

Prescriber Update

Vol. 36 No. 3

September 2015

www.medsafe.govt.nz

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

Contents

Oxycodone — Sometimes More Pain than Gain?	34
Complementary Corner — Olive Leaf Extract	34
Reminder: Interactions Resulting in Serotonin Syndrome	35
Therapeutic Products Regulatory Regime	35
Risks of Hydroxychloroquine	36
Medicines and Hyperkalaemia	37
M MEDICINES MONITORING: Melatonin and Hallucinations Added	39
Varicella Zoster Virus Vaccines — Medication Errors	40
Miracle Mineral Solution — Buyer Beware	41
Clomifene and Risk of Stroke	41
Ibuprofen and Cardiovascular Risk	42
MARC's Remarks: June 2015 Meeting	42
Reminder: Citalopram and QT Prolongation	43
Quarterly Summary of Medsafe's Early Warning System Communications	44

Oxycodone — Sometimes More Pain than Gain?

Key Messages

- ⌘ Oxycodone use can result in increased sensitisation to pain (hyperalgesia).
- ⌘ Opioid-induced hyperalgesia (OIH) should be suspected if the patient experiences increased pain in the absence of disease progression that is not managed by increasing the oxycodone dosage.
- ⌘ If OIH is suspected, opioid reduction, opioid rotation or the use of an alternative pain-control may be required.

Healthcare professionals should be aware that the use of oxycodone can result in hyperalgesia.

The Centre for Adverse Reactions Monitoring (CARM) has received a report of a female patient who was receiving oxycodone for neuropathic pain (post juvenile idiopathic arthritis) who reported a more intense pain that spread to involve her whole body. Her oxycodone dosage was increased in response. The patient was admitted to hospital where hyperalgesia was diagnosed. The patient was weaned off oxycodone and commenced on morphine. At the time of the report, the patient was improving.

Opioid-induced hyperalgesia (OIH) is a state of nociceptive (nerve cell) sensitisation caused by exposure to opioids whereby the patient receiving opioids for the treatment of pain may become more sensitive to pain¹.

It is important to note that OIH and analgesic tolerance can both result in a similar effect on opioid dose requirements¹. However, they are distinct pharmacologic phenomena¹. Tolerance occurs when there is a progressive lack of response to a medicine resulting in increased dosage². Tolerance can be overcome

by increasing the medicine dosage. In contrast, OIH cannot be overcome by increasing the dosage.

OIH is thought to result from neuroplastic changes in the central nervous system and peripheral nervous system leading to sensitisation of pro-nociceptive pathways¹.

OIH should be suspected if the opioid treatment effect wanes in the absence of disease progression, particularly if in association with unexplained pain or pain from ordinarily non-painful stimuli¹.

If OIH is suspected, opioid reduction, opioid rotation or the use of a non-opioid strategy for pain control should be considered¹⁻⁴.

The New Zealand data sheets for oxycodone lists the frequency of hyperalgesia as not known and includes the following precaution. *“Hyperalgesia that will not respond to a further dose increase of oxycodone may very rarely occur in particular at high doses. An oxycodone dose reduction or change in opioid may be required”*^{3,4}.

Healthcare professionals are encouraged to report any adverse events to the CARM. Reports may be submitted via the Medsafe website (www.medsafe.govt.nz/profs/adverse/reactions.asp) or by reporting directly to CARM (<https://nzphvc.otago.ac.nz/carm/>).

References

1. Chu LF, Angst MS, Clark D. 2008. Opioid-induced hyperalgesia in humans: molecular mechanisms and clinical considerations. *Clinical Journal of Pain* 24: 479–496.
2. Silverman SM. 2009. Opioid induced hyperalgesia: clinical implications for the pain practitioner. *Pain Physician* 12: 679–684.
3. BNM Group. 2014. *Oxycodone (BNM) Data Sheet*. 13 March 2014. URL: www.medsafe.govt.nz/profs/Datasheet/o/oxycodoneBNMtab.pdf (accessed 22 July 2015).
4. Mundipharma New Zealand Limited. 2014. *Oxycontin Data Sheet*. 2 October 2014. URL: www.medsafe.govt.nz/profs/Datasheet/o/OxyContinTab.pdf (accessed 22 July 2015).

Complementary Corner — Olive Leaf Extract

Healthcare professionals are reminded that dietary supplements can contain pharmacologically active ingredients that may cause adverse reactions. Olive leaf (*Olea europaea*) extract is one such dietary supplement,

which is predominantly marketed to ‘provide immune support’.

