

# Prescriber Update

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## Medicine Induced Anaphylaxis – Reporting is Vital!

### Key Messages

- ⌘ Anaphylaxis is reported most commonly with antibiotics, muscle relaxants, and NSAIDs but can occur with most medicines.
- ⌘ Allergy testing is useful to identify or confirm the medicine responsible for anaphylaxis.
- ⌘ A Medic Alert bracelet should be considered in all patients with a serious allergy to a medicine.
- ⌘ Please report all cases to CARM so that an alert can be entered in the Medical Warning System.

Anaphylaxis is a life-threatening, systemic hypersensitivity reaction that can occur with a wide range of medicines. Healthcare professionals are advised to report all cases of suspected or confirmed medicine induced anaphylaxis to the Centre for Adverse Reactions Monitoring (CARM) even if the reaction is well known.

Reporting will enable a 'Danger' to be entered against the patient's NHI on the Medical Warning System to alert other healthcare professionals to the patient's allergy<sup>1</sup>.

### Medical Warning System

The Medical Warning System is a national alert service that is linked to National Health Index (NHI) numbers<sup>1</sup>. CARM enters information

on serious and/or life threatening adverse reactions into this system as either a 'Warning' or a 'Danger'. Anaphylaxis is always entered as a 'Danger'.

Whenever the patient's NHI is accessed, the 'Danger' is automatically highlighted to ensure that healthcare professionals are aware of the patient's allergy. Unfortunately, although the system is visible to DHB's, the Medical Warning System is not currently accessible to the majority of GPs.

### Reports to CARM

From 1 January 2000 until 31 December 2013, CARM received a total of 1433 reports of anaphylactic or anaphylactoid reactions. The majority of patients were women (63%) and most patients had made a full recovery (>90%) by the time of reporting to CARM.

In New Zealand, anaphylaxis is most commonly reported following the administration of antibiotics, neuromuscular blocking agents (muscle relaxants), NSAIDs and anaesthetics (Figure 1).

While the pattern of reporting in New Zealand is consistent with that in the published literature, the proportion of reports in each of these classes is lower than in many studies. The lower rate may indicate that New Zealand healthcare professionals are less likely to report cases associated with medicines that are well known to cause anaphylaxis.

The most commonly implicated individual medicines were rocuronium (10%), amoxicillin/

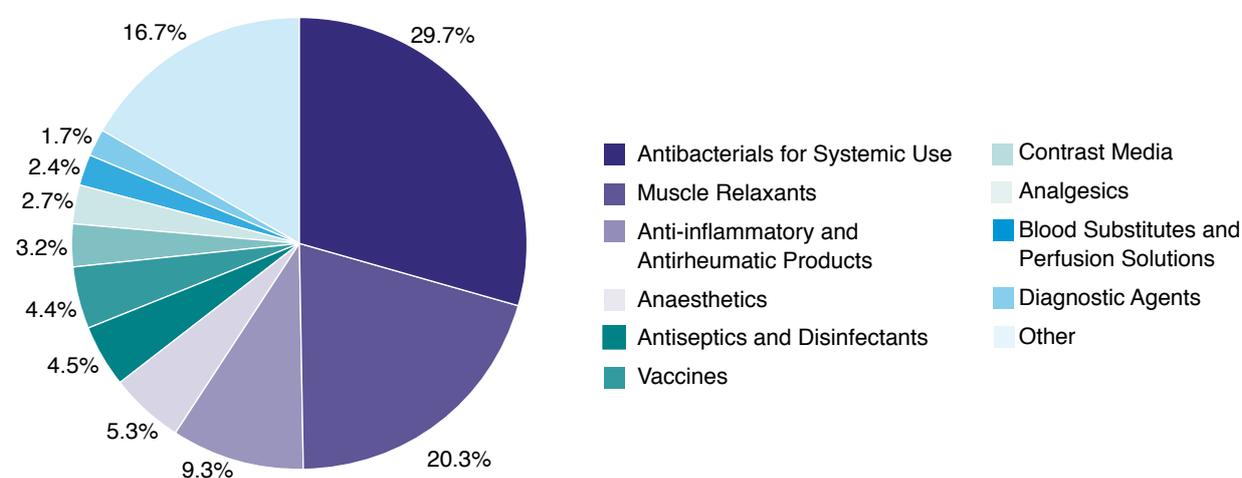


Figure 1: Top 10 classes of medicines associated with anaphylaxis in the CARM database

clavulanic acid (7%), suxamethonium (7%), diclofenac (5%) and cefazolin (5%).

Of note, 4.5% of the reports were for anaphylaxis to antiseptics such as chlorhexidine, which may not be well recognised as a cause of anaphylaxis<sup>2</sup>.

### Anaphylaxis Terminology

The term anaphylaxis has traditionally been used to describe IgE mediated allergic reactions and the term anaphylactoid reaction has been used to describe non-IgE mediated reactions. However, as the two types of reactions are not clinically distinguishable and are treated in the same way, anaphylaxis is now used to describe both categories of reactions.

In 2010, the World Allergy Organization divided anaphylaxis into three categories<sup>3</sup>.

1. Immunologic anaphylaxis (IgE mediated or non-IgE mediated).
2. Non-immunologic anaphylaxis.
3. Idiopathic anaphylaxis.

Medicines can cause both immunologic and non-immunologic anaphylaxis.

