

Prescriber Update

Vol. 39 No. 1

March 2018

www.medsafe.govt.nz

ISSN 1172-5648 (print)
ISSN 1179-075X (online)

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Idarucizumab – A Second Dose May Be Needed

Key Messages

- ⌘ Idarucizumab reverses the effect of dabigatran for patients requiring emergency procedures with a risk of uncontrolled bleeding.
- ⌘ Some patients may need a second dose.

Prescribers are alerted to the possibility that some patients may need a second dose of idarucizumab (Praxbind) to reverse the effects of dabigatran (Pradaxa).

Idarucizumab is a specific reversal agent for the direct-acting thrombin inhibitor dabigatran. Idarucizumab is a humanised monoclonal antibody fragment (Fab) that binds to dabigatran more strongly than thrombin (around 300-fold more potent). As a result of this strong binding affinity, idarucizumab rapidly neutralises the anticoagulant effect of dabigatran¹.

Idarucizumab is indicated in patients treated with dabigatran when rapid reversal of dabigatran's anticoagulant effect is required for emergency surgery/urgent procedures or in life-threatening or uncontrolled bleeding¹.

Idarucizumab comes in 50 mL vials containing 2.5 g per vial (50 mg/mL). The recommended dose of idarucizumab is 5 g (2 x 2.5 g/50 mL vials) administered intravenously either as two consecutive infusions over 5–10 minutes each or as a bolus injection.

Post-marketing experience with dabigatran has shown that a second dose of idarucizumab is sometimes required². Administration of a second 5 g dose of idarucizumab may be considered in patients with prolonged clotting times who develop a recurrence of bleeding or who require a second emergency surgery/urgent procedure.

The timing of the second dose depends on the timing of the recurrence of bleeding and the measurement of the elevated coagulation tests. Please refer to the data sheet for further information¹.

References

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2. Pollack CVJ, Reilly PA, van Ryn J, et al. 2017. Idarucizumab for Dabigatran Reversal – Full Cohort Analysis. *New England Journal of Medicine* 377: 431–41.

Aspirin in Chloroform – More Harm than Help?

Key Messages

- ⌘ The Centre for Adverse Reactions Monitoring (CARM) has received a report of hepatotoxicity suspected to be linked to the topical use of aspirin in chloroform.
- ⌘ Chloroform is a possible human carcinogen and has been associated with hepatotoxicity.
- ⌘ Patients and pharmacy staff are exposed to chloroform when applying or compounding aspirin in chloroform.
- ⌘ The benefit-risk balance of topical aspirin in chloroform is unfavourable and the use of this mixture should be avoided.

The Centre for Adverse Reactions Monitoring (CARM) has received a report of the death of a

72-year-old female, who developed hepatotoxicity suspected by the treating physicians to be linked to topical application of aspirin in chloroform.

Aspirin in chloroform is compounded by pharmacists and pharmacy technicians and is used in the treatment of post herpetic neuralgia. It is an unapproved medicine in New Zealand but is currently funded by PHARMAC¹.

A study conducted in 1993 found that chloroform did not improve the efficacy of the topical aspirin preparation, but improved its solubility². There is no convincing evidence in scientific literature that aspirin dissolved in chloroform is effective for post-herpetic neuralgia.

Chloroform is classified by the International Agency for Research on Cancer as a group 2B carcinogen, being possibly carcinogenic to humans³. It is readily absorbed into the body after inhalation and oral or dermal exposure⁴.

Significant exposure to chloroform has been associated with hepatotoxicity in humans^{3,5}. This is a potential risk for patients who are applying aspirin in chloroform multiple times per day for extended periods of time.

Acute exposure to chloroform can cause headaches, vertigo and dizziness⁵. Pharmacy staff and patients may experience these symptoms when compounding or applying aspirin in chloroform.

CARM has also received one report of a patient experiencing chemical burns after applying topical aspirin in chloroform.

Given the lack of evidence for efficacy and significant risk of harm, the benefit-risk balance for topical aspirin in chloroform is unfavourable and prescribers should use alternative medicines for their patients.

References

1. PHARMAC. 2018. *New Zealand Pharmaceutical Schedule 25(0)*. URL: www.pharmac.govt.nz/2018/02/01/Schedule.pdf (accessed 31 January 2018).
2. King, R.B. 1993. Topical aspirin in chloroform and the relief of pain due to herpes zoster and postherpetic neuralgia. *Archives of Neurology* 50: 1046–53.
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4. World Health Organization. 2004. *Concise International Chemical Assessment Document 58: Chloroform*. URL: www.who.int/ipcs/publications/cicad/en/cicad58.pdf?ua=1 (accessed 31 January 2018).
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The Risk of Hyperglycaemia with Systemic Glucocorticoids

Key Messages

- ⌘ Systemic glucocorticoids can cause hyperglycaemia in both diabetic and non-diabetic patients.
- ⌘ Monitor the blood glucose levels of diabetic patients taking glucocorticoids.
- ⌘ Non-diabetic patients treated with systemic glucocorticoids should be asked if they are experiencing any symptoms of hyperglycaemia.

Medsafe was recently notified of a case where a patient was treated with high dose dexamethasone who developed diabetic ketoacidosis requiring hospitalisation.

Healthcare professionals are reminded that systemic glucocorticoids, including dexamethasone, can cause hyperglycaemia (severe enough to cause ketoacidosis) in both diabetic and non-diabetic patients^{1,2}.

