Prescriber Update

Vol. 38 No. 3 September 2017

www.medsafe.govt.nz

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

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Aripiprazole and Impulse Control Disorders

In the previous edition of *Prescriber Update*, the association between impulse control disorders and the use of dopaminergic medicines was discussed[1]. Aripiprazole (currently available in New Zealand as Abilify tablets) is a novel antipsychotic medicine with partial dopamine agonist activity. Impulse control disorders have also been associated with the use of aripiprazole.

The New Zealand data sheet for Abilify was recently updated to include information on pathological gambling and impulse-control disorders[2].

Although impulse control disorders can be associated with the underlying disorder for which treatment with aripiprazole was initiated, in some cases impulsive urges were reported to have stopped when the dose was reduced or the medicine discontinued[2].

The Centre for Adverse Reactions Monitoring (CARM) recently received a case report concerning a 39-year-old male who developed compulsive gambling one month after changing from risperidone to aripiprazole. At the time of reporting, he was being changed back to risperidone and the outcome of stopping aripiprazole was not yet known.

References

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JC Virus — More than PML

Key Messages

- In immunocompromised patients infected with JC virus, mutation of the virus can lead to neurological infection causing clinically distinct entities: PML, granule cell neuronopathy, encephalopathy and meningitis.
- PML and granule cell neuronopathy have been diagnosed in patients treated with immune-suppressing medicines, particularly natalizumab and rituximab.
- Clinicians should be aware of JC virus-granule cell neuronopathy and should consider this in cases of progressive cerebellar syndrome of unknown origin in immunosuppressed patients.

JC Virus

The etiologic agent of progressive multifocal leukoencephalopathy (PML) is a small ubiquitous polyomavirus, the JC virus (JCV). At least 50% of the general population is seropositive to JCV[1].

It is believed that initial infection with JCV results in a transient viraemia before the virus establishes as a latent or persistent infection in the kidney, tonsils and gut[1,2]. JCV reactivation can occur particularly in the setting of cellular immune suppression[2].

Mutations in the JCV genome can allow JCV to infect other cell types, such as oligodendrocytes, astrocytes, neurones and meningeal cells. Clinically distinct entities occur depending on the location of infection including:

- PML
- JCV-granule cell neuronopathy (JCV-GCN)
- JCV encephalopathy
- JCV meningitis.

JCV meningitis, JCV encephalopathy, JCV-GCN and PML may occur separately or co-exist on a continuum as the virus mutates and spreads from one location to another[3]. These new features of JCV infection provide challenges for clinicians taking care of affected patients (Table 1)[3,4].

PML

PML has been described in previous *Prescriber Update* articles, *PML: a rare but serious disease* (**www.medsafe.govt.nz/profs/PUArticles/PMLSept2012.htm**) and *Reminder: immunomodulatory medicines and risk of progressive multifocal leukoencephalopathy*

(**www.medsafe.govt.nz/profs/PUArticles/March2016/ReminderImmunomodulatoryMedicinesAndRiskProgressiveMultifocalLeukoencephalopath.htm**).

Initially PML was mostly associated with HIV infection, but is now increasingly being associated with medicine-induced immune suppression. For example, in patients taking natalizumab, who have JCV antibodies and prior immunosuppressant use, the frequency of PML is 1%[5]. The features of PML are summarised in Table 1.

PML-Immune Reconstitution Inflammatory Syndrome (PML-IRIS)

A cellular immune response directed against JCV is beneficial in classic PML. However, a rapid global recovery of the immune system may not always be favourable. It can trigger an immune reconstitution inflammatory syndrome (IRIS).

IRIS is an inflammatory response to clinically apparent or subclinical pathogens associated with recovery of the immune system after a period of immunosuppression. Immune reconstitution is inferred by an increase in T lymphocyte counts. This can occur after starting combination anti-retroviral therapy in HIV positive patients or with stopping immunosuppressive therapy, for example with natalizumab[4].

Natalizumab has a biological activity of three months following discontinuation, during which time either PML can progress or the resulting return of lymphocytes in the CNS may lead to IRIS. Plasma exchange/immunoadsorption reduces the serum concentration of natalizumab more quickly. The rapid restoration of the immune system increases the risk of precipitating a severe IRIS reaction up to three weeks later. Aggressive use of corticosteroids has been recommended in this situation to reduce the risk of a fatal outcome[4].

Granule Cell Neuronopathy (JCV-GCN)

In JCV-GCN, JCV infects the granule cell layer of the cerebellum, but spares Purkinje cells[3]. Symptoms include ataxia, tremor, dysarthria, dysdiadochokinesia (inability to perform rapid alternating movements), dysmetria (lack of coordination) on finger to nose and heel to shin testing, incoordination and nystagmus[4].