The Centre for Adverse Reactions Monitoring (CARM) has received three reports of gastrointestinal adverse reactions with the use

of olive leaf extract products. In one case, the patient experienced nausea, epigastric pain and projectile vomiting soon after taking the product, followed by bouts of diarrhoea. In the other cases, the patients experienced vomiting or gastrointestinal pain.

Healthcare professionals are reminded to ask patients about their use of complementary medicines, including herbal and dietary supplements, and to report any suspected adverse reactions to CARM.

Reminder: Interactions Resulting in Serotonin Syndrome

Key Messages

- ⌘ Serotonin syndrome can result from a pharmacodynamic interaction between medicines with serotonergic effects.
- ⌘ Medicines with serotonergic effects also include medicines other than antidepressants such as tramadol, methylene blue and linezolid.
- ⌘ Healthcare professionals are reminded that patients taking more than one serotonergic medicine are at an increased risk of developing serotonin syndrome.

Healthcare professionals are reminded that the risk of developing serotonin syndrome is increased in patients taking more than one serotonergic medicine.

The Centre for Adverse Reactions Monitoring (CARM) has recently received two reports of patients taking regular fluoxetine who developed serotonin syndrome after tramadol was started. The symptoms improved after tramadol was stopped.

Although tramadol is an analgesic, it also has serotonergic effects and should be avoided in patients taking serotonin reuptake inhibitors.

Pharmacodynamic interactions include interactions that occur between medicines which have similar pharmacological effects or adverse effects¹. Serotonin syndrome is an example of a pharmacodynamic interaction where two or more medicines with serotonergic effects interact resulting in serotonin toxicity.

Further information on serotonin syndrome, including a summary table of serotonergic medicines, can be found in a previous edition of *Prescriber Update*².

Healthcare professionals are encouraged to report all suspicions of medicine interactions to CARM. Reports may be submitted on paper or electronically (<https://nzphvc.otago.ac.nz/>).

References

1. New Zealand Formulary. 2015. Drug interactions. NZF v37. URL: www.nzf.org.nz/nzf_9751 (accessed 14 July 2015).
2. Medsafe. 2010. Serotonin syndrome/toxicity — reminder. *Prescriber Update* 31(4): 30–31. URL: www.medsafe.govt.nz/profs/PUArticles/SerotoninSyndromeToxicityReminder.htm (accessed 14 July 2015).

Therapeutic Products Regulatory Regime

The New Zealand Government is currently developing a new, comprehensive domestic regulatory regime to regulate therapeutic products. This follows the cessation of the Australia New Zealand Therapeutic Products Agency (ANZTPA) project.

The new regulatory regime will replace the Medicines Act 1981, and is intended to cover medicines, medical devices, and cell and tissues. The new regulatory regime will support and enable the delivery of healthcare and disability support services now and as they evolve into the future.

The objectives of the new regulatory regime include the need to be an efficient regulator and be cost effective. In addition, there needs to be flexibility in the legislation to future proof regulation with emerging technology. The benefits of aligning regulation with international standards are clear and this is a key objective.

A website is being developed and there will be opportunities for all groups to be consulted throughout the process. The Medsafe website will provide links to this website (www.medsafe.govt.nz).

Risks of Hydroxychloroquine

Key Messages

- ⌘ Hydroxychloroquine is associated with several rare but serious adverse reactions that may warrant immediate discontinuation of the medicine.
- ⌘ Serious adverse reactions include ophthalmological, cardiomyopathy and QT prolongation, haematological, and neurological and neuromuscular reactions.
- ⌘ Routine monitoring is recommended for all patients, particularly those on long-term therapy.

The Centre for Adverse Reactions Monitoring (CARM) receives several reports each year of serious adverse reactions to hydroxychloroquine. Healthcare professionals are encouraged to report all suspicions of adverse reactions to hydroxychloroquine and other medicines to CARM (<https://nzphvc.otago.ac.nz/>).

Hydroxychloroquine, originally used as an antimalarial agent, has beneficial effects on mucocutaneous symptoms in systemic lupus erythematosus. It is also used for the skin rash of discoid lupus erythematosus. A number of rare but serious adverse reactions can occur with its use and are usually associated with long-term therapy.

Ophthalmological Reactions

In the last two years, CARM has received two reports of ophthalmological reactions associated with hydroxychloroquine. Of the two reports, one report was of scotoma and one report was of retinal disorder.

Retinopathy is a serious adverse reaction due to the progressive and irreversible nature of the changes¹. Retinopathy is usually associated with long-term use (greater than five years), although it can occur earlier.

