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New Zealand Government

Spotlight on Pembrolizumab (Keytruda)

Key Messages

- ⌘ Pembrolizumab (Keytruda) is an immune checkpoint inhibitor used in the treatment of some advanced or metastatic cancers.
- ⌘ Modify the dose for patients experiencing immune-mediated adverse reactions or infusion-related reactions.
- ⌘ Seek specialist advice before administering any vaccine to patients receiving immune checkpoint inhibitors, as well as those who have stopped treatment within the past six months.

The spotlight series continues with this article on pembrolizumab. Key information on pembrolizumab, including recent developments and adverse reaction reporting in New Zealand, is described.

Please refer to the medicine data sheet for full prescribing information (**www.medsafe.govt.nz/profs/Datasheet/k/Keytruda.pdf**).

What is pembrolizumab and what is it used for?

Pembrolizumab (Keytruda) is a monoclonal antibody used in the treatment of some advanced or metastatic cancers. These currently include:

- melanoma
- non-small cell lung carcinoma (NSCLC)
- classical Hodgkin Lymphoma (cHL)
- urothelial carcinoma.

Pembrolizumab is commonly known as an immune checkpoint inhibitor because it blocks the PD-1 pathway on immune dampening cells. This action helps the immune system to boost its response against cancer cells[1].

Recent developments

Immune-mediated adverse reactions are known to occur with immune checkpoint inhibitors, including pembrolizumab[1].

The pembrolizumab data sheet was recently updated to include dose modifications in the presence of immune-mediated adverse reactions or infusion-related reactions, including new recommendations for myocarditis. These dose modifications are stratified according to the severity of the adverse reaction. In general, the advice is to withhold treatment until adverse reactions improve, or to permanently discontinue treatment.

The following side effects have also been recently identified:

- thyroiditis
- myasthenic syndrome
- encephalitis
- sarcoidosis
- graft-versus-host-disease (GVHD) in patients with a history of allogeneic haematopoietic stem cell transplant (HSCT).

In March 2018, chapter four of the *Immunisation Handbook 2017* was updated to include information for vaccinators about oncology patients treated with immune checkpoint inhibitors[2].

Vaccinators are advised to seek specialist advice before administering any vaccine to patients who are currently being treated with immune checkpoint inhibitors, as well as those who have discontinued treatment within the past six months[2]. There are currently no international consensus statements on the use of vaccines in patients being treated with immune checkpoint inhibitors as this is a rapidly evolving therapeutic area. Caution is advised, particularly with live vaccines[2].

Adverse reactions reported in New Zealand

As at 30 June 2018, the Centre for Adverse Reactions Monitoring (CARM) has received 21 adverse reaction reports where pembrolizumab was considered to be the suspect medicine.

The following is a list of some interesting cases reported within the last two years:

- four reports of reactions relating to changes in renal function and/or nephritis (CARM ID numbers: 123300, 124915, 125854, 126553). Three of these patients were also taking omeprazole, which has been associated with acute interstitial nephritis[3]
- two reports describing reactions relating to diabetes (123772, 123983)

- one report describing symptoms likely to be hypophysitis (124301)
- one fatal case of pneumonitis (123805).

The reported reactions listed above, including monitoring requirements, are all listed in the pembrolizumab data sheet.

References

1. Medsafe. 2017. New anti-cancer therapy – immune checkpoint inhibitors. *Prescriber Update* 38(4): 50. URL: **www.medsafe.govt.nz/profs/PUArticles/December2017/NewAntiCancerTherapy.htm** (accessed 2 July 2018).
2. Ministry of Health. 2018. *Immunisation Handbook 2017* (2nd edn). Wellington: Ministry of Health. URL: **www.health.govt.nz/publication/immunisation-handbook-2017** (accessed 9 July 2018).
3. Medsafe. 2015. Keeping it renal: drug-induced acute interstitial nephritis. *Prescriber Update* 36(2): 26–7. URL: **www.medsafe.govt.nz/profs/PUArticles/June2015/June2015AcuteInterstitialNephritis.htm** (accessed 9 July 2018).