In non-diabetics, effects on blood glucose levels are dose-dependent usually with a mild increase

in fasting glucose levels and a greater increase in postprandial values². It is important to ask non-diabetic patients if they are experiencing any symptoms of hyperglycaemia during treatment with systemic glucocorticoids.

Diabetic patients may experience difficulties with glycaemic control while taking glucocorticoids². Regular monitoring of blood glucose levels is important during treatment with glucocorticoids and dose adjustments for insulin or oral hypoglycaemic agents may be required.

Medsafe is working with pharmaceutical companies to ensure all data sheets for systemic glucocorticoids include information on the risk of hyperglycaemia. Please continue to report any adverse reactions to medicines to the Centre for Adverse Reactions Monitoring (CARM).

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1. Tamez-Perez HE, Quintanilla-Flores DL, Rodriguez-Gutierrez R, et al. 2015. Steroid hyperglycemia: Prevalence, early detection and therapeutic recommendations: A narrative review. *World Journal of Diabetes* 6: 1073–81.
2. UpToDate. 2017. *Major side effects of systemic glucocorticoids* 15 June 2017. URL: www.uptodate.com/contents/major-side-effects-of-systemic-glucocorticoids (accessed 12 January 2018).

Adverse Reaction Reporting in New Zealand – 2017

Medsafe and the Centre for Adverse Reactions Monitoring (CARM) would like to thank all those who submitted reports of suspected adverse reactions in 2017. Your reports are important in contributing to the post-market monitoring of medicines in New Zealand.

In 2017, CARM received a total of 3,816 suspected adverse reaction reports. These included 2,550 reports associated with medicines, 1,238 reports associated with vaccines and 28 reports associated with complementary or alternative medicines (CAMs).

Of all the reports received in 2017, 26.8% were considered serious. Serious reports accounted for 38.3% of medicine reports, 3.2% of vaccine reports and 21.4% of CAM reports. According to internationally agreed criteria, a serious adverse reaction is defined as any reaction that results in death or is life-threatening, causes or prolongs hospitalisation, results in persistent or significant disability/incapacity, is a congenital abnormality or is a medically important event.

Additional information about suspected adverse reactions reported in New Zealand can be found on the Medsafe website using the Suspected Medicine Adverse Reaction Search (SMARS) (www.medsafe.govt.nz/projects/B1/ADRDisclaimer.asp).

The most frequent reporters of adverse reactions in 2017 were nurses, followed by GPs and hospital doctors (Figure 1).

Please report any suspected adverse reactions to medicines, vaccines or CAMs to CARM. Anyone can report suspected adverse reactions, including healthcare professionals and consumers.

If in doubt, report!

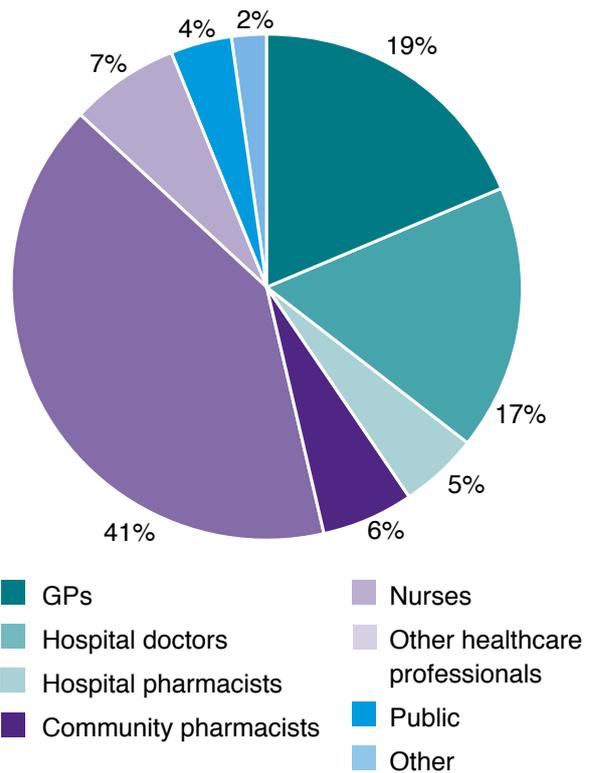


Figure 1: Source of suspected adverse reaction reports in New Zealand in 2017

Reports can be submitted by:

- filling an online reporting form at <https://nzphvc.otago.ac.nz/>
- electronic reporting through GP Practice Management Systems
- using the Apple iOS app on your iPhone or iPad (download from <https://nzphvc.otago.ac.nz/app/>)
- contacting CARM via phone on (03) 479 7247 or emailing carmnz@otago.ac.nz.

Subscribe to Printed Editions of *Prescriber Update*

In response to the *Prescriber Update* survey in March 2016, *Prescriber Update* will gradually move towards a predominantly online publication.

Print editions of *Prescriber Update* will continue to be supplied to organisations such as pharmacies and general practices, and will also be available to individuals who subscribe.

If you would like to continue to receive a print edition of *Prescriber Update*, you must re-subscribe by emailing prescriberupdate@atlantishealthcare.com with your name and postal address with the word 'subscribe' as the subject.

Subscription to an electronic copy of *Prescriber Update* can be found on the Medsafe website (www.medsafe.govt.nz/profs/subscribe.asp).