MRI typically shows cerebellar atrophy suggestive of neurodegeneration[3,4]. The diagnosis is established by cerebellar biopsy

Table 1: Clinical presentation of JCV infection (adapted from Tan)[4]

	Classic PML	PML–IRIS	JCV–GCN	JCV encephalitis	JCV meningitis
Onset	Subacute	Immune recovery	Chronic	Subacute	Acute
MRI findings	Asymmetric well demarcated non-enhancing subcortical white matter lesions	Contrast enhancement and mass effect	Cerebellar atrophy	Cortical lesions	No defined brain lesions, ventricular dilation
Neurological symptoms	Based on location	Based on location and inflammation	Cerebellar syndrome	Encephalopathy	Headache, stiff neck, fever
Diagnosis	JC virus detection in the CSF, brain biopsy, MRI findings and symptoms	JC virus detection in the CSF, brain biopsy, MRI findings and symptoms	Cerebellar biopsy, JC virus in CSF, radiological findings and symptoms	Brain biopsy, JC virus PCR in the CSF, radiographical findings and symptoms	JC virus in the CSF and exclusion of other viruses
Treatment	Decrease immunosuppression, plasma exchange for natalizumab-treated patients	Similar to PML, steroids in cases with notable worsening	Similar to classic PML	Similar to classic PML	Similar to classic PML

showing a lytic infection of granule cell neurons by JCV[4].

JCV-GCN has mainly been reported in patients with HIV infection, but also in patients treated with natalizumab and rituximab[2,3].

JCV-GCN can occur in isolation or concomitantly to PML. A histologic survey of archival PML samples indicated that infection of granule cell neurons may be found in up to half of patients with PML[3]. It is unclear whether JCV-GCN should be considered as a separate entity of JCV related disease or a PML subtype[2].

The reversal of the immunocompromised status is the only way to stop the disease evolution of JCV-GCN. Motor function can remain impaired, but the illness itself, unlike PML does not appear to be life-threatening[6].

Clinicians should be aware of this entity. JCV-GCN should be considered in cases of progressive cerebellar syndrome of unknown origin in immunosuppressed patients[6].

JCV Encephalitis

JCV encephalitis occurs when JCV infects cerebral pyramidal neurons and astrocytes in the cortical grey matter and grey-white junction. The pathology of JCV encephalitis is characterised by the infection and lysis of cortical grey matter[1,3,4].

JCV Meningitis

JCV meningitis has been associated with findings of JCV in the CSF of patients presenting with meningeal symptoms only[4]. Several studies have documented JCV as the only pathogen present in the CSF of patients with typical meningeal signs and symptoms such as neck stiffness and diplopia. Whether these cases result from JCV primary infection or reactivation is unclear[3].

Healthcare professionals should be aware that JCV infection can result in clinically distinct entities depending on the location of infection. JCV-GCN, in addition to PML, has been reported in patients with medicine-induced immune suppression.

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Drug Interactions with Lithium and Therapeutic Drug Monitoring

Key Messages

- ⌘ Prescribers and patients need to be mindful of factors that reduce lithium clearance due to its narrow therapeutic range.
- ⌘ Drug interactions with lithium mostly occur through the direct effect of other medicines on the kidney.
- ⌘ Prescribers are advised to regularly monitor serum lithium and assess patients for signs of toxicity during concomitant treatment with suspect medicines.
- ⌘ Adjust lithium dose or discontinue interacting medicines as appropriate.

NZ Case Report

A 72-year-old woman with impaired renal function was prescribed lithium and cilazapril (as well as other medicines). She was stable until a non-steroidal anti-inflammatory drug (NSAID) was added, leading to fatal lithium toxicity. It was suspected that the NSAID triggered lithium toxicity due to a pharmacokinetic interaction. The patient's lithium levels had only been sporadically monitored.

Drug Interactions with Lithium

Lithium is not metabolised and is almost entirely eliminated by the kidneys[1]. As a result, serum lithium levels are sensitive to physiological factors that affect renal function,

including age, dehydration, sodium balance and haemodynamics[1]. In addition, lithium has a narrow therapeutic index and minor changes in plasma concentrations can have significant clinical consequences[1].

Drug interactions with lithium mostly occur through the direct effect of other medicines on renal function, notably glomerular filtration rate and sodium absorption[1].

Medicines that interact with lithium are summarised in Table 1. Regular monitoring of serum lithium and assessment for signs of lithium toxicity (see below) should be performed for patients requiring concomitant treatment with lithium and interacting medicines[2–4]. The dose of lithium may require adjustment. In some cases, the concomitant treatment may need to be stopped[2–4].

Table 1: Medicines that may interact with lithium (adapted from data sheets)[2–4]

Interactions that may increase lithium concentrations	
Selective serotonin re-uptake inhibitors (SSRIs)	
Non-steroidal anti-inflammatory drugs (NSAIDs)	
Angiotensin-converting enzyme (ACE) inhibitors	
Angiotensin-II receptor antagonists	
Diuretics: thiazides, spironolactone, furosemide	
Other: metronidazole, tetracyclines, topiramate, medicines that affect electrolyte balance	
Interactions that may decrease lithium concentrations	
Xanthines: theophylline, caffeine	
Sodium bicarbonate and sodium chloride containing products	
Other: psyllium or ispaghula husk, urea, mannitol, acetazolamide	
Interactions that may cause or aggravate neurotoxicity	
Antipsychotics: haloperidol, risperidone, clozapine, phenothiazines	In rare cases: confusion, disorientation, lethargy, tremor, extrapyramidal symptoms, myoclonus.
SSRIs, sumatriptan, tricyclic antidepressants	Associated with episodes of neurotoxicity and may precipitate serotonin syndrome. Either presentation justifies immediate discontinuation of treatment.
Calcium channel blockers	May lead to ataxia, confusion and somnolence, reversible after discontinuation of the medicine. Lithium concentrations may be increased or decreased.
Carbamazepine, phenytoin	May lead to dizziness, somnolence, confusion, cerebellar symptoms.
Methyldopa	
Other interactions	
Neuromuscular blocking agents	Lithium may prolong the effects of these agents.
Iodine	May act synergistically with lithium to produce hypothyroidism.
Other: baclofen, cotrimoxazole, aciclovir, prostaglandin-synthetase inhibitors	Case reports of interactions with lithium. Clinical significance uncertain.

