Prescriber Update

Vol. 36 No. 4 December 2015

www.medsafe.govt.nz

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

Contents

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

MINISTRY OF HEALTH
MANATŪ HAUORA

New Zealand Government

Statins — More Than Just Myopathy

Key Messages

- Statins are known to cause myopathy and rhabdomyolysis.
- An immune-mediated necrotising myopathy has also been reported with the use of statins.
- Distinguishing between immune-mediated muscle problems and self-limiting myopathy is important as patients may need immunosuppressive therapy.

Self-Limiting Myopathy and Rhabdomyolysis

Statins can cause myopathy that presents as muscle pain, tenderness, or weakness with or without raised levels of creatine kinase. Rhabdomyolysis is a more severe form of skeletal muscle damage that occurs with muscle related symptoms and creatine kinase levels greater than 10 times the upper limit of normal[1].

These statin induced muscle effects are dose-dependent. Interactions of statins with CYP3A4 inhibitors may also increase exposure to statins. Therefore, it is important that the risks of myopathy and rhabdomyolysis are considered and managed when a statin is started or changed, during dose increases, and with the addition of any interacting medicines.

These direct myotoxic effects of statins are also referred to as "*self-limiting*" because symptoms tend to resolve either by lowering the dose, changing to a lower potency statin, or stopping the statin[2].

Immune-mediated Necrotising Myopathy

More recently, there have been reports of an immune-mediated necrotising myopathy associated with statin use. This autoimmune myopathy is characterised by progressive muscle weakness, elevated creatine kinase levels, and progression of signs and symptoms even when the statin is stopped[3].

A comparison of self-limiting muscle effects and immune-mediated necrotising myopathy associated with statins is provided in Table 1.

An anti-HMG-CoA reductase autoantibody has been identified in association with immune-mediated necrotising myopathies[4]. Identifying this autoantibody in patients suspected to have statin-induced necrotising autoimmune myopathy is useful to confirm the diagnosis[4].

Treatment should include stopping the statin. Immunosuppressive therapy with agents such as prednisone, methotrexate, azathioprine, or ciclosporin may be required[4].

Table 1: Comparison of self-limiting muscle effects and immune-mediated necrotising myopathy associated with statins[4]

	Self-limiting muscle effects	Immune-mediated necrotising myopathy
Incidence	Frequent	Rare
Proximal weakness	Infrequent	Common
Creatine kinase levels	Normal or mildly elevated (>100,000 IU/L in rhabdomyolysis)	Elevated, 1000–50,000 IU/L
Timing relationship to statin	Following initiation, resolve after discontinuation	May present after years of usage; may appear or persist after statin discontinuation
Anti-HMG-CoA reductase antibody	Absent	Present
Electromyography	Non-specific or normal	Irritable myopathy
Biopsy	Non-specific	Prominent muscle necrosis with minimal or no inflammation
Treatment	Statin withdrawal or dose reduction	Statin withdrawal and immunosuppressive therapy

New Zealand Reports

The Centre for Adverse Reactions Monitoring (CARM) has received 167 reports of self-limiting muscle effects associated with a statin during 2010 to 2014. These reports are summarised in Figure 1.

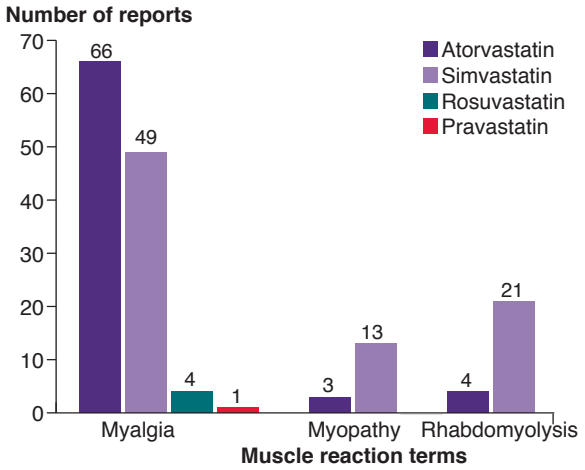

Figure 1: Reports to CARM of self-limiting muscle effects associated with a statin from 2010 to 2014

CARM has received one report of an immune-mediated necrotising myopathy associated with atorvastatin. This was reported to CARM in 2014.

Please continue to report any adverse reactions to statins, including muscle effects, to CARM. Reports can be submitted on paper or electronically (**https://nzphvc.otago.ac.nz/**).

References

1. Sathasivam S, Lecky B. 2008. Statin induced myopathy. *British Medical Journal* 337: a2286.
2. Mohassel P, Mammen A. 2013. The spectrum of statin myopathy. *Current Opinion in Rheumatology* 25(6): 747–752.
3. Merck Sharp & Dohme (New Zealand) Limited. 2014. *Lipex Data Sheet* 26 November 2014. URL: **www.medsafe.govt.nz/profs/datasheet/l/Lipextab.pdf** (accessed 23 October 2015).
4. Babu S, Li Y. 2015. Statin induced necrotizing autoimmune myopathy. *Journal of the Neurological Sciences* 351: 13–17.

Ocular Adverse Reactions: More than Meets the Eye

Prescribers are reminded that ocular reactions can occur with all medicines, not only those medicines administered directly into the eye. Prescribers should be aware of possible ocular adverse events and monitor where appropriate.

The top 10 ocular reactions reported to the Centre for Adverse Reactions Monitoring (CARM) up until 30 September 2015 are shown in Figure 1. Conjunctivitis and abnormal vision were the most commonly reported reactions.

