Prescriber Update

Vol. 40 No. 2 June 2019

www.medsafe.govt.nz

ISSN 1179-075X (online)

Contents

MEDSAFE
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NSAIDs and cardiovascular risk

Key messages

- All NSAIDs, including both traditional and COX-2 selective NSAIDs, increase the risk of a cardiovascular adverse event.
- It is not possible to differentiate or rank NSAIDs by their cardiovascular risk.
- Cardiovascular adverse events occur with both short-term and long-term use.
- Use NSAIDs at the lowest effective dose for the shortest time possible.

Background

The Medicines Adverse Reactions Committee (MARC) reviewed the cardiovascular safety of non-steroidal anti-inflammatory drugs (NSAIDs) at the 177th meeting on 14 March 2019.

Recent cardiovascular safety studies

Since the MARC previously discussed the cardiovascular safety of diclofenac in 2013[1] and ibuprofen in 2015[2], several new studies on the cardiovascular safety of NSAIDs have been published.

Medsafe presented a report on the recent literature to the MARC at the 177th meeting on March 2019[3]. These studies include two key clinical trials[4,5], and two large observational studies using healthcare databases[6,7]. In addition, there have been two meta-analyses of older studies[8,9], a Danish healthcare registry study examining the risk of out-of-hospital cardiac arrest with NSAIDs[10], and a case-control study nested in a cohort derived from European electronic healthcare databases that examines the risk of hospital admission for heart failure exacerbation in new users of NSAIDs[11].

The MARC reviewed these studies and concluded that it is currently not possible to differentiate NSAIDs by their individual cardiovascular risk profiles[12]. All NSAIDs increase cardiovascular risk, and the risk is increased with both short-term and long-term use.

Clinical implications

- Avoid using all NSAIDs in patients with established cardiovascular disease, and in those with significant risk factors.
- If required, use NSAIDs at the lowest effective dose for the shortest duration possible.
- Inform patients that NSAIDs increase the risk of cardiovascular adverse events, even in those without a history of cardiovascular disease, and about the symptoms and signs to look out for.

Mechanism of action

NSAIDs reduce inflammation by inhibiting the production of cyclo-oxygenase (COX), an important enzyme in prostaglandin synthesis. There are two major forms of the COX enzyme: COX-1 and COX-2. While COX-1 is present in most tissues all the time, COX-2 is expressed in response to inflammation. Both forms catalyse the conversion of arachidonic acid, via intermediates, to thromboxane A2 (pro-thrombotic) and prostacyclin (anti-thrombotic).

COX-selectivity is relative, not absolute

NSAIDs are generally divided into non-selective traditional NSAIDs and selective COX-2 inhibitors. Comparisons are often made between selective COX-2 inhibitors and traditional

NSAIDs in clinical studies. However, there is much overlap between the two classes in the degree of COX-2 inhibition. For example, among the traditional NSAIDs, indomethacin and naproxen are relatively COX-1 selective, while diclofenac and meloxicam are relatively COX-2 selective. Furthermore, celecoxib (a selective COX-2 inhibitor) and diclofenac (a traditional NSAID) have a similar degree of COX-2 selectivity[13].

The balance between COX-1 and COX-2 inhibition can change during the dose interval, depending on the potency and plasma half-life of the NSAID. For diclofenac, COX-1 inhibition drops off as the plasma concentration falls during the dose interval, leaving COX-2 inhibition relatively unopposed. In contrast, for both ibuprofen and naproxen, COX-1 inhibition exceeds COX-2 inhibition throughout the dose interval[14,15].

When COX-2 is inhibited relative to COX-1, the pro-thrombotic/antithrombotic balance on the endothelial surface shifts in favour of thrombosis, increasing the risk of cardiovascular thrombotic adverse events. Relative COX selectivity also influences the gastrointestinal adverse event profile of individual NSAIDs[16].

NSAID cardiotoxicity is multifactorial

In addition to potential pro-thrombotic effects, other factors contributing to the cardiovascular toxicity of NSAIDs include blood pressure elevation, reduced renal perfusion, fluid retention, and exacerbation of heart failure[13,17,18].

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Dabigatran – Reduced dose recommendations

The dabigatran (Pradaxa) dose recommendations for the treatment/prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE) are changing. The new recommendations concern elderly patients, patients with moderate renal impairment (creatinine clearance [CrCl]: 30–50 mL/min), and patients at risk of bleeding with one or more risk factors (Table 1).

