARM.

The Medical Warning System

The MWS is a national alert service linked to the National Health Index (NHI) numbers¹. The MWS alerts health care professionals to known risk factors that could be important when making clinical decisions about patient care. This includes information on serious and/or life-threatening adverse reactions to medicines, such as anaphylaxis.

The MWS system is currently visible to the district health boards (DHBs), but not to primary care. In some areas, however, general practitioners (GPs) can access the information via their DHB. Although GPs may also add a medicine allergy alert in their Patient Management System (PMS), this alert is only visible to their practice and is not automatically added to the MWS. Opportunities to make the MWS more accessible to primary care are under consideration.

Adding an alert

There are two types of medicine alerts: Danger and Warning.

- A Danger alert reflects a contraindication to further use for the patient. Used, for example, when the patient has had an anaphylactic-type reaction or any other life-threatening reaction.
- A Warning alert indicates that the medicine has caused the patient significant morbidity and should be avoided. Some alerts need to be qualified, for example, "tolerates at slow infusion rate".

CARM adds many of the medicine alerts to the MWS. The alerts are generated from adverse drug reaction (ADR) reports sent to them from health care professionals and the public. When CARM receives an ADR report, the medical team assess the case and, based on the nature of the event, may place a Danger or Warning alert on the MWS for the medicine, listing the associated reaction(s). Some hospitals/DHBs have systems in place and designated staff who enter Warning alerts into the MWS, but only CARM can place a Danger alert.

CARM receives approximately 4,000–5,000 ADR reports per year. Of these, about 1,500 are vaccine-related and only occasionally require an entry on the MWS. Of the remaining reports, about 2,500 are for therapeutic medicines and result in approximately 500 Danger entries and 1,000 Warning entries on the MWS.

ADR reporting is vital

Reporting adverse drug reactions is vital so that where necessary, CARM can add an alert to the MWS. Whenever the patient's NHI is accessed in the future, details of the alert (Danger or Warning) are available to health care professionals who can access the MWS. This is crucial in patients who are not able to speak for themselves, are confused or may have forgotten an event from distant history. The MWS alert may also be more reliable than asking the patient, especially when health literacy is low, or there are language barriers.

ADR reporting is easiest online: nzphvc.otago.ac.nz/reporting/

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MARC's Remarks: March 2020 meeting

The Medicines Adverse Reactions Committee (MARC) met on 12 March 2020 to discuss a number of medicine-related safety issues.

The MARC discussed dosing of **paracetamol** in obese children and if specific dosing instructions for this group of patients should be included in the data sheets and/or label statements. The MARC considered there is very limited data available on the pharmacokinetics of paracetamol or cytochrome P450 activity in obese children. The MARC determined there is insufficient evidence to recommend an update to the paracetamol data sheets and/or label statements.

The MARC discussed **ondansetron** exposure *in utero* and the risk of cleft palate. The MARC considered that there is some evidence suggesting a slightly increased risk of cleft palate when ondansetron is taken during the first trimester of pregnancy. The MARC considered this small risk should be highlighted in New Zealand data sheets. The MARC also recommended that the Committee's discussion is highlighted to the Society of Obstetric Medicine of Australia and New Zealand and included in a future edition of *Prescriber Update* (see the article on page 27).

The MARC reviewed the benefits and risks of Tdap vaccine (**Boostrix**) when administered to women in their second trimester of pregnancy. The MARC determined that the data did not indicate that use in the second trimester would expose pregnant women to additional risks and recommended a data sheet update to include this information.

See the Medsafe website for the MARC meeting minutes (medsafe.govt.nz/profs/MARC/Minutes.asp) and the reports presented to the MARC (medsafe.govt.nz/committees/MARC/Reports.asp).

Antipsychotic medicines: monitor cardiovascular risk

Key messages

- Antipsychotic medicines are associated with significant cardiovascular adverse effects.
- Routine monitoring for cardiovascular risk factors is recommended before and during treatment.