The top 10 medicines linked to cases reporting an ocular reaction in New Zealand in alphabetical order were: amiodarone, influenza vaccine (trivalent), iohexol, meningococcal B vaccine, metoprolol, MMR vaccine, nalidixic acid (no longer approved), simvastatin, thyroxine, and zoledronate. Interestingly, none of the top 10 medicines reported to CARM involved eye drops.

Consistent with the CARM reports, this finding has also been reported in the published literature. A 2015 review by four regulatory authorities suggested that from the safety alerts evaluated, most of the ocular adverse events were associated with non-ophthalmic drugs[1].

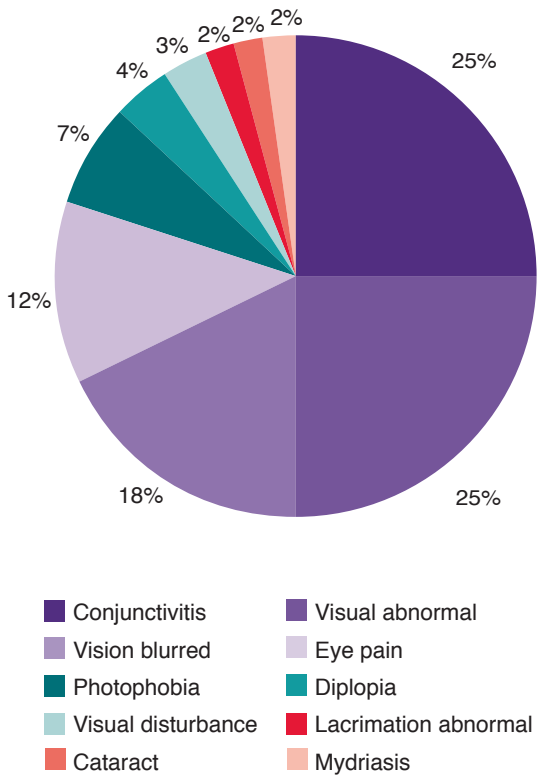

Figure 1: Top 10 ocular reactions reported to CARM (using the WHO Group 'Vision Disorders')

Another recent systematic review looked at ophthalmic adverse drug reactions to systemic drugs. This review concluded that medicines frequently involved with ocular adverse reactions include amiodarone, sildenafil, hydroxychloroquine and bisphosphonates[2].

In the New Zealand data, ocular reactions were also found to be commonly reported in association with vaccinations. This is possibly related to other vaccination-related adverse effects such as fainting and dizziness.

Further information regarding adverse reactions can be found in the data sheets for the specific medicine. In addition, *Prescriber Update* articles relating to ocular reactions (bisphosphonates and amiodarone) can be accessed on the Medsafe website (**www.medsafe.govt.nz/profs/PUArticles/BisphosphonatesSept2011.htm** and **www.medsafe.govt.nz/profs/PUArticles/AmiodaroneJune2011.htm**).

Healthcare professionals are encouraged to report all suspected adverse reactions to any medicine to CARM. Reports may be submitted on paper or electronically (**https://nzphvc.otago.ac.nz**).

References

1. Penedones A, Mendes D, Alves C, et al. 2015. Drug-Induced Ocular Adverse reactions: review of the Safety Alerts Issued During the Last Decade. *Journal of Ocular Pharmacology and Therapeutics* 31:5.
2. Miguel A, Henriques, Azevedo LF, et al. 2014. Ophthalmic adverse drug reactions to systemic drugs: a systematic review. *Pharmacoepidemiology and Drug Safety* 23:221–233.

Have Your Say on the Classification of Medicines

Key Messages

- The Medicines Classification Committee makes recommendations to the Minister of Health on the classification of medicines.
- Your comments are valuable to the Committee decision making process.
- To sign up to receive regular emails that will let you know when and how to comment, email **committees@moh.govt.nz** with '*MCC — Subscribe*' in the subject line.

The Medicines Classification Committee (MCC) is a Ministerial advisory committee that makes recommendations to the Minister of Health regarding access to medicines. The MCC advises whether a medicine should be classified as prescription, restricted (pharmacist-only) or pharmacy-only. Secretarial support for the MCC is provided by Medsafe.

The usual progression is for medicines to be '*down-scheduled*' (eg, prescription to restricted) as more market experience is gained and post-marketing surveillance provides a clearer picture of safety. Medicines suitable to be '*down-scheduled*' are for conditions or symptoms that can be diagnosed and managed by a pharmacist or patient. However, medicines can sometimes be reclassified to a more restricted classification or '*up-scheduled*' (eg, restricted to prescription).

Submissions for reclassification to the MCC usually come from pharmaceutical companies. However, anyone can make a submission. It takes approximately six months to change the legal classification of a medicine in New Zealand.

The closing date for submissions is at the end of January and July each year. Following this, the agenda for the meeting is published on the Medsafe website (**www.medsafe.govt.nz**). The submissions for reclassification are also published for public consultation. The consultation period lasts approximately six weeks. Any interested parties may comment on reclassification submissions during this time.

Further details on the MCC and the classification process can be found on the Medsafe website (**www.medsafe.govt.nz/committees/mcc.asp**).

To sign up to receive regular emails that will let you know when and how to comment on submissions for reclassification, email **committees@moh.govt.nz** with '*MCC — Subscribe*' in the subject line. You can also email the MCC Secretary at the same address for any specific queries.

Ingenol Mebutate (Picato) Correct Use and Adverse Reactions

Key Messages

- ⌘ Each tube of ingenol mebutate (Picato) contains a single dose.
- ⌘ Each tube should be spread evenly over an area of up to 25 cm^2 (5 cm x 5 cm).
- ⌘ Local skin reactions such as erythema, flaking, scaling and mild swelling commonly occur after topical application of ingenol mebutate (Picato).

