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MINISTRY OF HEALTH
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New Zealand Government

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Ondansetron: New Dose Restrictions

A new clinical study conducted by the company shows that there is a significant risk of QT prolongation in patients given high doses of ondansetron used to manage nausea and vomiting induced by highly emetogenic chemotherapy.

Consequently, the following changes and advice are recommended.

- The new maximum intravenous dose for adults is **16mg** infused over at least 15 minutes.
- Ondansetron should be avoided in patients with congenital QT syndrome.
- Caution should be used if ondansetron is administered to patients with risk factors for QT interval prolongation.
- Hypokalaemia and hypomagnesaemia should be corrected prior to ondansetron administration.

Ondansetron data sheets are currently being updated.

PML: A Rare but Serious Disease

Conjointly prepared by Medsafe and the Australian Therapeutic Goods Administration

Immunomodulatory medicines have emerged as a class of medicines associated with the development of progressive multifocal leukoencephalopathy (PML).

Awareness of risk factors and early recognition of symptoms is important as early diagnosis is likely to improve the prognosis[1].

What is PML?

PML is a rare, but often fatal, demyelinating disease of the central nervous system (CNS). PML is caused by lytic infection of oligodendrocytes and astrocytes resulting in multiple areas of demyelination in the CNS.

PML lesions are typically asymmetrical demyelinated plaque areas with irregular borders, surrounded by macrophages and irregular astrocytes with large, multiple nuclei[2]. On magnetic resonance imaging (MRI), the lesions usually do not show oedema, mass effect or gadolinium enhancement, which are common in multiple sclerosis[2].

Patients with PML can have a variety of symptoms including muscle weakness, sensory deficit, cognitive dysfunction, language impairment and/or coordination and gait difficulties[3].

What causes PML?

PML is caused by a human polyomavirus, the JC virus. The virus was named after the patient from whom the virus was initially cultivated, John Cunningham. Approximately 50% of the world's population are infected with the virus by the time they reach age 20, although most remain asymptomatic[4]. After initial virus infection, the virus remains quiescent in the kidneys, bone marrow and lymphoid tissue[3].

In immunocompromised individuals the quiescent virus can reactivate, enter the blood-stream and then gain entry to the CNS where it infects oligodendrocytes and astrocytes. Infection of these cells leads to cell death, and the resulting demyelination produces the neurological signs and symptoms of PML[5].

Viruses isolated from the brains of individuals with PML have a genomic rearrangement in the regulatory region that is not found in the strains responsible for initial infection[4,5].

What are the risk factors?

Patients who are immunosuppressed or have a malfunction of the immune system are at higher risk of developing PML. Cell-mediated immunity disorders are the major immunological disorders that predispose individuals to the development of PML[4].

PML cases have been reported in patients with HIV, lymphoproliferative disorders, malignancies, patients on immunosuppressive therapy after solid organ transplantation and in rheumatic diseases such as systemic lupus erythematosus[6,7].

Immunosuppressive medications that have been associated with PML include cyclophosphamide, corticosteroids, mycophenolate mofetil and monoclonal antibodies including natalizumab (Tysabri), rituximab (Mabthera) and alemtuzumab (MabCampath)[8].

How is PML diagnosed?

Diagnosis should be considered in any patient with risk factors who presents with progressive

neurological signs or symptoms and has MRI evidence of multiple characteristic lesions. The early signs of PML are often related to cognitive dysfunction, manifesting as mental slowness, disorientation and behavioural changes[2]. Motor and sensory disturbance, characterised by lack of coordination, gait disturbance, ataxia, hemiparesis or visual deficits may also be found at the time of presentation[2]. Seizures, language difficulties and headaches can occur but are less common. These signs and symptoms progress over the course of a few weeks and death can occur weeks to months after diagnosis.

The diagnosis can be confirmed by detection of JC virus DNA or proteins by *in situ* hybridization or immunohistochemistry on a brain biopsy sample, or by detection of JC virus DNA in the CSF by quantitative PCR[3]. However, a negative PCR result does not exclude the diagnosis of PML, particularly early in the disease.

How many cases have been reported?

A search of the Australian and New Zealand adverse event databases found 27 reports of PML (Table 1). Many of these reports had multiple risk factors including prior or concomitant immunosuppression therapies, underlying disease and chemotherapy. The majority of reports were associated with the monoclonal antibodies, rituximab and natalizumab. However, this may be due to greater awareness of PML in association with these particular medicines.

