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REMINDER: Avoid teratogenic medicines in pregnancy

Key messages

- Avoid prescribing teratogenic medicines for people of childbearing potential whenever possible.
- If a person of childbearing potential requires treatment with a teratogenic medicine, ensure they are aware of the risk of harm to the fetus and agree to adhere to the pregnancy prevention measures specified in the data sheet.
- The period for pregnancy avoidance after stopping a teratogenic medicine varies depending on the medicine. For example, the period is three years (36 months) after stopping treatment with acitretin (Novatretin).
- Caution is needed when prescribing a medicine that interferes with contraceptive effectiveness in a person being treated with a teratogenic medicine.

Use of medicines in pregnancy is common

Medicine exposure during pregnancy is common¹⁻⁴ and increasing.³ A recent study of prescription medicine dispensing patterns in pregnant women in New Zealand found that 67.2 percent of pregnancies in 2015 were exposed to a non-supplement prescription medicine.³

Use of medicines during pregnancy may be necessary to manage underlying chronic conditions (eg, diabetes mellitus, asthma, epilepsy), acute illness (eg, infection), or a pregnancy-related condition (eg, hyperemesis, gestational diabetes, hypertension, deep vein thrombosis). Treating such conditions is important for both maternal and fetal health.

Medicine exposure in pregnancy may occur inadvertently as over half of pregnancies in New Zealand are unplanned.⁵

Prescribing medicines to people of childbearing potential

Consider the possibility of pregnancy when prescribing medicines for a person of childbearing potential. If possible, select a therapeutic option that would be safe in pregnancy.

For short-term treatments, use the lowest effective dose for the shortest possible time to limit the possibility of exposure in the event of an unplanned pregnancy.

The [New Zealand Formulary](#) and the [New Zealand data sheets](#) are useful sources of information about medicine use in pregnancy.

Avoid teratogenic medicines in people of childbearing potential

Teratogenic medicines should be avoided in people of childbearing potential whenever possible.

If it is necessary to prescribe a teratogenic medicine to a person of childbearing potential, the person must be fully informed of the nature and level of risk of harm to the fetus if pregnancy occurs.

Pregnancy must be excluded before starting treatment with the teratogenic medicine. The person must use effective contraception without interruption from one month before treatment, for the duration of treatment and for a specified period (depending on the medicine) after stopping treatment. The period for continuing pregnancy prevention measures after treatment cessation varies for different medicines and is specified in the data sheet.

For example, pregnancy prevention measures must continue to be used for one month after stopping treatment with isotretinoin (Oratane).⁶ The person must not become pregnant for three years (36 months) after stopping treatment with acitretin (Novatretin).^{7,8}

See section 4.4 of the data sheet for detailed pregnancy prevention measures. Medsafe publishes pharmaceutical company data sheets on the Medsafe website.

- [Search for a data sheet](#)

Pharmaceutical companies may also publish educational materials for healthcare professionals and people about the risk of exposure in pregnancy. Educational materials are available for:

- [Epilim \(sodium valproate\)](#)
- [Oratane \(isotretinoin\)](#).

People should avoid unplanned pregnancy while taking a teratogenic medicine

People on treatment with a teratogenic medicine for a defined length of time, such as isotretinoin for acne, must defer pregnancy until after treatment.

Some people will want to have a child whilst taking a long-term teratogenic medicine such as sodium valproate. This requires careful planning before pregnancy to limit the risk of harm to the fetus and enable optimal treatment for the person during pregnancy.⁹

Sodium valproate for the treatment of bipolar disorder is contraindicated in pregnancy. A person on sodium valproate for bipolar disorder should be reviewed by a specialist experienced in the management of bipolar disorder and switched to a suitable alternative treatment prior to pregnancy.^{10,11}

In the treatment of epilepsy, sodium valproate is contraindicated in pregnancy unless there is no suitable alternative treatment.¹⁰ For these people, pregnancy must be carefully planned, including referral to a specialist experienced in the management of epilepsy for advice, prior to conception.¹⁰

If an unplanned pregnancy occurs while on treatment with sodium valproate, urgent specialist consultation is required to reassess the benefits and risks of continuing the medicine. Sudden discontinuation of antiepileptic therapy should be avoided as it may lead to breakthrough seizures, which could have serious consequences for both the person and fetus.^{10,12}