Picato gel contains ingenol mebutate. It is indicated for the topical treatment of solar keratoses in adults[1]. Each tube is a single dose and should be used over an area of up to 25 cm^2 (5 cm x 5 cm)[1]. The gel should be spread evenly over the entire treatment area[1].

Two different strengths are available for use in different areas of the body. Picato 0.05% can be applied on the trunk and extremities in adults. Picato 0.015% can be applied on the face and scalp in adults. If the lesion is near the eyes, nostrils or mouth a smaller treatment area may be used[2].

Administration of Picato is not recommended until the skin has healed from any previous treatments[1]. Patients should be instructed to wash their hands immediately after applying the gel[1]. Touching and washing the treatment area should be avoided for six hours after the application of Picato[1].

Most patients experience one or more local skin response(s) following application of this medicine[1]. These show that the treatment is working[2]. Application site reactions frequently reported include erythema, crusting, swelling, exfoliation, and scabbing. Internationally, there have been reports of severe allergic reactions and herpes zoster (shingles) associated with the use of Picato[3].

Local skin responses typically resolve within two weeks of treatment initiation on the face or scalp and within four weeks for treatment on the trunk and extremities[1].

Healthcare professionals are encouraged to report all suspected adverse reactions to Picato, and all other medicines, to the Centre for Adverse Reactions Monitoring (CARM). Reports may be submitted on paper or electronically (**https://nzphvc.otago.ac.nz**).

References

1. LEO Pharma. 2014. *Picato Gel Data Sheet* 19 February 2014. URL: **www.medsafe.govt.nz/profs/datasheet/p/picatogel.pdf** (accessed 5 October 2015).
2. LEO Pharma. 2013. *Picato Gel Consumer Medicine Information* April 2013. URL: **www.medsafe.govt.nz/consumers/cmi/p/picatogel005.pdf** (accessed 5 October 2015) and **www.medsafe.govt.nz/consumers/cmi/p/picatogel0015.pdf** (accessed 27 October 2015).
3. Food and Drug Administration. 2015. FDA warns of severe adverse events with application of Picato (ingenol mebutate) gel for skin condition; requires label changes. *FDA Drug Safety Communication* 21 August 2015. URL: **www.fda.gov/Drugs/DrugSafety/ucm459142.htm** (accessed 27 October 2015).

Mycophenolate Mofetil: Contraindicated in Pregnancy

The data sheets for mycophenolate mofetil (CellCept) are being updated to include new contraindications. Mycophenolate mofetil will be contraindicated in:

- pregnancy
- women of child bearing potential not using highly effective contraceptive methods
- women who are breastfeeding.

Mycophenolate mofetil is currently categorised as a Category D medicine. This is a medicine that is suspected to have caused, or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. Based on new information the company are updating this warning to a contraindication.

Healthcare professionals should inform and counsel patients of reproductive potential about the pregnancy associated risks of mycophenolate mofetil and the need to use effective contraception for both female and male patients.

Updated data sheets will be published on the Medsafe website (**www.medsafe.govt.nz/profs/Datasheet/DSForm.asp**).

Access to Medicinal Cannabis

There are numerous claims about the efficacy of medicinal cannabis products for a wide range of conditions and growing support internationally to allow access to medicinal cannabis on compassionate grounds. While evidence for the efficacy of cannabis in some conditions shows promise, further high quality research is needed to evaluate whether the claims can be justified.

In New Zealand cannabis is regulated under the Misuse of Drugs Act 1975 and Misuse of Drugs Regulations 1977. Cannabis preparations are Class B1 controlled drugs and cannabis seed and plant are Class C1 controlled drugs.

Both classes of cannabis products need ministerial approval (usually delegated to the Ministry of Health) prior to importing, prescribing, or administering.

To date Sativex is the only cannabinoid medicine with consent for distribution in New Zealand. Sativex is indicated as add-on treatment, for symptom improvement in patients with moderate to severe spasticity due to multiple sclerosis who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy.

Ministerial approval is required before prescribing any medicinal cannabis products including Sativex and is considered on a case-by-case basis. The Minister of Health's delegate has previously allowed access to Sativex for off-label use.

Information on accessing medicinal cannabis products and the application process, including application forms, can be found on the Ministry of Health website (**www.health.govt.nz/our-work/regulation-health-and-disability-system/medicines-control/medicinal-cannabis**). Please be aware the application forms differ depending on the type of cannabis product.

50 Years of Adverse Reaction Reporting

2015 marks 50 years of adverse drug reaction reporting in New Zealand. The first reports were received in April 1965, making the New Zealand programme one of the earliest established in the world.

Formation of adverse reaction monitoring centres were prompted by the thalidomide tragedy, where congenital abnormalities were observed in children born to mothers that had taken this medicine to manage morning sickness. Fortunately, the continued monitoring of adverse drug reactions have prevented another tragedy like this from occurring again.

The success of this scheme is in your hands, so please continue to report suspected adverse reactions to medicine (**https://nzphvc.otago.ac.nz**).

Use of Aspirin in Children is Not Recommended

Key Messages

- ⌘ Aspirin should not be used in children due to the risk of Reye's syndrome.
- ⌘ Aspirin is no longer recommended for the symptomatic management of joint pain in rheumatic fever.
- ⌘ Paracetamol, naproxen or ibuprofen can be used for the symptomatic management of joint pain in rheumatic fever.

Healthcare professionals are reminded that the use of aspirin in children is not recommended due to the risk of Reye's syndrome.

The Centre for Adverse Reactions Monitoring (CARM) recently received a report of a 16-year-old patient who was taking the maximum adult dose of aspirin as part of their management for acute rheumatic fever. In this case, the patient experienced nose bleeds, which is a known side effect of aspirin, but also a less common clinical feature of rheumatic fever.