Other risk factors include high dose (both daily dose and cumulative dose), an age greater than 60 years, and renal or hepatic dysfunction¹. Patients with a history of retinopathy or pre-existing maculopathy should not be treated with hydroxychloroquine.

Corneal changes can also occur with hydroxychloroquine use, although these often subside following a dose reduction or discontinuation of the medicine².

The data sheet recommends all patients should have an ophthalmological examination prior to treatment initiation and at least six monthly thereafter². Local guidance of monitoring requirements should also be considered.

Any indication of abnormality in the visual field or retinal macular areas, or any visual symptoms which are not fully explainable by difficulties of accommodation or corneal opacities require immediate discontinuation of hydroxychloroquine and the patient closely observed for possible progression^{1,2}.

There is some evidence that early detection means that retinal changes reverse upon discontinuation of the medicine².

Cardiomyopathy and QT Prolongation

CARM have received reports of cardiac arrest, cardiac failure, cardiomyopathy, endocarditis and myocarditis associated with hydroxychloroquine treatment.

Long-term use and high doses of hydroxychloroquine are risk factors for the development of cardiomyopathy. Cardiac failure, conduction disorders (including QT prolongation and Torsades de Pointes) and sudden cardiac death are consequences of the cardiomyopathy.

Diagnosis of cardiomyopathy can be difficult due to the lack of specificity of symptoms and concurrent cardiovascular involvement of the underlying disease³.

When detected early, hydroxychloroquine induced cardiomyopathy may be reversible⁴. Therefore, patients requiring long-term therapy should be appropriately monitored. If cardiac complications due to hydroxychloroquine are suspected, treatment should be discontinued.

In patients with risk factors for QT prolongation, hydroxychloroquine should be used with care. Reassessment of treatment should occur should any new risk factors for QT prolongation be identified for individual patients. Further information on risk factors for QT prolongation is available in a previous issue of *Prescriber Update*⁵.

Haematological Reactions

Two cases of blood dyscrasias requiring hospital treatment have been reported to CARM in the last two years.

Hydroxychloroquine treatment can cause bone marrow depression, anaemia, aplastic anaemia, leucopenia, thrombocytopenia, agranulocytosis, and porphyria exacerbation.

Risk factors include use of high doses and long-term use. Periodic full blood counts are recommended for patients on long-term therapy. Treatment should be discontinued if hydroxychloroquine treatment is identified as the cause of any of these serious blood dyscrasias².

Neurological and Neuromuscular Reactions

In New Zealand, there have been two reports of peripheral neuropathy associated with hydroxychloroquine use since 1 January 2010. In one report, the patient's symptoms improved after the drug was discontinued.

Reports of neuromyopathy in the literature generally involve proximal muscle weakness in the lower extremities together with diminished

tendon reflexes³. Muscle weakness may be progressive and atrophy of the proximal muscles can occur². The manifestations of neuromyopathy are reversible on discontinuation of treatment^{2,3}.

All patients on long-term therapy should be questioned and examined periodically for muscle weakness². Testing should include knee and ankle reflex response².

References

1. Rodriguez-Caruncho C, Bielsa Marsol I. 2014. Antimalarials in dermatology: mechanism of action, indications, and side effects. *Actas Dermosifiliograficas* 105(3): 243–252.
2. Sanofi-Aventis NZ Ltd. 2014. *Plaquenil Data Sheet*. URL: www.medsafe.govt.nz/profs/datasheet/p/Plaqueniltab.pdf (accessed 30 July 2015).
3. Tonnesmann E, Kandolf R, Lewalter T. 2013. Chloroquine cardiomyopathy — a review of the literature. *Immunopharmacology and Immunotoxicology* 35(3): 434–442.
4. Yogasundaram H, Putko BN, Tien J, et al. 2014. Hydroxychloroquine-Induced Cardiomyopathy: Case Report, Pathophysiology, Diagnosis and Treatment. *Canadian Journal of Cardiology* 30: 1706–1715.
5. 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 6 Aug 2015).

Medicines and Hyperkalaemia

Key Messages

- ⌘ Many frequently prescribed medicines can influence the serum potassium concentration and even a slight change can have significant clinical consequences.
- ⌘ Drug-drug interactions that result in increased potassium concentrations occur in up to 10% of hospitalised patients¹.
- ⌘ The clinically most important effect of hyperkalaemia is cardiac arrhythmias, which can be severe and life threatening.
- ⌘ Common causes of hyperkalaemia include diabetes, renal disease and medicines such as angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists.
- ⌘ Cautious dosing of potassium-increasing medicines and close monitoring of serum potassium is recommended in susceptible patients.