Table 1: Summary of new dabigatran dose recommendations in the treatment/prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE) indications

Special population	New dose recommendation	Previous dose recommendation
Patients aged ≥80 years	110 mg twice daily	150 mg twice daily
Patients aged 75–80 years	110 mg twice daily* OR 150 mg twice daily	150 mg twice daily
Patients with moderate renal impairment (CrCl 30–50 mL/min)	110 mg twice daily* OR 150 mg twice daily	150 mg twice daily
Patients at risk of bleeding with one or more risk factors	110 mg twice daily OR 150 mg twice daily	150 mg twice daily

* Use the lower recommended dose for patients with a lower thromboembolic risk and high bleeding risk.

Dabigatran dose recommendations were discussed at the December 2018 Medicines Adverse Reactions Committee meeting (**https://www.medsafe.govt.nz/profs/adverse/Minutes176.htm**). The Committee recommended harmonising the recommendations for reduced dabigatran dose for the DVT and PE indications with those for the SPAF indication (SPAF: prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation).

Medsafe is working with the sponsor to update the Pradaxa data sheet. Full prescribing information will be available in the Pradaxa data sheet in the coming weeks.

Phenytoin (Dilantin) capsules formulation change – How did it affect patients?

Key messages

- Changes in the brand of phenytoin should be avoided whenever possible. However, the reformulation of Dilantin meant that patients were exposed to an unavoidable change to their anti-epileptic medicine.
- Close monitoring and measurement of phenytoin blood levels were recommended for these patients.
- The Centre for Adverse Reactions Monitoring has received three reports of seizures associated with the formulation change.

Introduction

Changes to the brand of phenytoin taken by patients should be avoided. Even when different brands demonstrate bioequivalence, there are reports of clinically relevant differences[1].

In July 2018, Pfizer, the manufacturer of Dilantin, announced a formulation change for the 30 mg and 100 mg capsules[2]. Here we review reports made to the Centre for Adverse Reactions Monitoring (CARM) concerning adverse events associated with the formulation change.

Dilantin formulation changes

The manufacturer announced minor formulation changes to the Dilantin capsules[3]:

- addition of lactose to the 30 mg capsules
- in both the 30 mg and 100 mg capsules, pre-mixed sucrose and maize starch was used instead of individual excipients.

The new formulation demonstrated bioequivalence to the old formulation.

The manufacturer recommended close monitoring of patients during the change. This included measuring phenytoin levels 7 to 10 days after starting the new formulation and, if needed, adjusting the dose to achieve the clinically effective serum total concentration of phenytoin of 10 to 20 mcg/mL.

In 2018[4]:

- 1,096 patients were taking phenytoin 30 mg capsules
- 3,855 patients were taking phenytoin 100 mg capsules.

Reports to CARM

As of April 2019, CARM had received 4 reports of patients experiencing problems following the phenytoin formulation change (CARM ID numbers: 131358, 131605, 131438, 131917).

Three patients experienced seizures, and one patient experienced suicidal ideation. Of the three patients who had seizures, phenytoin levels were measured and found to be low.

- 131358: the seizure occurred before the patient could attend for a phenytoin level measurement.
- 131605: levels were measured 4 days after the change and were low. The phenytoin dose was increased, but the patient still experienced a life-threatening prolonged seizure.
- 131438: the patient declined phenytoin level testing. Levels were tested after the seizure and found to be low.

All three patients had previously experienced long periods of being seizure free.

The low number of cases illustrates that close monitoring of patients and obtaining timely phenytoin levels can ensure a smooth transition. However, even with appropriate monitoring, some patients still experienced problems, including life-threatening seizures and loss of driving licence.

Medsafe has approved a similar formulation change for Dilantin Infatabs (50 mg phenytoin, paediatric chewable tablets). Closely monitor patients when changing to the new formulation – this can include blood monitoring within the first 7 days after changing formulation.

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Acute pancreatitis – Sometimes triggered by medicines

Key messages

- Medicines are a rare cause of acute pancreatitis.
- If medicine-induced pancreatitis is suspected, withdrawal of the suspected medicine is usually effective.