Considered Crushing for Troublesome Throats

Key Messages

- ⌘ Many oral medicines cannot or should not be altered at the point of administration as doing so may cause harm, either to the patient or the person administering the medicine.
- ⌘ Regularly check the swallowing ability of patients before prescribing them medicines.
- ⌘ Do not assume a medicine can be altered (eg, crushed) prior to administration. Always consider the appropriateness of a formulation for your patient.

Background

Oral medicines are commonly altered for administration in patients who have swallowing difficulties or for administration down feeding tubes. Alteration methods include crushing or opening capsules. Some medicines can be altered for easier administration (eg, allopurinol tablets). However, such alteration is not appropriate for many medicines because the finished product is formulated to be swallowed as a whole tablet or capsule[1].

Some medicine names are accompanied by abbreviations that indicate they should be administered whole (Table 1, next page). When prescribing, dispensing or administering these medicines, care should be taken to ensure the patient is able to swallow them[1].

What can happen?

Adverse effects associated with the altering of tablets include local irritation, cytotoxic exposure, increased bioavailability or loss of effect. Dose dumping occurs when a modified release formulation (or similar) is not administered as a whole tablet/capsule. The patient receives the full dose at once, rather than over a period of time as intended.

Table 2 (next page) lists some commonly prescribed medicines and associated adverse effects that may occur if the medicine is not administered as a whole tablet/capsule. These types of adverse effects can result in hospital admissions[2].

A larger list is available at **www.saferx.co.nz/Crushing-table-RAC.pdf**.

Example of a serious adverse event

The Centre for Adverse Reactions Monitoring (CARM) recently received a report of a patient who developed an oesophageal ulcer next to their carotid artery. The patient had been attempting to take alendronate (as Fosamax Plus), despite their dysphagia (CARM ID: 129320). Attempted dilation of the oesophagus resulted in rupture, and the patient required Total Parenteral Nutrition (TPN) for many weeks. The original ulcer likely occurred due to improper passage of the alendronate tablet through the oesophagus. Alendronate is known to cause chemical burns if it is in contact with the oesophageal mucosa for too long (see Table 2).

Please report all adverse events that are suspected to be due to the incorrect administration of a medicine to CARM (**https://nzphvc.otago.ac.nz/report/**).

Table 1: Types of formulations that cannot be altered at the point of oral administration, with associated abbreviations and examples (this is not an exhaustive list)

Abbreviation	Type of formulation	Examples
CR	Controlled release	Metoprolol CR, Sinemet CR, Oxycodone CR (Oxycontin)
SR	Sustained release	Morphine SR (m-Eslon), Isosorbide mononitrate SR (Duride)
MR	Modified release	Ferrograd MR
CD	Controlled delivery	Diltiazem CD
EC	Enteric coated	Aspirin EC, Mesalazine EC (Asacol, Asamax, Pentasa)
HBS	Hydrodynamically balanced system	Madopar HBS
LA	Long acting	LA-Morph
ER	Extended release	Felodipine ER (Plendil)
FC	Film coated	Methotrexate, Sertraline

Source: SaferRx. 2018. *Crushing guide for oral medication in Residential Aged Care.* URL: **www.saferx.co.nz/RAC_crushing_intro.pdf** (accessed 12 July 2018).

Table 2: Commonly prescribed medicines and the adverse effects that may occur if not administered correctly

Medicine	Adverse effect
Metoprolol CR, Felodipine ER, Isosorbide mononitrate SR	Hypotension, falls, and loss of efficacy later in the day
Dabigatran (Pradaxa)	Opening the capsules increase bioavailability by 75%, increasing the risk of gastritis and bleeding
Levodopa + carbidopa/benserazide (Sinemet CR, Madopar HBS)	Dyskinesia, hallucinations, other motor complications
Oxycodone (Oxycontin, Oxycodone CR), Morphine (m-Eslon SR, LA-Morph)	Dose dumping causing respiratory depression, loss of consciousness and death
Alendronate (Fosamax), Risedronate	Local irritation and ulceration may occur if the tablet doesn't pass through the oesophagus quickly
Methotrexate, Azathioprine	Risk of exposure to cytotoxic medicine by person other than the patient
Mesalazine LA, Pantoprazole EC tablet	Loss of efficacy

Source: SaferRx. 2018. *Guide for crushing oral medication for residents with swallowing difficulties in Residential Aged Care* July 2018. URL: **www.saferx.co.nz/Crushing-table-RAC.pdf** (accessed 12 July 2018).