Background

The Centre for Adverse Reactions Monitoring was recently alerted to a case where a patient suffered a non-fatal cardiac arrest shortly after administration of an antipsychotic. Whilst the contribution of the medicine to the event was unclear, the patient had multiple risk factors for adverse cardiovascular outcomes. Medsafe would like to remind prescribers of the risks of antipsychotic medicines and the need for cardiovascular risk factor monitoring in patients taking them.

Cardiovascular adverse effects and risk factors

Antipsychotic medicines are associated with significant cardiovascular adverse effects. To varying extents, antipsychotic medicines may cause QT-interval prolongation, tachycardia, arrhythmias and changes in blood pressure^{1,2}. Clozapine is also associated with myocarditis and cardiomyopathy^{3,4}.

In addition to direct effects on the cardiovascular system, antipsychotic medicines are associated with metabolic changes including dyslipidaemia, hyperglycaemia and central obesity that further increase the risk of adverse cardiovascular outcomes. Compared to the general population, patients with psychotic disorders have higher rates of smoking and alcohol misuse, poorer nutrition and more sedentary lifestyles, which further increases their cardiovascular risk⁵⁻⁷.

Monitoring cardiovascular risk factors in patients prescribed antipsychotic medicines is necessary to minimise the risk of serious outcomes². Consult local clinical guidelines and data sheets to find recommended cardiovascular monitoring for individual medicines. Data sheets are available at: medsafe.govt.nz/Medicines/infoSearch.asp.

Communication between psychiatric and primary care providers about who will take responsibility for the patient's routine cardiovascular monitoring and risk factor management may help to ensure timely intervention of modifiable risk factors¹.

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Gathering knowledge from adverse reaction reports: June 2020

Adverse reaction reporting is an important component of medicine safety monitoring. Case reports can highlight significant safety issues concerning therapeutic products and their use.

The table below presents a selection of recent informative cases from the Centre for Adverse Reactions Monitoring (CARM) database.

Case details ^{a,b}	Reaction description and data sheet information ^{b,c}
<p>CARM ID: 134546</p> <p>Age: 54</p> <p>Gender: Female</p> <p>Medicine(s): Terbinafine</p> <p>Reaction(s): Systemic lupus erythematosus</p>	<p>Two months after starting oral terbinafine, the patient experienced a worsening eczematous rash across her abdomen, back and lower limbs. Laboratory results were positive for antinuclear antibodies, anti-Ro antibody and anti-histone antibody. She was diagnosed with terbinafine-induced lupus (flare of subacute cutaneous lupus erythematosus) and treated with topical clobetasol.</p> <p>The Deolate data sheet lists cutaneous and systemic lupus erythematosus as very rare adverse reactions (medsafe.govt.nz/profs/Datasheet/d/deolatetab.pdf).</p>
<p>CARM ID: 135335</p> <p>Age: 39</p> <p>Gender: Male</p> <p>Medicine(s): Atorvastatin</p> <p>Reaction(s): Pancreatitis</p>	<p>Three weeks after starting atorvastatin, the patient experienced abdominal pain, with laboratory tests showing raised amylase and bilirubin, and deranged LFTs. He was diagnosed with pancreatitis and the atorvastatin was discontinued.</p> <p>Liver derangements are well known with statins, and pancreatitis is listed as a rare adverse reaction in the Lorstat data sheet (medsafe.govt.nz/profs/Datasheet/l/lorstattab.pdf).</p> <p>See also the <i>Prescriber Update</i> article about pancreatitis (medsafe.govt.nz/profs/PUArticles/June2019/Acute-pancreatitis-Sometimes-triggered-by-medicines.htm).</p>
<p>CARM ID: 135630</p> <p>Age: 55</p> <p>Gender: Female</p> <p>Medicine(s): Flucloxacillin</p> <p>Reaction(s): Lip swelling, pruritis, urticaria</p>	<p>The patient experienced a delayed allergic reaction to flucloxacillin, with a rash appearing on the fifth day of treatment and lip swelling two days after stopping treatment.</p> <p>Allergic reactions, including rash, urticaria and angioedema, are described in the Staphlex data sheet (medsafe.govt.nz/profs/Datasheet/s/Staphlexcapsyr.pdf).</p> <p>See also the <i>Prescriber Update</i> article about delayed skin reactions reported with penicillins (medsafe.govt.nz/profs/PUArticles/March2016/DelayedSkinReactionsReportedWithPenicillins.htm).</p>