Table 1: Australian and New Zealand reports of PML associated with immunomodulatory medicines to June 2012

Medicine	No. of reports
Rituximab*	13
Natalizumab	12
Alemtuzumab	1
Cyclophosphamide*	1
Prednisolone*	1
Mycophenolate mofetil#	1
Tacrolimus#	1
Dexamethasone#	1

**Co-suspect medicines in one report*
#Co-suspect medicines in one report

How is PML treated?

Improved chance of survival is associated with early diagnosis, younger age at diagnosis and if the disease is limited to one lobe of the brain[1].

Current treatment of PML is limited and is generally supportive in nature. The current treatment strategy for PML in HIV-negative patients is to restore the host adaptive immune response by stopping or decreasing immunosuppression[3]. There are currently no specific antiviral drugs for the JC virus.

Recovery of the immune system can trigger immune reconstitution inflammatory syndrome (IRIS). In HIV-negative patients with PML-IRIS, the current treatment is corticosteroids to reduce the inflammatory response[3].

Key Messages

- PML is a rare but potentially fatal disease.
- Patients with compromised immune systems due to immunomodulatory medicines or disease are at risk of developing PML.
- A diagnosis of PML should be considered for any patient with risk factors who presents with progressive neurological signs or symptoms.
- Early diagnosis is associated with an improved chance of survival.

References

1. Vermersch P, Kappos L, Gold R, et al. 2011. Clinical outcomes of natalizumab-associated progressive multifocal leukoencephalopathy. *Neurology* 76: 1697–704.
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To SMARS and Beyond

Medsafe has now launched the Suspected Medicine Adverse Reaction Search (SMARS).

In a first for New Zealand, SMARS provides consumers, healthcare professionals and pharmaceutical companies with online access to information about *suspected* adverse reactions to medicines reported in New Zealand.

By searching on the active ingredient of a medicine you can now find out:

- the number of adverse reactions reported for a specific ingredient in New Zealand
- the suspected reaction profile reported for medicines in New Zealand
- single case reports that list the adverse reactions and medicine.

Importantly, the information contained in SMARS does not summarise the complete known safety profile of a medicine. The data available comes from spontaneous adverse reaction reports and only represent *suspected* adverse reactions.

Comprehensive information about the safety and efficacy of medicines approved in New Zealand can be found in medicine data sheets at **www.medsafe.govt.nz/profs/Datasheet/dsform.asp**

Medsafe stresses that consumers should not make decisions about their own medication without first discussing any concerns with a healthcare professional.

SMARS is available in concert with the Australian Database of Adverse Event Notifications (DAEN) and represents the first tangible development in the establishment of the Australia New Zealand Therapeutic Products Agency (ANZTPA).

SMARS addresses the growing public demand for access to more information about their medicines. SMARS also provides a resource for healthcare professionals to see what events are associated with different medicine ingredients.

Healthcare professionals and consumers are encouraged to report suspected adverse reactions to medicines to the Centre for Adverse Reactions Monitoring (CARM). Information about how to report is available at **https://nzphvc-01.otago.ac.nz/carm-adr/**

The SMARS database can be found at **www.medsafe.govt.nz**

Quinolones — A Tendoncy to Rupture

Tendon rupture and tendinitis are rare adverse events associated with the use of quinolone antibiotics. The Achilles tendon is most frequently involved but other sites can also be affected[1].

Although the mechanism for this toxicity is not yet fully understood, a direct toxic effect on collagen fibres has been suggested as occasionally symptoms occur after a single dose of a quinolone[2].

Currently, the known risk factors for tendon disorders associated with the use of quinolones include[1,2]:

- patients over 60 years of age
- concomitant steroid therapy
- chronic kidney disease
- previous kidney, heart or lung transplant.

Since 2007, there have been a total of 53 reports to the Centre for Adverse Reactions Monitoring (CARM) of tendon disorders in association with quinolone use. Of the 53 reports, 36 cases of tendon disorders were reported following treatment with ciprofloxacin, 16 cases following treatment with norfloxacin and one case following treatment with levofloxacin.

More than a third of reports (36%) were tendon ruptures, with the remainder mostly categorised as tendinitis. Only four patients were reported to be taking steroids together with a quinolone.