Use of teratogenic medicine by male partner

For some medicines, the teratogenic risk also extends to use by a male partner. For example, lenalidomide, which is indicated for the treatment of multiple myeloma and myelodysplastic disorders, is structurally related to thalidomide. Lenalidomide is present in semen during treatment. Males on treatment with lenalidomide must comply with contraception requirements detailed in the data sheet.¹³

Interactions with contraception

Caution is needed if prescribing a medicine that may interfere with contraceptive effectiveness in a person who is on treatment with a teratogenic medicine.

Medicines that induce hepatic metabolism by the CYP3A4 enzyme (eg, rifampicin, carbamazepine, phenytoin, St John's wort, topiramate) reduce the effectiveness of oral hormonal contraceptives.¹⁴

People taking a teratogenic medicine should also be aware that diarrhoea and vomiting reduce the absorption of oral hormonal contraceptive pills, which may result in contraceptive failure.¹⁴ They should seek medical advice on how to manage this situation.

New Zealand case reports

Up to 30 June 2021, the Centre for Adverse Reactions Monitoring (CARM) had received 70 reports of congenital malformation or neurodevelopmental adverse effects associated with exposure to one or more medicines during pregnancy. In recent years, most of these reports have been for fetal valproate syndrome or autism associated with sodium valproate exposure during pregnancy.

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Paediatric recommendations for chloramphenicol eye drops

Key messages

- When prescribing chloramphenicol eye drops to children aged under two years, the recommended dose is one drop in the affected eye(s) four times daily for five days.
- This recommended paediatric dose is associated with boron exposure that is below the threshold of concern for reproductive toxicity. Animal studies have found that boron exposure could be associated with reproductive toxicity, but the relevance to humans is uncertain.
- Boric acid and borates are boron-containing excipients contained in some eye drops, including chloramphenicol eye drops.

The paediatric dosing recommendations in the chloramphenicol eye drops data sheets are being updated to include dosing recommendations for children aged under two years. However, the updated dosing recommendations reflect conventional clinical practice.

Boric acid and borates

Boric acid and borates are excipients that are mainly used as pH buffers and antimicrobial preservatives in eye drops. These excipients contain boron. There has been concern that boron exposure may be associated with reproductive toxicity.¹

Advice for healthcare professionals

Eye infections are common in young children and require prompt treatment to prevent ocular complications. Chloramphenicol eye drops and ointment are a first-line treatment for superficial eye infections in children.²

The recommended dosage regimen for children aged under two years is one drop in the affected eye(s) four times daily for five days.³ This dose is associated with boron exposure that is below the threshold of concern for reproductive toxicity. In Europe, 1 mg of boron per day is the threshold for a safety warning for use in children aged under two years.¹

Chloramphenicol eye ointment is an alternative or additive to treatment with eye drops that does not contain boric acid or borates.³

New Zealand regulatory action

The Medicines Adverse Reactions Committee discussed the risk of reproductive toxicity with boron-containing excipients at the 186th meeting on 10 June 2021.⁴

The Committee noted that the data is limited to animal studies, which have shown toxicities such as effects on sperm parameters and decreased birth weight with high doses of boric acid.¹ The Committee considered that the relevance of the animal data to humans is uncertain. Although human studies have not shown reproductive toxicity, they were not sufficiently robust to rule out this risk.

Chloramphenicol eye drop products may contain more than 1 mg boron in the maximum daily dose. The Committee recommended that the data sheets for chloramphenicol eye drop products should reflect the conventional dosing regimen for children aged under two years: one drop in the affected eye(s) four times daily for five days. This paediatric dose is associated with a boron exposure below the threshold of concern for reproductive toxicity.

International regulatory action

The European Medicines Agency (EMA) reviewed the reproductive toxicity of boric acid and borates in 2017. The EMA requires consumer warnings about boron and fertility concerns for medicinal products that exceed certain thresholds for boron content.¹

In July 2021, the United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA) reviewed the risk of reproductive toxicity with the use of chloramphenicol eye drops containing boric acid and borates in children aged under two years. The MHRA concluded that benefits of chloramphenicol eye drops outweigh the risks in this age group.⁵

More information

- See the MARC [meeting minutes](#) and the [report](#) presented to the MARC.
- [Search for a data sheet.](#)

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MARC's remarks: September 2021 meeting

The Medicines Adverse Reactions Committee (MARC) convened via videoconference on 9 September 2021.