Medicinal Cannabis Update

The Misuse of Drugs (Medicinal Cannabis) Amendment Bill was tabled in Parliament on 20 December 2017, as part of the Government's 100 Day Plan, to introduce legislation to improve access to medicinal cannabis for terminally ill people and those in chronic pain. The intent of the Bill is to improve access to affordable cannabis products made to a quality standard.

The proposed changes are intended to strengthen the existing therapeutic model and improve access to medicinal cannabis based on principles of fairness, quality and safety, and compassion. The Bill is now progressing through the Parliamentary process and is anticipated to take up to a year, so any changes would come into force from 2019 onwards. An advisory committee will be

established and consultation on the Bill will be undertaken.

The Bill includes:

- compassionate measures for those that are terminally ill
- a regulation-making power to enable quality standards to be set for medicinal cannabis products available on prescription
- descheduling cannabidiol as a controlled drug.

For information on the current process for prescribing medicinal cannabis products, up-to-date information on the Bill and the Government's proposed Medicinal Cannabis Scheme please see our website (www.health.govt.nz).

Recent Approvals of Medicines Containing a New Active Ingredient

For period 16 October 2017 to 15 January 2018.

Trade Name (active ingredient)*	Dose Form and Strength	Therapeutic Area
Aldurazyme (laronidase) [†]	Concentrate for infusion 500 U/5 mL	Mucopolysaccharidosis I (MPS I; alpha-L-iduronidase deficiency)
Alecensa (allectinib)	Capsule 150 mg	Anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC)
Belkyra (deoxycholic acid)	Solution for injection 20 mg/2 mL (10 mg/mL)	Improvement in appearance of submental fat in adults
Darzalex (daratumumab)	Concentrate for infusion 100 mg/5mL and 400 mg/20 mL	Multiple myeloma
Esmya (ulipristal)	Tablet 5 mg	Uterine fibroids
Glassia (alpha-1 proteinase inhibitor)	Solution for injection 1000 mg/50 mL (20 mg/mL)	Emphysema due to congenital deficiency of alpha1-proteinase inhibitor (alpha1-antitrypsin deficiency).
Hexvix (hexaminolevulinat) [†]	Powder for injection 85 mg with diluent	Diagnostic use only. Used in cystoscopy to detect bladder cancer.
Ocrevus (ocrelizumab)	Concentrate for infusion 300 mg/10 mL	Multiple sclerosis (MS)
Venclexta (venetoclax) [†]	Film coated tablet 10 mg	Chronic lymphocytic leukaemia (CLL)
Xiaflex (collagenase clostridium histolyticum)	Powder for injection 900 mcg	Dupuytren's contracture and Peyronie's disease

* New active ingredient shown in bold type † Not available

The data sheets for currently marketed medicines are published on the Medsafe website (www.medsafe.govt.nz/Medicines/infoSearch.asp).

The Medsafe Files – Episode Five: Pharmacovigilance

Key Messages

- ⌘ Pharmacovigilance aims to identify emerging safety issues related to the real world use of medicines and vaccines as early as possible.
- ⌘ By submitting reports of suspected adverse reactions, you are contributing to medicines safety in New Zealand.
- ⌘ Stay informed about medicines safety issues by continuing to read *Prescriber Update* and keeping an eye on the Medsafe website.

Medsafe uses a variety of methods to collect information on the safety and quality of medicines and vaccines after they have been approved. These activities are known as pharmacovigilance. The main aim of pharmacovigilance is to identify emerging safety signals related to the use of medicines or vaccines or new information on known side effects.

What is pharmacovigilance?

Before a medicine is marketed, experience of its safety and efficacy is limited to its use in clinical trials. However, clinical trials do not always reflect the way a medicine or vaccine is used in real life. In addition, some populations such as pregnant women are not usually studied in clinical trials.

Although Medsafe may receive extensive information from clinical trials for a specific medicine, some adverse reactions are rare and may not be seen until a very large number of people have taken the medicine. For this reason, it is very important to continue to monitor all medicines after they have been approved.

What does pharmacovigilance involve?

Pharmacovigilance involves:

- monitoring the use of medicines in everyday practice to identify previously unknown adverse effects or changes in the patterns of adverse effects
- assessing the benefits and risks of harm of medicines to determine if action is required to improve their safe use
- providing information to healthcare professionals and consumers to promote medicines safety

- monitoring the impact of any action taken and assessing whether further action is required.

Where does this information come from?

Information from many sources are used for pharmacovigilance including:

- clinical and observational studies
- published medical literature
- pharmaceutical companies
- other regulatory authorities such as the United States Food and Drug Administration (FDA), European Medicines Agency (EMA) and Australia's Therapeutic Goods Administration (TGA)
- spontaneous suspected adverse reaction reports submitted to the Centre for Adverse Reactions Monitoring (CARM).

What are spontaneous suspected adverse reaction reports?

These are unsolicited case reports of suspected adverse reactions or adverse events that people have experienced while taking a medicine. Reports are collected by CARM in Dunedin.

Anyone can submit a report to CARM including healthcare professionals, consumers and pharmaceutical companies.

The advantages of these reports include that they are a very quick and effective way of finding potential safety signals with medicines and they can be used to monitor medicines safety in real life use over the lifetime of the medicine.

Limitations of spontaneous suspected adverse reaction reports include:

- under-reporting (ie, some cases may not be reported)
- lack of reliable information on the number of people taking the medicine
- incomplete information on diagnosis and history of the patient
- they are not very effective at detecting adverse reactions that occur a long time after starting the medicine.

