Prescriber Update

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MANATŪ HAUORA
MINISTRY OF HEALTH

Non-steroidal anti-inflammatory drugs (NSAIDs): avoid use in pregnancy

Key messages

- NSAIDs are contraindicated in the third trimester of pregnancy.
- NSAIDs should not be used during the first two trimesters of pregnancy unless the expected benefits to the mother outweigh the risks to the fetus. If there is a compelling need for NSAID treatment during the first or second trimester, limit use to the lowest effective dose and shortest duration possible.
- Enquire about NSAID use in people who are pregnant or planning pregnancy and advise them not to self-medicate with these medicines during pregnancy.

The Medicines Adverse Reactions Committee (MARC) recently reviewed the safety of non-steroidal anti-inflammatory drug (NSAID) use in the third trimester of pregnancy.

The MARC concluded that all NSAIDs should be contraindicated in the third trimester of pregnancy and recommended that the pregnancy information in the data sheets for all NSAIDs should be updated and aligned.

Non-steroidal anti-inflammatory drugs should be avoided in pregnancy

Maternal use of NSAIDs in the third trimester of pregnancy may have adverse effects for the mother, fetus and neonate.[1,2] Possible adverse effects include the following.

- **Maternal effects**: prolonged labour, post-partum haemorrhage.
- **Fetal effects**: premature closure of the ductus arteriosus, fetal renal impairment, oligohydramnios.
- **Neonatal effects**: respiratory distress syndrome, persistent pulmonary hypertension of the newborn (PPHN), bronchopulmonary dysplasia, renal failure, intraventricular haemorrhage, necrotising enterocolitis.

MARC recommendations

Medsafe is working with the New Zealand sponsors of NSAIDs to update the data sheets, as per the MARC recommendations, to contain the following information.

- NSAIDs are contraindicated in the third trimester of pregnancy.
- NSAIDs should not be used during the first two trimesters of pregnancy unless the expected benefits to the mother outweigh the risks to the fetus. If there is a compelling need for NSAID treatment during the first or second trimester, limit use to the lowest effective dose and shortest duration possible.
- NSAID use in early pregnancy is associated with an increased risk of miscarriage and congenital malformation.
- Use of NSAIDs in the second or third trimester may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Oligohydramnios is generally seen after days to weeks of treatment, although it has been reported as soon as 48 hours after NSAID initiation. Oligohydramnios is usually, but not always, reversible after treatment discontinuation. Consider ultrasound monitoring of amniotic fluid if treatment extends beyond 48 hours. Discontinue NSAID treatment if oligohydramnios occurs.

- NSAID use during the third trimester may cause premature closure of the fetal ductus arteriosus, fetal renal impairment, inhibition of platelet aggregation, and may delay labour and birth. NSAID use in the third trimester of pregnancy is therefore contraindicated.

Data sheets are available on the Medsafe website.

Advise people who are pregnant to avoid using NSAIDs

Some systemic NSAIDs are classified as pharmacy-only or general sale medicines. The package labelling for NSAIDs that are available over-the-counter states that the medicine should not be used in pregnancy.

Healthcare professionals are reminded to enquire about NSAID use in people who are pregnant or planning pregnancy and to advise them not to self-medicate with these medicines during pregnancy.

Health Navigator has information for consumers about the risks associated with taking NSAIDs.

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Opioids and serotonergic medicines: some combinations may increase the risk of serotonin syndrome

Key messages

- There is a risk of developing serotonin syndrome with concomitant use of opioids and serotonergic medicine(s). The risk varies depending on the medicine combination.
- Pethidine, dextromethorphan and tramadol are high-risk opioids for serotonin syndrome when used with serotonergic antidepressants.
- When prescribing opioids with serotonergic medicines, consider the risk of a drug-drug interaction leading to serotonin syndrome.

The Medicines Adverse Reaction Committee (MARC) recently reviewed the risk of serotonin syndrome with concomitant use of opioids and serotonergic medicines.

Medsafe is working with sponsors of opioid and serotonergic medicines to update the data sheets with information on this interaction (see MARC's remarks on page 37 of this edition of *Prescriber Update*).