CARM has received a total of 34 reports where aspirin was used in a child under 18 years of age. Of these, four had an indication of rheumatic fever with or without heart involvement. The indication for use was not reported in nine cases. There were no reports of aspirin being used for Kawasaki disease or prevention of thrombus formation following cardiac surgery.

The majority of reports described reactions involving the skin such as rash, urticaria, and angioedema. Of the 34 reports, only five were received by CARM in the last six years.

What is the Age Restriction?

In New Zealand, aspirin product labels are required to include the following statement *'Unless a doctor has told you to, do not use this product in children under 12 years of age or teenagers with chickenpox, influenza or fever'.*

The New Zealand Formulary for Children contraindicates the use of aspirin in children under 16 years of age unless it is being used for Kawasaki disease or for prevention of thrombus formation after cardiac surgery[1]. This is in-line with recommendations from the United Kingdom[2].

Should Aspirin be used in Rheumatic Fever?

Aspirin is no longer recommended for the symptomatic management of joint pain in rheumatic fever due to the risk of Reye's syndrome[3]. Mild joint pain and fever may respond to paracetamol alone.

Non-steroidal anti-inflammatory drugs (NSAIDs) can also be used. Naproxen is the evidence-based treatment of choice. However, there is no liquid formulation of naproxen available in New Zealand. Ibuprofen is available as a liquid and is often used but there is a lack of published evidence supporting use for this indication.

What is Reye's Syndrome?

Reye's syndrome is a very rare but serious condition that causes inflammation and swelling of the brain and fatty degeneration of the liver[4]. It occurs almost exclusively in children[4].

The exact cause is unknown but is often triggered by a viral infection and the use of aspirin[4]. Symptoms start with vomiting and varying degrees of neurologic impairment, including fluctuating personality changes and deterioration in consciousness[4].

Treatment is supportive with a primary focus on reducing increased intracranial pressure[5].

References

1. New Zealand Formulary for Children. 2015. Aspirin. *NZFC* v40. URL: **www.nzfchildren.org.nz/nzf_1529** (accessed 6 October 2015).
2. British National Formulary. March 2015 – September 2015. Aspirin monograph. *BNF* 69: 280.
3. Heart Foundation of New Zealand. 2014. *New Zealand Guidelines for Rheumatic Fever: Diagnosis, Management and Secondary Prevention of Acute Rheumatic Fever and Rheumatic Heart Disease: 2014 Update*. URL: **www.heartfoundation.org.nz/uploads/HF2227A_Rheumatic_Fever_Guideline_v3.pdf** (accessed 6 October 2015).
4. Belay ED, Bresee JS, Holman RC, et al. 1999. Reye's syndrome in the United States from 1981 through 1997. *The New England Journal of Medicine* 340(18): 1377–1382.
5. MSD. 2014. Reye Syndrome. *MSD Manual Professional Version*. URL: **www.msdmanuals.com/professional/pediatrics/miscellaneous-disorders-in-infants-and-children/reye-syndrome** (accessed 6 October 2015).

Nitrofurantoin — Not Suitable in Renal Impairment

Key Messages

- ⌘ Nitrofurantoin is contraindicated in patients with creatinine clearance under 60 mL/min.
- ⌘ Adverse reactions to nitrofurantoin may occur with both acute treatment and prophylaxis of genitourinary infections.
- ⌘ Pulmonary reactions, both acute and chronic, are the most commonly reported adverse reaction.

Nitrofurantoin is indicated for the treatment and prophylaxis of susceptible genitourinary infections[1]. Since nitrofurantoin use can be short or long term there are well defined acute and chronic adverse reactions to treatment. Long-term use is up to six months unless the benefits clearly outweigh the risk.

The efficacy of nitrofurantoin is dependent on its concentration in the bladder. As renal function deteriorates, the nitrofurantoin bladder concentration decreases and plasma levels increase. Therefore, in renal impairment

Table 1: Reported reaction type (by system organ class) to nitrofurantoin and onset time

System Organ Class	<1 week	>1 week <1 month	>1 month	Unknown	Total
Respiratory	36	23	63	14	**136**
Skin and appendages	72	17	6	4	**99**
Nervous system	19	9	25	3	**56**
Alimentary	39	9	4	2	**54**
Liver	7	5	22	4	**38**
Total reactions*	**261**	**93**	**139**	**43**	**536**

*Not all system organ classes are shown, therefore the total does not reflect the numbers in the table.

efficacy is reduced and the potential for adverse reactions increased. Nitrofurantoin is consequently contraindicated in patients with creatinine clearance less than 60 mL/min[1].

The Centre for Adverse Reactions Monitoring (CARM) has received 333 adverse reaction reports up until 30 September 2015 where nitrofurantoin was considered a suspect medicine. Respiratory symptoms are the most commonly reported adverse reaction (Table 1).

Acute pulmonary reactions include fever, chills, cough, chest pain, dyspnoea, pulmonary infiltration, and eosinophilia[1]. Chronic pulmonary reactions include malaise, dyspnoea, cough, and diffuse interstitial pneumonitis or fibrosis or both[1]. If any of these pulmonary reactions occur, nitrofurantoin should be discontinued and the patient should be advised to seek medical attention.

Alimentary and skin reactions are mostly reported in the first week of nitrofurantoin use, whereas liver reactions generally occur after one month. Respiratory and nervous system reactions are reported at all the time periods analysed (Table 1).

The reaction onset time by age group is shown in Table 2. As expected, the number of reports increases with the age of the patient, likely due to greater use and greater susceptibility to adverse reactions. Both acute and chronic reactions are reported in all age groups, with the exception of those aged under 20 years.