The majority of CARM reports from 2007 to mid-2012 described patients aged 60 years and over (83%) with over half (53%) occurring in patients age 75 years and over (Figure 1). There were no reports for patients younger than 30 years of age.

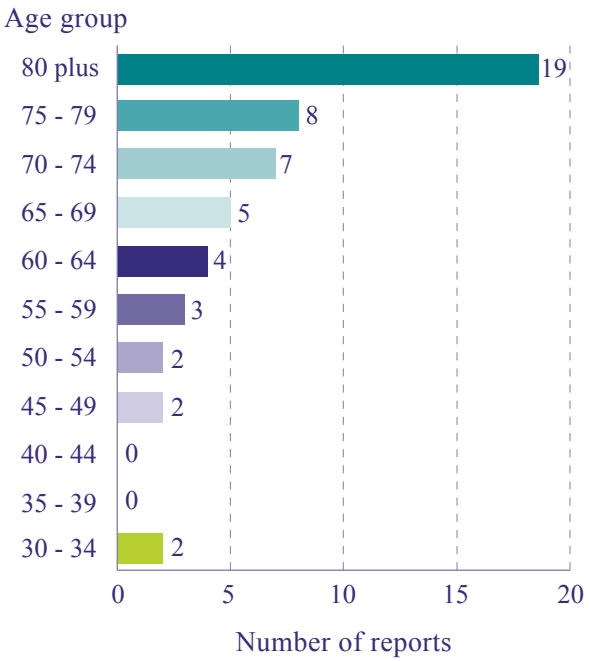

Figure 1: Age of patients in CARM reports of quinolone-associated tendon disorder from 2007 to mid-2012

A review of CARM reports since 2007 identified seven patients who experienced symptoms (tendinitis) in the first 24 hours after receiving a quinolone (Figure 2). In approximately half the cases (54%), the onset of the tendon disorder occurred within one week. In almost all reports (98%), symptoms developed within one month of starting treatment. However, one report described tendon rupture occurring more than six months following the use of a quinolone.

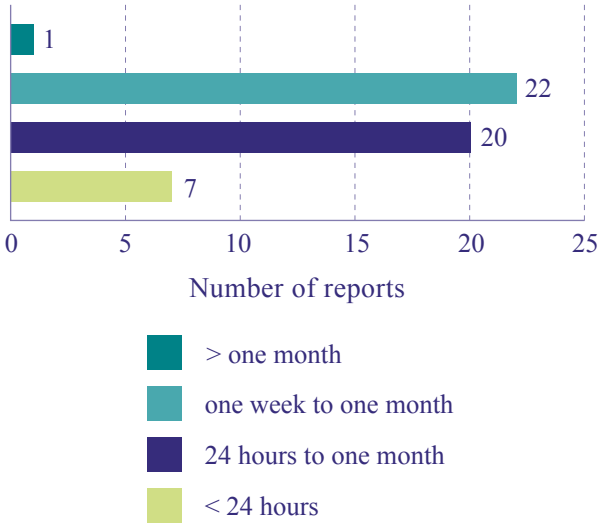

Figure 2: Latency of quinolone-associated tendon disorder reports to CARM from 2007 to mid-2012

Healthcare professionals are encouraged to report these reactions to CARM and to include as much information as possible to help identify other risk factors. More information on these cases can be found by searching SMARS on the Medsafe website.

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Statins — A Risk of Diabetes Mellitus?

Statins, HMG-CoA reductase inhibitors, are one of the most widely prescribed classes of medicinal products in New Zealand. PHARMAC estimates that over 1.7 million statin prescriptions were written for over 400,000 patients during 2011.

Recent publications have suggested that there may be an association of new-onset type 2 diabetes mellitus (T2DM) with the use of statins[1,2]. The Medicines Adverse Reactions Committee (MARC) have reviewed the relevant studies and concluded that there is a small, but statistically significant association, particularly in patients already at risk of T2DM. Nevertheless, the MARC considered that the benefits of statin treatment clearly outweigh any risk of developing new-onset T2DM.

A total of six meta-analyses were reviewed by the MARC. The studies all had limitations and suggest that other individual risk factors may also contribute to the association. The risk factors included:

- raised fasting glucose level (5.6 to 6.9mmol/L)
- body mass index greater than 30kg/m^2
- raised triglycerides
- history of hypertension.