Background

Potassium is an important electrolyte required for physiological functioning. A slight change in concentration can have a significant impact clinically². Hyperkalaemia is generally defined as a serum potassium concentration greater than 5.0 mmol/L³.

It is widely recognised that cardiac complications, including sudden death, are associated with hyperkalaemia making prevention of hyperkalaemia a priority⁴.

Medicines have been considered as a primary or contributing cause of hyperkalaemia in 35% to 75% of hospitalised patients⁵. Potassium increasing drug-drug interactions (DDIs) are also common, occurring in up to 10% of hospitalised patients¹.

Symptoms

Hyperkalaemia is often asymptomatic and discovered on routine laboratory tests. Severe hyperkalaemia (potassium >6.5 mmol/L) is life-threatening^{3,6}. Symptoms are predominantly cardiac or muscular related and include generalised weakness, paralysis, and cardiac arrhythmia^{3,6}.

Cardiac arrhythmias are the clinically most important symptom as these may lead to (sudden) death². Thus hyperkalaemia is associated with increased mortality⁷.

Medicines that Increase Serum Potassium

Medicines known to increase serum potassium are shown in Table 1. Medicines affecting the renin-angiotensin system are the most common cause of hyperkalaemia^{6,9}.

Important Drug Interactions

Potassium-increasing DDIs may induce hyperkalaemia and hence life-threatening cardiac arrhythmias¹. The risk for hyperkalaemia is increased with the number of concurrently administered potassium-increasing medicines¹.

Care needs to be taken when adding a potassium increasing medicine to a patient's treatment regimen which already includes a potassium increasing medicine. This is most likely to be overlooked when the patient requires short-term treatment with a nonsteroidal anti-inflammatory drug (NSAID) or anti-infective such as co-trimoxazole (trimethoprim-sulfamethoxazole).

Recent research has shown an increased risk of sudden death in patients taking spironolactone, angiotensin-converting enzyme (ACE) inhibitors

or angiotensin receptor antagonists who were also treated with co-trimoxazole for an infection^{5,9}.

Non-medicinal Causes

Other factors may contribute to the risk of a patient developing hyperkalaemia and include ⁶⁻⁸:

- increasing age
- dehydration
- renal disease
- hypoaldosteronism
- metabolic acidosis
- diabetes mellitus/insulin deficiency
- an increased potassium supply.

Management

Patients at risk of developing hyperkalaemia should have their serum potassium levels frequently monitored.

When potassium levels start to increase or in mild hyperkalaemia, the potassium-increasing medicine should be reduced and dietary potassium restricted. If this is not effective the medicine may need to be withdrawn⁶. In patients requiring diuretics, loop or thiazide diuretics should be used⁶. However, these may have reduced efficacy in patients with underlying kidney failure.

Table 1: Medicines known to increase serum potassium levels⁸

Mechanism	Medicine Type	Medicines
Reduction of potassium renal excretion due to hypoaldosteronism	Aldosterone antagonists	Spironolactone, canrenoate potassium, eplerenone, drospirenone
	Angiotensin-converting enzyme inhibitors	Captopril, enalapril, lisinopril
	Angiotensin II receptor antagonists	Candesartan, losartan
	Non-steroidal anti-inflammatory drugs	Ibuprofen, naproxen, diclofenac, meloxicam
	Heparins	Enoxaparin sodium
	Immunosuppressive drugs	Cyclosporin, tacrolimus
Reduction of potassium passive renal excretion	Potassium-sparing diuretics other than aldosterone antagonists	Amiloride, triamterene
	Anti-infective drugs	Trimethoprim, pentamidine
Reduction of potassium cellular transport	Beta-blockers	Propranolol, atenolol, metoprolol, bisoprolol
	Cardiac glycosides	Digoxin
	Mood stabiliser	Lithium
Excess of potassium supply	Potassium salts	Potassium chloride
Unknown mechanism	Epoetins	Epoetin alfa, epoetin beta

Patients who develop severe hyperkalaemia require immediate hospital attention.

Early measurement of potassium levels, cautious dosing (giving consideration to potassium-increasing medicines), close monitoring of a patient's electrolyte levels and avoidance of other drugs that cause hyperkalaemia is recommended to reduce the risk of hyperkalaemia⁹.