Reports of pulmonary reactions were reviewed to determine whether reduced renal function was a risk factor for the reaction. However, most reports contained little to no information on renal function. Of the 136 reports of pulmonary reactions, 11 were reported to have pre-existing renal disease. None of the reports provided the patient's creatinine clearance.

The Medicines Adverse Reactions Committee (MARC) recently reviewed the available information on use of nitrofurantoin in patients with renal impairment (**www.medsafe.govt.nz/profs/adverse/Minutes163.htm**). The MARC considered that the benefits of nitrofurantoin treatment do not outweigh the risks of harm in patients with creatinine clearance less than 60 mL/min.

References

1. W.M. Bamford & Company Limited. 2004. *Nifuran Data Sheet* 9 November 2004. URL: **www.medsafe.govt.nz/profs/datasheet/n/Nifurantab.pdf** (accessed 4 November 2015).

Table 2: Nitrofurantoin adverse reaction onset time by age group

Age	<1 week	>1 week <1 month	>1 month	Unknown	Total
<20 years	4	1	0	0	**5**
20–29 years	10	4	1	0	**15**
30–39 years	14	6	4	0	**24**
40–49 years	13	4	7	3	**27**
50–59 years	35	6	15	3	**59**
60–69 years	24	13	24	6	**67**
>70 years	44	18	59	14	**135**
Unknown	0	1	0	0	**1**
Total cases	**144 (43%)**	**53 (16%)**	**110 (33%)**	**26 (8%)**	**333**

MARC's Remarks: September 2015 Meeting

The Medicines Adverse Reactions Committee (MARC) met on 10 September 2015 to discuss a number of medicine-related safety issues.

A summary of published observational studies investigating the possible association between **human papillomavirus (HPV) vaccine** and autoimmune conditions was presented to and discussed by the MARC. The MARC considered that there is no safety concern relating to the development of autoimmune conditions after HPV vaccination.

In addition, the MARC was presented with the Coroner's draft report on the sudden death of an 18-year-old female six months following the third dose of HPV vaccination. This followed from the 141st meeting of the MARC held on 11 March 2010 when this case was first discussed. The MARC noted the Coroner's findings.

The MARC discussed the use of **nitrofurantoin** in patients with renal impairment. The MARC considered that the contraindication in patients with a creatinine clearance of less than 60 mL/min should remain. Further information can be found in this edition of *Prescriber Update*[1].

The MARC reviewed the available information on penicillin cross reactivity with **cephalosporins** and considered that advice from the Australasian Society of Clinical Immunology and Allergy would be useful to aid further discussion on this topic.

Finally, the MARC discussed the risk of interstitial lung disease with the use of **statins**. Healthcare professionals should be aware that interstitial lung disease can occur with the use of any statin and the statin should be stopped if this is suspected.

Further information on this meeting can be found on the Medsafe website (**www.medsafe.govt.nz/profs/adverse/Minutes163.htm**).

References

1. Medsafe. 2015. Nitrofurantoin — Not suitable in renal impairment. *Prescriber Update* 36(4): 51–52.

Prescribing Medicines to Athletes

Drug Free Sport NZ regards members of the medical profession as critical partners in their work. Athletes are encouraged to inform all medical professionals that they may be subject to doping control (drug testing).

Medical professionals are asked to check all medicines they wish to prescribe to athletes and not make assumptions about their status in sport. Although this can take extra time, the consequences of getting it wrong are serious for the athlete.

Drug Free Sport NZ has developed the following table to provide a quick and efficient reference that describes the status of commonly prescribed medications (Table 1 over page). Permitted medicines are in green. An online version of this table can be found on the Drug Free Sport website (**www.drugfreesport.org.nz/what-we-do/education/resources/**).

The status of all medicines can be checked in the New Zealand Formulary (**www.nzformulary.org/**) or MIMS.

If a prohibited medicine is necessary, a Therapeutic Use Exemption (TUE) application which meets the specific World Anti-Doping Agency (WADA) requirements accompanied by comprehensive medical supporting documentation will need to be submitted. This may be required in advance or following a test depending on the status of the athlete. Please see the Drug Free Sport NZ website (**www.drugfreesport.org.nz**) or contact 0800 DRUG FREE (0800 378 327) for more information.

To view the WADA prohibited list or to obtain TUE application paperwork go to the Drug Free Sport NZ website (**www.drugfreesport.org.nz**).

For all other information please contact Drug Free Sport NZ directly on 0800 DRUGFREE (0800 378 437), **info@drugfreesport.org.nz**, or text 4365 (text the medication name and we will respond with its status in sport).