Serotonin syndrome is a rare but potentially life-threatening condition

Serotonin toxicity/syndrome is a drug-induced condition caused by an excess of the neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) in the synapses of the brain.[1]

Signs and symptoms of serotonin syndrome range from mild to life-threatening and may include diarrhoea, diaphoresis (excessive sweating), agitation, tremor, hypertension, hyperthermia, tachycardia, hyperreflexia (twitching) and clonus (involuntary muscle movements).[2]

Serotonin syndrome usually follows from a combination of two or more serotonergic medicines.[1] These include most antidepressants, such as monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs).[1]

The serotonergic potential of opioids is increasingly recognised. When prescribing opioids with serotonergic medicines, consider the possibility of a drug-drug interaction leading to serotonin syndrome.[3]

If serotonin syndrome is suspected, and depending on the severity of the symptoms, consider discontinuing at least one of the serotonergic medicines. Initiate supportive care.[2]

The risk of developing serotonin syndrome varies between different opioid and serotonergic medicine combinations

Table 1 outlines the risk stratification and management of the drug-drug interaction between different opioids and antidepressant medicines.[4]

Pethidine, tramadol and dextromethorphan (a common ingredient in cough medicines) are opioids with a high risk of causing serotonin syndrome when used with serotonergic antidepressants.[4] Concomitant use of these medicines with MAOIs is contraindicated due to this interaction.[4] Individuals who misuse or abuse cough medicines containing dextromethorphan are at a greater risk of developing serotonin syndrome.[5]

Methadone and fentanyl also have serotonergic properties and are considered medium risk for inducing serotonin syndrome.[4] An interaction may occur with these opioids in combination with antidepressant medicines (see Table 1).[4] This interaction is more likely to occur with higher doses of methadone used in opioid substitution therapy and higher doses of fentanyl used in anaesthesia or post-operative recovery.[3]

Morphine, codeine, buprenorphine and oxycodone are not expected to interact with antidepressant medicines to cause serotonin syndrome.[4] Dihydrocodeine (not included in Table 1) is likely to act similarly to these low risk opioids.[3,6]

There is potential for serotonin syndrome to develop in individuals taking antidepressants with other opioid narcotics, such as methylenedioxymethamphetamine (MDMA or 'ecstasy').[6] Herbal products, such as St John's wort, may also increase 5-HT levels and potentially interact with serotonergic opioids.[1]

Some opioids act as serotonin reuptake inhibitors *in vitro*

The serotonin transporter (SERT) maintains serotonin (5-HT) plasma concentrations and is important for the rapid reuptake of serotonin into presynaptic nerve terminals.[6] Medicines that inhibit SERT may increase the plasma, synaptic cleft and postsynaptic serotonin concentrations, that, in turn, activate the postsynaptic 5-HT receptors.[6] Excessive activation of 5-HT receptors may lead to serotonin syndrome.

In vitro studies have investigated the potential mechanisms by which some opioids directly or indirectly increase serotonin levels.[6] Dextromethorphan, methadone, pethidine and tramadol inhibit SERT *in vitro*.[7] Fentanyl does not inhibit SERT *in vitro* but, unlike other opioids, shows affinity for both the 5-HT1A and 5-HT2A receptors.[7] As cases of serotonin syndrome have been reported with fentanyl, there may be some SERT-

independent effects on the 5-HT system *in vivo*.[7] Codeine, morphine, buprenorphine, oxycodone and dihydrocodeine do not inhibit SERT and do not have affinity for 5-HT receptors.[7]

Further research is needed to confirm the clinical implications of these *in vitro* findings.[6,7]

Table 1: The risk of serotonergic toxicity with combinations of antidepressants and opioids

	Antidepressants	
Opioids	**Low-intermediate risk** SSRIs, SNRIs, TCAs, St John's wort, lithium	**High risk** MAOIs (or previous history of serotonin toxicity)
Low risk Morphine, codeine,* buprenorphine, oxycodone	Should be safe	Possible rare interaction. Use with caution
Medium risk Fentanyl, methadone	Possible rare interaction. Use with caution	Increased risk of serotonin syndrome
High risk Tramadol,* pethidine, dextromethorphan	Increased risk of serotonin syndrome	Contraindicated

* risk of decreased analgesic effect

SSRI selective serotonin reuptake inhibitor

SNRI serotonin noradrenaline reuptake inhibitor

TCA tricyclic antidepressant

MAOI monoamine oxidase inhibitor

Source: Perananthan V and Buckley NA. 2021. Opioids and antidepressants: which combinations to avoid. *Australian Prescriber* 44(2): 41–4. DOI: https://doi.org/10.18773/austprescr.2021.004 (accessed 17 June 2022).