<p>CARM ID: 136107</p> <p>Age: 64</p> <p>Gender: Female</p> <p>Medicine(s): Zoledronic acid</p> <p>Reaction(s): Hypophosphataemia, malaise, vision blurred</p>	<p>Soon after receiving a zoledronic acid infusion, the patient reported symptoms of bloating, nausea and loss of appetite. This progressed to difficulty breathing, weakness, fever, chills, blurred vision and pain in her neck and shoulders. Seven days after the infusion, she was diagnosed with hypophosphataemia and treated with oral phosphate replacement therapy.</p> <p>The Aclasta data sheet lists hypophosphataemia as an adverse reaction derived from post-marketing experience, with an unknown frequency (medsafe.govt.nz/profs/Datasheet/a/Aclastainf.pdf).</p>
<p>CARM ID: 136158</p> <p>Age: 77</p> <p>Gender: Male</p> <p>Medicine(s): Methotrexate, sulfamethoxazole + trimethoprim (Co-trimoxazole)</p> <p>Reaction(s): Drug interaction, pancytopenia</p>	<p>While on treatment with methotrexate, the patient was prescribed co-trimoxazole. The patient subsequently experienced pancytopenia and methotrexate toxicity.</p> <p>The Trexate and Trisul data sheets state that methotrexate and co-trimoxazole have anti-folate effects. Co-trimoxazole (and trimethoprim alone) may also increase the free plasma levels of methotrexate by inhibiting renal excretion. Co-administration may therefore lead to increased bone marrow suppression. If co-trimoxazole is considered appropriate therapy in patients receiving other anti-folate drugs such as methotrexate, a folate supplement should be considered, and the full blood count closely monitored (medsafe.govt.nz/profs/Datasheet/t/Trisultab.pdf medsafe.govt.nz/profs/Datasheet/t/trexatetab.pdf).</p>

Notes:

- Only the medicines suspected to have caused the reaction are listed in the table.
- 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 to CARM, and do not always match the MedDRA term.
- If the suspect medicine's brand name is not described in the report to CARM, only the data sheet for the funded medicine is included in the table.

Information about suspected adverse reactions reported to CARM is available on the Medsafe website using the Suspected Medicines Adverse Reaction Search (SMARS) (www.medsafe.govt.nz/Projects/B1/ADRSearch.asp).

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

Recent approvals: new active ingredients or new indications

For the period 16 January 2020 to 15 April 2020.

Recent approvals of medicines with new active ingredients

Trade name (Active ingredient)	Dose form and strength(s)	Therapeutic area
Aimovig (erenumab)	Solution for injection 70 mg/mL 70 mg/mL pen	Migraine
Brintellix (vortioxetine)	Tablet 5 mg 10 mg 15 mg 20 mg	Major depressive disorder
Fasenra (benralizumab)	Solution for injection 30 mg/mL	Eosinophilic asthma
Lenvima (lenvatinib)	Capsule 4 mg 10 mg	Thyroid cancer Renal cell carcinoma Hepatocellular carcinoma
Nitisinone DiPharma (nitisinone)	Capsule 2 mg 5 mg 10 mg	Hereditary tyrosinemia type 1 (HT-1)
Oncaspar (pegaspargase)	Solution for injection 3750 U/5mL	Acute lymphoblastic leukaemia

