Prescriber Update

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Amiodarone Pulmonary Toxicity — Early Recognition is Vital

Key Messages

- ⌘ All patients receiving amiodarone should be monitored for the development of adverse effects including pulmonary toxicity.
- ⌘ Pulmonary toxicity should be suspected in all patients who develop new or worsening pulmonary symptoms whilst taking amiodarone.
- ⌘ Amiodarone should be stopped in all suspected cases of pulmonary toxicity.
- ⌘ Corticosteroids may be considered as a treatment option. Slow withdrawal of the corticosteroids (over at least two to six months) is recommended to prevent rebound pulmonary toxicity[1].

Pulmonary toxicity is estimated to occur in approximately 5% of patients taking amiodarone and is considered to be the most serious adverse effect associated with its use[1]. Early recognition of toxicity and withdrawal of amiodarone is associated with a good prognosis in the majority of patients.

Amiodarone is a class III anti-arrhythmic agent that is an effective treatment for ventricular and supraventricular tachyarrhythmias[2]. However, its use can be limited by the development of serious adverse effects including pulmonary, thyroid and liver toxicity.

Monitoring

All patients taking amiodarone require ongoing clinical review and monitoring for adverse effects (Table 1).

New Zealand Information

PHARMAC data indicate that approximately 7000 patients a year are receiving amiodarone. The majority of these patients (85%) are aged 60 years or over.

The Centre for Adverse Reactions Monitoring (CARM) has received a total of 65 reports of adverse reactions to amiodarone from January 2008 to September 2013. Of these reports, 16 were for pulmonary adverse reactions. These reports include interstitial pneumonia or pneumonitis (8 reports), pulmonary fibrosis (5), respiratory distress or cardio-respiratory failure (2) and unspecified pulmonary disorder (1).

The majority of reports were in men (10 compared with six) and in those aged over 60 (14 reports). The duration of use of amiodarone in these reports ranged from four days to over five years.

Presentation

Amiodarone-induced pulmonary toxicity can present acutely (hours to days after surgery or angiography) or chronically (months to years after starting amiodarone treatment). Acute toxicity (eg, acute respiratory distress syndrome) is rare but is associated with high mortality (up to 50%).

Table 1: Recommended minimum screening measures[3]

Type of test	Time when test is performed
Liver function tests	Baseline and every six months
Thyroid function tests	Baseline and every six months
Chest X-ray	Baseline and every 12 months
Ophthalmological evaluation	Baseline if visual impairment is present or for investigation of symptoms
Pulmonary function tests (including DLCO)	Baseline and for investigation of: • unexplained cough or dyspnoea, especially in patients with underlying lung disease • suggestive X-ray abnormalities • clinical suspicion of pulmonary toxicity
High resolution CT scan	If clinical suspicion of pulmonary toxicity
Electrocardiogram	Baseline and when clinically relevant

Chronic toxicity (eg, chronic interstitial pneumonitis, organising pneumonia) is more common and presents gradually with symptoms including non-productive cough, dyspnoea, fever, pleuritic chest pain, fatigue and/or weight loss. Mortality has been reported as up to 10% in some studies[1].

Risk Factors

Potential risk factors for amiodarone-induced pulmonary toxicity include high daily doses (greater than 400 mg/day), high cumulative doses (treatment duration greater than two months), male gender, increasing age (over 60 years) and pre-existing lung disease.

Recent surgery or pulmonary angiography is associated with acute amiodarone-induced pulmonary toxicity. Cases have occurred with low doses and short treatment durations.

Diagnosis

The diagnosis of amiodarone-induced pulmonary toxicity requires exclusion of other causes (eg, heart failure, infectious pneumonia, pulmonary embolism and malignancy). A reduction of more than 20 percent in the diffusing capacity of the lung for carbon monoxide (DLCO), and demonstration of infiltrates on a chest X-ray or other imaging is highly suggestive but not diagnostic of amiodarone-induced pulmonary toxicity.

Treatment

Treatment consists primarily of stopping amiodarone. Corticosteroids may also be beneficial (although no clinical trials have been performed).

Healthcare professionals should be aware that due to amiodarone's long half-life (estimated to be between 14 and 59 days) symptoms may initially worsen or be slow to resolve[4].

References

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3. Van Cott TE. Yehle KS, DeCrane SK, et al. 2013. Amiodarone-induced pulmonary toxicity: Case study with syndrome analysis. *Heart and Lung* 42: 262–266.
4. Sanofi-Aventis New Zealand Limited. 2012. *Cordarone X Data Sheet*. 12 December 2012. URL: **www.medsafe.govt.nz/profs/datasheet/cCordaroneXtabinj.pdf** (accessed 19 November 2013).