Lithium Toxicity

Patients and family members should be warned of the signs and symptoms of impending lithium toxicity such as:

- gastrointestinal: progressive anorexia, diarrhoea and vomiting
- central nervous system: muscle weakness, lack of coordination, drowsiness or lethargy (these may progress to dizziness, ataxia, tinnitus, blurred vision, dysarthria, coarse tremor and muscle twitching)[2–4].

If signs of toxicity appear, patients should be instructed to stop taking lithium immediately and seek medical attention[2–4].

Monitoring Requirements for Patients Taking Lithium

Routine monitoring of serum lithium levels should be performed weekly after initiation until levels are stable[2–4]. Once stabilised, levels should be monitored at least every three months[2–4].

Additional monitoring should occur if signs of lithium toxicity occur, following dose changes, development of intercurrent disease, signs of manic or depressive relapse, dehydration or other significant change in sodium intake or fluid balance[2–4]. Patients travelling to the tropics and/or experiencing gastroenteritis are at particular risk and should be appropriately advised.

It is also important to monitor renal function regularly to ensure early detection and management of renal impairment. Further information on renal monitoring is available in a previous edition of *Prescriber Update* (**www.medsafe.govt.nz/profs/PUArticles/RenalDanagersSept10.htm**).

Case Reports from New Zealand

The Centre for Adverse Reactions Monitoring (CARM) has received a total of nine case reports that identify a drug interaction with lithium. The interacting medicines identified by the reporter include venlafaxine, furosemide and a calcium channel blocker (two reports each).

References

1. Finley PR. 2016. Drug Interactions with Lithium: An Update. *Clinical Pharmacokinetics* 55(8): 925-41.
2. Mylan New Zealand Ltd. 2014. *Lithicarb FC Data Sheet*. 9 June 2014. URL: **www.medsafe.govt.nz/profs/Datasheet/l/LithicarbFCtab.pdf** (accessed 27 June 2017).
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Warfarin and Calciphylaxis — A Rare but Serious Adverse Event

Key Messages

- ⌘ Calciphylaxis is a very rare but serious condition most commonly observed in patients with known risk factors such as end-stage renal disease.
- ⌘ Calciphylaxis has been reported in patients taking warfarin, including those with normal renal function.
- ⌘ Patients treated with warfarin should be advised to consult their doctor if they develop a painful rash/ulcer.
- ⌘ If calciphylaxis is diagnosed, appropriate treatment should be started and consideration should be given to stopping treatment with warfarin.

Calciphylaxis is a very rare but serious condition characterised by vascular calcification and cutaneous necrosis. Calciphylaxis has been reported in patients taking warfarin[1]. These patients commonly had pre-existing renal disease, but some reports noted normal renal function[1].

The Centre for Adverse Reactions Monitoring (CARM) has received two reports of calciphylaxis associated with the use of warfarin. Both patients were reported to have multiple comorbidities, including severe chronic renal failure in the first case and stage 4 chronic kidney disease in the second case.

Calciphylaxis is generally seen in patients with end-stage renal disease on dialysis or in those with known risk factors such as protein C or S deficiency, hyperphosphataemia, hypercalcaemia or hypoalbuminaemia[1].

The exact pathogenesis of calciphylaxis is unknown. Small blood vessels deep in the skin become blocked due to calcification and thrombosis. The resulting skin lesions are typically purpuric, indurated plaques with central necrosis.

Patients with calciphylaxis usually experience severe pain, burning and sometimes itching at lesion sites. The mortality rate is very high, primarily caused by secondary infection of the ulcers and sepsis[2].

The mechanism by which warfarin causes calciphylaxis may be mediated through the matrix Gla protein, which is a vitamin-K-dependent protein that prevents calcium deposition in arteries. Warfarin inhibits Gla protein and may therefore promote vascular calcification in susceptible individuals[1].

The authors of a recent review suggest that warfarin-associated calciphylaxis is distinct from classic calciphylaxis in pathogenesis, course and particularly outcome as the survival rate of nonuremic patients was remarkably high (83%)[3].

Medsafe is working to ensure that all data sheets for warfarin products include calciphylaxis as a potential adverse effect.

References

1. Medicines and Healthcare Products Regulatory Agency. 2016. Calciphylaxis is a very rare but serious condition causing vascular calcification and skin necrosis. *Drug Safety Update*. 18 July 2016. URL: **www.gov.uk/drug-safety-update/warfarin-reports-of-calciphylaxis** (accessed 27 June 2017).
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Quarterly Summary of Recent Safety 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**).