Due to these limitations, spontaneous reports are generally only used to detect safety signals and are not used to investigate or confirm them. Information obtained from spontaneous reports needs to be interpreted with caution.

What is a safety signal?

A safety signal is an indication that there may be a safety problem related to a medicine. A signal could be a previously unknown adverse reaction or a change in the frequency or severity of a known side effect.

What does Medsafe do with this information?

Medsafe analyses adverse reaction reports together with other information to determine if the safety signal is real. Medsafe seeks the advice of independent experts through the Medicines Adverse Reactions Committee (MARC) or may also form working groups of experts to provide advice.

Medsafe undertakes a risk-benefit assessment on safety signals to see if any action is required.

The majority of safety signals that Medsafe investigates are not supported when all of the available information is closely examined. In this case, no action is considered necessary, although Medsafe may continue to closely monitor the issue.

A small number of safety signals are confirmed on close examination of the available information, and Medsafe takes appropriate action to improve the safe use of these medicines.

What action can Medsafe take if a safety concern is confirmed?

- Provide information directly to healthcare professionals and consumers on medicines safety issues.
- Require changes to medicine data sheets and/or the product label.

- Restrict the conditions that the medicine can be used for.
- Recommend that the legal status of a medicine is changed, for example from over-the-counter to prescription only.
- In rare circumstances, Medsafe can recommend removal of the medicine from the market.

How does Medsafe communicate with healthcare professionals and consumers?

Communication with healthcare professionals and consumers is one of the best ways to provide information about adverse effects and safe use of medicines.

Medsafe provides information by:

- requesting pharmaceutical companies to update medicine data sheets and consumer medicine information (CMI)
- publishing information here in *Prescriber Update*
- publishing safety alerts, media releases and consumer recalls on the Medsafe website.

You can subscribe to receive an electronic copy of *Prescriber Update* and alert communications on the Medsafe website (www.medsafe.govt.nz/profs/subscribe.asp).

Neither Medsafe nor CARM can say in individual cases that a medicine was the actual cause of a suspected adverse reaction. Any consumer who has concerns regarding medicines they are taking should discuss these with their healthcare professional.

WE NEED YOUR HELP!

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



Medicine	Potential Safety Issue	Active Monitoring Ends
Dabigatran	Gout or gout-like symptoms	31 July 2018

- **M²** is a Medsafe scheme designed to collect more information on potential safety signals for specific medicines.
- Safety signals are identified from reports of adverse medicine reactions sent to the Centre for Adverse Reactions Monitoring (CARM). For further information see the Medsafe website.
- The **M²** scheme does not replace routine adverse reaction reporting. Find out how to report at: www.otago.ac.nz/carm or www.medsafe.govt.nz



New Zealand Government



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

Spotlight on Colchicine

Key Messages

- ⌘ Colchicine is approved for the treatment of acute gout.
- ⌘ Patients should be counselled on the appropriate use of this medicine and the signs of toxicity to ensure its safe and effective use.
- ⌘ Serious adverse effects and toxicity may be potentiated by pharmacokinetic drug interactions.
- ⌘ Adverse effects predominantly affect the gastrointestinal tract, skin, and blood.

This article on colchicine continues the spotlight series where Medsafe reviews the safety information on a specific medicine or class of medicine.

Indication

Colchicine is indicated for the treatment of acute gout when nonsteroidal anti-inflammatory drugs (NSAIDs) are contraindicated, ineffective or not tolerated¹.

Dose

The toxicity of colchicine is directly related to dose and patients should be advised to take the lowest dose they can to provide relief from pain. The approved adult dose of colchicine for acute gout flares is 1 mg (two tablets), followed by 500 micrograms (one tablet) every six hours for the first 24 hours, to a maximum daily dose of 2.5 mg (five tablets)¹. After the first 24 hours, the dose should not exceed 1.5 mg (three tablets)². The total dose given in an acute attack should not exceed 6 mg over four days¹.

In older patients, patients with renal or hepatic impairment, or patients weighting less than 50 kg, the maximum dose in the first 24 hours should not exceed 1 mg, and the maximum cumulative dose over four days should not exceed 3 mg¹.

A course of colchicine should not be repeated within three days¹.

An alternative dosage regimen has also been recommended by the New Zealand Formulary².

Contraindications

Colchicine should not be used in:

- patients with severe or combined renal and hepatic impairment
- patients with mild to moderate hepatic impairment while taking a P-glycoprotein or strong CYP3A4 inhibitor
- patients with serious cardiac or gastrointestinal disorders, or pre-existing blood dyscrasias
- children
- breastfeeding mothers¹.

Warnings and Precautions

Fatal Overdose

Colchicine has a low toxic threshold and can be fatal in doses as small as 6 mg¹. Patients should be told to stop taking colchicine and to seek medical advice immediately if signs of toxicity occur, such as nausea, vomiting, diarrhoea (including bloody diarrhoea) or abdominal pain¹. There is no specific antidote for colchicine toxicity¹.

Renal Impairment

Clearance of colchicine is decreased in renal impairment¹. Adverse effects should be monitored for and dosage may be reduced, or the interval extended¹.

Blood Dyscrasias

Colchicine can have leukopenic and thrombocytopenic effects¹. This may result in an increased incidence of microbial infection, delayed healing, or gingival bleeding¹.