Discontinuation of Supply of Oral Ketoconazole

Key Messages

- ⌘ Oral ketoconazole (Nizoral) 200 mg tablets were discontinued on 1 December 2013.
- ⌘ Patients requiring long-term oral anti-fungal therapy will need to be changed to an alternative oral anti-fungal treatment.
- ⌘ Topical ketoconazole products are not affected and continue to be available.

Healthcare professionals are advised that Janssen-Cilag (New Zealand) have discontinued oral ketoconazole (Nizoral) 200 mg tablets.

Due to on-going safety concerns regarding liver toxicity with the use of oral ketoconazole tablets, the manufacturer has decided to stop making this medicine. This adverse reaction is well known with oral ketoconazole and was most recently discussed by the Medicines Adverse Reactions Committee (MARC) in September 2011.

Oral ketoconazole is used in the treatment of mycoses that cannot be treated topically due to the site or extent of lesions. Other effective oral antifungal treatment options are available.

Topical ketoconazole formulations, including shampoos and cream, have low systemic absorption and therefore are not affected by these safety concerns and continue to be available.

Further information about the discontinuation of oral ketoconazole was published last month on the Medsafe website (**www.medsafe.govt.nz/Projects/B2/2013/oral-ketoconazole.asp**).

Do Calcium Supplements Increase Cardiovascular Risk?

Key Messages

- The available evidence does not support an association between the use of calcium supplements and adverse cardiovascular events.
- The absence of evidence for cardiovascular risk does not negate the requirement for appropriate prescribing of calcium supplements.

The Medicines Adverse Reactions Committee (MARC) recently reviewed data on the risk of adverse cardiovascular outcomes associated with the use of calcium supplements. The MARC concluded that there is insufficient evidence to support an association at this time.

At the September 2013 MARC meeting, data were reviewed from recent meta-analyses and reanalyses of randomised controlled trials that reported cardiovascular events. This review identified contradictory outcomes in relation to the risk of cardiovascular events in patients taking calcium supplements. These differences included different outcomes when the same dataset was analysed by different groups[1,2].

One group identified an increased risk of myocardial infarction associated with calcium supplements but no increase of all-cause death in a meta-analysis[1]. However, another group's meta-analysis analysing similar data did not identify an increased risk[3].

Another analysis of a randomised controlled trial found that calcium supplements were protective in those individuals with pre-existing cardiovascular disease[4].

There were limitations to all the analyses reviewed. These limitations included an absence of cardiovascular events as primary outcomes, patient data were not always gathered in a standardised manner and there was a lack of information regarding dietary calcium intake. There were differences in the trials analysed with respect to the patient population. Adherence was also a factor in the trials with some trials reporting adherence as low as 50%.

The Centre for Adverse Reactions Monitoring (CARM) has received nine reports of suspected adverse reactions involving calcium supplements since 2008. Only one report involved a cardiovascular event of arrhythmia in a patient also taking clozapine.

The minutes of the September 2013 MARC meeting are available on the Medsafe website (**www.medsafe.govt.nz/profs/adverse/Minutes155.htm**). Medsafe will continue to monitor this issue as it does for all medicines.

References

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2. Prentice RL, Pettinger MB, Jackson RD, et al. 2013. Health risks and benefits from calcium and vitamin D supplementation: Women's Health Initiative clinical trial and cohort study. *Osteoporosis International* 24(2): 567–580.
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4. Lewis JR, Calver J, Zhu K, et al. 2011. Calcium supplementation and the risks of atherosclerotic vascular disease in older women: results of a 5-year RCT and a 4.5-year follow-up. *Journal of Bone and Mineral Research* 26(1): 35–41.

Reporting Adverse Effects from Psychoactive Substances

Key Messages

- The Psychoactive Substances Regulatory Authority seeks the assistance of healthcare professionals to report all adverse effects from patients using psychoactive products to the Centre for Adverse Reactions Monitoring (CARM).
- Reporting adverse effects plays a crucial role in the reduction of harm to individuals using psychoactive substances.
- A single report of a severe adverse effect, such as an epileptic seizure, is sufficient to identify a product as posing more than a low risk of harm.

Healthcare professionals are encouraged to report all adverse effects from patients using psychoactive products to the Centre for Adverse Reactions Monitoring (CARM).

The Psychoactive Substances Act requires that any psychoactive product approved for use must pose no more than a low risk of harm to individual consumers. The reporting of adverse effects therefore plays a crucial role in the reduction of harm to individuals using psychoactive substances.

A single report can make the difference!

A single report of a severe adverse effect, such as an epileptic seizure, is sufficient to identify a psychoactive product as posing more than a low risk of harm.

Since the Psychoactive Substances Act came into effect in July 2013, the number of retail outlets selling psychoactive products has reduced by an estimated 95%. The number of products legally available has reduced by an estimated 75%.