Consumer information leaflets provide information about medicines and medical devices or medical conditions to consumers.

Date	Communication	Topic
2 August 2017	Consultation	Changes to the Label Statements Database for sedating antihistamines available without prescription (Closes 29 Sep 2017)
20 July 2017	Consultation	Proposed change to warning statements on labels of oral non-steroidal anti-inflammatory drugs (NSAIDs) available without a prescription (Closes 15 Sep 2017)
11 July 2017	Alert Communication	UPDATE — Heater-cooler devices used during cardiac surgery: risk of infection with Nontuberculous Mycobacterium species – advice and recommendations
11 July 2017	Alert Communication	Consumer Level Recall — NovoPen® Echo®
7 July 2017	Alert Communication	Use of Tramadol During Breastfeeding
12 May 2017	Monitoring Communication	Direct-acting antiviral (DAA) regimens and liver failure
27 March 2017	Dear Healthcare Professional Letter	Zelboraf — Risk of Dupuytren's Contracture and Plantar Fascial Fibromatosis

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

Montelukast — Reminder about Neuropsychiatric Reactions

Key Messages

- Neuropsychiatric reactions have been reported in patients taking montelukast.
- Healthcare professionals should advise patients that neuropsychiatric reactions can occur.
- Patients and/or family members should be instructed to contact a healthcare professional should any neuropsychiatric reaction occur.

Montelukast is a leukotriene receptor agonist used for the treatment of asthma and rhinitis. Neuropsychiatric reactions have been reported in patients taking montelukast.

The Centre for Adverse Reactions Monitoring (CARM) has received 22 reports of suspected adverse reactions to montelukast to date. More than half of these reports (12) describe neuropsychiatric events. The most commonly reported neuropsychiatric reactions were abnormal dreaming, insomnia and aggression. In some reports, it was noted that the patient was also taking corticosteroids. However, in some cases montelukast was the only reported medicine.

The data sheets for montelukast products note that the following neuropsychiatric reactions have been reported: agitation including aggressive behaviour or hostility; anxiousness; depression; disorientation; disturbance in attention; dream abnormalities; hallucinations; insomnia; memory impairment; psychomotor hyperactivity (including irritability, restlessness, and tremor); somnambulism; suicidal thinking and behaviour (suicidality) and tic[1,2].

It is recommended that physicians discuss these adverse experiences with their patients and/or caregivers. Patients and/or caregivers should be instructed to notify their physician if these changes occur.

References

1. Merck Sharp & Dohme (NZ) Ltd. 2016. *Singulair Data Sheet*. 3 June 2016. URL: **www.medsafe.govt.nz/profs/Datasheet/s/Singulairtab.pdf** (accessed 4 July 2017).
2. Apotex NZ Ltd. 2016. *Apo-montelukast Data Sheet*. 9 December 2016. URL: **www.medsafe.govt.nz/profs/Datasheet/a/apo-montelukasttab.pdf** (accessed 4 July 2017).

MARC's Remarks: June 2017 Meeting

The Medicines Adverse Reactions Committee (MARC) met on 8 June 2017 to discuss a number of medicine-related safety issues.

The MARC discussed the safety of **antibiotic ear drops** in children with grommets. The MARC discussed the risk of ototoxicity when used in children with grommets or with a perforated tympanic membrane and differences in the risk of ototoxicity between different antibiotic-containing ear drops. The MARC considered the available evidence suggests that ciprofloxacin-containing ear drops have less toxicity than other antibiotic-containing ear drops and recommended updates to data sheets.

The MARC discussed the risk of spontaneous abortion from the use of **non-steroidal anti-inflammatory drugs (NSAIDs)**. The MARC considered the strength of the evidence to be equivocal for an association between NSAIDs and spontaneous abortion at this time. However, the MARC considered that a woman who is trying to get pregnant would want to know that spontaneous abortion from the use of NSAIDs is a potential concern and recommended updates to data sheets and labelling.

The MARC discussed the risk of major haemorrhage or ischaemic stroke from the use of **statins** in patients taking **dabigatran**. The MARC identified a number of limitations and confounding factors in the evidence presented to them and overall considered the strength of the available evidence to be weak. The MARC did not consider the evidence suggests a clinically relevant interaction between dabigatran and statins.

The MARC reviewed available evidence on the risk of gadolinium accumulation in the brain after use of **gadolinium-based contrast agents**. The available evidence indicates that gadolinium is deposited in the brain after administration of

gadolinium-based contrast agents. However, the MARC did not consider there was evidence of harm from deposition of gadolinium. Healthcare professionals and consumers should nonetheless be informed about this safety concern.

The MARC noted the United States Food and Drug Administration (FDA) has revised the contraindications for **tramadol**-containing products. Its use is restricted in children younger than 18 years to treat pain after surgery to remove the tonsils and/or adenoids[1]. The MARC discussed the use of tramadol in New Zealand and considered there is value in tramadol being available for use post-operatively. However, it is important to monitor for signs of toxicity or overdose when tramadol is used following recent tonsillectomy, adenoidectomy and throat surgery.