If a patient has swallowing difficulties but needs an oral medicine, discuss alternatives with a pharmacist, for example, changing to a different medicine in the same class where the formulation can be altered, or the use of patches or sublingual formulations.

References

1. SaferRx. 2018. *Crushing guide for oral medication in Residential Aged Care*. URL: **www.saferx.co.nz/RAC_crushing_intro.pdf** (accessed 12 July 2018).
2. SaferRx. 2018. *Guide for crushing oral medication for residents with swallowing difficulties in Residential Aged Care* July 2018. URL: **www.saferx.co.nz/Crushing-table-RAC.pdf** (accessed 12 July 2018).

WE NEED YOUR HELP!

Please send your reports **to CARM (https://nzphvc.otago.ac.nz/report/)** for the potential safety issue* listed in the table below.

Medicine	Potential Safety Issue	Active Monitoring Ends
Isotretinoin	Obsessive compulsive disorder	31 March 2019

- M² (Medicines Monitoring) is a Medsafe scheme designed to collect more information on potential safety signals for specific medicines.
- Please send your report to CARM (as for any suspected adverse reaction). This can be done even if the reaction happened some time ago. Please include as much information as possible as this helps the medical assessors at CARM to investigate whether the medicine caused the reaction.
- For further information about M², see the Medsafe website (**www.medsafe.govt.nz/profs/M2MedicinesMonitoring.asp**).

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

Some Asthma Inhalers Contain Very Small Amounts of Ethanol

Key Messages

- Ethanol is present in some metered dose inhalers.
- The quantity of ethanol released per actuation is very small (less than 10 mg), and is less than the ethanol content in a ripe banana (40 mg).
- The amount of ethanol is too low to have a pharmacological effect.

Medsafe has recently been contacted by health care professionals regarding the inclusion of ethanol in some metered dose inhalers (MDIs) for asthma. Medsafe and PHARMAC have previously responded to questions about ethanol in MDIs[1,2].

Ethanol is added to some MDIs to increase the solubility of the active ingredient. Ethanol has been used as an excipient in asthma MDIs since the late 1990s.

How much ethanol is in a metered dose inhaler?

The quantity of alcohol per actuation (puff) is very small – less than 10 mg.

Table 1 (next page) shows the ethanol content in asthma MDIs that are currently available in New Zealand, and for comparison, the amount of ethanol in a ripe banana[3] and a standard alcoholic drink[4]. There is considerably more ethanol in a ripe piece of fruit than in one actuation from an MDI. The amount of ethanol per actuation is too small to have a pharmacological effect.

Continue to use asthma inhalers according to the data sheets and clinical guidelines[5,6].