### Diagnosis

The diagnosis of anaphylaxis can be difficult. However, anaphylaxis is likely if the following features are present<sup>4,5</sup>.

- Acute onset and/or rapid progression of symptoms.
- Life-threatening airway compromise (swelling, hoarseness, stridor) and/or breathing difficulties (rapid breathing, wheeze, fatigue, cyanosis) and/or circulatory compromise (pale, clammy, faintness, hypotension).

- Skin reactions (eg, rash, urticaria, angioedema).

### Treatment

Intramuscular adrenaline is the core treatment for anaphylaxis. It should be given immediately to all patients with life-threatening clinical features. Anaphylaxis treatment algorithms should be followed<sup>4-6</sup>.

Long-term management should include patient education, referral for allergy testing and consideration of a Medic Alert bracelet.

For further advice on the diagnosis and management of anaphylaxis please refer to the the guidelines produced by the Best Practice Advocacy Centre (BPAC), NZ Resuscitation Council and Starship Children's Hospital<sup>4-6</sup>.

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## Intravenous Iron and Hypersensitivity

### Key Messages

- ⌘ Patients are at risk of hypersensitivity or allergic reactions with every dose of intravenous iron.
- ⌘ A test dose is no longer recommended.
- ⌘ Intravenous iron should not be used in pregnancy unless clearly necessary.
- ⌘ Patients should be monitored for 30 to 60 minutes after each administration.

The European Medicines Agency (EMA) has recently issued new recommendations to manage the risk of allergic reactions with intravenous iron. A test dose of intravenous iron is no longer recommended.

Patients are at risk of hypersensitivity or allergic reactions with every dose of intravenous iron. Allergic reactions can still occur even if patients have tolerated previous doses or have not reacted to a test dose.

The risk of hypersensitivity is increased in patients with known allergies, inflammatory conditions or a history of asthma, eczema or other atopy.

Intravenous iron should not be used in pregnancy unless clearly necessary and only if the benefits outweigh the potential risks to the mother and foetus. As currently stated in the New Zealand data sheets, use of these products in the first trimester of pregnancy is contraindicated<sup>1-3</sup>.

Intravenous iron should only be administered when resuscitation facilities are immediately available and with trained staff present. Each patient should be monitored for signs and symptoms of hypersensitivity during and after each administration for at least 30 to 60 minutes.

New Zealand has three approved intravenous iron medicines: Ferrosig and Ferrum H (both iron polymaltose), and Venofer (iron sucrose)<sup>1-3</sup>.

The Centre for Adverse Reactions Monitoring (CARM) has received a total of 103 reports of hypersensitivity for iron polymaltose and iron sucrose. Of these reports, 81 were for women and 25 were for pregnant women. All patients recovered and most of the reports were classified as not serious.

Medsafe is currently working with the relevant sponsors to ensure all data sheets for intravenous iron medicines contain these new recommendations.

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## Drug Metabolism – The Importance of Cytochrome P450 3A4

### Key Messages

- ⌘ CYP3A4 is responsible for the metabolism of more than 50% of medicines.
- ⌘ CYP3A4 activity is absent in new-borns but reaches adult levels at around one year of age.
- ⌘ The liver and small intestine have the highest CYP3A4 activity.
- ⌘ Some important CYP3A4 interactions are due to intestinal rather than hepatic enzyme inhibition (eg, grapefruit).
- ⌘ There is considerable variability in CYP3A4 activity in the population.
- ⌘ Women have higher CYP3A4 activity than men.
- ⌘ Potent inhibitors of CYP3A4 include clarithromycin, erythromycin, diltiazem, itraconazole, ketoconazole, ritonavir, verapamil, goldenseal and grapefruit.
- ⌘ Inducers of CYP3A4 include phenobarbital, phenytoin, rifampicin, St. John's Wort and glucocorticoids.

Cytochrome P450 enzymes are essential for the metabolism of many medicines and endogenous compounds. The CYP3A family is the most abundant subfamily of the CYP isoforms in the liver. There are at least four isoforms: 3A4, 3A5, 3A7 and 3A43 of which 3A4 is the most important<sup>1</sup>.

CYP3A4 contributes to bile acid detoxification, the termination of action of steroid hormones, and elimination of phytochemicals in food and the majority of medicines<sup>2,3</sup>.

Data sheets on the Medsafe website ([www.medsafe.govt.nz](http://www.medsafe.govt.nz)) and the New Zealand formulary ([www.nzf.org.nz](http://www.nzf.org.nz)) are useful sources of information on individual drug-drug interactions.

### Age-related Changes and Gender Differences

Foetal levels of CYP3A4 expression, content and activity are very low, but appear to reach adult levels at around one year of age<sup>1</sup>.

Clinical studies indicate that women metabolise drugs which are substrates of CYP3A4 more quickly than men (20–30% increase)<sup>4</sup>. Analyses have shown around two fold higher levels of CYP3A4 protein in female compared to male tissue samples<sup>3,4</sup>.

## Location

CYP3A4 is mainly located in the liver and small intestine and is the most abundant cytochrome in these organs<sup>1</sup>. However, CYP3A4 levels in the intestines are not correlated with those of the liver<sup>3</sup>.

Some medicines which are substrates of CYP3A4 have low oral (but not intravenous) bioavailability due to intestinal metabolism. The bioavailability of these substrates is dramatically changed by inhibition, induction or saturation of CYP3A4<sup>5</sup>.