Further information on the meeting held on 8 June 2017 can be found on the Medsafe website (**www.medsafe.govt.nz/profs/adverse/Minutes170.htm**). As of this meeting, papers presented to the MARC will be published on the Medsafe website (**www.medsafe.govt.nz/committees/MARC/Reports.asp**).

References

1. Food and Drug Administration. 2017. FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women. *FDA Drug Safety Communication*. April 2017. URL: **www.fda.gov/Drugs/DrugSafety/ucm549679.htm** (accessed 11 July 2017).

Zostavax Vaccine for Shingles — Do Not Use in Immunocompromised Patients

Key Messages

- ⌘ Zostavax vaccine is contraindicated in immunocompromised patients.
- ⌘ Vaccination of immunocompromised patients may result in disseminated herpes zoster infection.
- ⌘ Healthcare professionals should assess the patient's immunological status before vaccination.

The Australian Therapeutic Goods Administration (TGA) recently received a report of a death in an individual following vaccination with Zostavax[1]. The patient had a pre-existing compromised immune system. Healthcare professionals are reminded that Zostavax vaccination is contraindicated in immunocompromised patients due to the risk of disseminated herpes zoster infection[2].

Zostavax is a live, attenuated varicella-zoster virus vaccine that is indicated in individuals 50 years of age or older for:

- prevention of herpes zoster (shingles)
- prevention of postherpetic neuralgia
- reduction of acute and chronic zoster-associated pain[2].

Zostavax contains a higher titre of the live attenuated varicella vaccine, with nine to 14 times more virus than the childhood varicella vaccines (depending on the childhood varicella vaccine). Zostavax should not be administrated to children as it has the potential to cause harm in this population[2,3].

In the Shingles Prevention Study, the use of the zoster vaccine reduced the burden of illness due to herpes zoster in adults 60 years of age or older by 61.1%[4]. The incidence of post-herpetic neuralgia was also reduced by 66.5% in adults 60 years of age or older who received the vaccine[4].

Zostavax is contraindicated for use in patients with primary and acquired immunodeficiency states due to conditions such as acute and chronic leukaemias, lymphoma, other conditions affecting the bone marrow or lymphatic system, immunosuppression due to HIV/AIDS, and cellular immune deficiencies[2].

In addition, Zostavax is contraindicated in patients on immunosuppressive therapy including high dose corticosteroids[2]. However, Zostavax is not contraindicated in patients who are receiving topical/inhaled corticosteroids or low dose systemic corticosteroids, or in patients who are receiving corticosteroids as replacement therapy (eg, for adrenal insufficiency)[2]. Further information on immunisation of individuals with diseases or therapy causing immunocompromise can be found in the Ministry of Health's *Immunisation Handbook*[5].

Healthcare professionals should assess the patient's immunological status before vaccination. Any patient who is immunosuppressed or immunodeficient should not receive Zostavax.

Healthcare professionals are encouraged to report any suspected adverse reactions to vaccines or medicines to the Centre for Adverse Reactions Monitoring (CARM).

Information on how to report can be found on the Medsafe website (**www.medsafe.govt.nz/safety/report-a-problem.asp**) or the CARM website **(https://nzphvc.otago.ac.nz/reporting/**).

References

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Gathering Knowledge from Adverse Reaction Reports: Sept 2017

Adverse reaction reporting is an important component of medicine safety monitoring. Case reports can highlight significant safety issues concerning therapeutic products and their use.

A selection of recent informative cases from the Centre for Adverse Reactions Monitoring (CARM) database is presented below.

CARM ID: 124149 **Age:** 68 **Gender:** Male **Medicine(s):** Doxazosin **Reaction(s):** Priapism	The patient experienced unwanted, long-lasting painful erections at night.
	The Apo-Doxazosin data sheet (**www.medsafe.govt.nz/profs/Datasheet/a/ApoDoxazosintab.pdf**) states isolated cases of priapism have been reported to be associated with alpha-1-agonists, including doxazosin.
CARM ID: 123972 **Age:** 62 **Gender:** Male **Medicine(s):** Aspirin, ibuprofen **Reaction(s):** Blood clot, Drug interaction	The patient was taking regular ibuprofen with enteric coated aspirin and experienced a blood clot.
	The data sheet for Ibugesic (**www.medsafe.govt.nz/profs/Datasheet/i/ibugesictab.pdf**) states ibuprofen antagonises the irreversible inhibition of platelet COX-1 induced by low dose aspirin (ie, ibuprofen inhibits the anti-platelet effect of aspirin).
CARM ID: 119749 **Age:** 37 **Gender:** Female **Medicine(s):** Venlafaxine **Reaction(s):** Hypertension	The patient developed hypertension during pregnancy that required treatment with labetalol.
	Hypertension is a common adverse reaction to venlafaxine. The Efexor-XR data sheet (**www.medsafe.govt.nz/profs/Datasheet/e/Efexorxrcap.pdf**) states caution should be exercised in patients whose underlying conditions might be compromised by increases in blood pressure.

The Medsafe Files — Episode Four: New Medicines Assessment (Part 2)

Key Messages

- ⌘ Medsafe assesses the quality, safety and efficacy of every new medicine registered in New Zealand.
- ⌘ Medicines differ in how they are made, what they look like and what they are used for. Some contain active ingredients that are well established. Others are new to New Zealand.
- ⌘ The type of medicine determines how Medsafe assesses its acceptability for the New Zealand market.