References

1. Medsafe. 2005. *Salamol inhalers – New Zealand brand switching complaints investigation*. URL: **www.medsafe.govt.nz/hot/PapersReports/Salamol.asp** (accessed 10 May 2018).
2. PHARMAC. 2005. PHARMAC responds on salbutamol. New Zealand Medical Journal 118(1221): 112–20. URL: **www.nzma.org.nz/__data/assets/pdf_file/0007/17917/Vol-118-No-1221-26-August-2005.pdf** (accessed 11 May 2018).
3. Gorgus E, Hittinger M, Schrenk D. 2016. Estimates in ethanol exposure in children from food not labeled as alcohol-containing. *Journal of Analytical Toxicology* 40(7): 537–42. URL: **www.ncbi.nlm.nih.gov/pmc/articles/PMC5421578/** (accessed 10 May 2018).
4. Ministry of Health. 2017. *Alcohol*. URL: **www.health.govt.nz/your-health/healthy-living/addictions/alcohol-and-drug-abuse/alcohol** (accessed 10 May 2018).
5. Asher I, McNamara D, Davies C, et al. 2017. Asthma and Respiratory Foundation NZ child and adolescent asthma guidelines: a quick reference guide. *New Zealand Medical Journal* 130(1466): 10–33. URL: **www.nzasthmaguidelines.co.nz/childguidelines-654716.html** (accessed 10 May 2018).
6. Beasley R, Hancox RJ, Harwood M, et al. 2016. Asthma and Respiratory Foundation NZ adult asthma guidelines: a quick reference guide. *New Zealand Medical Journal* 129(1445): 83–102. URL: **www.nzasthmaguidelines.co.nz/adultguidelines.html** (accessed 10 May 2018).

Table 1: Ethanol content of currently available aerosol metered dose inhalers for asthma, and comparator food and drink items

Metered dose inhalers			
Active ingredient	Brand name	Strength of active ingredient (mcg)	Ethanol quantity (mg) per actuation
Beta$_2$ agonists			
Salbutamol	Salamol	100	4.8
	Respigen	100	4.1
	SalAir	100	1.5
	Ventolin	100	nil
Antimuscarinic bronchodilators			
Ipratropium	Atrovent	20	8.4
Inhaled corticosteroids			
Beclometasone dipropionate	Beclazone	50	2.1
		100	3.1
		250	6.0
	Qvar	50	4.7
		100	4.7
Fluticasone	Flixotide	125	nil
	Flixotide Junior	50	nil
	Floair	50	1.6
		125	1.6
Long-acting beta-agonists			
Salmeterol	Serevent	25	nil
	Meterol	25	1.6
Combination preventer products			
Fluticasone/salmeterol	Seretide	50/25	nil
		125/25	nil
		250/25	nil
Budesonide/formoterol	Vannair	100/6	nil
		200/6	nil
Comparator food and drink items[a,b]			
Food or drink			**Ethanol quantity (mg) per item**
Ripe banana (100 g)			40.0
One standard unit of alcohol			10,000.0

a. Gorgus E, Hittinger M, Schrenk D. 2016. Estimates in ethanol exposure in children from food not labeled as alcohol-containing. *Journal of Analytical Toxicology* 40(7): 537–42. URL: **www.ncbi.nlm.nih.gov/pmc/articles/PMC5421578/** (accessed 10 May 2018).

b. Ministry of Health. 2017. *Alcohol*. URL: **www.health.govt.nz/your-health/healthy-living/addictions/alcohol-and-drug-abuse/alcohol** (accessed 10 May 2018).

Corticosteroids and Central Serous Chorioretinopathy (CSCR)

Key Messages

- Central serous chorioretinopathy is a retinal disorder associated with use of topical and systemic corticosteroids.
- Refer patients who present with blurred vision or other visual disturbances while taking corticosteroids to an ophthalmologist or optometrist for evaluation of the underlying causes.

Central serous chorioretinopathy (CSCR) has been reported with both topical (inhaled, intranasal, epidural, intra-articular, dermal and periocular routes) and systemic corticosteroid use[1].

Up to 30 June 2018, the Centre for Adverse Reactions Monitoring (CARM) had received one case report of CSCR and two case reports of retinal detachment associated with corticosteroid use (CARM ID numbers: 128846, 023340, 120887).

CSCR occurs when fluid accumulates beneath the retina. This causes detachment of the retina from the underlying pigment epithelium and choroid[2]. Usually, just one eye is affected[3].

Symptoms of CSCR include blurred or distorted vision, blind spots, micropsia, sensitivity to bright light and reduced contrast sensitivity[3,4].

In addition to CSCR, other causes of blurred vision or visual disturbances may include cataracts or glaucoma, which are recognised adverse reactions for both systemic and topical corticosteroids[5–7].