## Polymorphisms

The population variability of CYP3A4 activity is extremely high (>100-fold)<sup>3,6</sup>.

Some variability can be attributed to allelic variation. A recently discovered single nucleotide polymorphism (CYP3A4\*22) appears to be associated with decreased expression and activity (1.7 to 5 fold less). However, the frequency of this variant at around 2% of the population limits its contribution to overall CYP3A4 variability<sup>1,3</sup>.

Another identified polymorphism is CYP3A4\*1B which occurs at a frequency of 2–9% in some populations. However, a functional effect of this variant has not been established<sup>3</sup>.

Hepatic and intestinal expression of CYP3A4 exhibits a unimodal distribution of activity suggesting that the population variability is not due to genetic polymorphism of the enzyme itself<sup>2</sup>.

Nevertheless, there are indications of substantial heritability<sup>3</sup>. Variation in CYP3A4 among healthy individuals is most likely to be the result of differences in homeostatic regulatory mechanisms<sup>2</sup>.

## Effect of Disease

In disease states, the inherent variability of CYP3A4 mediated drug metabolism is potentially exacerbated by many factors including alterations in hepatic haemodynamics, hepatocellular function, nutrition, circulating hormones, as well as drug-drug interactions<sup>2,3</sup>.

It has also been increasingly recognised that inflammatory mediators associated with a range of disease states are capable of having profound effects on CYP3A4 gene expression<sup>2</sup>.

Patients with inflammation, particularly elevated acute phase proteins such as C-reactive

protein (CRP) have been noted to have reduced CYP3A4 function<sup>2</sup>. This is clinically relevant in cancer patients because tumours can be a source of systemically circulating cytokines<sup>3</sup>.

Acute systemic hypoxia (eg, in chronic respiratory or cardiac insufficiency) appears to up-regulate CYP3A4 activity<sup>7</sup>.

Reports of CYP3A4 activity in critically ill children showed significantly lower CYP3A4 metabolism<sup>1,8</sup>.

## Inhibition

CYP3A4 is subject to reversible and mechanism-based (irreversible) inhibition. The latter involves the inactivation of the enzyme via the formation of metabolic intermediates that bind irreversibly to the enzyme and then inactivate it<sup>6</sup>. The clinical effects of a mechanistic inactivator are more prominent after multiple dosing and last longer than those of a reversible inhibitor<sup>6</sup>.

Medicines that are potent CYP3A4 inhibitors include (but are not limited to) clarithromycin, diltiazem, erythromycin, itraconazole, ketoconazole, ritonavir, and verapamil<sup>9</sup>.

Common drug-drug interactions involving CYP3A4 include:

- clarithromycin/erythromycin and simvastatin resulting in myopathy or rhabdomyolysis<sup>10</sup>
- diltiazem/verapamil and prednisone resulting in immunosuppression caused by increased prednisolone levels<sup>9</sup>.

One form of reversible inhibition occurs due to competition between CYP3A4 substrates (eg, oestrogen and antidepressants during the late luteal phase of the menstrual cycle)<sup>4</sup>.

## Induction

CYP3A4 activity is induced via the pregnane X receptor (PXR), the constitutive androstane receptor (CAR), peroxisome proliferator-activated receptor (PPAR $\alpha$ ) and probably the glucocorticoid receptor (GR)<sup>3,11</sup>.

The magnitude of CYP3A4 induction can be substantial. Induction becomes apparent more slowly than inhibition and it takes more time for the induction to stop affecting medicine metabolism. For example, the induction of CYP3A4 by rifampicin takes around six days to develop and 11 days to disappear<sup>11</sup>.

Induction normally results in a decrease in the effect of the medicine. However, it can lead to

increased toxicity if the increased metabolism of the parent compound is accompanied by an increase in exposure to a toxic metabolite<sup>11</sup>.

Medicines that are potent inducers include phenobarbital, phenytoin and rifampicin<sup>9</sup>. Many glucocorticoids in clinical use also induce CYP3A4. Some organochlorine pesticides such as dichlorodiphenyltrichloroethane and endrin also induce CYP3A4<sup>11</sup>.

### Herb and Food Interactions

Popular dietary supplements and foods that have a high risk for interaction with medicines metabolised by CYP3A4 include (but are not limited to) the following.

#### Goldenseal

Goldenseal (*Hydrastis Canadensis*) is often taken to try to prevent common colds and upper respiratory tract infections. It has been reported to reduce CYP3A mediated activity by 88%, equivalent to that seen with clarithromycin<sup>12</sup>.

#### Black pepper

Black pepper (*Piper nigrum*) has been used as a flavouring agent and medicine. When used for flavouring food it is not likely to affect the metabolism of most medicines<sup>12</sup>. However, excessive use or use in dietary supplements (piperine or piperamides greater than 10 mg) may produce clinically significant interactions, including CYP3A4 inhibition<sup>12</sup>.

#### Schisandra

Preparations of fruits from woody vines of *Schisandra* species are used in traditional Chinese, Japanese and Russian medicine, often as hepatoprotective agents<sup>12</sup>. Currently available clinical data strongly suggest that *Schisandra* extracts pose a significant risk for elevating blood levels of medicines that are CYP3A substrates<sup>12</sup>.