There was insufficient data to exclude an effect with any individual statin or to support a dose-dependent relationship. Further information on this issue can be found at **www.medsafe.govt.nz/profs/adverse/Minutes150.htm**

Healthcare professionals should be aware of the association of new-onset T2DM with the use of statins and are advised to monitor at risk patients according to best practice guidelines (see **www.bpac.org.nz** or **www.nzgg.org.nz** for further information).

Key Messages

- The MARC considered the evidence suggests an association of new-onset T2DM with the use of statins. However, any risk appears to be mainly in patients already at increased risk of developing diabetes.
- The cardiovascular benefits of statin therapy continue to outweigh the risk of patients developing diabetes.
- There is insufficient evidence to confirm or exclude an increased risk for individual statins or support a dose-dependent relationship.

References

1. Sattar N, Preiss D, Murray HM et al. 2010. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet* 375: 735–42.
2. Culver AL, Ockene IS, Balasubramanian R, et al. 2012. Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative. *Archives of Internal Medicine* 172: 144–52.

Publication of Recalls in New Zealand

Summary information about all recall actions initiated in New Zealand for medicines and medical devices is now available via a searchable database on the Medsafe website. The database, known as the Medsafe Online Recalls Database (MORD), provides publicly accessible information about medicine and medical device actions. These actions include recalls, recalls for product correction and hazard alerts.

For some recall actions there will be links to additional information about the recall (eg, media statements, questions and answers). These links will provide timely and targeted information to the public, healthcare professionals, healthcare organisations and other stakeholders about market actions in New Zealand.

It is anticipated that publishing this additional information will increase transparency and enhance the information and advice that is currently distributed as a consequence of a recall or other market action in New Zealand.

Please note that the database has not been backfilled and only contains information on products that were recalled after 1 July 2012. The online database is located on the Medsafe website **www.medsafe.govt.nz/hot/Recalls/RecallSearch.asp**

MARC's Remarks: June 2012 Meeting

The Medicines Adverse Reactions Committee (MARC) met on 21 June 2012 to review a number of possible medicine related safety issues.

The MARC was provided with a review of the risk of progressive multifocal leukoencephalopathy (PML) in association with the use of **monoclonal antibodies**. The MARC agreed that although PML is a very rare result of treatment with some monoclonal antibodies, it has very serious consequences. Further information about PML can be found in this edition of *Prescriber Update*[1].

The MARC reviewed the dosing and administration recommendations of **haloperidol**. The MARC agreed that evidence from the literature suggests that oral or intravenous doses greater than 10mg per day are unlikely to provide further benefit and may increase the risk of adverse events. The MARC recommended that initial and maximum doses for haloperidol be reviewed and changes clearly outlined in the data sheets.

The MARC was provided with a review of **statins** and the risk of development of new-onset type 2 diabetes mellitus (T2DM). The MARC recommended that data sheets be updated to include information on those patients more likely to be at risk of developing T2DM. Further information relating to this matter can be found in this edition of *Prescriber Update*[2].

The MARC reviewed a recent paper and a summary of published literature on **hypnotic** use and mortality. Additional information about this issue can be found in this edition of *Prescriber Update*[3].

Further information about all of these issues is available from the MARC meeting minutes published on the Medsafe website **www.medsafe.govt.nz/profs/adverse/Minutes150.htm**

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3. Medsafe. 2012. Hypnotics: no time to be weary. *Prescriber Update* 33(3): 29.

Antibiotics and Liver Injury — Be Suspicious!

Prescribers are advised to be aware of the risk of liver injury associated with antibiotic treatment. Early recognition is essential as withdrawal of the causative antibiotic is the most effective treatment[1]. Specialist advice should be sought in all cases of severe liver injury and in patients who fail to improve despite withdrawal of the antibiotic.

Drug-induced liver injury

Drug-induced liver injury (DILI) can be classified as hepatocellular, cholestatic or mixed depending on the specific liver function test abnormalities that occur. DILI has an estimated incidence of 1 in 10,000 to 1 in 100,000. As with other liver diseases, DILI can present with jaundice, malaise, abdominal pain, unexplained nausea and anorexia. There are no specific signs, symptoms or tests that can confirm a diagnosis of DILI.

Antibiotic-associated DILI

Antibiotics are a common cause of DILI, probably because of the high rate of exposure in the community. Most cases are idiosyncratic and are therefore rare, unpredictable (from the pharmacology of the antibiotic) and largely dose-independent[1,2].