The benefits and risks of **phentermine** were discussed. The Committee noted that although the evidence regarding safety and efficacy is limited, phentermine has a role in bariatric medicine. The Committee considered that the benefits of treatment with phentermine outweigh the risks of harm and no further action is needed.

The risk of fetal renal impairment and oligohydramnios with the use of **non-steroidal anti-inflammatory drugs (NSAIDs)** during the second trimester of pregnancy was discussed. The Committee recommended that the pregnancy information should be aligned across all NSAID data sheets and should include a warning about the risk of oligohydramnios in the second trimester. A harmonised statement will be agreed on at a future meeting. The Committee also recommended that the safety of NSAIDs in the third trimester of pregnancy should be discussed at this future meeting as this information is not consistent across NSAID data sheets.

See the Medsafe website for the [MARC meeting minutes](#) and the [reports presented to the MARC](#).

Test your knowledge: The *Prescriber Update* quiz 2021

Have you been reading *Prescriber Update* in 2021?

Have you kept up to date with emerging safety signals?

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

Answers to the quiz are on page 61 and the [Medsafe website](#).

- 1. Which of the following medicines can increase potassium levels?**
a. Amiloride b. Losartan c. Cilazapril d. All of the above
- 2. The increased risk of angioedema associated with concomitant use of vildagliptin and an ACE inhibitor is thought to be related to:**
a. Reduced degradation of bradykinin and substance P
b. Increased degradation of bradykinin and substance P
c. Increased activity of DPP-IV
d. Deficiency of CYP2D6
- 3. What is the recommended dose of chloramphenicol eye drops for children aged under two years?**
- 4. What is the reported frequency of thrombocytopenia and pancytopenia in the sodium valproate data sheet?**
a. Thrombocytopenia: uncommon; Pancytopenia: uncommon
b. Thrombocytopenia: common; Pancytopenia: common
c. Thrombocytopenia: common; Pancytopenia: uncommon
d. Thrombocytopenia: uncommon; Pancytopenia: common
- 5. In clinical trials for treatment of neuropathic pain, what were the most commonly reported reasons for patients discontinuing treatment with pregabalin or gabapentin?**
- 6. Fingolimod is an immunomodulating drug indicated for the treatment of relapsing multiple sclerosis. Which of the following are recognised adverse effects of this drug?**
a. Renal impairment b. Clinically significant liver injury c. Acute liver failure
d. a and c e. b and c
- 7. Omalizumab is a monoclonal antibody drug used in the treatment of asthma. Which component of the immune system is the target of this drug?**
a. IL-6 b. IL-5 c. IgE d. IgM
- 8. Which of the following is incorrect? To prevent adrenal insufficiency, dose tapering of prednisone is generally required for patients who have:**
a. Been given repeat prednisone doses in the evening
b. Received more than 10 mg of prednisone per day for more than one week
c. Recently had repeated courses
d. Received prednisone for more than 3 weeks
- 9. Which of the following is NOT a risk factor for developing diabetic ketoacidosis in patients being treated with empagliflozin?**
a. A low carbohydrate diet b. Increasing insulin dose
c. Prolonged fasting d. Surgery
- 10. What is the length of time that a patient must not become pregnant for after stopping treatment with acitretin (Novatretin)?**

Kratom – not such a nice cup of tea

Key messages

- Kratom is a herbal substance which has psychotropic and opioid-like effects and can be addictive. Kratom has not been shown to have any beneficial medical uses.
- Patients taking natural health products containing kratom may be at risk of serious adverse reactions, such as acute liver injury.
- Advise patients to always check the ingredients of any natural health products or dietary supplements carefully before use.

A case has been reported to the Centre for Adverse Reactions Monitoring (CARM) where the individual developed a hepatic reaction in relation to use of kratom.

What is kratom?