Use in Older People

Older patients, even those with normal renal and hepatic function, may be more susceptible to colchicine toxicity¹. All patients in this population should be closely monitored for signs of toxicity and doses may need to be reduced¹.

Use in Pregnancy

Colchicine should be avoided in pregnancy and women of child-bearing age should be advised to use effective contraception whilst taking colchicine¹. In animal studies, colchicine has been shown to have teratogenic effects¹.

Medicine Interactions

Colchicine is a substrate of the efflux transporter, P-glycoprotein, and is metabolised by CYP3A4¹. If colchicine is administered with medicines that inhibit P-glycoprotein and/or CYP3A4, increased blood concentrations of colchicine are likely¹. Medicines that interact with colchicine include ciclosporin, macrolide antibiotics, protease inhibitors, lipid lowering agents, calcium channel blockers and digoxin. Fatal medicine interactions have occurred¹.

The leukopenic and thrombocytopenic effects of colchicine may be intensified by concomitant or recent therapy with blood dyscrasia-causing medications, or bone marrow depressants¹.

Adverse Effects

Adverse effects associated with colchicine predominantly affect the gastrointestinal system, skin and blood. Adverse effects are summarised in Table 1.

New Zealand Reports of Adverse Reactions

From 1 January 2013 to 31 December 2017, the Centre for Adverse Reactions Monitoring (CARM) received 13 reports where colchicine was a suspect medicine. The most commonly reported adverse reactions were diarrhoea (4 reports), acute renal

failure (3), abdominal pain (2), myopathy (2), and vomiting (2). Ten reports concerned male patients, consistent with the higher prevalence of gout in males³.

One patient died from acute renal failure and severe metabolic acidosis due to incorrect self-administration of colchicine⁴. This report highlights the importance of counselling patients on the correct use of this medicine.

Health professionals should advise patients to seek medical advice immediately if they show any signs of toxicity. Please continue to report any adverse reactions to colchicine and any other medicine to CARM. Reports can be submitted on paper or electronically (<https://nzphvc.otago.ac.nz/>).

References

1. Pharmacy Retailing (NZ) Ltd. 2016. *Colgout New Zealand Data Sheet* 26 January 2016. URL: www.medsafe.govt.nz/profs/datasheet/c/Colgouttab.pdf (accessed 16 January 2018).
2. NZ Formulary. 2018. *New Zealand Formulary Release 67* 1 January 2018. URL: <http://nzf.org.nz/> (accessed 31 January 2018).
3. Roddy E, Doherty M. 2010. Epidemiology of gout. *Arthritis Research & Therapy* 12(6): 223.
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Table 1: Selected adverse effects associated with colchicine¹

System Organ Class	Adverse Effects
Blood and lymphatic system	Anaemia, leukopenia, neutropenia, thrombocytopenia, agranulocytosis, pancytopenia, aplastic anaemia and non-thrombocytopenic purpura
Cardiac	Generalised vascular damage
Eye	Corneal ulcers
Endocrine	Hypothyroidism
Gastrointestinal	Nausea, vomiting, abdominal pain, diarrhoea, paralytic ileus, stomatitis, steatorrhoea
Investigations	Blood alkaline phosphatase increased
Metabolism and nutrition	Vitamin B12 absorption decreased
Musculoskeletal and connective tissue	Myopathy, rhabdomyolysis
Renal and urinary	Bladder spasm, anuria, haematuria, oliguria, acute kidney injury
Reproductive system and breast	Azoospermia, oligospermia
Respiratory, thoracic and mediastinal	Acute respiratory distress syndrome
Skin and subcutaneous tissue	Rash, urticaria, dermatosis, dermatitis, alopecia

Mycobacterial Infections after Cardiac Surgery Using Heater-Cooler Devices

Key Messages

- ⌘ Cases of non-tuberculous mycobacterial infection have been identified in patients who have undergone cardiac surgery using heater-cooler devices.
- ⌘ These infections can manifest many months or years after surgery.
- ⌘ Consider non-tuberculous mycobacteria in patients who present with symptoms of an infection, have negative conventional cultures, do not respond to antibiotic treatment and have undergone surgery where heater-cooler devices have been used.
- ⌘ Patients with these infections have presented with fatigue, fever, pain, redness, heat or pus at the surgical site, muscle pain, joint pain, night sweats, weight loss, abdominal pain, nausea or vomiting.
- ⌘ Medical practitioners with patients who have undergone surgery using affected heater-cooler devices have been contacted.

Heater-cooler devices are used during cardiac surgery to maintain the patient's temperature. Following reports of unusual infections in patients who had undergone cardiac surgery, investigations identified a problem with contamination of heater-cooler devices. Bacterial contamination of the water within the device can result in transmission of bacteria by aerosol from the device's exhaust vent into the operating theatre. The type of bacteria involved in the infections were non-tuberculous mycobacteria.

Non-tuberculous mycobacteria include a number of different bacterial species, many of which are widespread in nature and can be found in water, including tap water. They are not usually a major cause of infection in the community. However, in rare cases they may cause infection in very ill or immune-compromised patients, or in situations where prosthetic material is implanted.

The organism is slow-growing so may present as infection months or even years after exposure.

Mycobacterial infection should be suspected in patients who have had cardiac surgery who present with any of the following symptoms: fatigue, fever, pain (including muscle or joint pain), redness, heat or pus at the surgical site, night sweats, weight loss, abdominal pain, nausea or vomiting. Cultures will be negative and the patient will not respond to conventional antibiotic treatment.