Note: Oxymorphone, hydromorphone, tapentadol are not currently available in New Zealand.

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Prostaglandin-associated periorbitopathy

Key messages

- Prostaglandin-associated periorbitopathy (PAP) has been associated with the use of ocular prostaglandin analogues.
- Before initiating treatment, inform patients of the possibility of changes to the eye during treatment.
- Ocular prostaglandin analogues are commonly used to treat glaucoma. Bimatoprost, travoprost and latanoprost are currently available in New Zealand.

The Medicines Adverse Reactions Committee (MARC) reviewed the risk of prostaglandin-associated periorbitopathy (PAP) at the 190th meeting in June 2022.

The MARC considered that the evidence showed the risk of PAP was a class effect. Medsafe has asked the sponsors to update their data sheets with information on this adverse reaction.

Ocular prostaglandin analogues

Ocular prostaglandin analogues are a class of medicines commonly used to treat glaucoma.[1] They bind to prostaglandin F (FP) receptors in the eye, leading to increased aqueous outflow through the uveoscleral pathway.[2] The increased outflow reduces the elevated intraocular pressure associated with glaucoma.[2,3]

Bimatoprost, travoprost and latanoprost are the ocular prostaglandin analogues currently available in New Zealand.

Prostaglandin-associated periorbitopathy (PAP)

The term 'prostaglandin-associated periorbitopathy' describes clinical and cosmetic changes in the eye associated with prostaglandin analogues.[4] Patients may experience one or more of the following:[4]

- deepening of the upper eyelid sulcus
- flattening of the lower eyelid bags
- upper eyelid ptosis (drooping eyelid[5])
- orbital fat atrophy
- mild enophthalmos (posterior displacement of the eye[6])
- inferior scleral show (sclera visible between the cornea and lower eyelid margin[7])
- tight orbit
- ciliary hypertrichosis
- hyperpigmentation of the periorbital skin
- dermatochalasis (redundant eyelid skin[5]).

Figure 1 shows a patient with PAP in one eye.

The risk of PAP is likely to be the highest for bimatoprost and the lowest for latanoprost.[8] It has been reported in more than 10 percent of patients treated with bimatoprost.[1] Clinical and cosmetic changes can occur as early as one month after starting treatment.[1] The changes may be partially or fully reversible upon discontinuation or switching to alternative treatments.[1]

The mechanism of prostaglandin-associated periorbitopathy is not fully understood. Stimulation of the FP receptors by prostaglandin analogues may inhibit adipogenesis, leading to orbital fat atrophy.[8]

Figure 1: Patient with prostaglandin-associated periorbitopathy in one eye

Following unilateral treatment with a prostaglandin analogue, the patient developed PAP in the treated eye (arrow).

The images are used with the kind permission of the patient.

Advice for healthcare professionals[1]

Before starting treatment, inform patients of the possibility of changes to the eye during treatment. These changes are typically mild, can occur as early as one month after initiation of treatment and may cause impaired field of vision. Patients should also be aware that unilateral treatment may lead to differences in appearance between the eyes (as seen in Figure 1).

More information

- Minutes of the 190th MARC meeting
- Report presented to the MARC
- Search for a data sheet

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MARC's remarks: June 2022 meeting

The Medicines Adverse Reactions Committee (MARC) convened on 9 June 2022.