New Zealand Cases

The Centre for Adverse Reactions Monitoring (CARM) has received 60 reports of hyperkalaemia (Figure 1). These 60 reports involved 79 suspect medicines as two or more suspect medicines were described in some reports.

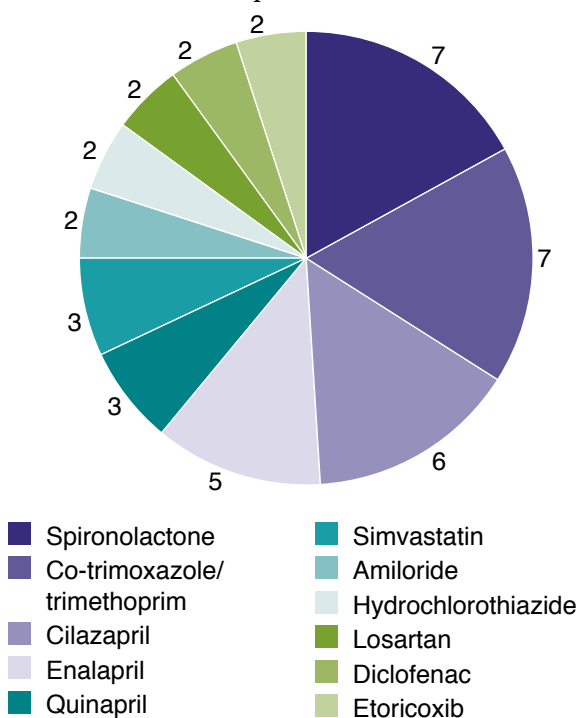


Figure 1: Medicines associated with hyperkalaemia that have been reported to CARM more than once.

ACE inhibitors and aldosterone antagonists accounted for 25% and 9% of the suspect medicines, respectively. This is consistent with hyperkalaemia causing medicines reported in the literature.

The suspect medicine was withdrawn in 40 of the 60 reports and in 33 of those 40 reports a definite improvement of hyperkalaemia was reported.

Healthcare professionals are encouraged to report any adverse events to medicines, including hyperkalaemia, to CARM. Reports may be submitted on paper or electronically (<https://nzphvc.otago.ac.nz/>).

References

1. Eschmann E, Beeler PE, Kaplan V, et al. 2014. Patient- and physician-related risk factors for hyperkalaemia in potassium-increasing drug-drug interactions. *European Journal Clinical Pharmacology* 70: 215–223.
2. Karmacharya P, Poudel DR, Pathak R, et al. 2015. Acute hyperkalemia leading to flaccid paralysis: a review of hyperkalemic manifestations. *Journal of Community Hospital Internal Medicine Perspectives* 5: 27993.
3. Rastegar A, Soleimani M. 2001. Hypokalaemia and Hyperkalaemia. *Postgraduate Medical Journal* 77: 759–764.
4. Ponce SP, Jennings AE, Madias NE, et al. 1985. Drug-induced hyperkalemia. *Medicine (Baltimore)* 64: 357–370.
5. Perazella MA. 2000. Drug-induced hyperkalemia: old culprits and new offenders. *American Journal Medicine* 109: 307–314.
6. Ben Salem C, Badreddine A, Fathallah N, et al. 2014. Drug-induced hyperkalemia. *Drug Safety* 37: 677–692.
7. Henz S, Maeder MT, Huber S, et al. 2008. Influence of drugs and comorbidity on serum potassium in 15,000 consecutive hospital admissions. *Nephrology Dialysis Transplant* 23: 3939–3945.
8. Noize P, Bagheri H, Durrieu G, et al. 2011. Life-threatening drug-associated hyperkalemia: a retrospective study from laboratory signals. *Pharmacoepidemiology Drug Safety* 20: 747–753.
9. Antoniou T, Hollands S, Macdonald EM, et al. 2015. Trimethoprim-sulfamethoxazole and risk of sudden death among patients taking spironolactone. *Canadian Medical Association Journal* 187: E138–143.

WE NEED YOUR HELP!

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



Medicine	Potential safety issue	Active monitoring ends
Guaifenesin (Guaiphenesin)	Tinnitus	31 October 2015
Melatonin	Hallucinations	31 January 2016



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.

Varicella Zoster Virus Vaccines — Medication Errors

Key Messages

- ⌘ Healthcare professionals should take care when preparing and administering varicella zoster vaccines to ensure the correct product is administered.
- ⌘ Mix ups between the paediatric (Varilrix and Varivax) and adult (Zostavax) formulations have recently occurred.
- ⌘ Zostavax contains a much higher titre of the virus than Varilrix and Varivax and has the potential to cause harm when administered to children.
- ⌘ Healthcare professionals should consider risk mitigation strategies to prevent future errors.