The exact number of cases worldwide is unclear, but the risk to patients is thought to be very low (roughly 1 in every 5000 procedures or 0.02%). However, these infections can be serious if they are not identified and treated. Due to the slow onset of symptoms, there is the potential for patients to present with these infections in the community.

To date, one case of infection attributable to non-tuberculous mycobacteria has been detected in New Zealand. Approximately 120 such cases have been identified worldwide. The New Zealand case was identified in 2015 and the patient was treated successfully.

Hospitals that use heater-cooler devices have been advised to consult with their infection prevention and control services to ensure that the decontamination and disinfection of these devices is performed according to the manufacturer's instructions.

The Ministry of Health has asked district health boards and private providers to notify patients who underwent surgery at their centre during which cardiac prosthetic material was inserted and a heater-cooler device was used after 1 January 2013.

All adverse events relating to medical devices should be reported to Medsafe. The reporting forms are available on the Medsafe website (www.medsafe.govt.nz/regulatory/DevicesNew/9AdverseEvent.asp) and should be emailed to devices@moh.govt.nz.

Further information about heater-cooler devices used during cardiac surgery is published on the Medsafe website (www.medsafe.govt.nz/safety/EWS/2016/H&C.asp).

Transdermal Opioid Patches – Stick to the Correct Application

Key Messages

- ⌘ Risks of harm are associated with the incorrect use of transdermal opioid patches.
- ⌘ Continue to monitor patients for adverse reactions after a transdermal opioid patch is removed as opioid concentrations decline gradually after removal.

Medsafe was recently notified of a case where the administration of a buprenorphine transdermal patch may have contributed to the death of a patient.

There are two types of transdermal opioid patch currently available in New Zealand, the Norspan Transdermal Patch which contains buprenorphine and Fentanyl Sandoz which contains fentanyl^{1,2}.

The risk of harm from transdermal opioid patches can be managed by:

- starting with a low dose
- discontinuing all other regular opioids when the patch is initiated
- avoiding concomitant prescribing of benzodiazepines and other central nervous system depressants where possible because

of the risks of profound sedation, respiratory depression, coma and death

- not discontinuing patches abruptly, a gradual downward titration should be used
- telling patients how to dispose of a patch safely and to keep them out of reach and sight of children
- monitoring for adverse reactions and interactions after patch removal as removal of the patch does not instantly reduce opioid concentrations¹.

The Health Quality and Safety Commission has published a medication alert to highlight the risks associated with the use of all transdermal patches³.

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MARC's Remarks: December 2017 Meeting

The Medicines Adverse Reactions Committee (MARC) met on 7 December 2017 to discuss a number of medicine-related safety issues.

The MARC noted a case reported to the Centre for Adverse Reactions Monitoring (CARM) where a patient required a second dose of **idarucizumab**. Further information is available in this edition of Prescriber Update¹.

The MARC discussed the potential risk of disabling and persistent musculoskeletal and nervous system adverse reactions from the use of **fluoroquinolones**. The MARC considered data sheets and consumer medicine information for fluoroquinolones should be updated with information on this potential risk. The MARC discussed antibiotic stewardship by prescribers to reduce antimicrobial resistance. The MARC noted the 2017 edition of the antibiotic guide produced

by the Best Practice Advocacy Centre recommends fluoroquinolones are used second-line for urinary tract infections and are not listed as first choice or alternatives for respiratory indications.

The MARC discussed the risk of overdose with **modified-release paracetamol** products. The MARC considered consumers should receive counselling and advice on the dosing regimen of modified-release products which is different from immediate-release products. Likewise, the management of overdose is different for modified-release products compared with immediate-release products. This topic will be discussed by the Medicines Classification Committee. Keep an eye on future editions of Prescriber Update and the Medsafe website for updates on this topic.

The MARC was presented with the **Influvac Tetra** risk management plan (RMP). The MARC

considered the RMP should include a few additional (potential) risks, including febrile seizures in children under five years of age and interaction with immune checkpoint inhibitors leading to severe muscle injury as potential safety concerns.

The MARC discussed the risk of respiratory depression when **gabapentin** is used without concomitant opioids. Patients with compromised respiratory function, respiratory or neurological disease, renal impairment and older people are at higher risk of experiencing respiratory depression. Concomitant use of central nervous system depressants with gabapentin also increases the risk of respiratory depression. Medsafe is working with the pharmaceutical companies to ensure this information is included in all gabapentin data sheets.

The MARC discussed the risk of haematological abnormalities in newborns whose mothers were

treated with **natalizumab** during pregnancy. The MARC considered there is a potential for haematological abnormalities, including increased white blood cell counts, thrombocytopenia and anaemia, to occur in newborns whose mothers were treated with natalizumab during pregnancy. Medsafe is working with the pharmaceutical company to ensure this information is included in the natalizumab data sheet.

Further information on this meeting can be found on the Medsafe website (www.medsafe.govt.nz/profs/adverse/Minutes172.htm). Papers presented to the MARC are also published on the Medsafe website (www.medsafe.govt.nz/committees/MARC/Reports.asp).