The characteristics of DILI associated with specific antibiotics are summarised below (Table 1).

Risk factors

Genetic variability is considered to be the most important risk factor, although specific genetic markers have not yet been elucidated for most antibiotics[1].

Table 1: Estimated frequency and characteristics of DILI associated with selected antibiotics[2]

Antibiotic	Incidence and liver injury	Onset	Time to recovery
Flucloxacillin	1.8–3.6 per 100,000 prescriptions *Cholestatic*	Can be early (1–9 weeks after starting) or delayed after treatment has stopped	Usually within 12 weeks of stopping. Up to 30% have a protracted course
Amoxicillin/ Clavulanic acid	1–17 per 100,000 prescriptions *Hepatocellular, cholestatic or mixed*	Within 4 weeks of starting but typically after stopping	Within 16 weeks of stopping therapy
Ceftriaxone	Up to 25% adults and 40% children develop *cholelithiasis*	After 9–11 days of treatment	Within 2–3 weeks of stopping
Erythromycin	< 4 cases per 100,000 prescriptions *Cholestatic*	Within 10–20 days of starting	Within 8 weeks of stopping
(Trimethoprim/ Sulfamethoxazole) Cotrimoxazole	< 2 per 10,000 prescriptions *Cholestatic or mixed*	Unknown	Within a few weeks of stopping
Doxycycline	< 1 per 18 million daily doses *Cholestatic*	Long latency of over 1 year	Variable. Most recover on stopping
Ciprofloxacin	Isolated cases only *Hepatocellular and cholestatic*	Unknown	Unknown

Other potential risk factors include[1]:

- previous hepatotoxic reaction to a specific antibiotic
- female sex
- increasing age
- comorbid illnesses.

An important exception are tetracyclines, where high doses seem to be a predictor of liver injury[2].

Diagnosis and treatment

Diagnosis requires a temporal association with antibiotic use and exclusion of other causes of acute liver injury (eg, alcohol, viral hepatitis, autoimmune liver disease, metabolic liver disease, ischaemic hepatitis and extra-hepatic biliary obstruction)[3]. The pattern of liver injury may also aid diagnosis (Table 1).

Treatment consists primarily of withdrawal of the causative antibiotic and supportive care if required. Most cases are mild and self-limiting[1]. However, rare cases of acute liver failure and death have been reported[1]. Chronic liver disease is a very rare complication but is more likely to develop if the antibiotic is continued despite evidence of liver injury.

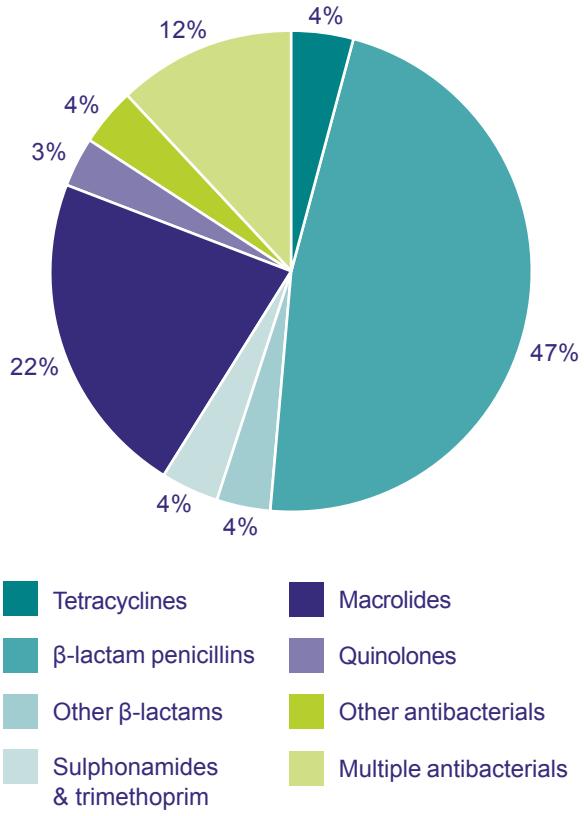

Figure 1: Classes of non-tuberculosis antibiotics associated with liver injury in New Zealand

New Zealand case reports

The Centre for Adverse Reactions Monitoring (CARM) has received a total of 360 reports of liver injury associated with the use of non-tuberculosis antibiotics since January 2000. Most reports were in adults aged over 50 years (71%), with 13 reports in patients aged less than 20 years. Seven reports (2%) involved a fatality.