The Committee reviewed the risk of developing **serotonin syndrome from taking an opioid in combination with another serotonergic medicine**. The Committee considered that this risk differed between different opioids. The Committee recommended that where the interaction is clinically significant, the opioid data sheets should have a standardised warning statement on the risk of serotonin syndrome when taken with a serotonergic medicine. This includes the data sheets for opioids that are high risk (tramadol, pethidine and dextromethorphan) and those that are medium risk (higher doses of fentanyl and methadone). The Committee also recommended updates to the serotonergic medicine data sheets to reflect this interaction. See the Opioids and serotonergic medicines article on **page 32** of this edition of *Prescriber Update*.

The risk of birth defects and fetal cardiac malformations with **methylphenidate** exposure in the first trimester was discussed. The Committee considered that recent observational studies did not suggest an overall increased risk of birth defects. However, one study showed a small increased risk of cardiac malformations. The Committee recommended data sheet updates to reflect this study's results and to emphasise that prescribers should discuss the medicine's benefits and risks with the individual.

The Committee reviewed the risk of prostaglandin-associated periorbitopathy (PAP) with the **ocular prostaglandin analogues**: bimatoprost, latanoprost and travoprost. The Committee considered that the overall evidence indicated a class effect and that bimatoprost had the highest risk of PAP. The Committee recommended updates to the ocular prostaglandin analogue data sheets to include information on PAP. See also the Prostaglandin-associated periorbitopathy article on **page 35** of this edition of *Prescriber Update*.

The benefits and risks of **methenamine hippurate** were discussed. The Committee noted that the current evidence supporting its efficacy for the suppression or elimination of urinary tract bacteria is weak. However, it may play a role in antimicrobial stewardship. Overall, the Committee considered the risk-benefit balance was favourable. The Committee recommended that the sponsor provide a data sheet and consumer medicine information leaflet to ensure appropriate information is available for healthcare professionals and consumers. The Committee also considered that patients with recurrent urinary tract infection symptoms should consult with a healthcare professional. They recommended that the Medicines Classifications Committee review the general sale classification of methenamine hippurate.

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

Re-ad-DRESS-ing the risk of DRESS with cautious titration

Key messages

- Drug reaction with eosinophilia and systemic symptoms (DRESS) is a serious medicine-induced hypersensitivity reaction.
- Antiepileptic medicines, antibiotics and allopurinol are most frequently associated with DRESS.
- Titrate these medicines when commencing treatment to decrease the risk of DRESS.

The Centre for Adverse Reactions Monitoring (CARM) recently received a case report (CARM ID: 143028) of a patient who was started on allopurinol and developed drug reaction with eosinophilia and systemic symptoms (DRESS) and subsequently Stevens-Johnson syndrome (SJS).

DRESS[1]

DRESS is a serious, potentially life-threatening medicine-induced hypersensitivity reaction. This reaction is characterised by an extensive skin rash, visceral organ involvement, lymphadenopathy, eosinophilia and atypical lymphocytosis.

Most cases of DRESS have a clear medicine exposure. Pharmacogenetic studies have also identified an association between the risk of DRESS and several human leukocyte antigen (HLA) haplotypes and genetic variants.

Most patients recover from DRESS following cessation of the offending medicine. However, recovered patients are at risk of long-term autoimmune sequelae. DRESS can also be fatal, with a mortality rate between 2 and 10 percent. Severe organ involvement and multiorgan failure are the leading causes of death in DRESS patients.

Importance of titration

Titration involves changes to medicine doses to achieve the best clinical response at the lowest dose possible, with the intention of reducing unnecessary medicine use and adverse events.[2] There is indirect evidence that the risk of DRESS for certain medicines is dose-dependent.[1] For example, a review of DRESS cases induced by phenytoin has identified delayed phenytoin clearance and accumulation.[1]

High starting doses and rapid titration rates contribute to the risk of adverse effects such as DRESS.[3] Therefore, starting treatment with a low dose and gradual titration may decrease this risk.[3] Additionally, the latency between medicine initiation and the onset of DRESS is prolonged, typically between two to eight weeks.[1,4] A slow drug titration may allow more time to notice and diagnose early symptoms of DRESS.

Common offenders

Antiepileptics (carbamazepine, phenytoin, lamotrigine), allopurinol, vancomycin and sulfonamide-containing antibiotics are commonly associated with DRESS.[1] Refer to the medicine data sheets for information about the risk of DRESS and how to manage it.