Approved medicines with new indications

Trade name (Active ingredient)	Dose form and strength(s)	New therapeutic area(s)
Keytruda (pembrolizumab)	Powder for infusion 50 mg Concentrate for infusion 25 mg/mL	Renal cell carcinoma
Praluent (alirocumab)	Solution for injection 75 mg/mL 150 mg/mL	Prevention of cardiovascular events
Xgeva (denosumab)	Solution for injection 70 mg/mL	Multiple myeloma Giant cell tumour of bone Hypercalcaemia of malignancy

See the Medsafe website for more information about these medicines (medsafe.govt.nz/regulatory/DbSearch.asp). Data sheets of currently marketed medicines are also available (medsafe.govt.nz/Medicines/infoSearch.asp).

Anticholinergic burden – a cause of adverse reactions for older patients

Key messages

- Medicines with anticholinergic effects are associated with an increased risk of adverse reactions in older people and should be avoided whenever possible.
- If use of these medicines is unavoidable, start treatment at a low dose, increase slowly to the lowest effective dose, and use for the shortest duration possible.
- Aim to reduce the anticholinergic burden for older patients.

Medicines with anticholinergic effects

Anticholinergic medicines (also called antimuscarinic medicines) antagonise the effect of the neurotransmitter acetylcholine on muscarinic (M1–M5) receptors in the central and peripheral nervous system¹⁻³.

Medicines with anticholinergic activity are used to treat a wide range of conditions. The anticholinergic effect may be intended (eg, hyoscine for gastrointestinal muscle spasm, oxybutynin, benztropine, procyclidine) or unintended (eg, tricyclic antidepressants, sedating antihistamines, clozapine, olanzapine, chlorpromazine).

Many commonly used medicines such as warfarin, metoprolol, furosemide, venlafaxine and loratadine have weak anticholinergic effects, which may be inconsequential when used alone but have an additive effect when used in combination⁴.

Undesirable anticholinergic effects

Peripheral anticholinergic effects include constipation, dry mouth, dry eyes, blurred vision (mydriasis), tachycardia and urinary retention. Central nervous system effects include agitation, confusion, delirium, hallucinations and cognitive impairment³. Consequential effects include problems such as tooth decay, falls or gastrointestinal obstruction.

Problems with anticholinergics in older patients

Older patients are more susceptible to adverse reactions associated with anticholinergic medicines. Effects such as cognitive impairment, dizziness and blurred vision increase the risk of falls in older patients,⁴ and may increase the risk of hospitalisation and limit their ability to perform activities of daily living^{3,5,6}. Combined use of sedative and anticholinergic medicines further increases the risk of falls and cognitive impairment in the older patients and should be avoided^{7,8}.

Recent studies suggest a possible association between the use of strong anticholinergic medicines and a risk of dementia^{2,9,10}. Further investigation is needed to confirm the association¹¹. Nevertheless, these data provide further need for caution in the use of these medicines.

Minimising risk

When prescribing medicines for older patients, it is important to consider the overall 'anticholinergic burden' (ie, the combined anticholinergic effect of all the medicines a patient is taking). Where clinically possible, aim to reduce the anticholinergic burden by avoiding, reducing, or deprescribing medicines with anticholinergic activity¹⁻⁴.

It may be possible to replace certain medicines with alternatives that do not have anticholinergic properties¹¹. If an anticholinergic medicine is unavoidable, start treatment at a low dose and increase slowly to the lowest effective dose¹².

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Quarterly summary of recent safety communications

The table below is a summary of recent safety communications to health care professionals and consumers, published on the Medsafe website (medsafe.govt.nz).