Background

Acute pancreatitis (AP) is a major gastrointestinal cause of hospitalisation. The condition is commonly caused by gallstones or excessive alcohol use. AP is characterised by inflammation of the pancreas and elevated levels of pancreatic enzymes (amylase and lipase) in the blood. It is likely that very few AP cases are triggered by medicines – estimates range from 0.1 to 2% of cases of AP[1]. However, as the incidence of all-cause AP is high[2], drug-induced pancreatitis (DIP) is still an important consideration.

Drug-induced pancreatitis

DIP does not have any unique clinical features to distinguish it from AP. In some cases a drug-rash and/or eosinophilia may occur. Diagnosis requires careful exclusion of other aetiologies. However, the presence of other causes of AP does not entirely exclude DIP[3].

The prognosis is generally excellent upon withdrawal of the medicine, and the DIP mortality rate is low[1].

DIP can occur through multiple mechanisms, including direct toxicity, immunologic reactions, accumulation of toxic metabolites, ischaemia, intravascular thrombosis, and increased viscosity of pancreatic secretions. The time to onset varies depending on the mechanism, ranging from weeks to months after initiation of the medicine[4].

New Zealand reports

Since 2009, the Centre for Adverse Reactions (CARM) has received 49 reports concerning 66 medicines suspected of causing pancreatitis. Table 1 shows some of the medicines reported to CARM and the number of positive dechallenges (withdrawal of medicine and cessation of symptoms) and rechallenges (restarting the medicine and reccurrence of symptoms).

Table 1: Selected medicines with reports received by CARM for pancreatitis reactions, 1 January 2009 to 31 December 2018

Medicine	Reports	Positive dechallenge[a]	Positive rechallenge[b]
Azathioprine	7	7	
Simvastatin	5	5	
Codeine	3	3	1
Ibuprofen	3	3	
Mesalazine	3	3	
Leflunomide	2	1	1
Olanzapine	2	2	1
Cannabis	1	1	1

Notes: a. Positive dechallenge: withdrawal of the medicine and cessation of symptoms.
b. Positive rechallenge: restart the medicine and recurrence of symptoms.

Advice for healthcare professionals

Healthcare professionals should consider medicines as a potential cause of pancreatitis, particularly when there is a temporal relationship with starting a medicine. If you suspect a medicine has caused pancreatitis, withdraw the medicine. Report any suspected cases of DIP to CARM (**https://nzphvc.otago.ac.nz/reporting/**).

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Zopiclone – Indicated for short-term use only

Key messages

- Zopiclone is indicated for short-term treatment of insomnia.
- Treatment with zopiclone should not exceed 4 weeks.
- If zopiclone is needed, also initiate non-pharmacologic measures to improve sleep.
- Use a lower starting dose in elderly patients.
- Adverse effects are common, especially in elderly patients.

Zopiclone should be used at the lowest effective dose and only for short periods

Zopiclone is indicated for the short-term treatment of insomnia in adults[1]. The approved adult dose is 7.5 mg taken shortly before bedtime for up to a maximum of 4 weeks. Medsafe has not assessed the safety and efficacy of longer-term use. Use of zopiclone for longer than 4 weeks should be considered 'off-label'.

If zopiclone is needed to manage insomnia, it should be used in conjunction with non-pharmacological approaches, such as managing expectations about sleep duration, improving sleep hygiene, modifying lifestyle factors, and addressing underlying health issues and psychological stress[2–4].

Long term use of zopiclone may cause tolerance and dependence, leading to withdrawal and rebound insomnia if the medicine is stopped abruptly. A gradual reduction in dose and/or frequency of use can reduce the likelihood of withdrawal effects after long-term use[1–3].

Zopiclone is eliminated via hepatic metabolism, therefore, hepatic impairment increases the risk of adverse effects. In healthy adults, the elimination half-life of zopiclone after a single dose is 5 hours. In patients with hepatic failure, the elimination half-life is prolonged to nearly 12 hours[1].

Risk of adverse effects greater in the elderly

The recommended dose for elderly patients is 3.75 mg. The dose may be increased if the lower dose is not effective, but a higher dose is more likely to cause central nervous system side effects in the elderly[1].

In elderly patients, the elimination half-life of zopiclone is prolonged to approximately 7 hours, compared to 5 hours in younger adults. The risk of next-day 'hangover' effects such as drowsiness, cognitive impairment and dizziness is, therefore, higher in the elderly. These 'hangover' effects put elderly patients at greater risk of falls, and may also affect their ability to drive.