The majority of CARM reports of liver injury were associated with β-lactam penicillins (Figure 1). Amoxicillin/clavulanic acid, flucloxacillin and erythromycin were the antibiotics most often implicated in the development of liver injury in New Zealand.

Key Messages

- Antibiotics are a common cause of drug-induced liver injury.
- Most cases of antibiotic-induced liver injury are idiosyncratic, unpredictable and largely dose-independent.
- In New Zealand, the antibiotics most often implicated with liver injury are amoxicillin/clavulanic acid, flucloxacillin and erythromycin.
- Withdrawal of the causative antibiotic is the most effective treatment.

References

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2. Andrade RJ, Tulkens PM. 2011. Hepatic safety of antibiotics used in primary care. *Journal of Antimicrobial Chemotherapy* 66: 1431–46.
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Classification of Medicines

Healthcare professionals are advised of medicine classification changes recommended by the Medicines Classification Committee (MCC) in May 2012.

Although still a prescription medicine, **seasonal influenza vaccine** has been reclassified to a prescription medicine except when administered to an adult by an accredited pharmacist. Pharmacists must have successfully completed the New Zealand Qualifications Authority approved vaccinator's course and comply with Ministry of Health immunisation standards. This will improve consumer access to the influenza vaccine.

Trimethoprim has also been reclassified to a prescription medicine except when administered by an authorised pharmacist. Pharmacists will be able to supply trimethoprim in packs of three tablets to women, aged 16 to 65 years, for the treatment of an uncomplicated urinary tract infection (UTI). The intention is to provide a more convenient method for women to access appropriate treatment for uncomplicated UTIs.

Pharmacists must successfully complete the New Zealand College of Pharmacists' training in the treatment of UTIs before participating in this scheme. Medsafe is to review the training material for pharmacists before the New Zealand College of Pharmacists' training is approved.

Further information on the classification process and the minutes of the MCC meetings are available at **www.medsafe.govt.nz/profs/class/clascon.asp**

Complementary Corner: Dangerous Liaisons

A fatal adverse reaction report involving warfarin and an unknown Chinese herbal remedy is a reminder of the importance in asking patients about the use of complementary and alternative medicines (CAMs).

The patient suffered a fall resulting in extensive bruising and was admitted to hospital two days later. On admission the patient's INR was raised (6.2); although the INR was corrected, the patient's condition deteriorated and they passed away. The patient's INR was reported to be well controlled on warfarin before beginning the herbal medicine.

The use of CAMs is extensive amongst the elderly, as high as 27.7% according to one US study[1]. Concomitant use of CAMs with conventional medicines, both prescription and non-prescription is also widespread in the elderly[2].

Herbal products may interact with anticoagulants in a number of different ways[3]. For example, mistletoe may have coagulant activity, while products such as feverfew, garlic, ginger and ginkgo may have anticoagulant activity[3]. Meadowsweet, poplar and willow may contain salicylate components and St John's wort has been suggested to increase the metabolism and clearance of some anticoagulants[1,3].

Research has shown that over 40% of patients do not discuss the use of CAMs with their doctor[4]. This has also been seen in a New Zealand study, where 54% of patients had not discussed their CAM use with their oncologist[5].

Prescribers and pharmacists are in a key position to determine those patients who are taking both CAMs and conventional medicines concurrently. Healthcare professionals are reminded to ask patients about use of CAMs and to report any suspected adverse drug reactions to the Centre for Adverse Reactions Monitoring (CARM).

References

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2. Elmer GW, Lafferty WE, Tyree PT, et al. 2007. Potential interactions between complementary/alternative products and conventional medicines in a Medicare population. *Annals of Pharmacotherapy* 41: 1617–24.
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4. Giveon SM, Liberman N, Klang S, et al. 2004. Are people who use "natural drugs" aware of their potentially harmful side effects and reporting to family physician? *Patient Education and Counseling* 53: 5–11.
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Metal-on-Metal Hips — Updated Recommendations

The UK Medicines and Healthcare products Regulatory Agency (MHRA) has recently updated its recommendations on the management of patients implanted with metal-on-metal hip

replacements. Medsafe and the New Zealand Orthopaedic Association endorse the MHRA recommendations for patients in New Zealand.