Adverse effects to psychoactive products can be reported to CARM by:

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

Further information about how to report adverse effects can be found on the CARM website (**carm.otago.ac.nz/**).

More information about the new Psychoactive Substances Act and the Psychoactive Substances Regulatory Authority can be found on the Ministry of Health website (**www.health.govt.nz/our-work/regulation-health-and-disability-system/psychoactive-substances**).

Bruce Atmore
Psychoactive Substances Regulatory Authority

Smoking Can Interact with Medicines

Key Messages

- ⌘ The doses of clozapine, olanzapine, theophylline, and warfarin may need to be reduced when a patient quits smoking.
- ⌘ Consider reducing the doses of other medicines metabolised by CYP1A2 when a smoker quits.
- ⌘ A dose increase may be required for some medicines if a patient starts smoking.
- ⌘ Patients exposed to second-hand smoke may also metabolise medicines faster than non-smokers and this may need to be considered in their treatment plan.
- ⌘ Nicotine replacement therapy does not induce CYP P450 activity.

Christmas and the New Year are the most popular time for smokers to try to quit. Similarly some patients may stop smoking if they are admitted to a hospital with a no smoking policy. Smoking has important effects on the metabolism of some medicines. Quitting smoking can increase the risk of patients experiencing adverse reactions to medicines.

The polycyclic aromatic hydrocarbons found in cigarette smoke induce hepatic cytochrome P450 (CYP) isoenzymes: 1A1, 1A2, 2A6, 2B6 and 2E1[1,2,3]. Smoking may also influence the glucuronidation of medicines[4].

The net effect of this is to increase the speed by which some medicines are removed from the body. Therefore, smokers may require higher doses of medicines that are metabolised by these induced cytochrome P450s.

Importantly, on quitting smoking the metabolic activity of CYP enzymes reduces. This means that the patient may now be exposed to a relative overdose of the medicine. Predicting the required dose after quitting is difficult and therapeutic medicine monitoring should be used when possible.

A number of medicines metabolised by CYP1A2 also have narrow therapeutic ranges further increasing the risk of toxicity. Medicines that have a narrow therapeutic range have a less than two-fold difference between the median lethal and median effective dose, or a less than two-fold difference between the minimum toxic and minimum effective concentration in the blood.

Nicotine does not have the same effects on CYP P450s. Patients using nicotine replacement to help quit smoking will require changes to their medicines as for smokers quitting without assistance[2].

Clozapine

Clozapine is metabolised by CYP1A2. It has been estimated that the average plasma levels of clozapine in smokers are approximately 80% those of non-smokers[1]. Dose reduction is highly recommended in patients who quit or who are hospitalised and unable to smoke. Recommendations are to reduce the dose by about 36% within one week of quitting smoking[2]. A dose increase may be required for patients starting smoking.

Olanzapine

Smokers have been found to have approximately five-fold lower dose-corrected steady state plasma concentrations of olanzapine compared to non-smokers[1]. Olanzapine is also metabolised by CYP1A2. After quitting smoking doses should be reduced by 36% over the first week[2]. Similar to clozapine a dose increase may be required in patients who start smoking whilst taking olanzapine.

Theophylline

The clearance of theophylline is increased by 58–100% and the half-life decreased by 63% in smokers compared to non-smokers[1]. Theophylline clearance has been estimated to be increased by 50% in children exposed to the second-hand smoke of parents who smoked at least 20 cigarettes daily[1]. After quitting smoking the clearance of theophylline decreases and the dose should be reduced[1].

Warfarin

It has been reported that patients taking warfarin who stopped smoking required a dose reduction of 14–23%[2]. The INR should be closely monitored when there is a change in the patient's smoking status[2].

Clopidogrel

An enhanced response to clopidogrel has been seen in smokers who are CYP1A2 (163CA) A-allele carriers[3].

Caffeine

Caffeine is a component of some analgesics and is almost entirely metabolised by CYP1A2. Caffeine clearance is increased by more than 50% in smokers[1]. When a patient quits smoking they should reduce their consumption of caffeine by half to avoid toxicity. Symptoms of caffeine overdose include irritability and insomnia, which can be mistaken for nicotine withdrawal symptoms[1].

Other medicines may also be affected such as: verapamil, propranolol, diazepam, naratriptan, fluvoxamine, lamotrigine[1,2,4]. Patients taking these medicines should be monitored for overdose effects and dose adjustments should be made if necessary.

Smoking may also cause pharmacodynamic interactions such as:

- increased risk of cardiovascular adverse effects with the combined hormonal contraceptive[1]
- decreased efficacy of inhaled corticosteroids[1]
- enhancing the effect of methadone on opiate withdrawal symptoms[3].