Psychiatric adverse events, including depression, suicidality, psychosis and schizophrenia, have been associated with the use of zopiclone. Psychiatric adverse reactions and paradoxical effects such as restlessness, irritability and aggression are more likely to occur in the elderly[1].

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Paraffin-based emollients and the risk of severe and fatal burns

Key messages

- From May 2020, some paraffin-based emollients will be required to include the following warning:

  Caution: This product may make dressings and clothing catch fire more easily.

- Change clothing, bedding and bandages regularly – preferably daily – because paraffin-based emollients soak into fabric, build up and can become a fire hazard.
- Advise patients not to smoke, use naked flames (or be near people who are smoking or using naked flames) or go near anything that may cause a fire while using paraffin-based emollients.

Background

Although there have not been any reports in New Zealand to date, the Medicines and Healthcare products Regulatory Agency in the UK is currently aware of 11 cases in which paraffin-based emollients are suspected to have contributed to the speed and intensity of a fire, resulting in a fatal burns injury[1].

The hazards of paraffin-based emollients have been documented in the UK for over 10 years[2].

The New Zealand Formulary includes safety information on a fire hazard with paraffin-based emollients[3]. However, there has been limited safety information in New Zealand regarding these emollients and the risk of severe and fatal burns.

What's new?

From May 2020, some paraffin-based emollients will be required to include the following warning:

Caution: This product may make dressings and clothing catch fire more easily.

This warning statement will only apply to products containing 50% or more of paraffin and in packs of 100 g or more.

Medsafe consulted on this warning statement at the end of 2018 – you can read more about it on the Medsafe website (**www.medsafe.govt.nz/consultations/Paraffin%20Based%20Skin/Outcome%20of%20Consultation.asp**).

Avoiding the risk of burns

Healthcare professionals should provide the following advice when prescribing, recommending, dispensing (including compounding and repacking), selling or applying paraffin-based emollients to patients and their carers[1,2].

- Paraffin-based emollients are not themselves flammable.
- Clothing, bedding or medical dressings covered in paraffin-based emollients are at risk of catching fire and are the main hazard.
- Patients should not smoke, use naked flames (or be near people who are smoking or using naked flames) or go near anything that may cause a fire while paraffin-based emollients are in contact with their clothing, bedding or medical dressings.

- Change patient clothing, bedding and medical dressings regularly – preferably daily – because paraffin-based emollients soak into fabric, build up and can become a fire hazard.
- Very high-risk patients are likely to be elderly smokers, with an even higher risk for those receiving home oxygen.
- No risk has been identified for paraffin-based products with other uses, such as paraffin-based eye ointments.

Further information

A Consumer Information Leaflet, 'Fire hazard from skin products containing paraffin', is available on the Medsafe website (**www.medsafe.govt.nz/consumers/educational-material.asp**).

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The fantastic four of adverse drug reaction reporting

Key messages

- There are only four requirements for a valid adverse drug reaction report: patient identifier, medicine, reaction, reporter details.
- You don't need to be certain – just suspicious!

Background

All medicines can cause adverse drug reactions. These reactions can range from minor discomfort to serious harm. A recent study of medication-related harm in New Zealand hospital settings estimated that 28% of patients experienced one or more medicine-related harms[1]. This study suggests medicine-related harms, including adverse drug reactions, are common.

Reporting suspected adverse drug reactions enables Medsafe to quickly identify and respond to emerging medicine safety issues.

Reporting adverse drug reactions

You don't have to be certain that a medicine caused a reaction. A *suspicion* of an adverse drug reaction is all that is required to prompt a report.

There are only four requirements for a valid adverse drug reaction report:

1. one patient identifier (eg, name, initials, gender, date of birth, age)
2. suspect medicine(s)
3. suspected reaction(s)
4. reporter details.

The patient can remain anonymous – only the age and/or sex are needed. Inclusion of the patient's name, date of birth, and NHI in the report is optional.

Anyone can report an adverse drug reaction, including all healthcare professionals and patients/consumers (Figure 1).

The four requirements listed above are the minimum requirements. However, including more information in your report will help Medsafe to investigate the reaction more quickly.