Date	Communication	Topic
21/05/2020	Monitoring	 Update – Possible risk of vasculitis with dabigatran (Pradaxa)
21/05/2020	Monitoring	 Potential interaction between fluoxetine and levothyroxine
28/04/2020	Dear Healthcare Professional letter	Use of Hydroxychloroquine (Plaquenil) in the context of COVID 19 – Risk of QT prolongation and drug/drug interactions (PDF 358 KB, 4 pages)
1/04/2020	Dear Healthcare Professional letter	Supply of Typhim Vi under labelling exemption (PDF 680 KB, 2 pages)

1/04/2020	Dear Healthcare Professional letter	Discontinuation of Reopro (abciximab) 10mg/5mL solution for injection vials as of 30 June 2020 - information for healthcare professionals (PDF 78 KB, 2 pages)
27/03/2020	Alert	Mentor Siltex breast implants and anaplastic large cell lymphoma
27/03/2020	Alert	Allergan breast implants and anaplastic large cell lymphoma
12/02/2020	Dear Healthcare Professional letter	Nozinan (Swiss Stock) Change in supply of Nozinan (levomepromazine) tablets to product sourced from Switzerland - information for healthcare professionals (PDF 299 KB, 2 pages)
7/02/2020	Dear Healthcare Professional letter	Nozinan (Swiss Stock) Change in supply of Nozinan (levomepromazine) tablets to product sourced from Switzerland - information for patients (PDF 233 KB, 1 page)

Flucloxacillin – sometimes bad news for kidneys

Key Messages

- Flucloxacillin is a very rare cause of interstitial nephritis.
- Early recognition and prompt treatment results in better outcomes.

Flucloxacillin can injure the kidneys as well as the liver. Both interstitial nephritis and hepatitis are listed as very rare undesirable effects in the flucloxacillin data sheets^{1,2}. However, in the last five years (1 January 2015 to 31 December 2019) the Centre for Adverse Reactions Monitoring (CARM) has received 39 reports of liver-related reactions and 13 reports of kidney-related reactions. These reports suggest interstitial nephritis may be an under-recognised reaction to flucloxacillin.

Of the 13 reports of renal reactions, the majority occurred in patients aged over 70 years. The median time to onset was three days, and the longest reported onset time was 20 days. Where the information was provided, two patients were reported to have died, three patients had recovered, and the majority (seven) had not yet recovered. Early recognition of flucloxacillin-induced interstitial nephritis and prompt treatment reduces the risk of long-term renal impairment³.

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3. Medsafe. 2015. Keeping it renal: Drug-induced acute interstitial nephritis. *Prescriber Update* 36(2): 26. URL: medsafe.govt.nz/profs/PUArticles/June2015/June2015AcuteInterstitialNephritis.htm (accessed 21 April 2020).

WE NEED YOUR HELP!



Please send your reports to CARM (nzphvc.otago.ac.nz/reporting/) for the potential safety issues* listed in the table below.

Medicine(s)	Potential safety issue	Active monitoring ends
Fluoxetine and levothyroxine	Interaction	30 November 2020

- **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 (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 (medsafe.govt.nz/profs/M2MedicinesMonitoring.asp).

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

Medicines associated with fistulas

Key messages

- Medicines such as axitinib, bevacizumab, nicorandil, pazopanib and tocilizumab are associated with the development of fistulas.

Background

The Centre for Adverse Reactions Monitoring (CARM) received a report concerning a 68-year-old female patient on long-term tocilizumab (CARM ID: 124763). The patient developed a colovaginal fistula, secondary to tocilizumab-induced diverticulitis. Both undesirable effects are described in the Actemra (tocilizumab) data sheet¹.

Fistulas

A fistula is an abnormal connection between two hollow spaces or organs and can occur in many different parts of the body²⁻⁴. Fistulas are often named according to the spaces or organs that are connected together, for example, rectovaginal (rectum and vagina), tracheoesophageal (trachea and oesophagus) or enterocutaneous (small bowel and skin).

Causes of fistula include surgery, trauma, infection or inflammation²⁻⁴. Diverticulitis is inflammation and/or infection of a diverticulum (a sac-like protrusion of the colonic wall)⁴. Fistula formation is one of the complications of diverticulitis, with most diverticular fistulas occurring between the colon and the bladder (colovesical) and the colon and the vagina (colovaginal)⁴.