References

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3. Lucas C, Martin J. 2013. Smoking and drug interactions. *Australian Prescriber* 36: 102–104.
4. Reinsberger C, Dorn T, Kraemer G. 2008. Smoking reduces serum levels of lamotrigine. *Seizure* 17: 651–653.

Joint Adverse Events Notification System for Medical Devices

Information about adverse events relating to medical devices can now be searched online. The joint adverse event notification system for medical devices (JAENS-MD) is a searchable database of medical device adverse event report information for Australia and New Zealand.

Summary information from the medical device adverse event reports is published in the JAENS-MD. This includes general information about the device involved as well as a list of reports associated with the device and a description of the adverse event.

Medsafe and the Australian Therapeutic Goods Administration (TGA) regularly receive adverse event reports associated with medical devices. These reports come from a wide range of sources, including members of the public, GPs, nurses, other healthcare professionals and the therapeutic products industry. These reports may be indicative of a quality or safety issue that needs to be addressed in some form.

The reports in the JAENS-MD commence from 1 July 2012 (for TGA) and from 1 Jan 2013 (for Medsafe). There is a lag of up to three months between a report being received and it appearing in the database. The lag allows time to analyse each adverse event report and to request additional information if needed.

It is important to read the information on the website about how to use the JAENS-MD. In particular, it is important to understand its limitations and that the reports provide only limited information about a device and its use.

The JAENS-MD can be found on the Australia New Zealand Therapeutic Products Agency (ANZTPA) website (**www.anztpa.org/projects/aem.htm**).

Preventing Medication Errors: Kadcyla and Herceptin

Key Messages

- ⌘ Kadcyla (trastuzumab emtansine) and Herceptin (trastuzumab) are NOT the same product.
- ⌘ Prescribers should always use the brand name Kadcyla, in addition to its generic name (trastuzumab emtansine), to help reduce medication errors.
- ⌘ Care should be taken when preparing and administering Kadcyla or Herceptin to ensure that this is the intended medicine.

In September 2013, Kadcyla was approved for use in New Zealand. Kadcyla (trastuzumab emtansine) and Herceptin (trastuzumab) are NOT the same product. Kadcyla is an antibody–drug conjugate and Herceptin is an antibody.

When writing a prescription, prescribers should always use the brand name Kadcyla, in addition to its full generic name (trastuzumab emtansine), to help reduce medication errors.

Healthcare professionals should also take care when preparing and administering Kadcyla or Herceptin to ensure that the intended medicine is administered.

In New Zealand, Kadcyla was approved for the following indication[1].

> *Kadcyla, as a single agent, is indicated for the treatment of patients with HER2-positive metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either:*
>
> - *Received prior therapy for metastatic disease, or*
> - *Developed disease recurrence during, or within six months of completing adjuvant therapy.*

Herceptin (trastuzumab) is also indicated for HER2-positive breast cancers[2]. However, these medicines have different dosing and treatment schedules. Confusing the products could lead to harm to the patient.

Trastuzumab emtansine and trastuzumab are both International Non-proprietary Names (INN). These names are selected through the World Health Organization's (WHO's) INN system. Experts from the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations have in the past discussed whether to use a one word versus a two word name for antibody-drug conjugates.

References

1. Roche Products (New Zealand) Limited. 2013. *Kadcyla Data Sheet*. 3 October 2013. URL: **www.medsafe.govt.nz/profs/datasheet/k/kadcylainj.pdf** (accessed 18 November 2013).
2. Roche Products (New Zealand) Limited. 2012. *Herceptin Data Sheet*. 25 September 2012. URL: **www.medsafe.govt.nz/profs/datasheet/h/Herceptininf.pdf** (accessed 18 November 2013).

Update: QT Prolongation with Antidepressants

Key Messages

- ⌘ QT prolongation appears to be a class effect for all selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs), and also occurs with venlafaxine.
- ⌘ The potential for QT prolongation to occur should be considered as part of the risk benefit assessment prior to prescribing an antidepressant.
- ⌘ There are no high quality data comparing the risk of QT prolongation between different antidepressants (other than citalopram and escitalopram).
- ⌘ If QT prolongation or symptomatic arrhythmia occurs during antidepressant treatment, the antidepressant should be stopped or the dose reduced and specialist advice sought.

The data sheets for antidepressants have been updated to include detailed information on the risk of QT prolongation particularly in overdose. Individual product data sheets should be consulted for advice on the risk associated with a specific antidepressant.

In December 2012, the Medicines Adverse Reactions Committee (MARC) concluded that QT prolongation/Torsades de Pointes is a risk with most of the antidepressants approved for use in New Zealand.

At the MARC's recommendation, a warning has been added to all selective serotonin reuptake inhibitor (SSRI), tricyclic antidepressant (TCA) and venlafaxine data sheets. This warning includes the following information.