Reporting is easiest online: **https://nzphvc.otago.ac.nz/reporting/**

Figure 1: Screenshot of the Centre for Adverse Reactions Monitoring (CARM) online reporting page (https://nzphvc.otago.ac.nz/reporting/)

Want to know more?

Complete the eLearning module and earn continuing professional development (CPD) points (**www.medsafe.govt.nz/profs/ADR-training/story_html5.html**).

Each year, the March edition of *Prescriber Update* includes a summary of adverse drug reactions reporting in New Zealand. Read about adverse reaction reporting in 2018 here: **https://medsafe.govt.nz/profs/PUArticles/March2019/Adverse%20reaction%20reporting%20in%20New%20Zealand%20%E2%80%93%202018.htm**

Search for suspected adverse drug reactions reported in New Zealand using the Suspected Medicine Adverse Reaction Search (SMARS) (**https://medsafe.govt.nz/Projects/B1/ADRDisclaimer.asp**).

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Medicines classification update: November 2018

There were a number of medicine classification changes recommended at the 61st meeting of the Medicines Classification Committee (MCC) held on 2 November 2018.

The following substances were reclassified.

- **Modified release paracetamol** containing up to 665 mg per dosage form is now a pharmacist-only medicine.
- **Dextromethorphan-containing medicines** are now pharmacist-only or prescription medicines. Dextromethorphan is no longer legally available for sale as a pharmacy-only or a general sale medicine.
- **Opium tincture and squill oxymel** (in combination known as **Gees linctus**) is now a prescription medicine.

The MCC considered two proposals to amend the classification statement for **melatonin** and recommended that melatonin prolonged release 2 mg tablets and 3 mg tablets should be classified as 'prescription except when' with the following conditions:

- supplied for the treatment of primary insomnia for adults aged 55 years or older for up to 13 weeks
- by a NZ registered pharmacist who has completed an approved training programme in mental health and insomnia
- in a pack that has received consent from the Minister of Health or the Director-General.

This recommendation has not yet been confirmed by the Minister's Delegate.

The MCC considered a proposal to amend the classification of **pholcodine** and recommended that it should remain unchanged.

More information

The Medsafe website has information on the classification process and minutes of the MCC meetings (**https://medsafe.govt.nz/committees/mcc.asp**). See also the **Medsafe Files** article on page 41 of this edition of *Prescriber Update*.

You can search the classification database to check the classification of an active ingredient (**https://medsafe.govt.nz/profs/class/classintro.asp**).

Proton pump inhibitors and rebound acid hypersecretion – A recurring issue

Key messages

- For many people, short-term proton pump inhibitor (PPI) use is appropriate.
- Rebound acid hypersecretion has been reported in patients after stopping prolonged treatment with a PPI.
- Consider a step-down approach when stopping PPI therapy.

Background

Concerns have been raised that rebound acid hypersecretion (RAHS) may be one of the explanations for the increasing long-term use of proton pump inhibitors (PPIs).

Proton pump inhibitors

PPIs inhibit gastric acid secretion. The PPIs currently available in New Zealand are omeprazole, lansoprazole or pantoprazole.

PPIs are indicated for[1]:

- the short-term treatment of benign duodenal and gastric ulcers
- the eradication of *Helicobacter pylori*, in combination with antibacterials
- the treatment of dyspepsia and gastro-oesophageal reflux disease
- the prevention and treatment of NSAID-associated ulcers
- Zollinger–Ellison syndrome.

PPIs are widely used in New Zealand. In 2018, omeprazole was the third most commonly dispensed medicine, after paracetamol and atorvastatin[2].

For many people, short-term PPI use (4–8 weeks) is appropriate. See the medicine data sheets for more information (**www.medsafe.govt.nz/Medicines/infoSearch.asp**).

Rebound acid hypersecretion

RAHS is the recurrence of symptoms due to an increase in gastric acid secretion above pre-treatment levels after stopping PPI therapy[3]. Symptoms of RAHS may include heartburn, regurgitation or dyspepsia.

According to the proposed RAHS mechanism, reduced gastric acidity caused by PPIs induces hypergastrinemia and growth of histamine-releasing enterochromaffin-like cells, which leads to an increased acid secretory capacity once the PPI therapy is discontinued[3].

Concerns have been raised that RAHS may contribute to the increasing long-term use of PPIs[3]. The symptoms of RAHS are similar to the underlying condition for which the PPI was used. Therefore, a reinforcing loop can develop where initial treatment creates the need for further treatment[4].