Search for a data sheet

Allopurinol

When commencing allopurinol treatment for gout, start with a low dose and then gradually increase it until the serum urate target is achieved.[5] The medicine may be used long-term but must be stopped if a rash or other signs of allergy appear.[5]

The excretion of allopurinol and its metabolites is prolonged in patients with renal impairment.[5] Therefore, doses may be halved or reduced even further when beginning therapy and then slowly increased depending on patient response.[5,6] Additionally, renal impairment has an additive effect to genetic predisposition on the risk of allopurinol-induced DRESS and other severe cutaneous adverse reactions.[1]

Lamotrigine

Skin rash is a common adverse effect of lamotrigine and is likely to occur within the first eight weeks of treatment.[7] Skin rashes are usually mild, but may develop into a severe skin reaction in rare cases.[7] Lamotrigine-induced DRESS has been reported and is a well-known example of the relationship between dose, titration rate and rash.[3] When initiating lamotrigine treatment, it is important to start low and titrate slowly, as high initial doses or a rapid dose escalation increases the risk of severe adverse effects such as DRESS.[7–9]

Phenytoin[10]

DRESS has also been reported in patients taking phenytoin. Individualise the dose of phenytoin to obtain maximum benefit for the patient. Increase the dose at two-weekly intervals.

New Zealand case reports

Up until 17 June 2022, CARM had received 132 reports of DRESS. Some reports had more than one suspect medicine. The most frequently reported suspect medicines were allopurinol, vancomycin, carbamazepine and trimethoprim-sulfamethoxazole (Table 1). The data sheets for these medicines include warnings for DRESS.

Table 1: Suspect medicines* and number of DRESS reports

Suspect medicine	Number of DRESS reports
Allopurinol	37
Vancomycin	13
Carbamazepine	12
Trimethoprim-sulfamethoxazole	9
Amoxicillin	8
Piperacillin-tazobactam	8
Flucloxacillin	6
Lamotrigine	5

* The table only shows suspect medicines with 5 or more reports of DRESS.

Source: Centre for Adverse Reactions Monitoring

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Recent approvals: new active ingredients or new indications

For the period 16 April 2022 to 15 July 2022.

Recent approvals of medicines with new active ingredients

Trade name (active ingredient)	Dose form and strength(s)	Therapeutic area
Zematane (alitretinoin)	Liquid filled capsule 10 mg 30 mg	Eczema
Zeposia (ozanimod)	Capsule 920 mcg	Relapsing multiple sclerosis
Zeposia (ozanimod)	Combination capsule 230 + 460 mcg	Relapsing multiple sclerosis
Spikevax* (elasomeran)	Injection 0.2 mg/mL	COVID-19 prevention

* Provisional approval

Approved medicines with new indications

Trade Name (active ingredient)	Dose form and strength(s)	New therapeutic area(s)
Cabometyx (cabozantinib)	Tablet 20 mg 40 mg 60 mg	Advanced renal cell carcinoma
Actemra (tocilizumab)	Concentrate for infusion 20 mg/mL	COVID-19 treatment

See the Medsafe website for:

- **more information about these medicines**
- **data sheets of currently marketed medicines**.

Paradoxical acute inflammatory syndrome with mycophenolate mofetil

Key messages

- Acute inflammatory syndrome is a paradoxical pro-inflammatory adverse reaction associated with de novo purine synthesis inhibitors such as mycophenolate mofetil (MFM) and mycophenolic acid (MPA).
- Patients with this syndrome may present with fever, arthralgias, arthritis, muscle pain and elevated inflammatory markers.
- To date, the syndrome has only been associated with MFM and MPA, but it may occur with other purine synthesis inhibitors.

The New Zealand data sheet for **CellCept** (mycophenolate mofetil) was updated in January 2021 to include de novo purine synthesis inhibitor-associated acute inflammatory syndrome as a newly described paradoxical pro-inflammatory reaction.[1] This article provides information about this adverse reaction.

De novo purine synthesis inhibitors

Purines are the building blocks of DNA and RNA molecules and provide energy and cofactors to promote cell survival and proliferation.[2] They are involved in many biological processes, including immune responses and host–tumour interaction.[2] The *de novo* synthetic pathway is essential to replenish the purine pool.[2] De novo purine synthesis inhibitors interrupt this pathway and are therefore used as immunosuppressant medicines.