Quality ensures that a medicine does what it is supposed to do every time

The quality of a new medicine is assessed to ensure that it is safe and consistently effective to minimise adverse events. The quality section of a New Medicine Application (NMA) is split into two main parts. One part focusses on the active ingredient of the medicine and the other part on the final dosage form, including any excipients and fillers.

Medsafe evaluates both parts against national legislation and international guidance to ensure that:

- the proposed formulation of the medicine has been suitably optimised and is appropriate for the intended route of administration
- the manufacturing processes are suitable and limit any impurities
- sufficient testing is done during and after manufacture
- the analytical methods used for testing are valid
- there is consistency between different batches
- the physical, chemical and biological properties of the medicine meet the requirements for the specific dosage forms
- the proposed packaging is appropriate
- the shelf-life is well established.

The information required for a NMA is specific to the type of medicine (chemical, biological), dosage form (tablet, solution for injection) and classification (prescription, over-the-counter).

It also depends on the risk profile of the medicine. For example, the quality review of a prescription medicine that contains a new active ingredient (considered higher risk) relies extensively on comparison of the provided data against international guidance. However, in the case of a generic prescription medicine (considered intermediate risk), evaluations are largely based on existing knowledge and comparisons with the innovator medicine that was originally approved. This has implications for the degree of clinical data required, as discussed in the next section.

The safety of new and generic medicines is established in different ways

For a new medicine (one that has not previously been approved in New Zealand), the results of full clinical trials are evaluated (see the previous edition of *Prescriber Update*)[1]. These trials have been carried out in human patients. The sample size, demographics and disease states are selected depending on the medicine's phase of development and intended use.

The main purpose of these clinical trials is to completely characterise the medicine's safety, efficacy and pharmacokinetic profile. However, for a new generic medicine, a specific type of clinical trial is used instead: **bioequivalence studies**.

Bioequivalence studies are based on the concept that if the systemic concentration of a generic medicine, once administered, is the same as the innovator then it will have the same therapeutic effect. This conclusion is made on the condition that the two medicines are the same in every other way, underlining the importance of quality assurance.

Bioequivalence studies are carried out with healthy human subjects and involve determining the amount of active ingredient present in the blood over time. Some dosage forms generally do not need these studies to establish bioequivalence (eg, injections), while others require multiple trials under different conditions (eg, modified release tablets). Further information on generic medicines and bioequivalence can be found in a previous edition of *Prescriber Update* (**www.medsafe.govt.nz/profs/PUArticles/Mar2013GenericMedBioqueivalence.htm**).

All clinical studies (including bioequivalence studies) must receive ethics approval and adhere to Good Clinical Practice, as discussed previously in *The Medsafe Files – Episode Two*[2].

Ensuring the safety of a medicine is not limited to the product itself

Beyond pharmaceutical chemistry and clinical performance, several other aspects of a new medicine are regulated to enhance patient safety.

To minimise the likelihood of medication errors, Medsafe undertakes a thorough review of the proposed name of the medicine, how it is labelled and the supporting documentation produced by the company to ensure its correct use (data sheet and consumer medicine information).

The site(s) where the medicine is manufactured, tested and packaged are also inspected to ensure that they comply with the requirements of Good Manufacturing Practice (GMP). GMP will be described in more detail in the next edition of *Prescriber Update*.

The outcome of Medsafe's evaluation — approval or referral

Following the assessment of an NMA, Medsafe provides advice to the Minister's delegate on whether the medicine has an acceptable risk/benefit profile. If it does, consent will be granted for distribution of the medicine in New Zealand.

If the safety, efficacy and/or quality of the medicine is not considered to meet the required standards, the NMA is referred to the Medicines Assessment Advisory Committee for further review (refer to *The Medsafe Files – Episode Four, Part 1* for more information)[1].

References

1. Medsafe. 2017. The Medsafe Files — Episode Four: New Medicines Assessment (Part 1). *Prescriber Update* 38(2): 27–8. URL: **www.medsafe.govt.nz/profs/PUArticles/June2017/TheMedsafeFiles.htm** (accessed 4 August 2017).
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Recent Approvals of Medicines Containing a New Active Ingredient

From 16 April 2017 to 15 July 2017.

Trade Name (active ingredient)*	Dose form and strength	Therapeutic area
Akynzeo (**netupitant**/palonosetron)†	Combination capsule 300 mg/0.5 mg	Chemotherapy-induced nausea and vomiting
Ibrance (**palbociclib**)	Capsule 75 mg, 100 mg and 125 mg	Hormone-receptor positive, HER2-negative, advanced breast cancer
Idelvion (**albutrepenonacog alfa**)	Powder for injection 250 IU, 500 IU, 1000 IU and 2000 IU	Haemophilia B
Nucala (**mepolizumab**)	Powder for injection 100 mg/mL	Eosinophilic asthma
Ranexa (**ranolazine**)	Modified release tablet 375 mg, 500 mg and 750 mg	Angina

*New active ingredient shown in bold type

† Not available

The data sheets for currently marketed prescription medicines are published on the Medsafe website (**www.medsafe.govt.nz/profs/Datasheet/dsform.asp**)

Update: Olanzapine Pamoate Depot and Post-injection Syndrome

Key Messages

- Olanzapine pamoate depot injection carries a risk of post-injection syndrome.
- Healthcare professionals are advised to discuss this potential risk before each injection.
- Patients must be monitored for at least two hours after each injection.