Kratom is a herbal substance made from the leaves of a tropical evergreen tree (*Mitragyna speciosa* or kratom tree – Figure 1), which belongs to the coffee family.¹ This tree is indigenous to South East Asia, the Philippines, New Guinea and parts of Africa but also cultivated elsewhere.¹⁻³ The main active alkaloid substances in kratom are called mitragynine and 7-hydroxymitragynine (7-HMG).³

Use and misuse of kratom¹

Extracts from the leaves of the kratom tree have shown psychotropic (mind-altering) and opioid-like activity and kratom has been used in traditional medicine to treat chronic pain and diarrhoea, increase energy and stamina and as a substitute for opium or for opium withdrawal. In many countries in Southeast Asia, chewing *Mitragyna speciosa* leaves is a common practice. However, kratom has not been shown to have any beneficial medical uses. Instead, these effects of kratom leaves have led to their use and misuse as a recreational drug. Regular kratom use can be addictive and result in adverse reactions.

Effects and side effects

The plant's dark green leaves are usually dried and either crushed or powdered and turned into a paste, capsules, tablets or brewed as a tea. In general, the effects of kratom in humans are dose-dependent: small doses produce 'cocaine-like' stimulation, while larger dosages cause 'morphine-like' sedative-narcotic effects.^{2,3} Higher doses can cause agitation, hypertension, psychosis, respiratory depression, seizures, depression and confusion, and overdoses can be fatal, especially if kratom is used together with other potent substances.^{1,4}

Chronic use of kratom recreationally has in rare cases been associated with acute liver injury.¹ Onset of injury was within 1 to 8 weeks of starting regular use of kratom powder or tablets, with symptoms of fatigue, nausea, pruritus, and dark urine followed by jaundice. The liver injury was cholestatic or mixed, sometimes severe, and complicated by acute renal failure and bone marrow toxicity. Recovery usually occurred if kratom was stopped.

Figure 1: *Mitragyna speciosa*



Source: Wikimedia Commons contributors. File: Mitragyna speciosa (Korth.) Havil.jpg
Wikimedia Commons, the free media repository. URL: commons.wikimedia.org/w/index.php?title=File:Mitragyna_speciosa_(Korth.)_Havil.jpg

Regulation of kratom

Kratom use is prohibited in many countries and parts of the United States.^{3,5} In New Zealand, *Mitragyna speciosa* is classified as a prescription medicine to control use, and it is prohibited to be used in herbal remedies under section 2 of the Medicines Act 1981. Kratom is not approved for any kind of medical use or allowed in dietary supplements.

As Medsafe does not monitor the safety or purity of herbal substances unless they are in an application for approval of a medicine, there is no quality control over any kratom that may be imported in unapproved medicines (which includes herbal products).

As for all herbal products, kratom products may be of poor quality, may be sub or super potent, contaminated, adulterated or counterfeit, and its use can put people at serious risk of unpredictable or severe adverse reactions.

Imported kratom for personal use that is detected at the border is referred to Medsafe and can only be released on the authority (and responsibility) of a medical practitioner.

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Recent approvals: new active ingredients or new indications

For the period 16 July 2021 to 15 October 2021.

Recent approvals of medicines with new active ingredients

Trade name (active ingredient)	Dose form and strength(s)	Therapeutic area
Xofluza (baloxavir marboxil)	Film-coated tablet 20 mg 40 mg	Influenza
Calquence (acalabrutinib)	Capsule 100 mg	Mantle cell lymphoma Chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL)
Piqray (alpelisib)	Film-coated tablet 200 mg 250 mg (200 mg + 50 mg) 300 mg (150 mg +150 mg)	Hormone receptor positive, HER2-negative, advanced or metastatic breast cancer with a PIK3CA mutation
Trumenba (<i>Neisseria meningitidis</i> group B factor H binding protein subfamily A + subfamily B)	Suspension for injection 120 mcg/0.5 mL	Meningococcal B disease
Trulicity (dulaglutide)	Solution for injection 3 mg/mL	Type 2 diabetes mellitus

Approved medicines with new indications

Trade name (active ingredient)	Dose form and strength(s)	New therapeutic area(s)
Rinvoq (upadacitinib hemihydrate)	Modified release tablet 15 mg	Atopic dermatitis
Vicks Vaporub (eucalyptus oil; menthol)	Topical ointment 1.33%; 2.82%	Headache
Keytruda (pembrolizumab)	Concentrate for infusion 25 mg/mL	Oesophageal cancer