References

1. Medsafe. 2018. Idarucizumab — A Second Dose May Be Needed. *Prescriber Update* 39(1):2.

Spontaneous Reports: Seasonal Influenza Vaccination 2017

Influenza has a significant impact on public health in New Zealand. The rate of influenza-associated hospitalisations for all causes and all ages in New Zealand has been estimated as 62.4 per 100,000 (1). The age groups with the highest rates were those 80 years of age and older (327.8 per 100,000) and children under one year (244.5 per 100,000)¹.

In addition, seasonal influenza in New Zealand has been estimated to be associated with all-cause medical deaths at a rate of 10.6 per 100,000 persons per year with the majority of deaths occurring in those 65 years and over².

During 2017, there was a total of 335 Intensive Care Unit cases of influenza-like illness of which 27 of

the 352 collected specimens tested positive for influenza viruses³.

In 2017, the Centre for Adverse Reactions Monitoring (CARM) received 191 reports of adverse reactions to seasonal influenza vaccines (Table 1). There were 467 suspected adverse reactions described in these 191 reports.

The majority of these reports were submitted by nurses (74.9%). The most commonly reported reactions were injection site inflammation, arm pain, headache, fever and vasovagal reaction (Table 2).

Table 1: Number of reports of adverse events following influenza vaccination received by CARM and number of influenza vaccine doses distributed, 2013–2017

	2013	2014	2015	2016	2017
Reports of adverse event reports following influenza vaccination	290	253	241	212	191
Influenza vaccine doses distributed*	1,253,600	1,206,573	1,211,152	1,245,934	1,217,494
Estimated reporting rate per 100,000 doses	23.1	21.0	19.9	17.0	15.7

*The number of doses distributed is not equal to number of people to whom the vaccine was administered.

Table 2: Top five reported suspected adverse reactions to the 2017 seasonal influenza vaccines

Adverse reaction	Number of events	Percentage of total events	Percentage of total report
Injection site inflammation	46	9.9%	24.1%
Arm pain	29	6.2%	15.2%
Headache	20	4.3%	10.5%
Fever	13	2.8%	6.8%
Vasovagal reaction	13	2.8%	6.8%

There were 10 reports that were classified as serious. Of these 10 reports, seven reports involved hospitalisation (3.7% of reports) and three reports were classified as life-threatening (severe allergic reactions) (1.6%).

In 2018, the funded influenza vaccine will be quadrivalent rather than trivalent. Please continue to report any suspected adverse reaction(s) to vaccines to CARM.

References

1. Khieu TQ, Pierse N, Telfar-Barnard LF, et al. 2015. Estimating the contribution of influenza to hospitalisations in New Zealand from 1994 to 2008. *Vaccine* 33: 4087–92.
2. Kessaram T, Stanley J, Baker MG. 2015. Estimating influenza-associated mortality in New Zealand from 1990 to 2008. *Influenza and Other Respiratory Viruses* 9: 14–9.
3. ESR. 2017. *Community and Hospital Surveillance: ILL, SARI ICU, Influenza and Respiratory Pathogens, 2017 Influenza Season, December 2017* 17 January 2018. URL: https://surv.esr.cri.nz/virology/influenza_surveillance_summary.php (accessed 31 January 2018).

Gathering Knowledge from Adverse Reaction Reports: Mar 2018

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

A selection of recent informative cases from the Centre for Adverse Reactions Monitoring (CARM) database is presented below.

<p>CARM ID: 125952 Age: 60 Gender: Female Medicine(s): Ciprofloxacin Reaction(s): Anxiety, Agitation, Paranoid thoughts</p>	<p>A 60-year-old patient experienced anxiety, agitation and paranoid thoughts one day after taking ciprofloxacin.</p> <p>The Cipflox data sheet (www.medsafe.govt.nz/profs/Datasheet/c/Cipfloxtabinf.pdf) states that psychiatric reactions may occur even after the first administration of fluoroquinolones, including ciprofloxacin. In these cases, ciprofloxacin should be discontinued and the appropriate measures instituted.</p>
<p>CARM ID: 125838 Age: 23 Gender: Male Medicine(s): Paracetamol Reaction(s): Steven Johnson Syndrome (SJS)</p>	<p>A 23-year-old male took several medicines and experienced wide spread ulcers on the tongue, mouth, lips with angioedema. Upon dermatologist review, paracetamol was identified as the most likely cause.</p> <p>The data sheet for Panadol (www.medsafe.govt.nz/profs/Datasheet/p/panadotab.pdf) lists Stevens-Johnson Syndrome as a very rare adverse reaction.</p>
<p>CARM ID: 125845 Age: 70 Gender: Female Medicine(s): Zoledronic acid and others Reaction(s): Osteonecrosis of both ear canals</p>	<p>The patient was being treated with zoledronate infusions and was found to have osteonecrosis of both ear canals that was successfully treated.</p> <p>The data sheet for Aclasta (www.medsafe.govt.nz/profs/Datasheet/a/Aclastainf.pdf) states that cases of osteonecrosis of bones other than the jaw have been reported.</p>

Drug-Induced Immune Thrombocytopenia

Key Messages

- ⌘ Drug-induced immune thrombocytopenia is a relatively uncommon adverse reaction caused by drug-dependent antibodies.
- ⌘ Always consider medicines as a possible cause of immune thrombocytopenia purpura.
- ⌘ Discontinuation of the offending medicine usually resolves the condition.