Some medicines are also associated with the development of fistulas. Table 1 provides a few examples (not a comprehensive list), including the information in the data sheet.

Table 1: Examples* of medicines that have been associated with the development of fistulas

Trade name (active ingredient)	New Zealand data sheet information regarding fistulas (data sheet URL)
Inlyta (axitinib)	In clinical trials, fistulas were reported in 0.6% of patients, and gastrointestinal perforation and fistula reported in 2% of patients. (medsafe.govt.nz/profs/Datasheet/i/inlytatab.pdf)
Avastin (bevacizumab)	Depending on the study population being treated, gastrointestinal fistula formation was reported in 2.0–8.2% of patients and non-gastrointestinal fistula reported in 0.1–1.8% of patients. Fistulas have also been reported in the post-marketing setting (frequency unknown). (medsafe.govt.nz/profs/Datasheet/a/Avastininf.pdf)
Ikorel (nicorandil)	Patients with diverticular disease may be at particular risk of fistula formation or bowel perforation during nicorandil treatment. Gastrointestinal ulcers are reported as a rare (≥ 0.01 and $< 0.1\%$) adverse reaction. If advanced, these ulcers may develop into fistulating disease. (medsafe.govt.nz/profs/Datasheet/i/ikoreltab.pdf)
Votrient (pazopanib)	In clinical studies, gastrointestinal fistula was reported as an uncommon (≥ 0.1 and $< 1\%$) adverse reaction. (medsafe.govt.nz/profs/Datasheet/v/votrienttab.pdf)
Actemra (tocilizumab)	In clinical trials, gastrointestinal perforation was reported at a rate of 0.26–0.28 events per 100 patient years. Gastrointestinal perforation was primarily reported as a complication of diverticulitis, including generalised purulent peritonitis, lower gastrointestinal perforation, fistula and abscess. Diverticulitis is reported as an uncommon ($\geq 0.1\%$ and $< 1\%$) adverse reaction. (medsafe.govt.nz/profs/Datasheet/a/Actemrainf.pdf)

* This table contains examples only and is not a comprehensive list.

References

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Medicinal Cannabis Scheme – now operational

**MEDICINAL
CANNABIS
AGENCY**

The Medicinal Cannabis Scheme is now operational

The Medicinal Cannabis Scheme (the Scheme) started on 1 April 2020 with the commencement of the Misuse of Drugs (Medicinal Cannabis) Regulations 2019. The Medicinal Cannabis Agency (the Agency) administers the Scheme, which includes a licensing regime for medicinal cannabis cultivation, manufacture and supply. The Scheme also includes the requirement for all medicinal cannabis products under the Scheme to consistently meet minimum standards of quality before they can be supplied.

Those who want to work in the industry need to hold a medicinal cannabis licence or work for a person or company that holds a licence. The licence specifies the types of activities that a licence holder may carry out, such as commercial cultivation of cannabis or manufacture and supply of medicinal cannabis products.

Medicinal cannabis products are prescription medicines and are only available to patients on prescription from a doctor.

Frequently asked questions

When will products be available to prescribe?

Doctors can prescribe Sativex™ now for any indication (approved or unapproved) without needing to apply for approval to prescribe from the Ministry of Health. Sativex™ is currently the only medicinal cannabis product that has been approved as a medicine under the Medicines Act.

Currently all other medicinal cannabis products are unapproved medicines, therefore they can only be prescribed by medical practitioners under the Medicines Act 1981. Doctors can prescribe medicinal cannabis products that have been verified by the Agency as meeting the minimum quality standard, but these will not be available immediately. The availability of new medicinal cannabis products depends on suppliers submitting evidence to the Agency to verify that their products meet the quality standard before they can be supplied.