- Cases of QTc prolongation and Torsades de Pointes, have been reported during post-marketing use.
- The antidepressant should be used with caution in patients with risk factors for QT prolongation.
- Hypokalaemia and hypomagnesaemia should be corrected prior to treatment.
- For high risk patients (eg, congenital long QT syndrome or multiple risk factors), ECG monitoring should be performed.
- Consideration should be given to stopping the antidepressant or reducing the dose if the QT interval is >500ms or increases by >60ms.

QT prolongation is a measure of delayed ventricular repolarisation and is a surrogate marker for the risk of developing the potentially fatal arrhythmia Torsades de Pointes.

The definition of QT prolongation depends on the age and gender of the patient. A QT >500ms or an increase of >60ms during treatment confers a high risk of Torsades de Pointes.

QT prolongation with medicines, including antidepressants, is more likely to occur in the presence of other risk factors. Major risk factors include a genetic predisposition or pre-existing QT prolongation[1]. Other risk factors include increasing age, female gender, hypokalaemia and hypomagnesaemia, and medicine interactions[1].

Further information can be found in the *Prescriber Update* articles 'Do All Antidepressants Cause QT Prolongation?', 'Citalopram and Escitalopram — Similar Risk of QT Prolongation?' and 'Drug-induced QT prolongation and Torsades de Pointes — the facts'[1–3].

Please report any suspected cases of QT prolongation/Torsades de Pointes or arrhythmias with any antidepressant to the Centre for Adverse Reactions Monitoring (CARM).

References

1. Medsafe. 2010. Drug-induced QT prolongation and Torsades de Pointes — the facts. *Prescriber Update* 31(4): 27–29. URL: **www.medsafe.govt.nz/profs/PUArticles/DrugInducedQTProlongation.htm** (accessed 8 November 2013).
2. Medsafe. 2012. Do all antidepressants cause QT prolongation? *Prescriber Update* 33(4): 33–35. URL: **www.medsafe.govt.nz/profs/PUArticles/Dec2012AntidepressantsQTProlongation.htm** (accessed 8 November 2013).
3. Medsafe. 2012. Citalopram and Escitalopram — Similar Risk of QT Prolongation? *Prescriber Update* 33(1): 3–4. URL: **www.medsafe.govt.nz/profs/PUArticles/CitalopramAndEscitalopramMarch2012.htm** (accessed 8 November 2013).

Hazardous Substances Tool: Disease and Injury Reporting

Key Messages

- ⌘ Any disease or injury that a medical practitioner suspects is caused by a hazardous substance must be notified to the local Medical Officer of Health.
- ⌘ Hazardous substances include household chemicals, cosmetics, industrial chemicals and fireworks. Medicines are not included.
- ⌘ An electronic form linked to practice management systems has been developed to make primary care notification simple and quick.
- ⌘ The form also incorporates reporting for high blood lead levels and poisoning arising from chemical contamination of the environment.

Which hazardous substances do I have to notify?

Medical practitioners must inform the local Medical Officer of Health of the following conditions.

- Lead absorption equal to or exceeding 0.48micromol/L.
- Poisoning arising from chemical contamination of the environment.
- Hazardous substances disease and injury.

A hazardous substance is legally defined as anything that can explode, catch fire, oxidise, corrode or be toxic to humans. This definition does not include medicines in finished dose form (and therefore most over-the-counter and prescription drugs), alcohol other than industrial alcohol, or radioactive materials.

Events that should be reported include ingestion of cleaning products or cosmetics by children, overdose with agrichemicals (including spray drift incidents), carbon monoxide poisoning, illness caused by exposure to solvents or chlorine, contact dermatitis due to chemicals, a fireworks injury and 'huffing' (inhaling) of butane.

How should I notify a case?

If you are working in primary care, look for the 'Hazardous Substances & Lead Notifications' module on the *bestpractice* Decision Support dashboard. Submitting the short form will send it to your local Medical Officer of Health via a secure system.

If your practice does not currently have access to the *bestpractice* dashboard, or you work in an emergency department or other secondary care service, you can contact your local Public Health Unit to notify them of a case (or suspected case).

What happens to the information?

Information is used in two ways. At a local level, the Medical Officer of Health and Public Health Unit staff will assess the notification and determine if further patient (or event) follow-up is required.

At a national level, the Centre for Public Health Research at Massey University uses the anonymised data for surveillance. The hazardous substances disease and injury reporting tool will provide additional information about primary care presentations, to enable more complete national surveillance.

Reports from the surveillance system are provided periodically to the Ministry of Health and each Public Health Unit to support disease and injury prevention and control activities. For example, following reports of injuries to children regulatory changes were made to the pH of dishwashing powder. This has decreased the number of children presenting following dishwashing powder ingestion.