Healthcare professionals should take care when prescribing, preparing and administering Zostavax, Varivax or Varilrix to ensure the correct varicella zoster virus vaccine is administered. The New Zealand Pharmacovigilance Centre has received five reports of medication error involving administration of the incorrect varicella zoster virus vaccine to a child or adult.

The Centre for Adverse Reactions Monitoring (CARM) has received four reports and the newly established Medication Error Reporting Programme (MERP) has received one report. In four of the five reports, children were administered Zostavax in error. In the fifth case, an elderly patient was prescribed and administered Varilrix for the prevention of shingles. In all five reports, there was no patient harm at the time of the report.

Varicella zoster virus is responsible for both chickenpox (varicella) and shingles (herpes zoster). Chickenpox is the primary infection and most commonly occurs in children. Shingles occurs when latent varicella zoster virus is reactivated and is more common in older adults¹.

In New Zealand, three varicella zoster virus vaccines are approved and available. Two of these, Varilrix and Varivax are used to vaccinate against chickenpox and can be used from ages

nine and 12 months respectively^{2,3}. The third, Zostavax is used for the prevention of shingles in individuals 50 years of age and above⁴.

Zostavax contains a much higher titre of the virus than Varilrix and Varivax and has the potential to cause harm when administered to children. It is not recommended for use in the paediatric population⁴.

To reduce the risk of medication errors, consider the following strategies:

- separate storage of Zostavax and other adult vaccines from childhood vaccines
- implementing independent double check procedures prior to vaccine administration
- alerting staff to the differences in the various products.

In cases where the correct product is not available, the patient should be asked to return at a time when the correct product will be available.

Healthcare professionals are encouraged to report to CARM or MERP (anonymously if preferred) any actual or potential 'near miss' medication and vaccine errors (<https://nzphvc.otago.ac.nz/>).

Information on the approved indication(s) as well as correct dosing and administration of each product can be found in the respective data sheets, available on the Medsafe website (www.medsafe.govt.nz/profs/Datasheet/DSForm.asp).

References

1. Immunisation Advisory Centre. 2014. *Chickenpox (Varicella) Fact Sheet*. URL: www.immune.org.nz/sites/default/files/factsheets/DiseaseVaricellaImac20140915V02Final_0.pdf (accessed 9 July 2015).
2. GlaxoSmithKline NZ Ltd. 2014. *Varilrix Data Sheet*. 18 October 2014. URL: www.medsafe.govt.nz/profs/Datasheet/v/Varilrixinj.pdf (accessed 9 July 2015).
3. Merck Sharp and Dohme (New Zealand) Limited. 2013. *Varivax Data Sheet*. 7 November 2013. URL: www.medsafe.govt.nz/profs/Datasheet/v/Varivaxinj.pdf (accessed 9 July 2015).
4. Merck Sharp and Dohme (New Zealand) Limited. 2015. *Zostavax Data Sheet*. 29 April 2015. URL: www.medsafe.govt.nz/profs/Datasheet/z/zostavaxinj.pdf (accessed 9 July 2015).

Miracle Mineral Solution — Buyer Beware

Key Messages

- ⌘ Miracle Mineral Solution (MMS) products contain sodium chlorite (an industrial bleach) and are not approved medicines.
- ⌘ Consumers who have bought MMS to take orally are advised to stop using the products immediately.
- ⌘ Medsafe is not aware of any research showing that MMS is effective for any illness when taken orally.
- ⌘ Ingesting MMS products can cause nausea, vomiting, diarrhoea and symptoms of severe dehydration.

Miracle Mineral Solution (MMS) products contain sodium chlorite (an industrial bleach) and are not approved medicines. The quality of the products is unknown.

MMS products are promoted as highly effective destroyers of pathogens, fungi, disease, bacteria and viruses to treat a variety of conditions. Medsafe is not aware of any scientific evidence that MMS products are effective for any illness when taken orally.

Whilst sodium chlorite may be an effective disinfectant when used on household surfaces or for water purification, this is not the same as ingesting the product. In fact, these products produce chlorine dioxide which can cause serious harm to health when ingested.

Symptoms include nausea, vomiting, diarrhoea and those of severe dehydration which may be life threatening. Any suspected adverse reactions to MMS product should be reported to the Centre for Adverse Reactions Monitoring (CARM).