Background

Drug-induced Immune Thrombocytopenia (DITP) is characterised by a low platelet count (typically less than $50 \times 10^9/L$). Presentations vary from petechia, bruising and bleeding from mucosal membranes (eg, epistaxis), to potentially life-threatening intracranial haemorrhage.

DITP is caused by drug-dependent antibodies that react with platelet membrane glycoproteins when the offending drug is present, resulting in platelet destruction¹. This mechanism differs from thrombocytopenia induced by some cytotoxic drugs that affect the bone marrow².

The typical time to presentation of DITP is within one to two weeks of starting the medicine. Previously sensitised patients can experience rapid drops in platelet counts within one to two hours on repeat exposure¹. Platelet count usually returns to normal within one week of stopping the offending medicine. Patients with severe thrombocytopenia or haemorrhage may require platelet transfusion¹.

Glycoprotein IIb/IIIa inhibitors (tirofiban, abciximab, and eptifibatide) have been associated with rapid onset DITP³. This can occur within minutes after exposure to the medicine.

Heparin induced thrombocytopenia (HIT) is a similar condition. Further information on HIT be found in the *Prescriber Update* article 'Don't get HIT: Heparin-induced Thrombocytopenia'⁴.

Medicines Known to Cause DITP

Over 100 medicines have been associated with DITP¹. Examples of medicines associated with DITP are shown in Table 1 (the list is not exhaustive).

New Zealand Cases

To date, a total of 25 cases of DITP have been reported to the Centre for Adverse Reaction Monitoring (CARM). In 20 of these reports a vaccine was the suspected medicine. The reported vaccines included Measles/Mumps/Rubella (6 reports), Meningococcal B (5), Diphtheria/Tetanus/Pertussis (4), Pneumococcal conjugate (2), Hepatitis B (2), Influenza trivalent (1), ADT Booster (1), and Haemophilus influenzae type B (1). Other suspected medicines were salmeterol (2 reports), tacrolimus (1), ciprofloxacin (1), and acyclovir (1).

References

1. Curtis BR. 2014. Drug-induced immune thrombocytopenia: incidence, clinical features, laboratory testing, and pathogenic mechanisms. *Immunohematology* 30(2): 55–65.
2. Aster RH, Curtis BR, McFarland JG, et al. 2009. Drug induced immune thrombocytopenia: pathogenesis, diagnosis, and management. *Journal of Thrombosis and Haemostasis* 7(6): 911–8.
3. Visentin GP, Liu CY. 2007. Drug-induced thrombocytopenia. *Hematology/oncology clinics of North America* 21(4): 685–96.
4. Medsafe. 2016. Don't get HIT: Heparin-induced Thrombocytopenia. *Prescriber Update* 37(4): 59–60. URL: www.medsafe.govt.nz/profs/PUArticles/December%202016/HeparinInducedThrombocytopenia.htm (accessed 7 February 2018).

Table 1: Examples of medicines associated with drug-induced immune thrombocytopenia^{1,2}

Medicine Classification	Examples of Implicated Medicines
Antibiotics	Cephalosporins, linezolid, penicillins, sulphonamides, trimethoprim, vancomycin
Antimalarials	Quinine
Antimycobacterials	Ethambutol, rifampicin
Antiepileptics	Carbamazepine, phenytoin, sodium valproate
NSAIDs	Ibuprofen, naproxen
Cardiovascular drugs	Abciximab, amiodarone, eptifibatide furosemide, quinidine, thiazides, tirofiban
Vaccines	Diphtheria, Tetanus, Pertussis (DTaP), Haemophilus influenzae type B, Influenza, MMR, pneumococcal, varicella zoster
Others	Haloperidol, paracetamol, irinotecan, mirtazapine, oxaliplatin

Quarterly Summary of Recent Safety Communications

The early warning system provides current and historical information on safety concerns for medicines and medical devices. These warnings are intended to help consumers and healthcare professionals make informed decisions about their use of medicines and medical devices.

More information about the early warning system can be found on the Medsafe website (www.medsafe.govt.nz/Projects/B2/EWS.asp).

Consumer information leaflets provide information about medicines and medical devices or medical conditions to consumers.

Date	Communication	Topic
15 February 2018	Alert Communication	Arthrem — potential risk of harm to the liver – statement under section 98 of the Medicines Act 1981
9 February 2018	Alert Communication	UPDATE – Heater-cooler devices used during cardiac surgery: risk of infection with nontuberculous
31 January 2018	Monitoring Communications	M² Update to Viekira Pak and Viekira Pak-RBV – possible effects on blood glucose control when used in patients with type 2 diabetes
31 January 2018	Monitoring Communications	M² Dabigatran and gout or gout-like symptoms
31 January 2018	Media Release	Surgical Mesh Implants — Regulatory action on surgical mesh products
13 December 2017	Safety Information	Surgical Mesh Implants — Update
12 December 2017	Media Release	Medsafe introduces surgical mesh restrictions
5 December 2017	Monitoring Communication	Update — Possible risk of hypothyroidism in infants exposed to iodine-containing contrast agents added to the medicines monitoring scheme

If you would like to receive Medsafe's early warning communications you can subscribe at www.medsafe.govt.nz/profs/subscribe.asp

Subscribe to 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.

Sign up to receive emails that will let you know:

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New Zealand Medicines and Medical Devices
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A business unit of the Ministry of Health

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Acknowledgement

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Prescriber Update is published and distributed by Medsafe in the interests of safer, more effective use of medicines and medical devices.

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

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