Dr Maria Poynter
Centre for Public Health Research

MARC's Remarks: September 2013 Meeting

The Medicines Adverse Reactions Committee (MARC) met on 12 September 2013 to review a number of medicine related safety issues.

The MARC reviewed the safety of **hydroxyethyl starch** containing solutions following concerns about mortality and renal injury.

The MARC noted that the meta-analyses and clinical studies had limitations sufficient to preclude a firm conclusion being made on the benefits and risks of these medicines in critically ill patients. The use in surgical patients did not raise any safety concerns.

The MARC considered that there were differences in the effects of different starches and recommended that a statutory benefit risk review should be performed.

The MARC reviewed recently published studies that indicated a direct increased risk of acute kidney injury or renal failure with the use of high-potency **statins**. The MARC concluded that the evidence that statins cause acute kidney injury through a direct effect rather than secondary to rhabdomyolysis was weak and the balance of benefits and risks of harm for statins remains positive.

The MARC agreed that more information would be valuable and that the topic of acute kidney injury, not associated with rhabdomyolysis, be added to Medsafe's M² scheme.

The MARC reviewed the use of **N-acetylcysteine** in the treatment of paracetamol overdose following changes to the United Kingdom guidelines. The MARC noted the efficacy of n-acetylcysteine and recommended changing the data sheet indications to state more clearly when n-acetylcysteine could be used.

In addition, the MARC recommended removal of the hypersensitivity contraindication, using the Australasian poisons centres recommended treatment nomogram, adding weight based dosing tables and adding additional information on adverse effects.

Calcium supplements and the risk of adverse cardiovascular outcomes was also reviewed by the MARC. The MARC concluded that there is insufficient evidence to support an association between the use of calcium supplements and adverse cardiovascular outcomes. Further information can be found in this edition of *Prescriber Update*[1].

The MARC discussed a Medsafe risk-benefit review of **propofol** when used to sedate paediatric patients undergoing ICU care. After reviewing the available data, the MARC concluded that the benefits of short-term propofol use outweigh the potential risks. The MARC recommended that all propofol data sheets be updated to include more detailed information on the risk of propofol related infusion syndrome occurring.

Further information on these issues can be found on the Medsafe website (**www.medsafe.govt.nz/profs/adverse/Minutes155.htm**).

Reference

1. Medsafe. 2013. Do Calcium Supplements Increase Cardiovascular Risk? *Prescriber Update* 34(4): 40.

Blood Testing of Patients with Metal-on-Metal Hip Implants

Medsafe reminds orthopaedic surgeons and GPs of the recommendations regarding blood test monitoring for patients who have received a metal-on-metal hip implant.

The majority of patients who receive a metal-on-metal hip replacement do well with the implant and are thought to be at low risk of developing serious problems. A small number of patients may develop a problem with metal debris deposition that can lead to a progressive soft tissue reaction in proximity to the joint (metallosis).

The metal debris deposition occurs through the build-up of microscopic metal debris through wear at the articular surface of the joint. This issue can be monitored through a heightened level of trace amounts of cobalt and chromium in the blood of a patient. Early revision surgery of poorly performing hip replacements is likely to lead to a better outcome.

The type of monitoring and frequency required is dependent on the nature of the implant used. Further information about monitoring and blood testing of patients with metal-on-metal hips is published on the Medsafe website (**www.medsafe.govt.nz/hot/alerts/mom-hip-implants.asp**).

Reminder: Unapproved Medicines and the *Code of Rights*

Key Messages

- ⌘ While unapproved medicines are able to be prescribed in New Zealand, the *Code of Rights* applies.
- ⌘ Unapproved medicines have not been assessed by Medsafe for quality, efficacy or safety.
- ⌘ The patient has the right to be provided with information about the medicine, including in writing if requested.
- ⌘ Informed consent should be obtained. In some circumstances, written consent should be obtained.

Prescribers are reminded that while the Medicines Act 1981 allows for the use of unapproved medicines in New Zealand, the *Code of Rights* applies.

The Medicines Act and Unapproved Medicines

Prescribers may be aware that Section 25 of the Medicines Act permits practitioners to prescribe any medicine for a particular patient in their care. This includes the use of approved or unapproved medicines.

In addition, Section 29 of the Medicines Act enables a New Zealand company/pharmacy to legally obtain and supply an unapproved medicine to a patient when authorised by a prescriber (reporting requirements apply).

Prescribers are reminded that unapproved medicines prescribed and supplied in New Zealand are not regulated by Medsafe. As a result, Medsafe has not assessed the quality, safety and efficacy of the medicine or the information provided with the product.

Medicines prescribed under Section 29 of the Medicines Act do not usually have a data sheet published on the Medsafe website and sometimes information can be hard to find. The New Zealand Formulary is a valuable resource that provides information about approved and some unapproved medicines (**www.nzf.org.nz**).