See the Medsafe website for:

- [more information about these medicines](#)
- [data sheets of currently marketed medicines.](#)

A bitter pill to swallow – medicines that can cause taste disturbances

Key messages

- Medicines have been reported to cause taste disturbances by altering the perception of taste, decreasing or heightening taste sensitivity, or causing a total loss of taste. The mechanisms behind these disturbances are often unknown.
- Although medicine related taste disturbances may not be considered a life-threatening adverse reaction, healthcare professionals should be aware that this can impact on patients' medication adherence, food intake and nutritional status.

Medicines have been reported to cause taste disturbances by:^{1,2}

- altering the perception of taste giving a markedly sweet, sour, salty, bitter, or metallic taste (dysgeusia)
- decreasing taste perception (hypogeusia)
- heightening taste sensitivity (hypergeusia)
- causing a total loss of taste (ageusia).

The mechanisms responsible for taste disturbances are often unknown

Each medicine has unique, often unknown, mechanisms that cause taste disturbances.¹ Some mechanisms may involve the following.

- The direct actions of the medicine through drug-receptor interaction, disturbance of action potential propagation in cell membranes of afferent and efferent neurons, and alteration of neurotransmitter function.³
- Limiting the access of taste substances to sensing receptors (ie, through drying the mucosa, increasing nasal congestion, and closing off taste pores) which can alter the perception of taste.³
- Changing the composition or quantity of saliva. Saliva plays a role as a solvent and transportation medium for taste substances to the taste bud.⁴
- A drug-drug pharmacokinetic interaction resulting in elevated blood-plasma levels of one medicine beyond therapeutic concentrations.¹

There are also significant individual differences in vulnerability to medicine related taste disturbances. Factors likely involved include differences in the dose of the medicine and patient-specific factors, such as genetic polymorphism, age, and other medical conditions.¹

Medicines reported as causing taste disturbances

Table 1 outlines examples of medicines reported to CARM causing taste disturbances.

Table 1: Examples of medicines reported to the Centre for Adverse Reactions Monitoring as causing taste disturbances

Medicine	What the data sheet says
Terbinafine	The Deolate data sheet states taste disturbances, including taste loss has been observed as uncommon ^a in clinical trials or during post-marketing experience. Taste may recover several weeks after discontinuing terbinafine. Remote situations of extended taste disturbances have been observed.
Atorvastatin	The Lorstat data sheet states that in post-marketing experience, dysgeusia has been reported as rare adverse event.
Metoprolol succinate	The Betaloc CR data sheet states taste disturbances is a very rare ^a adverse reaction.
Omeprazole ^b	The Losec data sheet states taste disturbance has been identified in clinical trials and post-marketing setting as rare. ^a
Varenicline	The Varenicline Pfizer data sheet states dysgeusia has been reported in studies at a rate $\geq 1\%$ and with an incidence higher than that for placebo.
Zopiclone	The Zopiclone Actavis data sheet states taste alteration (bitter taste) is the most commonly seen adverse reaction in clinical trials.

Notes:

- Adverse reactions are graded under frequency using the following principle: very common (1/10); common (1/100 to < 1/10); uncommon (1/1,000 to < 1/100); rare (1/10,000 to < 1/1,000); and very rare (< 1/10,000).
- In 2009, there was an increase in the number of adverse event case reports for omeprazole. While most of the cases were reporting a brand switch, taste disturbances were co-reported for some of them.

Complications and practice considerations

Although a medicine causing taste disturbances may not be considered a life-threatening adverse reaction, it can have a negative impact on patients' medication adherence, food intake and nutritional status.¹ Patients may compensate for bitter taste or dry mouth by increasing their fluid intake and the resulting increase in urinary frequency can increase the risk of falls or incontinence particularly in the elderly. Increased salt or sugar intake may complicate the management of underlying medical conditions such as diabetes and hypertension.⁵

Healthcare professionals should consider whether poor medication adherence, changes in eating habits or weight loss are attributed to medicine related taste disturbances. Monitoring weight and the early provision of dietary advice can help minimise effects on nutritional status.⁵

There is no standard treatment for medicine related taste disturbances as each medicine will have a unique, often unknown, mechanism causing this disturbance.¹ For most medicines, stopping or changing the dose of the suspected medicine or switching to another medicine are logical approaches to reversing taste disturbance over time.⁶

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Consider thromboembolic events in patients given omalizumab

Key messages

- Omalizumab is a monoclonal antibody indicated for the treatment of allergic asthma and chronic idiopathic urticaria.
- Thromboembolic events have been observed in patients being treated with omalizumab.