The Centre for Adverse Reactions Monitoring (CARM) continues to receive reports of reactions that suggest post-injection syndrome has occurred following administration of olanzapine pamoate depot injection. Patients experienced reactions including agitation, anxiety, ataxia, confusion, dizziness, drowsiness, disorientation, dysarthria, sedation, slurred speech and somnolence.

In the June 2014 *Prescriber Update* article *Reminder: Olanzapine Depot and Post-injection Syndrome*, CARM had received 14 reports of reactions consistent with the signs and symptoms of post-injection syndrome following an olanzapine pamoate depot injection[1]. CARM has now received a total of 75 reports.

Of these 75 reports, 26.7% were in females, 72.0% were in males and 1.3% unknown. Approximately half of the patients (52%) were hospitalised following olanzapine injection while the remaining reports (48%) were classified as not serious. At the time of the report to CARM, two-thirds of the patients recovered without sequelae (69.3%), with the remaining patients not yet recovered (9.3%) or outcome unknown (21.3%). The patients who were reported to have experienced post-injection syndrome were from all age groups (Figure 1).

During pre-marketing clinical trials, initial signs and symptoms related to post-injection syndrome appeared within one hour following injection and full recovery was reported to have occurred within 24–72 hours after injection in most cases[2].

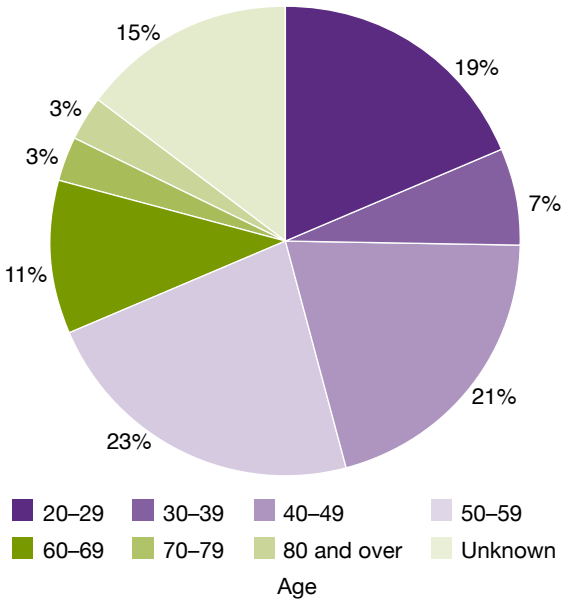

Figure 1: CARM reports of post-injection syndrome following olanzapine injection by patient age group as of 31 March 2017

Olanzapine pamoate is an antipsychotic depot injection formulation, designed to release olanzapine slowly from the intramuscular site. It is administered by deep intramuscular injection into the gluteal region every two to four weeks.

Healthcare professionals are reminded that the potential risk of post-injection syndrome should be discussed with patients prior to administering each olanzapine pamoate depot injection. Patients must be monitored for at least two hours after each injection[2].

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

References

1. Medsafe. 2014. Reminder: Olanzapine depot and post-injection syndrome. *Prescriber Update* 35(2): 28–9. URL: **www.medsafe.govt.nz/profs/PUArticles/June2014OlanzapineDepotAndPostInjectionSyndrome.htm (accessed 28 July 2017**).
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New Zealand is on Form for Medical Devices

Medsafe has now completed the redesign of the adverse event reporting forms for medical devices[1]. The new forms are specific for New Zealand users and allow for more information to be provided than the previous forms.

There are now separate adverse event reporting forms for:

- patients/consumers
- healthcare professionals
- suppliers/manufacturers.

In addition to these forms, there is a separate quality reporting form to identify an issue with a medical device that may not have caused an adverse event but has the potential to do so.

The new reporting forms are available from the Medsafe website (**www.medsafe.govt.nz/regulatory/devicesnew/9AdverseEvent.asp**).

Medsafe accepts reports from patients and their carers or relatives, healthcare professionals, and New Zealand suppliers/manufacturers of the medical devices.

Any adverse event or quality issue suspected of being associated with the use of a medical device should be reported to Medsafe. Adverse events and quality reports are reviewed by Medsafe to identify the cause of the issue and any consequential corrective actions. Following a review, Medsafe may publish a monitoring or alert communication (**www.medsafe.govt.nz/safety/alerts.asp**).

References

1. Medsafe. 2016. Adverse Event Reporting for Medical Devices. *Prescriber Update* 37(4): 58. URL: **www.medsafe.govt.nz/profs/PUArticles/December%202016/AdverseEventReportingMedicalDevices.htm** (accessed 3 August 2017).