Sian Clancy
Drug Free Sport NZ

drugfree sport
new zealand

Table 1: Drug Free Sport NZ status of commonly prescribed medicines

Asthma medications	
Permitted	**Prohibited at all times (requires TUE)***
Salbutamol by inhalation	Terbutaline
Salmeterol by inhalation	Bambuterol
Formoterol by inhalation	
Glucocorticoids	
Permitted	**Prohibited in competition (requires TUE)**
Glucocorticoids; non-systemic route of administration (eg, intra-articular, peritendinous, intra-bursal, epidural, subcutaneous injections)	Glucocorticoids; systemic route of administration (eg, intravenous, intramuscular, oral, rectal)
Glucocorticoids inhaled	Glucocorticoid suppositories
Glucocorticoid applied topically; eye/ear drops, nasal sprays or ointments for dermatitis	
Cold/flu/sore throat medications	
Permitted	**Prohibited in competition (consider permitted alternatives)**
Phenylephrine (eg, Lemsip, Maxiclear)	Pseudoephedrine; stop taking 24 hours before competition
Paracetamol	Morphine-based cough syrup (Gees Linctus)
Pain/inflammation	
Permitted	**Prohibited in competition (requires TUE)**
Nonsteroidal anti-inflammatories (NSAIDs)	Narcotics (eg, Fentanyl, Pethidine, Morphine, Oxycodone)
Ibuprofen	
Diclofenac	
Paracetamol	
Tramadol	
Antibiotics	
Permitted	
All antibiotics available in New Zealand	Note: Probenecid is prohibited
Diuretics and masking agents	
	All diuretics and masking agents are prohibited in competition (requires TUE)
	Furosemide
	Probenecid
	Thiazide diuretics
Hormone and metabolic modulators	
Permitted	**Prohibited in competition (requires TUE)**
	Tamoxifen
	Clomiphene
	Spironolactone
	Insulin
Stimulants	
Permitted	**Prohibited (requires TUE)**
	Methylphenidate
	Pseudoephedrine

*TUE = Therapeutic Use Exemption

Monitor Renal Function in Elderly Patients taking Dabigatran

Key Messages

- Dabigatran is contraindicated in patients with severe renal impairment (creatinine clearance (CrCl) <30 mL/min).
- A reduced daily dose of 220 mg (110 mg twice daily) is recommended for patients aged 80 years and above, or patients with reduced renal function.
- Renal function must be assessed prior to the initiation of treatment with dabigatran in elderly patients and at least once every year of treatment.
- More frequent monitoring may be needed in certain situations where it is suspected that renal function could decline.

The Centre for Adverse Reactions Monitoring (CARM) continues to receive reports of bleeding in elderly patients taking dabigatran.

Age-related decline of renal function is expected in older patients (>75 years of age)[1]. Renal insufficiency causes an increase in plasma concentration of dabigatran which increases the risk of bleeding[2].

Renal function must be monitored in elderly patients taking dabigatran. Monitoring should start prior to treatment and at least once yearly thereafter. If the patient is at risk of worsening renal impairment more frequent monitoring is recommended[3].

Patients with impaired renal function and those over 80 years of age should take the reduced daily dose of 220 mg (110 mg twice daily).

Dabigatran is contraindicated in patients with severe renal impairment (CrCl <30 mL/min)[1].

Bleeding is a well-recognised side effect seen with all anticoagulants. All patients should be monitored for signs of bleeding.

The main risk factors for dabigatran associated bleeding are age of 75 years old and greater, renal impairment (CrCl 30–50 mL/min) and use with other medicines that can cause bleeding such as aspirin or SSRIs.

CARM Cases

CARM have received a total of 720 reports where dabigatran was the medicine suspected of causing an adverse reaction. Of these, 75 reports described bleeds associated with dabigatran use (at a daily dose of 300 mg). Twenty-six (35%) of these 75 reports were in patients aged 75 years and over. In nine of the 75 cases (12%) pre-existing renal disease was reported.

Further information on bleeding and the use of dabigatran can also be found in the *Prescriber Update* articles *'Dabigatran – is there a bleeding problem*?' and '*Acute kidney injury – dangerous to continue some medicines*'[3,4].

Please continue to report adverse reactions to CARM. Reports can be submitted on paper or electronically (**https://nzphvc.otago.ac.nz/reporting/**)

References

1. Boehringer Ingelheim Limited. 2015. *Pradaxa Capsule Data Sheet* 7 May 2015. URL: **www.medsafe.govt.nz/profs/datasheet/p/Pradaxacap.pdf** (accessed 2 October 2015).
2. MHRA. 2011. Dabigatran (Pradaxa): risk of serious haemorrhage – need for renal function testing. *Drug Safety Update* December 2011. URL: **http://webarchive.nationalarchives.gov.uk/20141205150130 http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON137771** (accessed 2 October 2015).
3. Medsafe. 2011. Dabigatran – is there a bleeding problem? *Prescriber Update* 32(3): 19–20. URL: **www.medsafe.govt.nz/profs/PUArticles/DabigatranSept2011.htm** (accessed 2 October 2015).
4. Medsafe. 2014. Acute Kidney Injury — Dangerous to Continue Some Medicines. *Prescriber Update* 35(1):9–10. URL: **www.medsafe.govt.nz/profs/PUArticles/March2014AcuteKidneyInjury.htm** (accessed 2 November 2015).

Metformin — Renal Impairment and Risk of Lactic Acidosis

Key Messages

- ⌘ Metformin is generally considered to be first line treatment for type 2 diabetes mellitus.
- ⌘ The most important adverse effect is lactic acidosis due to the high fatality rate.
- ⌘ Renal impairment is a risk factor for the development of lactic acidosis in patients taking metformin.
- ⌘ Metformin can still be used in patients with stable renal impairment but the dose **MUST** be reduced.
- ⌘ Patients should be advised to seek medical attention if they experience symptoms of lactic acidosis or acute kidney injury.

Metformin is recommended as the first line oral hypoglycaemia medicine for patients with type 2 diabetes in international guidelines[1]. However, use has been restricted in patients with renal impairment due to the increased risk of lactic acidosis.

The New Zealand metformin data sheets have recently been updated to allow for the use of metformin in patients with stable renal impairment. The contraindication cut-off level for creatinine clearance has changed from <60 mL/min to <15 mL/min. Patients with renal impairment MUST take a lower dose of metformin to avoid toxic concentrations. The maximum daily dose to be used in renal impairment is specified in the metformin data sheet, according to degree of impairment.

The metformin data sheets can be found on the Medsafe website (**www.medsafe.govt.nz/profs/datasheet/DSForm.asp**).