Stopping PPIs

Consider a 'step down' approach for people taking a PPI who are no longer experiencing symptoms and/or do not require long-term treatment[2]. Stepping down involves gradually reducing the dose over time, before stopping the medicine completely. Alternative treatments, such as histamine H2-receptor antagonists or antacids, may be useful to manage rebound symptoms.

See the Best Practice Advocacy Centre NZ (bpac) PPI stepping down protocol for more information (**https://bpac.org.nz/2019/ppi.aspx**).

References

1. New Zealand Formulary. 2019. *New Zealand Formulary v82.1: Proton pump inhibitors* 4 April 2019. URL: https://nzf.org.nz/nzf_763 (accessed 10 April 2019).
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3. Lødrup A, Reimer C and Bytzer P. 2013. Systematic review: symptoms of rebound acid hypersecretion following proton pump inhibitor treatment. *Scandinavian Journal of Gastroenterology* 48(5): 515–22. URL: https://doi.org/10.3109/00365521.2012.746395 (accessed 10 December 2018).
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Recent approvals of medicines containing a new active ingredient

For the period 16 January 2019 to 15 April 2019.

Trade name (Active ingredient)	Dose form and strength(s)	Therapeutic area
Agrylin (anagrelide)	Capsule 0.5 mg	Essential thrombocythaemia
Phenasen (arsenic trioxide)	Concentration for injection 10 mg/10 mL	Acute promyelocytic leukaemia (APL)

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

Gathering knowledge from adverse reaction reports: June 2019

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]	Reaction description and data sheet information[b]
CARM ID: 129304 **Age:** 60 **Gender:** Male **Medicine(s)**: Atorvastatin, ticagrelor **Reaction(s):** Drug interaction, jaundice, abnormal hepatic function, urine discolouration	One month after being treated for myocardial infarction, a 60-year-old man experienced jaundice and dark urine. His liver function tests were abnormal. A ticagrelor-atorvastatin drug interaction was suspected. The symptoms resolved upon discontinuation of atorvastatin.
	Atorvastatin is metabolised by cytochrome P450 3A4 (CYP3A4). Ticagrelor is primarily a CYP3A4 substrate and a mild inhibitor of CY3A4. The Lorstat (**www.medsafe.govt.nz/profs/Datasheet/l/lorstattab.pdf**) and Brilinta (**www.medsafe.govt.nz/profs/Datasheet/b/Brilintatab.pdf**) data sheets state that co-administration of atorvastatin and ticagrelor increases the concentration of atorvastatin in plasma, although the increase was not considered clinically significant.
CARM ID: 130207 **Age:** 84 **Gender:** Female **Medicine(s):** Tranexamic acid **Reaction(s):** Pulmonary embolism	An 84-year-old woman presented to hospital after developing shortness of breath, nausea and sweating. She was diagnosed with pulmonary embolism. Three weeks earlier, tranexamic acid had been used after a dental extraction to prevent bleeding. The tablet had been dissolved in water to soak the gauze packing (it was not swallowed).
	Pulmonary embolism is listed as an uncommon (0.1 to <1%) adverse event in the Cyklokapron data sheet (**www.medsafe.govt.nz/profs/Datasheet/c/Cyklokaprontabinj.pdf**).
CARM ID: 130978 **Age:** 66 **Gender:** Male **Medicine(s):** Gliclazide, sulfamethoxazole + trimethoprim (co-trimoxazole) **Reaction(s):** Drug interaction, hypoglycaemia	A diabetic patient on long-term gliclazide had reduced blood glucose levels after starting co-trimoxazole treatment for an infection.
	The Glizide (**www.medsafe.govt.nz/profs/Datasheet/g/glizidetab.pdf**) and Trisul (**www.medsafe.govt.nz/profs/Datasheet/t/Trisultab.pdf**) data sheets state that sulfonamides can potentiate the blood glucose lowering effect of sulfonylureas.
CARM ID: 131210 **Age:** 70 **Gender:** Male **Medicine(s):** Quinine **Reaction(s):** Disseminated intravascular coagulation	A 70-year-old male taking quinine for cramps experienced disseminated intravascular coagulation.
	Quinine is not indicated for treatment of cramps. Intravascular coagulation is listed as an undesirable effect in the Q300 data sheet (**www.medsafe.govt.nz/profs/Datasheet/q/q300tab.pdf**).