#### St John's Wort

This is used for its antidepressant activity. The active substance is hyperforin, the most potent known activator of PXR<sup>12</sup>. Clinical studies have demonstrated that products containing less than 1% hyperforin are less likely to produce interactions<sup>12</sup>. However, most products contain 3% hyperforin<sup>12</sup>.

#### Grapefruit

Grapefruit (all sources) is a potent inhibitor of intestinal CYP3A4 that has been proposed to interact with more than 44 medicines and result in serious adverse effects<sup>13</sup>.

Healthcare professionals should ask patients about their use of complementary and alternative medicines when considering the use of a medicine that is altered by CYP3A4.

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## Update: PPIs and Clopidogrel Interaction

The Medicines Adverse Reactions Committee (MARC) has reviewed information on clinical outcomes in patients taking proton pump inhibitors (PPIs) and clopidogrel. Previous *in vitro* studies had shown an interaction between omeprazole resulting in reduced efficacy of clopidogrel<sup>1</sup>.

The MARC observed that available data indicate that patients who take PPIs have a greater number of co-morbidities that may predispose them to cardiovascular endpoints. The MARC recommended that whilst there is evidence that PPIs affect clopidogrel activity *ex vivo*, the available evidence suggests that this does not translate into adverse clinical outcomes.

In addition, the MARC also recommended that the available evidence does not show an increased risk of adverse cardiovascular outcomes when PPIs are used with aspirin or whether it is a direct effect of PPIs.

The possible interaction between PPIs and clopidogrel was first reviewed by the MARC in

2010<sup>2</sup>. At this time, there was limited information on the clinical significance of this interaction. Advice has previously been provided in *Prescriber Update*<sup>3,4</sup>.

Further information on this topic can be found on the Medsafe website ([www.medsafe.govt.nz/profs/adverse/Minutes156.htm#3.2.1](http://www.medsafe.govt.nz/profs/adverse/Minutes156.htm#3.2.1)).

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## Adverse Reaction Reporting in New Zealand – 2013

Medsafe and the Centre for Adverse Reactions Monitoring (CARM) would like to thank all those who have submitted reports of suspected adverse reaction and in doing so have contributed to pharmacovigilance in New Zealand.

Reporting of adverse reactions provides valuable information about the use of medicines in clinical practice. Reporting also makes an important contribution to post-market monitoring (pharmacovigilance) in New Zealand.

Before a medicine is approved in New Zealand, safety and efficacy experience is usually limited to its use in clinical trials. However, clinical trials do not always reflect the use of a medicine or vaccine in real life.

In addition, some important reactions are rare and may not be observed until a large number of people have received the medicine or have taken the medicine for a long period. Therefore, it is important to monitor all medicines after they have been approved.

In New Zealand, monitoring of adverse reactions is coordinated by Medsafe and CARM. Medsafe contracts CARM to collect and analyse adverse reaction reports submitted in New Zealand. Medsafe then uses this information to identify possible safety issues.

After further investigation, Medsafe may need to take appropriate action to ensure that the safety of these medicines is improved.

If further information is required to investigate a safety concern, the medicine and safety issue can be placed on Medsafe's **M** scheme. The aim of the **M** scheme is to highlight potential safety concerns to healthcare professionals and encourage reporting.

Information regarding medicines currently being monitored is available on the Medsafe website ([www.medsafe.govt.nz/profs/M2MedicinesMonitoring.asp](http://www.medsafe.govt.nz/profs/M2MedicinesMonitoring.asp)).

If information needs to be communicated about safety concerns, Medsafe uses its early warning system to publish information on its website.

Further information about the early warning system, including how to sign up for email alerts, can be found on the Medsafe website ([www.medsafe.govt.nz/projects/B2/EWS.asp](http://www.medsafe.govt.nz/projects/B2/EWS.asp)).

### Adverse Reaction Reports in 2013

In 2013, CARM received a total of 4159 reports of suspected adverse reactions. The number of reports submitted annually in New Zealand has remained consistent over the last five years.

Reports of adverse reactions to medicines make up the majority of the total reports received by CARM (63.9%) during 2013. The remainder of the reports of suspected adverse reactions were associated with vaccines (35.4%) and complementary and alternative medicines (CAMs) (0.7%). The comparative figures for 2012 were 67.8%, 31.8% and 0.3% respectively.

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

Of the reports received, 37% of the medicine reports and only 3% of the vaccine reports were considered serious. For CAMs, 50% of reports described reactions considered as serious.

A serious adverse reaction is determined by the CARM medical assessors according to internationally agreed criteria (ie, resulting in hospitalisation, is life-threatening, fatal, results

in disability or requires intervention to prevent permanent disability, or results in a congenital abnormality).

### Source of Reports

In 2013, nurses continue to be the healthcare professionals that report the most adverse reactions, followed by GPs and hospital doctors (Figure 1).