In the meantime, the Scheme includes a transition period where medicinal cannabis products (including cannabidiol (CBD) products) that were imported and supplied prior to 1 April 2020 can continue to be supplied until 1 October 2020 without having to meet the quality standard. Suppliers have six months to submit evidence to the Agency to verify that their existing products meet the quality standard in order to continue to be supplied after 1 October 2020.

Does a doctor need a recommendation from a specialist before they can prescribe a medicinal cannabis product that meets the quality standard?

No, a doctor can prescribe any medicinal cannabis product that has been verified by the Agency as meeting the minimum quality standard. If a doctor is unsure whether to prescribe a product, they may choose to seek advice from their colleagues, but a recommendation from a specialist is not required before they can prescribe a product. Note that a product that has been assessed and verified as meeting the minimum quality standard does not mean that the product has been assessed for safety and efficacy. It remains an unapproved medicine.

How will healthcare professionals know which products meet the quality standard?

The Agency will publish a list of products which have been assessed and verified as meeting the quality standard on the Ministry of Health website (see the More information section below).

How can I find out more information on a particular medicinal cannabis product?

You can ask the medicinal cannabis product supplier for information. As they are unapproved medicines, suppliers are prohibited from advertising their products in any way, however they can respond to enquiries from healthcare professionals regarding their product(s). The Agency is encouraging suppliers of medicinal cannabis products to have product information available to provide to healthcare professionals who request it. Medicines data sheets will not be available from Medsafe unless the product has been assessed and approved as a medicine under the Medicines Act 1981.

What is the difference between hemp and cannabis?

Hemp and cannabis are both varieties of the *Cannabis* plant. However, the difference between them is the tetrahydrocannabinol (THC) content: hemp varieties have a low THC content. In New Zealand, hemp varieties of cannabis can be cultivated under an industrial hemp licence for industrial purposes (eg, for fibre) and must have a THC level of less than 0.35 percent dry weight. Cannabis plants, including hemp varieties, can be cultivated for medicinal cannabis purposes under a medicinal cannabis licence and there is no specified limit on the level of THC. Therapeutic products (ie, medicinal cannabis products) can be manufactured from the plants cultivated for this purpose.

Are hemp products that are available in health stores and the supermarket medicinal cannabis products?

No, these hemp products are not medicinal cannabis products. Hemp products often seen in health stores and supermarkets are made from hulled, low-THC hemp seeds (or the oil that is extracted) and are permitted to be in foods. Hemp seed products have limits on the levels of cannabinoids (eg, THC or CBD) permitted, and they cannot make therapeutic claims or state that they contain CBD or THC.

More information

The Ministry of Health website has information about the Agency and the Scheme. You'll find information for industry (including guidelines and forms), health professionals and consumers. You can also subscribe to receive updates from the Agency.

- Medicinal Cannabis Agency: health.govt.nz/our-work/regulation-health-and-disability-system/medicinal-cannabis-agency
- Subscribe to receive updates: health.govt.nz/our-work/regulation-health-and-disability-system/medicinal-cannabis-agency/subscribe-medicinal-cannabis-updates
- Email the Medicinal Cannabis Agency: medicinalcannabis@health.govt.nz

Misuse of Drugs (Medicinal Cannabis) Regulations 2019:

legislation.govt.nz/regulation/public/2019/0321/latest/LMS285243.html

Prescribing unapproved medicines: medsafe.govt.nz/profs/RIss/unapp.asp

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Regulatory Web Update emails

These emails outline new and updated data sheets and consumer medicine information, changes to the Regulatory Guidelines, publication dates of Gazette Notices and other regulatory-related changes published on the Medsafe website.

To subscribe: medsafe.govt.nz/regulatory/subscribe.asp

Medicine Classification emails

The Medicines Classification Committee (MCC) makes recommendations to the Minister of Health on the classification of medicines. Your comments are valuable to the MCC decision-making process.

To subscribe, email committees@health.govt.nz with the words 'classification – subscribe' in the subject line.

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