Thromboembolic events associated with omalizumab treatment (brand name Xolair) have been observed in clinical trials and reported in the post-marketing setting, including in New Zealand. The Health and Disability Commissioner recently reported on a case where the patient had been treated with omalizumab and experienced fatal ischaemic bowel.

Omalizumab

Omalizumab is a recombinant monoclonal antibody that selectively binds to free but not receptor-bound human immunoglobulin E (IgE).^{1,2} IgE plays an important role in many diseases such as allergic asthma and chronic idiopathic urticaria.³ Omalizumab blocks acute IgE-mediated responses to inhaled and ingested allergens and late-phase responses to inhaled allergens.²

Xolair is approved for the treatment of allergic asthma and chronic idiopathic urticaria.¹

Thromboembolic events

The Xolair data sheet states that a higher rate of arterial thromboembolic events in Xolair-treated patients has been shown in studies compared with control patients.¹ Arterial thromboembolic events included stroke, transient ischemic attack, myocardial infarction, unstable angina and cardiovascular death.¹

A review of safety studies by the United States Food and Drug Administration suggested a slightly increased risk of adverse reactions involving the heart and blood vessels supplying the brain in patients being treated with omalizumab.⁴ The United Kingdom's Medicines and Healthcare products Regulatory Agency also highlighted a potential risk of thrombotic adverse reactions with omalizumab; however, the finding was not statistically significant at the 95 percent level.⁵

Prescribers should be observant of thromboembolic events in patients being treated with omalizumab.

Refer to the [Xolair data sheet](#) and the [Health and Disability Commissioner's report](#) on the case mentioned above for more information.

References

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Gathering knowledge from adverse reaction reports: December 2021

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: 141199</p> <p>Age: 16</p> <p>Gender: Female</p> <p>Medicine(s): Tramadol, sertraline</p> <p>Reaction(s): Seizure</p>	<p>A patient taking tramadol and sertraline experienced seizures.</p> <p>The Arrow-Tramadol data sheet states that tramadol can induce convulsions and increase the potential for selective serotonin re-uptake inhibitors (eg, sertraline) and other seizure threshold lowering agents to cause convulsions. The Setrona data sheet states that the risk of serotonin syndrome with SSRIs is increased with concomitant use of serotonergic medicines, including tramadol. Co-administration of sertraline with other medicines that enhance the effects of serotonergic neurotransmission, such as tramadol should be undertaken with caution and avoided whenever possible.</p>
<p>CARM ID: 141227</p> <p>Age: 13</p> <p>Gender: Male</p> <p>Medicine(s): Terbinafine</p> <p>Reaction(s): Stevens-Johnson syndrome</p>	<p>Three weeks after starting treatment with terbinafine, the patient developed a rash and mouth ulcers. He also had deranged liver function tests. Stevens-Johnson syndrome was suspected.</p> <p>Stevens-Johnson Syndrome is listed as a very rare adverse reaction in the Deolate data sheet. Treatment must be discontinued if a skin rash develops.</p>