The Code of Rights

The *Code of Rights,* published by the Health and Disability Commissioner, establishes the rights of consumers and the obligations and duties of providers to comply with the Code.

The *Code of Rights* states that the consumer has the right to treatment of an appropriate ethical and professional standard, and the provider has the responsibility to ensure treatment, whether approved or unapproved, meets this standard.

Importantly, the consumer has the right to be fully informed. If the use of a medicine is unapproved, the consumer should be advised and the provider should be frank about the standard of support for the use and any safety concerns.

Right 6 of the *Code of Rights* specifies that every consumer, on request, has the right to receive a written summary of the information provided.

Informed consent can be written or verbal. Written consent is generally required in situations where:

- there is minimal evidence to support the use of the medicine
- the evidence of the efficacy or safety of the medicine used in this manner is equivocal
- the use is part of a clinical trial.

Further information about the use of unapproved medicines, including example scenarios, can be found on the Medsafe website (**www.medsafe.govt.nz/profs/RIss/unapp.asp**).

Further information about the *Code of Rights* can be found on the Health and Disability Commissioner website (**www.hdc.org.nz/the-act--code/the-code-of-rights**).

Mefloquine and Visual Disturbances

Key Messages

- Lariam (mefloquine) may be associated with an increased risk of eye disorders.
- Adverse events may occur or persist up to several weeks after finishing treatment.
- Treatment may need to be stopped in those who experience adverse events.

The Lariam (mefloquine) data sheet has recently been updated to include new safety information about the potential for visual disorders[1]. This has arisen following the sponsor's review of non-clinical studies, the global drug safety database, the UK General Practice Research Database and the published literature.

The review found that treatment with Lariam, an anti-malarial drug, may be associated with an increased risk of eye disorders, including (but not limited to) cataracts, retinal disorders and optic neuropathy. Common presenting symptoms include visual impairment and blurred vision.

Due to the long half-life of Lariam, visual disturbances may occur during treatment or for several weeks afterwards. There were also some reports of permanent after-effects.

Lariam treatment may need to be stopped in patients who experience visual disorders.

The following has been added to the Warnings and Precautions section of the data sheet.

> *Eye disorders, including but not limited to optic neuropathy and retinal disorders, have been reported during treatment with mefloquine. Any patient presenting with a visual disorder should be referred to the treating physician, as certain conditions may require stopping treatment with Lariam.*

'Eye disorders' has also been added to the list of adverse events.

In New Zealand, the Centre for Adverse Reactions Monitoring (CARM) has received three reports of visual disturbances while using mefloquine. None were classed by CARM as serious.

As always, please report any adverse events to CARM. This can be done via either the Medsafe website (download form at: **www.medsafe.govt.nz/profs/adverse.asp)** or by reporting directly to CARM **(http://carm.otago.ac.nz/**).

Reference

1. Roche Products (New Zealand) Limited. 2013. *Lariam Data Sheet*. 9 July 2013. URL: **www.medsafe.govt.nz/profs/datasheet/l/lariamtab.pdf** (accessed 18 November 2013).

Harpagophytum and Valerian, a Pain in the Pancreas

Key Messages

- Acute pancreatitis has been reported with the use of *Harpagophytum procumbens* and *Valerian radix*.
- Healthcare professionals are reminded to ask patients about the use of herbal or complementary medicines.

Healthcare professionals are reminded that herbal formulations, like conventional medicines, have both benefits and risks associated with use. Healthcare professionals are reminded to ask patients about their use of herbal and complementary medicines, and to report any adverse reactions to the Centre for Adverse Reactions Monitoring (CARM).

Acute pancreatitis has a variety of causes including alcohol abuse and gallstones, as well as medicines such as thiazide diuretics, azathioprine and corticosteroids.

A recently published case-control study determined that the risk of acute pancreatitis is also increased with the use of some plant extracts, in particular *Harpagophytum procumbens* (also known as 'devil's claw') and *Valerian radix*[1].

Harpagophytum procumbens has traditionally been used for its anti-inflammatory and analgesic properties in arthritis, gout and rheumatic disease[2]. It has also been used to alleviate post-partum and menstrual pain, and used topically for sprains, ulcers and boils[3].

Valerian radix is commonly used as a mild sedative and hypnotic for those who have difficulty in falling asleep and to support mental relaxation[2].

The exact mechanism of action of *Harpagophytum procumbens* is not fully understood. *Valerian radix* is reported to increase GABA concentrations, an inhibitory neurotransmitter, which decreases central nervous system activity.

Both plant extracts contain the secondary metabolites, iridoids. Iridoids increase the volume of bile secretion, which may increase the risk of gallstone formation and increase the risk of acute pancreatitis[1].