Mycophenolate mofetil (MPM) is a pro-drug that is rapidly metabolised to mycophenolic acid (MPA). MPA is an inhibitor of inosine monophosphate dehydrogenase, which inhibits the *de novo* pathway for guanosine nucleotide synthesis and subsequent proliferation of T- and B-lymphocytes.[1]

CellCept is the only MPM product available in New Zealand. It is indicated for the prophylaxis of solid organ rejection in adults receiving allogeneic organ transplants and in paediatric patients receiving allogeneic renal transplants.[1] There are no MPA products available in New Zealand.

De novo purine synthesis inhibitors-associated acute inflammatory syndrome

Acute inflammatory syndrome is a paradoxical pro-inflammatory adverse reaction associated with MPM and MPA.[3] The post-market frequency of this adverse reaction is uncommon (≥1/1,000 to <1/1000). Case reports describe a close temporal relationship between medicine use and the onset of acute inflammatory syndrome. Positive medicine de-challenge and re-challenge suggests a causal relationship.[3,4]

The mechanism behind acute inflammatory syndrome is not completely understood. Systemic pro-inflammatory cytokine release induced by MPA-acyl glucuronide (a metabolite of MPA) may contribute to syndrome onset.[5]

Patients with acute inflammatory syndrome may present with fever, arthralgias, arthritis, muscle pain and elevated inflammatory markers. Discontinuation of the medicine can lead to a rapid improvement in symptoms.[1]

To date, the syndrome has only been described with MPM and MPA, but it may occur with other purine synthesis inhibitors.

New Zealand information

As of 7 July 2022, the Centre for Adverse Reactions Monitoring had not received any reports of de novo purine synthesis inhibitors-associated acute inflammatory syndrome.

Advice for prescribers

- Be aware of the risk of acute inflammatory syndrome when prescribing mycophenolate mofetil.
- Consider acute inflammatory syndrome if patients show signs and symptoms of pyrexia, arthritis, arthralgia, myalgia and elevated inflammatory markers.
- If clinically appropriate, discontinue treatment. The available information suggests symptoms rapidly improve following treatment discontinuation.[1]

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We need your help!

MEDICINES MONITORING

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

Medicine(s)	Potential safety issue	Active monitoring ends
Oral anticoagulants	Abnormal uterine bleeding	28 February 2023

- 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.

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

Gathering knowledge from adverse reaction reports: September 2022

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]
CARM ID: 139501 **Age:** 77 **Gender:** Male **Medicine(s):** Finasteride **Reaction(s):** Breast cancer male	A patient taking long-term finasteride was diagnosed with male breast cancer.
	The **Ricit** data sheet states that a small number of cases of male breast cancer have been seen in clinical trials and in the post-market setting, but a causal relationship has not been established. The data sheet also states that physicians should counsel patients to report any breast changes or symptoms during treatment.
CARM ID: 140096 **Age:** 8 **Gender:** Male **Medicine(s):** Montelukast **Reaction(s):** Epistaxis	The patient experienced epistaxis within hours of commencing montelukast. He had no previous history of nosebleeds.
	Increased bleeding tendency (rare) and epistaxis (uncommon) are listed as adverse reactions in the **Montelukast Mylan** data sheet.
CARM ID: 143342 **Age:** 73 **Gender:** not reported **Medicine(s):** Tolvaptan **Reaction(s):** Hepatorenal syndrome, hepatic failure, encephalopathy	Two months after starting tolvaptan, the patient developed mild hepatic impairment. This worsened to severe impairment and tolvaptan was stopped. The patient subsequently developed liver failure, hepato-renal syndrome and hepatic encephalopathy.
	Section 4.4 of the **Jinarc** data sheet provides detailed safety measures to mitigate the risk of significant and irreversible liver injury. This includes blood testing for hepatic transaminases and bilirubin before initiating treatment and regularly throughout treatment. Monitoring for symptoms of liver injury is also recommended. Treatment must be interrupted at the onset of symptoms or signs consistent with liver injury and may need to be permanently discontinued.