Case details ^{a,b}	Reaction description and data sheet information ^{b,c}
<p>CARM ID: 141350</p> <p>Age: 79</p> <p>Gender: Male</p> <p>Medicine(s): Digoxin</p> <p>Reaction(s): Toxicity to various agents</p>	<p>A patient taking a daily dose of 500 mcg of digoxin developed signs of toxicity, including blurred vision, bradycardia, visual hallucinations, confusion and unsteadiness. His digoxin level was measured at 8.6 nmol/L.</p> <p>The therapeutic serum digoxin concentration range is 0.8 to 2 ng/mL (1 to 2.6 nmol/L). The Lanoxin data sheet states that digoxin toxicity is more commonly associated with serum digoxin concentration greater than 2 ng/mL. However, serum digoxin concentration should be interpreted in the clinical context. Toxicity may occur with lower digoxin serum concentrations. In deciding whether a patient's symptoms are due to digoxin, the clinical state together with the serum potassium level and thyroid function are important factors. For elderly patients, high serum digoxin levels and associated toxicity can occur quite readily, unless doses lower than those in non-elderly patients are used.</p>
<p>CARM ID: 141825</p> <p>Age: 51</p> <p>Gender: Male</p> <p>Medicine(s): Ciprofloxacin</p> <p>Reaction(s): Arthralgia, muscular weakness, tendonitis, dyspnoea, disturbance in attention</p>	<p>The patient experienced ongoing symptoms several months after stopping ciprofloxacin.</p> <p>The Cipflox data sheet states that fluoroquinolones, including ciprofloxacin, have been associated with disabling and potentially persistent adverse reactions involving different body systems that have occurred together in the same patient. These include, but are not limited to, serious adverse reactions involving the nervous system and the musculoskeletal system. Tendinitis and tendon rupture (predominantly Achilles tendon) sometimes bilateral, may occur with ciprofloxacin, even within the first 48 hours of treatment. Cases occurring up to several months after completion of ciprofloxacin therapy have been reported. Advise patients that if any sign of tendonitis occurs (eg, painful swelling, inflammation), they should rest the affected extremity, avoid inappropriate physical activity and seek medical advice. The antibiotic treatment should be discontinued.</p>
<p>CARM ID: 135982</p> <p>Age: 43</p> <p>Gender: Male</p> <p>Medicine(s): Clozapine</p> <p>Reaction(s): Death, colitis, megacolon, sepsis</p>	<p>A patient taking clozapine experienced constipation and was prescribed laxatives. Some months later, the patient was found unresponsive in bed and he subsequently passed away. The post-mortem identified megacolon with evidence of colitis, possibly leading to sepsis.</p> <p>The Clopine and Clozaril data sheets state that careful monitoring for constipation is required during treatment with clozapine and patients should be questioned about their bowel habits. Onset of constipation must be identified early and managed effectively to prevent complications. 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.</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 \(SMARS\)](#).

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
	COVID-19	Adverse events following immunisation with COVID-19 vaccines
17/11/2021	Monitoring	Menstrual disorders and unexpected vaginal bleeding – Comirnaty (Pfizer COVID-19 vaccine)
17/11/2021	Monitoring	COVID-19 vaccination in pregnancy: no safety concerns with Comirnaty (Pfizer COVID-19 vaccine)
15/11/2021	Alert	Consent to distribute medicines containing bufexamac was revoked on 9 November 2021
21/10/2021	Dear Healthcare Professional Letter	Supply of Actemra (tocilizumab) 162 mg/0.9 mL solution for subcutaneous (PDF, 4 pages, 753 KB)
11/10/2021	Dear Healthcare Professional Letter	Supply of Actemra (tocilizumab) for hospital use (PDF, 4 pages, 753 KB)
06/09/2021	Dear Healthcare Professional Letter	Notification of temporary supply shortage for Actemra (tocilizumab) (PDF, 2 pages, 215 KB)
06/09/2021	Alert	Risks of importing or prescribing ivermectin for prevention or treatment of COVID-19

Hypocalcaemia – increased risk with concomitant use of denosumab and cinacalcet

Key messages

- Hypocalcaemia is a well-established risk of treatment with both denosumab and cinacalcet, and concomitant use may worsen the risk.
- See the respective data sheets for recommendations for reducing the risk of hypocalcaemia, and closely monitor serum calcium levels if concomitant treatment with denosumab and cinacalcet is required.

The denosumab data sheets are being updated to include a warning for increased risk of hypocalcaemia with concomitant use of denosumab and cinacalcet.

Denosumab

Denosumab is a monoclonal antibody that inhibits osteoclast formation, function and survival, thereby decreasing bone resorption and increasing bone mass and strength.^{1,2}

Denosumab is indicated to prevent skeletal-related events from osteoporosis and metastatic bone disease.³ There are two denosumab products approved and available in New Zealand: Prolia and Xgeva.