Case details[a]	Reaction description and data sheet information[b]
CARM ID: 131491 **Age:** 65 **Gender:** Female **Medicine(s):** Candesartan, bendroflumethiazide, ibuprofen **Reaction(s):** Drug interaction, acute kidney injury, orthostatic hypotension	A 65-year-old female patient on long-term ibuprofen and a thiazide diuretic developed reduced renal function and orthostatic hypotension after starting an angiotensin receptor antagonist. The Candestar (**www.medsafe.govt.nz/profs/Datasheet/c/candestartab.pdf**) and Brufen SR (**www.medsafe.govt.nz/profs/Datasheet/b/brufenretardtab.pdf**) data sheets state that concomitant use of NSAIDs, angiotensin receptor antagonists and thiazide diuretics increases the risk of renal impairment, especially in older patients or those with pre-existing renal impairment. The Arrow-Bendrofluazide data sheet states that enhanced hypotensive effects may follow the concomitant use of thiazides and other antihypertensives (**www.medsafe.govt.nz/profs/Datasheet/a/arrow-bendrofluazidetab.pdf**). See also the 'Triple whammy' discussion in the June 2013 *Prescriber Update* article 'NSAIDs and acute kidney injury' (**www.medsafe.govt.nz/profs/PUArticles/June2013NSAIDS.htm**).

Notes: a. Only the medicines suspected to have caused the reaction are listed in the table.

b. If the suspect medicine's brand name is not described in the report to CARM, only the data sheet for the funded medicine is included in the table.

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

By selecting the ingredient of a medicine you can find out:

- the number of reports and suspected adverse reactions for that ingredient. The suspected reactions are grouped by body system or organs (Summary report)
- single case reports, listing the medicines involved that contain the ingredient and the suspected adverse reactions (Detail report).

MARC's remarks: March 2019 meeting

The Medicines Adverse Reactions Committee (MARC) met on 14 March 2019 to discuss a number of medicine-related safety issues.

The Committee discussed **fingolimod** and tumefactive lesions. The Committee stated that it is difficult to determine whether tumefactive lesions occur due to multiple sclerosis or fingolimod. The Committee considered that there was no strong evidence of an association with fingolimod. However, the Committee determined that due to the severity of tumefactive lesions, a warning should be included in the data sheet. Medsafe is currently working with the sponsor to update the data sheet.

The Committee discussed recent publications describing the cardiovascular risks associated with **NSAIDs**. For further information, please see the **NSAIDs article** on page 26 of this edition of *Prescriber Update*.

The Committee discussed the use of **methadone** during breastfeeding. The Committee concluded that the benefit of breastfeeding while taking methadone for opioid substitution therapy outweighs the risks of harm from the transfer of methadone to the infant via breast milk. Increased monitoring during the first three weeks of life is important to ensure infant

safety, and Medsafe is working with the sponsors of methadone products to include this information in the data sheets.

The Committee reviewed newly published literature on the use of **nitrofurantoin** in renal impairment. The Committee concluded that the overall evidence was insufficient to warrant any changes to the data sheets. Use of nitrofurantoin remains contraindicated in patients with a creatinine clearance below 60 mL/min.

The Committee discussed **ergotamine-containing medicines** and pancreatitis. The Committee considered that the single case received by CARM describing Cafergot and pancreatitis (CARM ID 129940) did not provide sufficient evidence of an association. However, the Committee noted that there is limited evidence of benefit and that these medicines have been removed from multiple overseas markets. The Committee recommended that Medsafe undertakes a risk-benefit review of Cafergot under section 36 of the Medicines Act 1981.

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

Quarterly summary of recent safety communications

The table below is a summary of recent safety communications to healthcare professionals and consumers, published on the Medsafe website (**medsafe.govt.nz/safety/alerts.asp**).