Lactic Acidosis

Lactate is produced by most tissues and is rapidly cleared by the liver. Levels of lactate increase as a consequence of intracellular acidosis and help to slow down the onset of acidosis. High lactate levels are generally considered to be those above 4 mmol/L[2]. Lactic acidosis is a condition of high lactate and a pH below 7.35[2].

There are many causes of elevated lactate including[2]:

- sepsis and septic shock
- regional tissue ischaemia for example due to burns
- anaerobic muscle activity for example as a result of seizures
- use of drugs such as alcohol
- use of medicines such as metformin or linezolid
- diabetic ketoacidosis
- cardiac arrest
- trauma
- liver dysfunction.

Risk factors for the development of lactic acidosis in patients taking metformin include[3]:

- renal impairment
- acute kidney injury for example due to dehydration
- hepatic insufficiency
- poorly controlled diabetes
- alcohol intoxication
- acute tissue hypoxia for example in sepsis.

Symptoms of lactic acidosis are generally non-specific and include malaise, myalgia, muscle cramps, respiratory distress, nausea, vomiting and abdominal pain[3].

The general nature of the symptoms can make diagnosis difficult and may be confused with other causes, which may in turn result in lactic acidosis. The difficulty in determining the cause of lactic acidosis in some cases has led to debate about the existence of metformin associated lactic acidosis (MALA). However, the occurrence of lactic acidosis in people who have taken an overdose of metformin provides evidence that MALA does occur[3].

The incidence of lactic acidosis in patients taking metformin is also difficult to estimate. A Cochrane review failed to identify any cases of lactic acidosis in patients taking metformin[4]. Whereas, a Dutch observational study found an incidence of 47 cases of MALA per 100,000 patient years[5]. The Centre for Adverse Reactions Monitoring (CARM) has received 19 cases of lactic acidosis in patients taking metformin to 30 October 2015.

The mortality of MALA is high. Previous estimates were around 50%[6]. However, more recently the

estimate has been revised to 25%[7]. The decrease in mortality may be due to changes in clinical practice including better use of haemodialysis to remove metformin[7]. Of the 19 cases of lactic acidosis reported to CARM, 12 patients (63%) were reported to have died.

Using Metformin Safely in Patients with Renal Impairment

Metformin is not metabolised and is entirely cleared by renal excretion. Studies have indicated that plasma levels of metformin below 5 mg/L are not associated with lactic acidosis[8].

Since metformin excretion is entirely dependent on renal function a dose reduction is required in patients with stable renal impairment. The new advice on metformin doses in renal impairment is derived from a population pharmacokinetic study[8]. This study included patients with varying levels of renal impairment (Table 1)[8].

Table 1: Maximum recommended doses of metformin in renal impairment[3,8]

Renal function (creatinine clearance)	Maximum daily metformin dose
15–30 mL/min	500 mg
30–60 mL/min	1000 mg
60–120 mL/min	2000 mg

Renal function should be measured at least twice a year in patients with renal impairment taking metformin[3]. Dosage adjustments should be made as and when necessary. For more information see the metformin data sheets.

Information for Patients

Patients should be informed of the symptoms of lactic acidosis and acute kidney injury and told to seek medical attention if these occur. Patients should be warned against excessive alcohol intake.

References

1. National Institute for Health and Care Excellence. 2009. Type 2 diabetes: The management of type 2 diabetes. *NICE Guideline* CG87.2009. URL: **www.nice.org.uk/guidance/cg87/resources/the-management-of-type-2-diabetes-975693927877** (accessed 3 November 2015).
2. Andersen LW, Mackenhauer J, Roberts JC, et al. 2013. Etiology and therapeutic approach to elevated lactate levels. *Mayo Clinic proceedings* 88: 1127–1140.
3. Apotex NZ Ltd. 2015. *Apotex Metformin Data Sheet* 5 August 2015. URL: **www.medsafe.govt.nz/profs/datasheet/m/Metformintab.pdf** (accessed 17 November 2015).
4. Salpeter SR, Greyber E, Pasternak GA, et al. 2010. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane database of systematic reviews*: CD002967.
5. van Berlo-van de Laar IR, Vermeij CG, Doorenbos CJ. 2011. Metformin associated lactic acidosis: incidence and clinical correlation with metformin serum concentration measurements. *Journal of Clinical Pharmacy and Therapeutics* 36: 376–382.
6. Pillans P. 1998. Metformin and Fatal Lactic Acidosis. *Prescriber Update* 16: 22–24.URL: **www.medsafe.govt.nz/profs/PUarticles/5.htm** (accessed 18 November 2015).
7. Kajbaf F, Lalau JD. 2014. Mortality rate in so-called "metformin-associated lactic acidosis": a review of the data since the 1960s. *Pharmacoepidemiology and Drug Safety* 23: 1123–1127.
8. Duong JK, Kumar SS, Kirkpatrick CM, et al. 2013. Population pharmacokinetics of metformin in healthy subjects and patients with type 2 diabetes mellitus: simulation of doses according to renal function. *Clinical Pharmacokinetics* 52: 373–384.

SGLT2 Inhibitors and Diabetic Ketoacidosis

Key Messages

- ⌘ Sodium glucose co-transporter 2 (SGLT2) inhibitors (dapagliflozin, empagliflozin, canagliflozin) have been associated with cases of diabetic ketoacidosis (DKA).
- ⌘ SGLT2 inhibitor-associated DKA may occur within the first few months of treatment and have an atypical presentation.
- ⌘ Patients should be informed of the signs and symptoms of DKA and advised to seek immediate medical attention should they experience these symptoms.