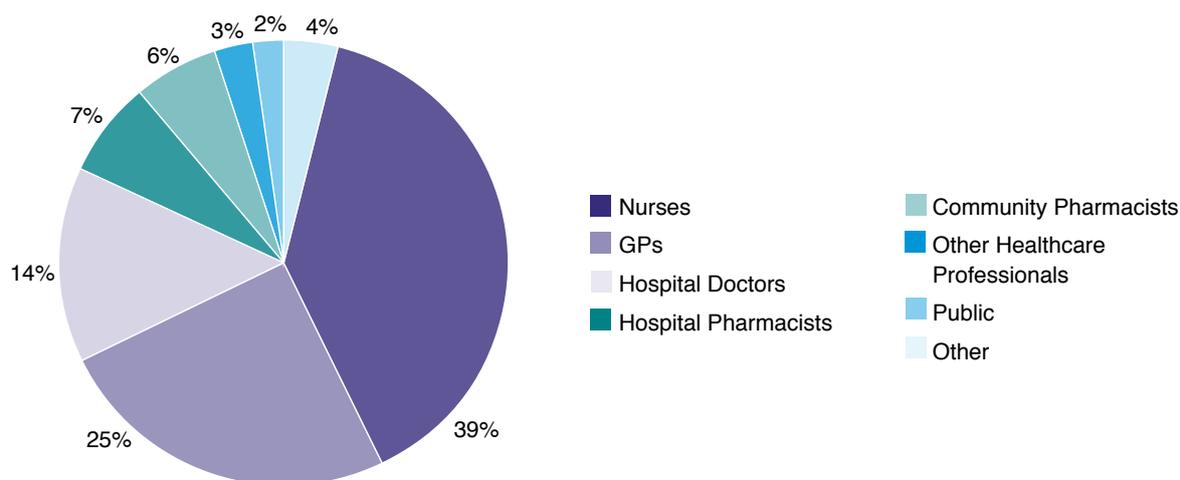
### How to Report

Healthcare professionals and consumers are encouraged to report any suspected adverse reaction to a medicine, vaccine or CAM to CARM.

Information about how to submit an adverse reaction report can be found on the Medsafe website ([www.medsafe.govt.nz/profs/adverse .asp](http://www.medsafe.govt.nz/profs/adverse.asp)) or on the CARM website (<https://nzphvc-01.otago.ac.nz/carm-adr/>).

Suspected adverse reactions to medicines, vaccines and CAMs can be reported by:

- completing a yellow card
- phoning the CARM line 0800 4 Monitor (0800 466648)
- downloading a form from either the CARM or Medsafe websites
- completing an online report available from either the CARM or Medsafe websites
- electronic reporting through GP software
- using the iPhone application (ADR Online).



**Figure 1: Source of adverse reaction reports from healthcare professionals and consumers in New Zealand in 2013**

## Acute Kidney Injury – Dangerous to Continue Some Medicines

### Key Messages

- ⌘ Overdose effects can result from continuing intake of renally metabolised medicines in patients with acute kidney injury (AKI).
- ⌘ Prescribers should review the appropriateness of all medicines in patients at risk of AKI and be prepared to stop treatment if AKI develops.
- ⌘ Some medicines may need dose adjustment whilst other medicines may need to be withheld until kidney function is restored.
- ⌘ Data sheets provide specific advice for individual medicines.

There are a number of medicines that are almost exclusively renally excreted and may have toxic effects in overdose. When taking these medicines patients who experience acute kidney injury (AKI) are at risk of adverse effects. These medicines may need to be withheld until kidney function has been restored.

AKI represents a continuum of renal injury that is characterised by a rapid (hours to days) decrease in renal function with the accumulation of waste products such as creatinine and urea<sup>1</sup>.

The causes of AKI can be divided into three categories<sup>1,2</sup>.

#### 1. Pre-renal injury due to a reduction in blood flow to the kidney

Causes include (but are not limited to) diarrhoea, vomiting, diuretics, haemorrhage, trauma, sepsis, decompensated heart failure, major surgery, infection, and medicines such as NSAIDs, angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs).

#### 2. Intrinsic injury due to direct kidney damage

Causes include (but are not limited to) vasculitis, glomerulonephritis, interstitial nephritis, rhabdomyolysis, malignant disease and nephrotoxic medicines such as NSAIDs, lithium and aminoglycosides.

#### 3. Post-renal injury due to a blockage to the flow of urine

Causes include (but are not limited to) kidney stones, prostatic hypertrophy and obstructed urinary catheter.

A number of cases have been reported in the literature in which patients experienced adverse events due to the combination of a medicine and AKI.

#### Dabigatran

A patient taking dabigatran experienced AKI due to dehydration after a brief gastrointestinal illness<sup>3</sup>. The patient's creatinine increased to more than 1.5 times baseline. The AKI resulted in decreased clearance and increased plasma concentration of dabigatran as manifested by standard measures of coagulation. Dabigatran was withheld with resolution of coagulopathy over four days.

The data sheet for dabigatran states that renal function should be assessed in clinical situations when it is suspected that renal function could decline or deteriorate<sup>4</sup>. Treatment with dabigatran is contraindicated in severe renal impairment<sup>4</sup>.

#### Metformin

In this report for two patients, metformin related lactic acidosis symptoms emerged shortly after the patients experienced AKI<sup>5</sup>. In the first case, use of oral NSAIDs along with dehydration caused by persistent vomiting contributed to AKI. In the second case, fluid loss from diarrhoea probably induced AKI. Both patients were successfully treated with haemodialysis.

The data sheet states that renal insufficiency is a risk factor for systemic accumulation of metformin and consequently lactic acidosis<sup>6</sup>. Metformin is contraindicated in patients with creatine clearance less than 60 mL/minute<sup>6</sup>.