Temporary blurred vision may occur when a topical corticosteroid eye product is administered[8]. This will not usually require medical attention.

Medsafe is working with sponsors to include safety information about CSCR in the New Zealand data sheets for all corticosteroid-containing products.

Refer patients who present with symptoms such as blurred vision or other visual disturbances while taking corticosteroids to an ophthalmologist or optometrist for evaluation of possible causes.

References

1. Medicines and Healthcare products Regulatory Agency. 2017. Corticosteroids: rare risk of central serous chorioretinopathy with local as well as systemic administration. *Drug Safety Update* 11(1): 2. URL: **www.gov.uk/drug-safety-update/corticosteroids-rare-risk-of-central-serous-chorioretinopathy-with-local-as-well-as-systemic-administration** (accessed 4 July 2018).
2. Arroyo G. 2018. Retinal detachment. In: *UpToDate* 10 January 2018. URL: **www.uptodate.com/contents/retinal-detachment** (accessed 4 July 2018).
3. Royal National Institute of Blind People. 2018. *Central serous retinopathy.* URL: **www.rnib.org.uk/eye-health/eye-conditions/central-serous-retinopathy** (accessed 4 July 2018).
4. Liew G, Quin G, Gillies M, et.al. 2013. Central serous chorioretinopathy: a review of epidemiology and pathophysiology. *Clinical & Experimental Ophthalmology* 41: 201–14. URL: **www.ncbi.nlm.nih.gov/pubmed/22788735** (accessed 4 July 2018).
5. Apotex NZ Ltd. 2018. *APO-Prednisone Tablets New Zealand Data Sheet*. 11 June 2018. URL: **www.medsafe.govt.nz/profs/datasheet/a/Apoprednisonetab.pdf** (accessed 4 July 2018).
6. GlaxoSmithKline NZ Limited. 2015. *Flixotide Inhaler New Zealand Data Sheet*. 5 October 2015. URL: **www.medsafe.govt.nz/profs/Datasheet/f/FlixotideCFCfree.pdf** (accessed 4 July 2018)
7. Mylan New Zealand Limited. 2015. *Alanase Aqueous Nasal Spray New Zealand Data Sheet*. 16 June 2015. URL: **www.medsafe.govt.nz/profs/datasheet/a/Alanasenasalspr.pdf** (accessed 4 July 2018).
8. Novartis New Zealand Limited. 2018. *Maxidex Ophthalmic Suspension and Ointment New Zealand Data Sheet*. 26 March 2018. URL: **www.medsafe.govt.nz/profs/Datasheet/m/Maxidexeyedropsoint.pdf** (accessed 4 July 2018).

CARM
CENTRE FOR ADVERSE REACTIONS MONITORING

Report Adverse Drug Reactions

Reporting adverse reactions contributes to the safety of medicines in New Zealand.

If you think your patient has had an adverse reaction to a medicine, report it to CARM.

Online reporting is easiest (**https://nzphvc.otago.ac.nz/report/**).

Intussusception: A Very Rare Risk After Rotavirus Vaccination

Key Messages

- Intussusception is the most common abdominal emergency in young children.
- About 1–6 in 100,000 children may experience intussusception due to vaccination with rotavirus vaccine.
- The benefits of rotavirus vaccination continue to outweigh the risks of harm.
- Parents and/or guardians should be advised to seek prompt medical assistance if any of the symptoms of intussusception occur.

Introduction

Intussusception is the most common abdominal emergency in young children[1]. Intussusception refers to the telescoping of a segment of the intestine into itself[1,2].

It typically presents between 6 and 36 months of age[1]. The incidence of intussusception is highest in the first to third years of life, although about 10 percent of cases occur in children aged over 5 years[1]. Most episodes occur in otherwise healthy and well-nourished children. There is a slight male predominance, with a male: female ratio around 3:2[1].

If intussusception is not relieved, the blood supply to the affected segment of the intestine may be compromised, resulting in ischaemia and possibly perforation. Untreated intussusception may be fatal[3].