A number of serious cases of diabetic ketoacidosis (DKA) have been reported in patients taking sodium glucose co-transporter 2 (SGLT2) inhibitors (dapagliflozin, empagliflozin, canagliflozin) for type 2 diabetes mellitus[1]. Up to half the reported cases occurred during the first two months of treatment[1].

DKA is usually associated with raised blood glucose levels. However, in a number of reported cases, patients presented atypically with only a slight increase in blood glucose levels.

Early signs and symptoms of ketoacidosis include difficulty breathing, nausea, vomiting, anorexia, excessive thirst, abdominal pain, confusion and unusual fatigue or sleepiness[1]. More serious

signs and symptoms include dehydration, deep gasping breathing, confusion and coma. Patients should be informed of these signs and symptoms and advised to seek immediate medical attention should they experience any of these symptoms.

To prevent delayed diagnosis, patients taking SGLT2 inhibitors with symptoms of acidosis should be tested for raised ketones, even if blood glucose levels are near normal. If ketoacidosis is suspected, treatment with SGLT2 inhibitors should be discontinued.

Internationally, DKA has also been associated with off-label use of SGLT2 inhibitors in patients with type 1 diabetes mellitus. Healthcare professionals are reminded that in New Zealand type 1 diabetes is not an approved indication for SGLT2 inhibitors.

Please continue to report any cases of diabetic ketoacidosis or other suspected adverse reactions associated with SGLT2 inhibitors to the Centre for Adverse Reactions Monitoring (CARM).

Further information can be found in the Dear Healthcare Professional letter distributed by AstraZeneca in July 2015 to inform prescribers of safety information regarding Forxiga (dapagliflozin)[1].

References

1. AstraZeneca Limited. 2015. *Forxiga (Dapagliflozin) Dear Healthcare Professional Letter* 9 July 2015. URL: **www.medsafe.govt.nz/safety/DHCPLetters/Forxiga9July2014.pdf** (accessed 17 November 2015).

TEST YOUR KNOWLEDGE

Have you read your copy of *Prescriber Update* in 2015?

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/PUPDF.asp**

1. **True or false: Each single dose tube of Picato gel should cover an area of approximately 5 cm x 5 cm.**

2. **During treatment with dabigatran, renal function must be assessed:**
   a) at least once a year during treatment.
   b) only in situations where renal function is suspected to decline.
   c) only prior to initiation of treatment.
   d) prior to initiation of treatment and at least once every year of treatment, and more frequently in certain situations.

3. **What medicine is currently on Medsafe's M² scheme associated with a possible risk of hallucinations?**

4. **Who of the following can make a submission to reclassify a medicine to the Medicines Classification Committee?**
   a) Pharmaceutical companies
   b) Health professionals and their professional bodies
   c) Medsafe
   d) Members of the public
   e) All of the above

5. **The risk of bleeding when taking new oral anticoagulant medicines dabigatran etexilate (Pradaxa), rivaroxaban (Xarelto), and apixaban (Eliquis) is not increased when taken together with which of the following:**

   a) verapamil b) fluoxetine c) carbamazepine d) amiodarone

6. **Which of the following anti-depressants has a low risk of causing sexual dysfunction?**

   a) citalopram b) mirtazapine c) sertraline d) venlafaxine

7. **Name one condition/adverse reaction for which clozapine treatment must be permanently discontinued.**

8. **Which of the following medicines have serotonergic effects?**

   a) tramadol b) methylene blue c) linezolid d) all of the above

9. **Which of the following statements is false?**

   a) Varilrix is indicated for use in individuals from the age of nine months.

   b) Zostavax is indicated for use in individuals 50 years of age and over.

   c) Zostavax is indicated for use in individuals from the age of 12 months.

   d) Varivax is indicated for use in individuals 12 months of age and older.

10. **Which of the following medicines is it okay to take with grapefruit juice?**

    a) warfarin b) simvastatin c) tacrolimus d) amiodarone

WE NEED YOUR HELP!

M² MEDICINES MONITORING

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

Medicine	Safety concern	Active monitoring ends
Melatonin	Hallucinations	31 January 2016

- 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.

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
25 September 2015	Alert	Medical Devices Manufactured by Silimed, Brazil
28 September 2015	Alert	Use of Sodium Valproate (Epilim) in Pregnancy

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

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

Editor
Dr Amanda Taylor, PhD
Medsafe, PO Box 5013,
Wellington, New Zealand
Ph: (04) 819 6800, Fax: (04) 819 6806
E-mail: Amanda_Taylor@moh.govt.nz

Editorial Team
Andrea Kerridge, Advisor Pharmacovigilance
Jo Prankerd, Advisor Pharmacovigilance
Lily Chan, Advisor Pharmacovigilance
Rowan Pollock, Senior Advisor Pharmacovigilance
Dr Samantha Stubbs, PhD, Advisor Pharmacovigilance
Sharon Woollaston, Senior Policy Analyst
Dr Susan Kenyon, PhD, Acting Manager Clinical Risk

Acknowledgment
Dr Janine Ryland
Dr Meghan Sandle
Dr Niki Stefanogiannis
Dr Sisira Jayathissa
Sue Scott

Clinical Advisor
Dr Geraldine Hill

Acting Group Manager
Chris James

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

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

An electronic version of *Prescriber Update* is available at **www.medsafe.govt.nz/profs/PUarticles.asp**

To receive *Prescriber Update* electronically, please register at **www.medsafe.govt.nz/profs/profs.asp**

Data sheets, consumer medicine information, media releases, medicine classification issues and adverse reaction forms can be found at **www.medsafe.govt.nz**

Prescriber Update is a member of the

INTERNATIONAL SOCIETY OF DRUG BULLETINS

New Zealand Government