#### Gabapentin

An elderly lady with AKI taking prescribed gabapentin experienced serious mental status changes resulting in the need for transfer to intensive care<sup>7</sup>. Consciousness was restored in this patient by stopping gabapentin treatment and starting continuous venovenous haemofiltration. The data sheet recommends a dose adjustment in renal impairment<sup>8</sup>.

## Olanzapine

An 80-year-old man was admitted to hospital with altered mental status and hypothermia. He had a recent history of gastroenteritis with dehydration resulting in AKI<sup>9</sup>. The patient was taking, among other medicines, olanzapine, to which the authors attributed the hypothermia.

The data sheet advises that olanzapine is used with caution in those with severe renal impairment<sup>10</sup>. Olanzapine is not removed by haemodialysis<sup>10</sup>.

These cases illustrate the need to consider dose adjustment of renally excreted medicines in patients with established AKI or patients who are developing AKI.

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## Spontaneous Reports: Seasonal Influenza Vaccination 2013

In 2013, the Centre for Adverse Reactions Monitoring (CARM) received 290 reports of adverse events following seasonal influenza vaccination (Table 1). Some reports contained more than one suspected event.

The most commonly reported events were injection site inflammation (65 reports), headache (39), arm pain (35), and fever (25).

Three percent (10 reports) of the influenza vaccine-related reports in 2013 were considered serious. A serious adverse reaction is determined by CARM according to internationally agreed criteria (ie, resulting in hospitalisation, is life-threatening, fatal, results in a disability or

requires intervention to prevent permanent disability, or results in a congenital abnormality).

One death was reported with a temporal association to influenza vaccination. This patient, with a history of myocardial infarction, cardiac arrhythmia, congestive heart failure and diabetes, died of a further myocardial infarction.

In 2013, most reports were submitted by nurses (72%), followed by GPs (21%), pharmacists (1.7%), and hospital doctors (1.0%).

In 2014, the influenza vaccine includes two new strains. The funded vaccines are Fluarix (GSK) and Influvac (Abbott). Both may be used in children from 6 months of age.

**Table 1: Numbers of reports received by CARM and number of influenza vaccine doses distributed, 2009–2013**

	2009	2010	2011	2012	2013
Reports of adverse events following influenza vaccination	138	409	207	193	290
Influenza vaccine doses distributed*	960,900	1,046,000	993,500	1,000,600	1,253,600
Estimated reporting rate per 100,000 doses	14.4	39.1	20.8	19.3	23.1

\* The number of doses distributed is not equal to number administered (eg, some doses may have been destroyed at the end of the influenza season and not used).

## Combinations: A Bleeding Reason to be Careful

Healthcare professionals are reminded about the risks of additive effects when combining both complementary and conventional medicines.

The Centre for Adverse Reactions Monitoring (CARM) has received a report of an elderly patient who developed epistaxis requiring topical anaesthetic/vasoconstriction treatment. The patient was taking aspirin, resveratrol and Lester's oil (amongst other medicines). The epistaxis occurred following an increase in dose of Lester's oil.

No further epistaxis occurred following cessation of the Lester's oil. However, the patient's epistaxis recurred once the Lester's oil was restarted.

Lester's oil is reported to be omega-3 based oil that contains omega-3 fatty acids (fish oil), co-enzyme Q10, astaxanthin, vitamin D3, lutein, zeaxanthin and natural mixed tocopherols<sup>1</sup>. Product information for Lester's oil contains a precaution that it should not be taken with strong blood thinning medication, unless under the close supervision of your doctor<sup>1</sup>. However, it notes that it is fine to use with low dose aspirin<sup>1</sup>.

Two components of Lester's oil, fish oil and tocopherols, may affect platelet aggregation when used at high doses and when taken with

other antiplatelet/anticoagulant medicines may increase the risk of bleeding<sup>2,3</sup>.

Resveratrol is a polyphenol found in grapes that is used for its claimed anti-aging effect and antioxidant properties<sup>4</sup>. In addition, resveratrol is thought to have clinically significant antiplatelet effects and these may be additive with other medicines with antiplatelet effects<sup>4</sup>.

The combination of three medicines (one conventional, two complementary) all with antiplatelet effects seems likely to have increased the risk of bleeding in this patient.

Healthcare professionals are encouraged to report all adverse events associated with both conventional and complementary medicines to CARM.

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### Quarterly Summary of Medsafe's Early Warning System 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](http://www.medsafe.govt.nz/Projects/B2/EWS.asp)).

Date	Communication	Topic
3 December 2013	Alert	Black salve — buyer beware
3 February 2014	Monitoring	<b>M</b> <sup>3</sup> Amitriptyline and a possible risk of peripheral coldness (cold hands and/or feet) or Raynaud's phenomenon added to the medicines monitoring ( <b>M</b> <sup>3</sup> ) scheme
11 February 2014	Alert	Utrogestan (progesterone) formulation change — important information for patients with a peanut allergy
27 February 2014	Monitoring	Effectiveness of emergency contraception — reduced in women weighing more than 70kg

If you would like to receive Medsafe's early warning communications you can subscribe at [www.medsafe.govt.nz/profs/subscribe.asp](http://www.medsafe.govt.nz/profs/subscribe.asp)

## Statins and CYP Interactions

### Key Messages

- ⌘ Simvastatin and to a lesser extent atorvastatin are metabolised by the hepatic isoenzyme CYP3A4.
- ⌘ CYP3A4 inhibitors may increase the plasma concentration of these statins, increasing the risk of adverse reactions such as myopathy and/or rhabdomyolysis.
- ⌘ If a potent CYP3A4 inhibitor such as erythromycin must be used, then simvastatin or atorvastatin therapy should be stopped for the duration of therapy.
- ⌘ Fluvastatin, pravastatin and rosuvastatin are not significantly metabolised by CYP3A4 and are less susceptible to CYP interactions.
- ⌘ CYP3A4 inducers may reduce the effectiveness of some statins; therefore, lipid profiles should be monitored if co-prescribed.