Date	Communication	Topic
16 May 2019	Monitoring	Risk of infections with Prolia (denosumab)
15 May 2019	Dear HealthCare Professional letter	Actemra – New important identified risk: Hepatoxicity (PDF 361 KB, 3 pages)
7 May 2019	Monitoring	Review of the risks of harm and chance of benefit of Cafergot (ergotamine tartrate + caffeine) under section 36 of the Medicines Act 1981
24 April 2019	Alert	Take care when prescribing and dispensing levodopa-containing products (Madopar, Sinemet, Kinson)
23 April 2019	Alert	Consumer level recall – baby teething powder and baby colic powder
16 April 2019	Alert	Hydrochlorothiazide: risk of non-melanoma skin cancer
11 April 2019	Monitoring	Breast implants and anaplastic large cell lymphoma
26 March 2019	Dear HealthCare Professional letter	Darzalex (PDF 103 KB, 2 pages) – New important identified risk: Hepatitis B reactivation
22 March 2019	Alert	Consumer level recall – Normal saline, a component of The Trusts first aid kits
6 March 2019	Monitoring	Losartan approved medicines supplied in New Zealand not affected by recalls overseas
4 March 2019	Alert	Use of sodium valproate (Epilim) in girls and women – Change to indications and contraindications
15 February 2019	Dear Healthcare Professional letter	Esmya – Important safety update following reports of serious liver injury (PDF 115 KB, 2 pages)
11 February 2019	Alert	Consumer level recall – Bronchi-cough pills (Qiguanyan Kesou Tanchuanwan)

The Medsafe Files – Episode 10: Medicines classification

Key messages

- Medicines are generally classified according to their active ingredients.
- The Medicines Act 1981 defines three classifications for medicines: prescription medicine, restricted medicine (pharmacist only) and pharmacy-only medicine.
- Medicines not listed in the classification schedules are deemed to be unclassified, and are referred to as general sales medicines.
- The Medicines Classification Committee provides advice to the Minister of Health's delegate on the classification of medicines.

The Medsafe Files series continues with this article on classification of medicines.

Medicines are classified according to their active ingredients

Schedule 1 of the Medicines Regulations 1984 contains a list of active ingredients grouped under their respective classifications. Active ingredients are listed by their International Non-Proprietary Name (INN).

If a medicine has more than one active ingredient, the active ingredient with the most restrictive classification determines the classification of that medicine.

To find out the classification of an active ingredient you can search Medsafe's classification database (**https://medsafe.govt.nz/profs/class/classintro.asp**). Alternatively, you can refer to the latest amendment of the Medicines Regulations 1984 (available at **www.legislation.govt.nz**) and any subsequent notices published in the New Zealand Gazette (**https://gazette.govt.nz**).

Legislation defines three different classifications of medicines

The Medicines Act 1981 defines three classifications for medicines.

- **Prescription medicines** may be supplied only on the prescription of an authorised prescriber.
- **Restricted medicines** (also referred to as Pharmacist-Only medicines) may be sold without a prescription, but the sale must be made by a registered pharmacist in a pharmacy, and the details of the sale must be recorded.
- **Pharmacy-only medicines** may only be sold in a community or hospital pharmacy, and the sale may be made by any salesperson.

Medicines not listed in Schedule 1 are deemed to be unclassified and are referred to as **general sales medicines**. These medicines may be sold from any outlet.

Medicines Classification Committee

The Medicines Classification Committee (MCC) is an advisory committee that makes recommendations to the Minister of Health's delegate regarding the classification of medicines. The MCC considers applications for the reclassification of medicines and recommends the classification of new active ingredients. The MCC meets twice a year and secretarial support is provided by Medsafe. You can find out more information about the MCC on the Medsafe website (**https://medsafe.govt.nz/committees/mcc.asp**).

Anyone can make a submission to the MCC to reclassify a medicine. Guidance on how to change the legal classification of a medicine in New Zealand is published on the Medsafe website (**https://medsafe.govt.nz/downloads/How_to_change_medicine_classification.pdf** [PDF 408 KB, 22 pages]).

We need your help!

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

Medicine	Potential safety issue	Active monitoring ends
Tramadol	Opioid effects in breastfeeding babies	30 June 2019
Zoster (shingles) vaccine or Influenza vaccine	Lichen planus	31 July 2019
Denosumab	Risk of infections	30 November 2019

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

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

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To subscribe: **www.medsafe.govt.nz/profs/subscribe.asp**

Regulatory web update emails

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

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

Medicine classification emails

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

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

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Acknowledgement
Dr Michael Tatley, Centre for Adverse Reactions Monitoring
Dr Ruth Savage, Centre for Adverse Reactions Monitoring
Medsafe also acknowledges the contribution of the New Zealand Pharmacovigilance Centre in providing data and analysis for articles.

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