Causes

Approximately 75 percent of intussusception cases are idiopathic as no clear disease trigger or lead point is found[1]. (A lead point is a lesion or variation in the intestine that is trapped by peristalsis and dragged into a distal segment of the intestine, causing intussusception[1].)

When a cause is identified, it may include viral infection, bacterial enteritis or an underlying medical condition[1,4] (Table 1).

Table 1: Identified causes of intussusception[a,b]

Viral infections	Bacterial enteritis (caused by the following infections)	Underlying medical conditions
Rotavirus (including rotavirus vaccine)	*Salmonella spp.*	Meckel diverticulum
Adenovirus	*Escherichia coli*	Polyps
	Shigella spp.	Small bowel lymphoma
	Campylobacter spp.	Duplication cysts
		Vascular malformations
		Immunoglobulin A vasculitis
		Cystic fibrosis

a. Vo NJ, Sato TT. 2018. Intussusception in children. In: *UpToDate* 29 June 2018. URL: **www.uptodate.com/contents/intussusception-in-children** (accessed 18 July 2018).

b. Kodikara H, Lynch A, Morreau P, et al. 2010. Ten-year review of intussusception at Starship Hospital: 1998–2007. *New Zealand Medical Journal* 123(1324): 32–40. URL: **www.nzma.org.nz/__data/assets/pdf_file/0010/37459/kodikara.pdf** (accessed 18 July 2018).

Rotavirus vaccine is the only medicine associated with the development of intussusception. A low level risk of 1–6 excess cases per 100,000 vaccinated infants has been documented in some countries[5]. The incidence of intussusception in New Zealand prior to the introduction of routine rotavirus vaccination was estimated as 56.1 cases per 100,000 per year in children aged under 1 year, similar to the worldwide average estimate of 74 cases per 100,000[6].

The benefits of rotavirus vaccination continue to outweigh the risks of harm, but the vaccine should not be given to children with a history of intussusception or an uncorrected congenital malformation of the gastrointestinal tract[2,7].

Symptoms

The classic presentation is an infant or toddler with sudden onset of intermittent, severe, crampy,

progressive abdominal pain accompanied by inconsolable crying and drawing up of the legs towards the abdomen. Episodes usually occur at 15- to 20-minute intervals and become more frequent and severe over time. Vomiting may occur. A sausage-shaped abdominal mass may be felt in the abdomen. The stool is grossly bloody in nearly half of cases. In some cases, the stool may be a mixture of blood and mucous, giving it the appearance of redcurrant jelly. However, up to 20 percent of young infants have no obvious pain. Generally, some form of imaging is needed to confirm a diagnosis[1].

Parents and/or guardians should be advised to seek prompt medical advice if these symptoms occur after rotavirus vaccination[7]. Most children can be successfully treated with an enema (either air or fluid). However late diagnosis increases the likelihood that the child will require surgery[4].

New Zealand cases linked to rotavirus vaccination

Rotavirus vaccine (as RotaTeq) was added to the New Zealand National Immunisation Schedule in 2014. Rotarix replaced RotaTeq on the Schedule in 2017.

As of 30 June 2018 the Centre for Adverse Reactions Monitoring had received 565 reports of suspected adverse reactions to rotavirus vaccine, in 11 cases the reaction was reported to be intussusception. The vaccine brand was reported as RotaTeq in nine cases and Rotarix in two cases. In nine cases the affected child was male. Ethnicity was reported as Māori in five cases, European in five cases and Pacific in one case. Intussusception was reported after the first and subsequent doses, consequently the age of the affected child ranged from 6 weeks to 5 months. The time between vaccination and onset of the reaction was reported in all cases and ranged from four days to two months. Recovery was reported in 10 of the 11 cases (in one case the outcome was unknown).