Simvastatin and atorvastatin, two widely prescribed cholesterol lowering medicines, are both metabolised by the isoenzyme cytochrome P450 3A4 (CYP3A4). Simvastatin undergoes more pre-systemic metabolism than atorvastatin. This results in lower bioavailability and simvastatin is therefore more susceptible to medicine interactions<sup>1</sup>.

Nevertheless, the co-prescription of a CYP3A4 inhibitor may lead to an increase in the plasma concentration of either statin, increasing the risk of adverse effects such as myopathy and/or rhabdomyolysis.

Symptoms of myopathy include muscle pain, weakness and tenderness, which may occur with or without raised concentrations of creatine kinase. Rhabdomyolysis, a more severe form of skeletal muscle damage, is the occurrence of muscle related symptoms with creatine kinase greater than 10 times the upper limit of normal<sup>2</sup>.

The risk of rhabdomyolysis is estimated at approximately 3.4 cases per 100,000 person-years with standard-dose statin therapy<sup>3</sup>.

**Table 1: Examples of medicines that interact with simvastatin and atorvastatin**

Interacting medicines	Simvastatin	Atorvastatin
<b>Potent CYP3A4 Inhibitors</b>		
Macrolide Antibiotics (eg, Erythromycin, Clarithromycin) Azole Antifungals (eg, Itraconazole, Ketoconazole, Posaconazole, Voriconazole) Protease Inhibitors (eg, Ritonavir, Telaprevir, Boceprevir) Gemfibrozil Ciclosporin Danazol	Combination contraindicated	Use with caution and monitor. Avoid combination if possible
<b>Moderate CYP3A4 Inhibitors</b>		
Amiodarone Amlodipine Verapamil Diltiazem Nicotinic Acid (>1 g/day)	Do not exceed 20 mg/day	Use with caution and monitor
<b>Minor CYP3A4 Inhibitors</b>		
Azithromycin Roxithromycin	Case reports of rhabdomyolysis. Use with caution and monitor	No clinically significant interactions
<b>CYP3A4 Inducers</b>		
Carbamazepine Phenytoin Rifampicin St John's Wort	Probable reduction in concentration. Monitor lipid profile	Possible reduction in concentration. Monitor lipid profile

However, this increases with higher therapeutic doses and by prescribing statins in combination with interacting medicines<sup>3</sup>.

Statin therapy should be discontinued immediately if myopathy is suspected or diagnosed. Patients using lipophilic statins (atorvastatin and simvastatin) may be more susceptible to the risk of myopathy due to an increased ability to enter muscle cells and alter membrane structure<sup>4</sup>.

Strong CYP3A4 inhibitors are contraindicated with the use of simvastatin (Table 1). The dose of simvastatin should be restricted with the concomitant use of moderate CYP3A4 inhibitors<sup>5</sup>. Other CYP3A4 inhibitors should be used with caution or the combination avoided if possible<sup>6</sup>.

If use of a potent CYP3A4 inhibitor is unavoidable (eg, macrolide antibiotic), then the statin should be stopped during the duration of therapy.

CYP3A4 inducers, such as carbamazepine and rifampicin, may reduce the plasma concentrations of atorvastatin and simvastatin. If a CYP3A4 inducer is co-prescribed, then lipid profiles should be monitored and a dose adjustment made if necessary.

Fluvastatin, pravastatin and rosuvastatin are not significantly metabolised by CYP3A4.

Fluvastatin and to a minor extent rosuvastatin are metabolised by CYP2C9, and are less subject to clinically significant CYP interactions. However, caution is still recommended when co-prescribing known CYP inhibitors.

Pravastatin is excreted largely unchanged from the parent compound (is not significantly metabolised by CYP enzymes) and therefore is not subject to CYP interactions.

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## Reporting Medical Device Adverse Events

Adverse events that cause injury and that are associated with medical devices should be reported to Medsafe. These events may indicate a quality or safety issue that needs to be addressed. By reporting these to Medsafe, seemingly isolated incidents may be collated and action taken if necessary.

### Who can report an adverse event?

Anyone can submit a medical device adverse event report. Patients, caregivers, healthcare professionals and suppliers are all encouraged to lodge an adverse event report if an adverse event has occurred and there is a concern about the safety of the device or its use.

On the Medsafe website there is an adverse event reporting form for healthcare professionals and patients ([www.medsafe.govt.nz/downloads/device.doc](http://www.medsafe.govt.nz/downloads/device.doc)) and another for sponsors and manufacturers ([www.medsafe.govt.nz/downloads/iris\\_mdir03a.doc](http://www.medsafe.govt.nz/downloads/iris_mdir03a.doc)).