The hospital-based case-control study showed a significantly increased risk of acute pancreatitis associated with *Harpagophytum procumbens* (odds ratio 12.0, 95% confidence interval 1.9–74.3) and an increased risk associated with *Valerian radix* (10.3, 1.7–53.4), when adjusted for age, sex and all drugs[1].

As with conventional medicines, please report any adverse reactions associated with herbal or complementary medicines to CARM.

References

1. Douros A, Bronder E, Andersohn F, et al. 2013. Drug-induced acute pancreatitis: results from the hospital-based Berlin case-control surveillance study of 102 cases. *Alimentary Pharmacology and Therapeutics* 38: 825–834.
2. Barnes J, Anderson LA, Phillipson JD. 2007. *Herbal Medicines* (3rd Edition) London: Pharmaceutical Press.
3. Grant L, McBean DE, Fyfe L, et al. 2007. A review of the biological and potential therapeutic actions of *Harpagophytum procumbens*. *Phytotherapy Research* 21: 199–209.

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**).

Date	Communication	Topic
4 October 2013	Alert	Pradaxa (dabigatran etexilate) and oesophageal ulcer
1 November 2013	Monitoring	Statins and a possible risk of acute kidney injury (without rhabdomyolysis)
1 November 2013	Monitoring	Ornidazole and adverse effects on the eye
11 November 2013	Alert	m-Captopril tables 12.5mg, 25mg, 50mg, 100mg — Manufacturing Issues
12 November 2013	Alert	Discontinuation of oral ketoconazole (Nizoral) 200mg tablets
12 November 2013	Monitoring	Update: Hydroxyethyl starch solutions (Voluven, Volulyte 6%) associated with increased risk of mortality and renal impairment

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

TEST YOUR KNOWLEDGE

Have you read your copy of *Prescriber Update* in 2013?

Have you kept up to date with emerging safety signals?

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

Answers to the quiz are available at:

www.medsafe.govt.nz/profs/PUarticles/QuizAnswersDec2013.htm

1. Fill in the spaces for the potential safety issues that are currently on Medsafe's M² scheme?

a) Varenicline and interaction with _____

b) _____ and adverse effects on the eye

c) Statins and _____ _____ _____ without rhabdomyolysis

2. Which statement is correct?

a) Sedating antihistamines are contraindicated for use in children less than six years of age for all indications.

b) Sedating antihistamines are contraindicated for use in children less than two years of age for all indications.

c) Sedating antihistamines are effective for use in treating symptoms of the common cold in children.

d) Sedating antihistamines do not cause paradoxical stimulation.

3. Pradaxa (dabigatran) is now contraindicated under which of the following conditions?

a) Prosthetic heart valve replacement b) Atrial fibrillation

c) Symptomatic heart failure d) Prevention of venous thromboembolic events

4. Which of these medicines may require a dose reduction when a patients stops smoking

a) Clozapine b) Olanzapine c) Theophylline d) Warfarin e) All of these

5. Which statement regarding methotrexate and proton pump inhibitors (PPIs) is false?

a) PPI use increases the risk of methotrexate-related side effects.

b) Some PPIs are available over the counter.

c) The interaction risk is greatest with the use of high-dose methotrexate.

d) Methotrexate use increases the risk of PPI-related side effects.

6. Atypical femoral fractures are associated with the use of _____?

a) Etidronate, strontium, alendronate, zolendronate

b) Alendronate, zolendronate, pamidronate, denosumab

c) Denosumab, teriparatide, conjugated oestrogen, alendronate

d) Zolendronate, pamidronate, raloxifene, quinapril

7. **True or false: All patients should be screened for hepatitis B virus before starting treatment with rituximab?**

8. **Miconazole (oral gel) inhibits the metabolism of warfarin by inhibiting:**
   a) PGP b) CYP2C9 c) CYP3A4 d) Glucuronidation

9. **What adverse effect is caused by the 'triple whammy' of an ACE inhibitor/ARB, diuretic and an NSAID?**

10. **Which healthcare professionals reported the most adverse reactions in 2012?**
    a) General Practitioners
    b) Hospital Doctors
    c) Nurses
    d) Pharmacists

WE NEED YOUR HELP!

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

M² MEDICINES MONITORING

Medicine	Potential safety issue	Active monitoring ends
Varenicline	Interaction with alcohol	31 December 2013
Ornidazole	Adverse effects on the eye	30 June 2014
Simvastatin, Atorvastatin, Pravastatin, Rosuvastatin	Acute kidney injury without rhabdomyolysis	30 June 2014

- 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**

MEDSAFE
NEW ZEALAND MEDICINES AND MEDICAL DEVICES SAFETY AUTHORITY
A BUSINESS UNIT OF THE MINISTRY OF HEALTH
www.medsafe.govt.nz

CARM
CENTRE FOR ADVERSE REACTIONS MONITORING

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.

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