Cinacalcet

Cinacalcet is a calcimimetic – a medicine that mimics the action of calcium on tissues and reduces secretion of parathyroid hormone. This action decreases the serum calcium and phosphate levels.⁴

Cinacalcet is indicated for treatment of secondary hyperparathyroidism in dialysis patients with end-stage renal disease, hypercalcaemia in adult patients with parathyroid carcinoma, and primary hyperparathyroidism in adult patients for whom parathyroidectomy is not a treatment option.⁵ Sensipar is the only cinacalcet product that is approved and available in New Zealand.

Hypocalcaemia

The clinical manifestations of hypocalcaemia depend upon the severity and chronicity of hypocalcaemia and can range from few (if any) symptoms if the hypocalcaemia is mild, to life-threatening symptoms if it is severe.⁶

Due to their mechanisms of action, denosumab and cinacalcet are both independently associated with hypocalcaemia. Clinical manifestations of hypocalcaemia reported following treatment with either medicine include paraesthesias, muscle stiffness, twitching, spasms and muscle cramps.^{1,2,5} Life-threatening events, including seizures, QT prolongation and tetany, and fatal outcomes have also been reported.^{1,2,5}

See the respective data sheets for recommendations for reducing the risk of hypocalcaemia, including testing of serum calcium levels prior to initiation of treatment and monitoring levels during treatment:

- [Prolia \(denosumab\) data sheet](#)
- [Xgeva \(denosumab\) data sheet](#)
- [Sensipar \(cinacalcet\) data sheet.](#)

Concomitant use of denosumab and cinacalcet may worsen the risk of hypocalcaemia. The denosumab data sheets are being updated to include this information. The cinacalcet data sheet already includes warnings about concomitant use with medicines known to lower serum calcium.

Closely monitor serum calcium levels if concomitant denosumab and cinacalcet treatment is required.

New Zealand case reports

Up to 30 June 2021, the Centre for Adverse Reactions Monitoring (CARM) had received two reports of hypocalcaemia associated with use of denosumab (CARM IDs: 128578 and 139291). There have been no reports of hypocalcaemia associated with use of cinacalcet and no reports with concomitant use of denosumab and cinacalcet.

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Quiz answers

1. **d.** Potassium-sparing diuretics, ACE inhibitors and angiotensin receptor blockers are associated with hyperkalaemia. (September 2021)
2. **a.** Substance P and bradykinin are vasodilators involved in the pathogenesis of angioedema. ACE and DPP-4 are involved in the degradation of substance P, and ACE is one of the enzymes that degrade bradykinin. Compared with inhibition of ACE or DPP-4 alone, inhibition of both enzymes by the combined use of an ACE inhibitor and vildagliptin increases the risk of accumulation of substance P and bradykinin, resulting in angioedema. (March 2021)
3. The recommended dose of chloramphenicol eye drops for children aged under two years is one drop in the affected eye(s) four times daily for five days. (December 2021)
4. **c.** Sodium valproate treatment is associated with adverse haematological effects. Thrombocytopenia is a common adverse reaction, while pancytopenia is an uncommon adverse reaction. (September 2021)
5. Dizziness and somnolence. In clinical trials for treatment of neuropathic pain, dizziness and somnolence were the most commonly reported adverse events for pregabalin and gabapentin compared to placebo. Dizziness and somnolence were also the most commonly reported reasons for treatment discontinuation for both medicines. (March 2021)
6. **e.** Clinically significant liver injury and acute liver injury are recognised adverse effects of fingolimod. (September 2021)
7. **c.** Omalizumab is a monoclonal antibody which binds to free Immunoglobulin E. (December 2021)
8. **b.** Dose tapering is required for patients who have received more than 40 mg of prednisone per day for more than one week (not 10 mg per day). (June 2021)
9. **b.** Increasing the insulin dose is not a risk factor for DKA in patients being treated with empagliflozin. However, insulin dose reduction is a risk factor. (September 2021)
10. Three years (36 months). Pregnancy must be excluded before starting treatment with acitretin. The patient must use effective contraception without interruption from one month before treatment, for the duration of treatment and for three years (36 months) after stopping treatment. (December 2021)

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