Further information on MMS products is available on the Medsafe website (www.medsafe.govt.nz/safety/EWS/2015/MiracleMineralSolution.asp).

Clomifene and Risk of Stroke

Key Messages

- ⌘ Clomifene is a medicine used to induce ovulation.
- ⌘ There have been isolated reports of stroke in patients taking clomifene.
- ⌘ Patients should be advised to seek immediate medical attention if they experience any signs and symptoms of a stroke.

The Centre for Adverse Reactions Monitoring (CARM) recently received a report of ischaemic stroke in a patient taking clomifene. The patient was not reported to be taking any other medicines at the time of the stroke.

Clomifene (clomiphene) is a medicine used to induce ovulation in anovulatory women. It is indicated for the treatment of ovulatory failure in women desiring pregnancy¹. The ovulatory response to cyclic clomifene occurs through

increased output of pituitary gonadotrophins stimulating the release of eggs from the ovaries².

Patients should be advised to stop taking clomifene and seek emergency treatment if they experience numbness, weakness or paralysis on one side of the body, slurred speech, sudden blurred vision, confusion or unsteadiness — these could be signs of a stroke³.

Please continue to report any adverse reactions to medicines, including clomifene, to CARM. Reports may be submitted on paper or electronically (<https://nzphvc.otago.ac.nz/>).

References

1. Healthcare Logistics. 2015. *Serophene Data Sheet*. 26 June 2015. URL: www.medsafe.govt.nz/profs/datasheet/s/serophenetab.pdf (accessed 27 July 2015).
2. Sanofi. 2014. *Clomid Summary of Product Characteristics*. 19 August 2014. URL: www.medicines.org.uk/emc/medicine/820 (accessed 14 July 2015).
3. Sanofi. 2013. *Clomid Patient Information Leaflet*. August 2013. URL: www.medicines.org.uk/emc/medicine/3070 (accessed 14 July 2015).

Ibuprofen and Cardiovascular Risk

Key Messages

- ⌘ There is a small increased risk of cardiovascular events with high doses of ibuprofen (2400 mg per day).
- ⌘ Lower doses (1200 mg per day or less) of ibuprofen are not associated with an increased risk of cardiovascular events.
- ⌘ The overall benefit to risk of harm balance of ibuprofen as well as other non-steroidal anti-inflammatory drugs (NSAIDs) remains positive.
- ⌘ The lowest effective dose of ibuprofen should be used for the shortest possible duration.
- ⌘ Patients requiring high dose ibuprofen therapy should have their treatment reviewed to check for efficacy, adverse effects and the development of cardiovascular risk factors.

Medsafe and the Medicines Adverse Reactions Committee (MARC) recently evaluated the risk of cardiovascular events with the use of ibuprofen. The available data suggested that a dose-response relationship exists.

The MARC concluded that there is a small increased risk of cardiovascular thrombotic events when ibuprofen is used at high doses (2400 mg per day). Lower doses of ibuprofen of 1200 mg per day or less (the dose generally used for over-the-counter [OTC] preparations) were not associated with this increased risk.

Overall, the benefit to risk of harm balance for ibuprofen as well as other non-steroidal anti-inflammatory drugs (NSAIDs) remains positive

(www.medsafe.govt.nz/profs/adverse/Minutes161.htm#3.2.3).

It is recommended that the lowest effective dose of ibuprofen should be used for the shortest possible duration. Patients requiring high dose ibuprofen therapy should be reviewed regularly to check for efficacy of treatment, adverse effects and the development of cardiovascular risk factors.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease should only be treated with high dose ibuprofen after careful consideration of potential risks and benefits. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (eg, hypertension, hyperlipidaemia, diabetes mellitus and smoking).

There is no consistent evidence that the concurrent use of aspirin mitigates the possible increased risk of cardiovascular events associated with NSAIDs but aspirin will significantly increase gastrointestinal risk.

As a result of the MARC review, several changes have been made to the ibuprofen data sheets to ensure they contain the most up-to-date information. There is currently no legal requirement for data sheets for OTC preparations. Data sheets are published on the Medsafe website (www.medsafe.govt.nz/profs/datasheet/dsform.asp).

Further information on ibuprofen and cardiovascular safety, including a summary of data, is available on the Medsafe website (www.medsafe.govt.nz/safety/EWS/2015/Ibuprofen.asp).

MARC's Remarks: June 2015 Meeting

The Medicines Adverse Reactions Committee (MARC) met on 11 June 2015 to discuss a number of medicine-related safety issues.