The new recommendations apply to symptomatic patients with either hip resurfacing implants or stemmed metal-on-metal hip replacements with femoral heads of less than 36mm. It is now recommended these patients are to be followed up annually for the life of the implant.

For more information about metal-on-metal hip implants please refer to the Medsafe website **www.medsafe.govt.nz/profs/device-issues.asp#17April2012**

Hypnotics: No Time to be Weary

Healthcare professionals are reminded of the importance of appropriate use of hypnotics and to only prescribe these medicines for short periods.

The Medicines Adverse Reactions Committee (MARC) recently reviewed the potential association between use of hypnotics and an increased risk of mortality. This review was prompted by a paper published in the *BMJ Open* earlier this year[1]. The MARC agreed that the study had significant limitations and that the current data are inadequate to determine whether the association is causal.

The *BMJ Open* study concluded that patients prescribed any hypnotic had an increased risk of dying compared with patients who had never been prescribed hypnotics[1]. The authors concluded that there was a dose response as the risk of dying increased with the amount of hypnotics prescribed.

After exclusions, approximately 10,500 hypnotic users and 23,600 matched non-user controls were included in the study. The researchers concluded that patients with prescriptions for hypnotics had approximately 4.6 times the hazard of dying than non-users of hypnotics over an average observation period of two and a half years.

The results of the study are restricted by several significant limitations. There was no data on the cause of death in the study, which prevents an assessment of a causal association between hypnotic use and death. The study controlled for various co-morbidities. However, disease severity was not measured or controlled for. Importantly, psychiatric diagnoses were not available and were not controlled for. The study was conducted in a single US state that is predominantly rural and of low socioeconomic status. It is therefore not clear if the findings can be extrapolated to the greater population.

The MARC considered that the relationship between sleep disturbance and the development of medical and psychiatric conditions, including death, is highly complex and not well understood. The MARC agreed that more studies were needed in order to determine the risk of mortality in association with both sleep disturbance generally and with the use of hypnotics.

Further information about managing insomnia has been published by the Best Practice Advocacy Centre (BPAC)[2].

Key Reminders

- Hypnotics should only be used for short periods (ie, two to four weeks) for the treatment of severe or disabling insomnia. Continuous or long term use is not recommended.
- The lowest effective dose of hypnotic should be used.
- Avoid or use hypnotics with caution in patients with a history of substance abuse, myasthenia gravis, respiratory impairment or acute cerebrovascular accident.
- Review patients for adverse effects — in particular, daytime sleepiness.
- Give advice about the increased risk of use when prescribing for older patients and enquire about difficulties with balance, which may indicate an increased susceptibility to falls.

References

1. Kripke DF, Langer RD, Kline LE. 2012. Hypnotics' association with mortality or cancer: a matched cohort study. *BMJ Open* 2: e000850.
2. Best Practice Advocacy Centre. 2008. Managing insomnia. *Best Practice Journal* 14: 6–11. URL: **www.bpac.org.nz/magazine/2008/june/insomnia.asp**

The New Zealand Formulary is Now Available

The New Zealand Formulary (NZF) is available free of charge for use across primary and secondary care. The NZF is based on the British National Formulary (BNF) and specifically adapted for New Zealand.

The NZF is a concise and comprehensive resource for healthcare professionals looking for high quality and up to date information about medicines that are used in New Zealand. It also provides Medsafe and PHARMAC information in one place.

This information available at the point of care will promote consistency of practice across New Zealand, reduce medication errors and promote safer and more appropriate medicines management.

The NZF is available via **www.nzformulary.org** and a downloadable eBook.

WE NEED YOUR HELP!

M² MEDICINES MONITORING

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

Medicine	Potential safety issue	Active monitoring ends
Sildenafil	Thromboembolism	30 September 2012
Cetirizine	Severe Mood Disorder	30 September 2012
SRIs	Thunderclap headache/RCVS	31 December 2012
Triptans	Thunderclap headache/RCVS	31 December 2012
Lithium	Diabetes mellitus	31 December 2012
Lansoprazole, Pantoprazole, Omeprazole	Hypocalcaemia	31 December 2012
NEW Ibuprofen	Hypokalaemia/Renal tubular acidosis	31 March 2013

- M² is a new 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**

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

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