Case details[a,b]	Reaction description and data sheet information[b,c]
CARM ID: 143508 **Age:** 66 **Gender:** Female **Medicine(s):** Clozapine, codeine phosphate, oxybutynin **Reaction(s):** Constipation, megacolon	A patient taking long-term clozapine was prescribed oxybutynin and codeine. She was admitted to hospital with a severe bowel obstruction.
	The **Clopine** and **Clozaril** data sheets state that clozapine has been associated with varying degrees of impairment of intestinal peristalsis, ranging from constipation to intestinal obstruction, faecal impaction, paralytic ileus, megacolon and intestinal infarction/ischaemia. Particular care is necessary in patients who are receiving concomitant medicines known to cause constipation. Constipation is described as a common side effect in the **Codeine phosphate PSM** data sheet. There are no approved oxybutynin products in New Zealand. However, the **New Zealand Formulary monograph for oxybutynin** lists constipation as an adverse effect.
CARM ID: 143793 **Age:** 61 **Gender:** Female **Medicine(s):** Amitriptyline **Reaction(s):** Blindness, glaucoma	The patient was prescribed daily amitriptyline for an unapproved use. Approximately a year later, she developed acute angle glaucoma in one eye that progressed to permanent blindness.
	Acute glaucoma is listed as a very rare ADR in the **Arrow-Amitriptyline** data sheet.
CARM ID: 144121 **Age:** 89 **Gender:** Female **Medicine(s):** Nirmatrelvir + ritonavir**,** felodipine, donepezil, candesartan **Reaction(s):** Drug interaction, syncope, hypotension, bradycardia	A patient with severe renal impairment was prescribed a full dose of Paxlovid. Concomitant medicines included felodipine, donepezil and candesartan. On day 4 of Paxlovid treatment, she experienced collapse, hypotension and bradycardia. An interaction with felodipine was suspected.
	The **Paxlovid** data sheet states that the appropriate dose for patients with severe renal impairment has not been determined and it is contraindicated in these patients. Paxlovid inhibits CYP3A and may increase plasma concentrations of medicines that are primarily metabolised by CYP3A. Caution is warranted when Paxlovid is co-administered with calcium channel blockers, including felodipine. Clinical monitoring of patients is recommended, and a dose decrease of the calcium channel blocker may be needed. The **Felo ER** data sheet states that felodipine is metabolised by CYP3A4. Concomitant administration of medicines which interfere with CYP3A4 may affect plasma concentrations of felodipine.

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 to CARM, and do not always match the MedDRA term.

c. 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)**.

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).

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**.

Date	Communication	Topic
29/08/2022	Monitoring	Update – Possible risk of vasculitis with vildagliptin products (Galvus, Galvumet)
25/08/2022	Monitoring	Abnormal uterine bleeding and oral anticoagulants (blood thinners)
27/07/2022	Consultation	Outcome of the consultation on the proposed warning and advisory statements relating to the harm of opioid abuse
13/07/2022	Alert	Medsafe is publishing a warning that the product Nhan Sam Tuyet Lien Truy Phong Hoan should not be consumed
11/07/2022	Consultation	Proposed warning and advisory statement for ocular decongestants used for eye redness and/or minor eye irritation
30/06/2022	Alert	Accuretic found to contain nitrosamines
27/07/2022	Consultation	Outcome of the consultation on the proposed warning and advisory statements relating to harm of long-term use and overuse of stimulant laxatives
20/06/2022	Dear Healthcare Professional Letter	Comirnaty – Presentations available in New Zealand (PDF, 2 pages, 813 KB)
09/06/2022	Dear Healthcare Professional Letter	Supply of Canadian-labelled Coversyl 2 mg, 4 mg and 8 mg perindopril erbumine tablets in New Zealand (PDF, 3 pages, 260 KB)
07/06/2022	Alert	Typographical error in Healgen Rapid COVID-19 Antigen Self-Test (RATs) patient instruction leaflet

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Data sheets, consumer medicine information, media releases, medicine classification issues and adverse reaction forms are available at **medsafe.govt.nz**

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