The MARC discussed the value of **consumer reporting** of adverse drug reactions and gave advice to Medsafe on how to encourage and promote direct reporting from consumers.

The MARC discussed the risk of bladder cancer with **pioglitazone**. The MARC considered that the current information in the pioglitazone data sheet was sufficient and concluded that no further action or advice on this risk is required.

The MARC reviewed the available information on **statin**-associated autoimmune myopathy.

An article on the spectrum of muscle effects associated with statin treatment will be included in a future edition of *Prescriber Update*.

Further information on this meeting can be found on the Medsafe website (www.medsafe.govt.nz/profs/adverse/Minutes162.htm).

Reminder: Citalopram and QT Prolongation

Key Messages

- ⌘ The maximum dose of citalopram for elderly patients, patients with hepatic impairment, and patients who are CYP2C19 poor metabolisers, or who are taking CYP2C19 inhibitors is 20 mg daily due to increased risk of QT prolongation.
- ⌘ The maximum dose for other patients is 40 mg daily.
- ⌘ Patients should be screened for risk factors for QT prolongation before starting treatment with citalopram.
- ⌘ Citalopram should be stopped and specialist advice sought in patients who have significant QTc prolongation (QTc > 500 ms or an increase of > 60 ms) unless there are compelling reasons to continue.
- ⌘ Patients should be advised to contact a healthcare professional immediately if they experience signs and symptoms of an abnormal heart rate or rhythm while taking citalopram.

The Centre for Adverse Reactions Monitoring (CARM) has received a report of a 63-year-old female who was taking 40 mg of citalopram daily. The patient experienced a ventricular tachycardia leading to cardiac arrest and was found to have a prolonged QT interval.

The patient was in end stage renal failure. Although citalopram is eliminated more slowly in patients with mild to moderate renal impairment a dose adjustment is not necessary. However, no information is available on treatment of patients with severely reduced renal function and prescribers are advised to use caution¹.

Healthcare professionals are reminded that citalopram is associated with a dose dependent increase in the risk of QT prolongation². The maximum dose of citalopram is 40 mg a day due to the increased risk of QT prolongation with no additional benefit¹.

In elderly patients, patients with reduced hepatic function, patients who are CYP2C19 poor metabolisers, and patients taking CYP2C19 inhibitors (eg, cimetidine and omeprazole), the maximum dose should not exceed 20 mg a day because these factors lead to increased blood levels of citalopram¹.

QT prolongation is a measure of delayed ventricular repolarisation, which can cause Torsades de Pointes, ventricular tachycardia, and sudden death. A corrected QT interval (QTc) of greater than 500 ms or an increase in the QTc of greater than 60 ms is considered to confer a high risk of Torsades de Pointes³.

Citalopram should be discontinued and specialist advice sought in patients who are found to have persistent QTc greater than 500 ms or an increase of greater than 60 ms unless there are compelling reasons to continue.

QT prolongation risk factors include female gender, increasing age, genetic predisposition, structural heart disease, hypokalaemia, hypomagnesaemia, and interactions with other medicines³.

Prescribers should advise patients to contact a healthcare professional immediately if they experience signs and symptoms of an abnormal heart rate or rhythm while taking citalopram.

Further information on QT prolongation can be found in the *Prescriber Update* article '*Drug-induced QT prolongation and Torsades de Pointes — the facts*'³.

References

1. Actavis New Zealand Limited. 2014. *Arrow - Citalopram Data Sheet*. 24 April 2014. URL: www.medsafe.govt.nz/profs/datasheet/a/ArrowCitalopramtab.pdf (accessed 28 July 2015).
2. Food and Drug Administration. 2012. Revised recommendations for Celexa (citalopram hydrobromide) related to a potential risk of abnormal heart rhythms with high doses. *FDA Drug Safety Communication* 28 March 2012. URL: www.fda.gov/Drugs/DrugSafety/ucm297391.htm (accessed 28 July 2015).
3. 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 28 July 2015).

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.

17 June 2015	Alert	Ibuprofen and cardiovascular safety
19 June 2015	Alert	Miracle Mineral Solution — Buyer beware
22 June 2015	Monitoring	Influenza vaccine and mild hypersensitivity reactions
20 July 2015	Monitoring	Melatonin and the possible risk of hallucinations added to the medicines monitoring (M ²) scheme
31 July 2015	Alert	UPDATE — Utrogestan (progesterone) formulation change — important information for patients with a peanut allergy
31 July 2015	Alert	Advice on serotonin syndrome

New Zealand Government