Nicorandil — Updated Indication and Risk of Ulcerations

Key Messages

- Nicorandil is indicated for symptomatic treatment of stable angina pectoris that is inadequately controlled or in patients who have a contraindication or intolerance to first-line anti-anginal therapies.
- Patients should be reviewed to make sure they are receiving nicorandil for the correct indication.
- Nicorandil can cause serious skin, mucosal, and eye ulceration, including gastrointestinal ulcers, which may progress to perforation, haemorrhage, fistula, or abscess.
- Stop nicorandil treatment if ulceration occurs — consider the need for alternative treatment or specialist advice if angina symptoms worsen.

Nicorandil (Ikorel) is a vasodilator agent that works by relaxing the muscles in the walls of the blood vessels that supply the heart thereby improving blood flow to the heart muscle and relieving the symptoms of angina[1].

The indication for nicorandil has been updated after a review by the European Medicines Agency[1].

Nicorandil is indicated for second line treatment of stable angina in patients whose angina is inadequately controlled by first line anti-anginal therapies, or who have a contraindication or intolerance to first line anti-anginal therapies such as beta-blockers or calcium antagonists[1,2].

On rare occasions, Nicorandil use may lead to gastrointestinal, skin, mucosal, corneal or conjunctival ulceration, which may be serious. Ulcers may develop at different sites in the same patient, at the same time or one after another. Ulceration can occur at any time during nicorandil treatment, including years after starting treatment[3].

Ulcers that result following nicorandil treatment do not respond to conventional treatment, including surgery. Treatment with nicorandil should be withdrawn if ulceration occurs and the need for alternative treatment or specialist advice should be considered if angina symptoms worsen. It may take weeks or months for the ulcers to heal, depending on the severity[3].

Patients with risk factors such as diverticular disease may be at risk of fistula formation or bowel perforation. Concomitant use of aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids with nicorandil increases the

risk of gastrointestinal ulceration, perforations or haemorrhage[3].

At 30 June 2017, the Centre for Adverse Reactions Monitoring (CARM) had received one case of ulceration associated with the use of nicorandil. Ulcerative stomatitis and pharyngitis were reported in a 61-year-old female who was treated with nicorandil for less than a week.

Please continue to report any adverse reactions for nicorandil, and any other medicine, to CARM. Reports can be submitted on paper or electronically (**https://nzphvc.otago.ac.nz/**).

References

1. European Medicines Agency. 2015. *Ikorel and Dancor*. 27 March 2015. URL: **www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Ikorel_and_Dancor/human_referral_000387.jsp&mid=WC0b01ac05805c516f** (accessed 27 July 2017).
2. Sanofi-Aventis New Zealand Limited. 2016. *Ikorel Data Sheet*. 25 November 2016. URL: **www.medsafe.govt.nz/profs/Datasheet/i/ikoreltab.pdf** (accessed 14 July 2017).
3. Medicines and Healthcare Products Regulatory Agency. 2016. Updated advice on use of nicorandil as second-line treatment for stable angina — some ulcers may progress to complications unless treatment is stopped. *Drug Safety Update*. 21 January 2016. URL: **www.gov.uk/drug-safety-update/nicorandil-ikorel-now-second-line-treatment-for-angina-risk-of-ulcer-complications** (accessed 27 June 2017).

Bisphosphonates and Osteonecrosis—the Bare Bones

Key Messages

- ⌘ Osteonecrosis of the jaw has been associated with both oral and intravenous bisphosphonates.
- ⌘ Healthcare professionals should advise patients to maintain good oral hygiene, have routine dental check-ups and report any adverse oral symptoms immediately.
- ⌘ Osteonecrosis at other sites such as the hip, femur and auditory canal have also been reported with the use of some bisphosphonates.

Osteonecrosis of the Jaw

Healthcare professionals are reminded that osteonecrosis of the jaw (ONJ) has been associated with bisphosphonate treatment. All bisphosphonate data sheets include information on ONJ.

ONJ is predominantly reported in patients with cancer receiving treatment with intravenous bisphosphonates[1–3]. Many of these patients were also receiving chemotherapy and corticosteroids[2,3].

ONJ has also been rarely reported with oral bisphosphonates[1]. These cases were generally associated with tooth extraction and/or local infection with delayed healing[1].

Healthcare professionals should advise patients at risk of experiencing ONJ to maintain good oral hygiene, have routine dental check-ups and report any adverse oral symptoms immediately to their doctor and dentist[2,4].

From 1 January 2012 to 31 December 2016, the Centre for Adverse Reactions Monitoring (CARM) has received 14 case reports of ONJ where a bisphosphonate was considered to be the suspect medicine.

Further information on ONJ is available in a previous edition of *Prescriber Update* (**www.medsafe.govt.nz/profs/PUArticles/OsteonecrosisJune2012.htm**).

Osteonecrosis at Other Sites

More recently, osteonecrosis at other sites including the hip, femur and external auditory canal has been reported with the use of some bisphosphonates[1,2,5,6].

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1. Merck Sharp & Dohme (New Zealand) Limited. 2015. *Fosamax Data Sheet*. 31 August 2015. URL: **www.medsafe.govt.nz/profs/Datasheet/f/Fosamaxtab.pdf** (accessed 21 June 2017)
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3. Hospira NZ Limited. 2015. *Pamisol Data Sheet*. 3 June 2015. URL: **www.medsafe.govt.nz/profs/Datasheet/p/Pamisolinj.pdf** (accessed 21 June 2017).
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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.

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