### What adverse events should be reported?

Medical devices that are associated with adverse events that cause injury should be reported to Medsafe. Further information about what adverse events should be reported to Medsafe can be found on the Medsafe website ([www.medsafe.govt.nz/regulatory/devicesnew/9AdverseEvent.asp](http://www.medsafe.govt.nz/regulatory/devicesnew/9AdverseEvent.asp)).

### What happens to reports

All adverse event reports submitted to Medsafe are reviewed. Medsafe may then issue advice or an alert as required. If a product issue is found, Medsafe will work with the supplier on an appropriate corrective action to address the issue.

Information about adverse events relating to medical devices that have been reported to Medsafe can be searched online in the Joint Adverse Event Notifications System-Medical devices (JAENS-MD) database ([www.anztpa.org/devices/summary/search](http://www.anztpa.org/devices/summary/search)).

## MARC's Remarks: December 2013 Meeting

The Medicines Adverse Reactions Committee (MARC) met on 5 December 2013 to review a number of medicine related safety issues.

The MARC reviewed information on clinical outcomes in patients taking both **clopidogrel** and **proton pump inhibitors** (PPIs). The MARC concluded that the available evidence suggests this interaction does not translate into adverse clinical outcomes. Further information can be found in this edition of *Prescriber Update*<sup>1</sup>.

The MARC reviewed the benefits and risks of **bromocriptine** when used for the suppression of lactation due to a concern over rare but potentially serious or fatal adverse effects. These included cardiovascular, neurological and psychiatric adverse effects.

The MARC noted that the data sheets for bromocriptine appropriately outlined the risks of these adverse effects.

The MARC concluded that the benefit-risk profile of bromocriptine remained positive. However, the MARC recommended that bromocriptine should be restricted to second-line therapy for the suppression of lactation.

The MARC reviewed the latest update regarding the risk of mortality with **tiotropium** (Spiriva) (in particular the Respimat device). This review included the recently published trial designed to assess mortality of tiotropium Respimat and HandiHaler (the TIOSPIR trial).

The TIOSPUR randomised, double-blind, parallel group trial conducted by Boehringer Ingelheim found that Respimat (at either 2.5 mcg daily or 5 mcg daily) was non-inferior to HandiHaler (18 mcg daily) with regards to risk of death. Respimat was also not associated with a greater risk of COPD exacerbation compared to HandiHaler.

The MARC noted that the TIOSPIR study was very well-designed. The MARC was reassured that there is no evidence of increased mortality for the Respimat device compared with the HandiHaler device when used at the approved doses.

Due to concerns about the risk of serious cardiovascular events, the MARC reviewed the risks and benefits of using **short acting beta agonists** (SABAs) to delay delivery in women presenting with premature labour.

The MARC noted that injectable SABAs (including salbutamol) have established efficacy in delaying delivery for at least 48 hours. This allows time for the administration of steroids and/or magnesium, or transfer to a neonatal intensive care unit. However, the MARC noted that tocolysis with SABAs has not been shown to have an independent beneficial effect on neonatal outcomes.

The MARC concluded that the benefits of short term treatment ( $\leq$  48 hours) with intravenous salbutamol outweigh the risks when used in appropriate patients to inhibit premature labour.

However, the MARC agreed with the European Medicines Agency's (EMA's) conclusion that the risks associated with maintenance treatment with oral salbutamol outweigh any possible benefits in women presenting with premature labour. The MARC recommended that oral salbutamol be contraindicated for use in obstetric indications.

Further information on these issues can be found on the Medsafe website ([www.medsafe.govt.nz/profs/adverse/Minutes156.htm](http://www.medsafe.govt.nz/profs/adverse/Minutes156.htm)).

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## Atypical Antipsychotics Interacting with CNS Depressants

Healthcare professionals are reminded that the concomitant use of atypical antipsychotics (eg, quetiapine and risperidone) with other central nervous system (CNS) depressant medicines (eg, benzodiazepines) should be undertaken with caution.

Concomitant use of these centrally acting medicines has the potential to increase adverse effects such as somnolence, drowsiness and sedation. This is particularly important in obese patients or those with a history of sleep apnoea,

who may be more sensitive to the effects of these medicines.

Healthcare professionals are encouraged to report any adverse events, including the potential interaction between atypical antipsychotics and other CNS depressant medicines, to the Centre for Adverse Reactions Monitoring (CARM).

Reports may be submitted via the Medsafe website ([www.medsafe.govt.nz/profs/adverse/reactions.asp](http://www.medsafe.govt.nz/profs/adverse/reactions.asp)) or by reporting directly to CARM (<http://carm.otago.ac.nz>).

### WE NEED YOUR HELP!

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



MEDICINES  
MONITORING

Medicine	Potential safety issue	Active monitoring ends
Amitriptyline	Peripheral coldness/ Raynaud's phenomenon	31 July 2014
Ornidazole	Adverse effects on the eye	30 June 2014
Simvastatin, Atorvastatin, Pravastatin, Rosuvastatin	Acute kidney injury without rhabdomyolysis	30 June 2014

- **M<sup>2</sup>** 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 **M<sup>2</sup>** scheme does not replace routine adverse reaction reporting. Find out how to report at: [www.otago.ac.nz/carm](http://www.otago.ac.nz/carm) or [www.medsafe.govt.nz](http://www.medsafe.govt.nz)



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\* 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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