References

1. Vo NJ, Sato TT. 2018. Intussusception in children. In: *UpToDate* 29 June 2018. URL: **www.uptodate.com/contents/intussusception-in-children** (accessed 18 July 2018).
2. Ministry of Health. 2018. *Immunisation Handbook 2017* (2nd edn). Wellington: Ministry of Health. URL: **www.health.govt.nz/publication/immunisation-handbook-2017** (accessed 18 July 2018).
3. Jiang J, Jiang B, Parashar U, et al. 2013. Childhood intussusception: A literature review. *PLoS ONE* 8(7): e68482. URL: **www.ncbi.nlm.nih.gov/pmc/articles/PMC3718796/** (accessed 18 July 2018).
4. Kodikara H, Lynch A, Morreau P, et al. 2010. Ten-year review of intussusception at Starship Hospital: 1998–2007. *New Zealand Medical Journal* 123(1324): 32–40. URL: **www.nzma.org.nz/__data/assets/pdf_file/0010/37459/kodikara.pdf** (accessed 18 July 2018).
5. Burnett E, Parashar U, Tate J. 2018. Rotavirus vaccines: effectiveness, safety, and future directions. *Paediatric Drugs* 29(3): 223–33. URL: **www.ncbi.nlm.nih.gov/pubmed/29388076** (accessed 23 July 2018).
6. Rosie B, Dalziel SR, Wilson E, et al. 2016. Epidemiology of intussusception in New Zealand pre-rotavirus vaccination. *New Zealand Medical Journal* 129(1442): 36–45. URL: **www.nzma.org.nz/__data/assets/pdf_file/0016/51424/Best-FINAL.pdf** (accessed 20 July 2018).
7. GlaxoSmithKline NZ Limited. 2018. *Rotarix Human Rotavirus (Live Attenuated Oral Vaccine) Oral Liquid New Zealand Data Sheet* 30 April 2018. URL: **www.medsafe.govt.nz/profs/Datasheet/r/Rotarixliquidvac.pdf** (accessed 18 July 2018).

Recent Approvals of Medicines Containing a New Active Ingredient

For the period 16 April 2018 to 15 July 2018.

Trade name (active ingredient)	Dose form and strength	Therapeutic area
Acarizax (*Dermatophagoides farinae* allergen extract; *D. pteronyssinus* allergen extract)	Sublingual tablet 12 SQ-HDM	House dust mite allergy
Afstyla (lonoctocog alpha)	Injection with diluent 250, 500, 1000, 1500 2000, 2500 and 3000 IU	Haemophilia A (congenital FVIII deficiency)
Cystadane (betaine)	Powder for oral solution 180 g	Homocystinuria
Lonquex (lipegfilgastim)	Solution for injection 6 mg/0.6 mL	Neutropenia associated with cytotoxic chemotherapy
Maviret (glecaprevir, pibrentasvir)	Film coated tablet 100 mg/40 mg	Chronic hepatitis C infection

See the Medsafe website for data sheets of currently marketed medicines (**www.medsafe.govt.nz/Medicines/infoSearch.asp**).

Quarterly Summary of Recent Safety Communications

The table below is a summary of recent safety communications to healthcare professionals and consumers. (See page 47 for information about subscribing to Medsafe's updates and alerts.)

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 is available on the Medsafe website (**www.medsafe.govt.nz/Projects/B2/EWS.asp**).

Date	Communication	Topic
14 August 2018	Medicines Monitoring	M² Isotretinoin and possible risk of obsessive compulsive disorder added to the Medicines Monitoring scheme
13 August 2018	Alert Communication	Codeine – new restrictions on use in children and young adults
13 August 2018	Dear Healthcare Professional Letter	Bicillin – changes to expression of product strength
6 August 2018	Monitoring Communication	Dolutegravir and the possible risk of neural tube defects when taken early in pregnancy
27 July 2018	Alert Communication	Consumer Level Recall – Melatonin 3 mg tablets (Worldwide Labs)
25 July 2018	Consumer Information leaflet	Taking metformin for gestational diabetes – now available in te reo Māori and Samoan
19 July 2018	Dear Healthcare Professional Letter	Dissolution profile of Dilantin® 30 mg and 100 mg capsules (New Formulation)
3 July 2018	Dear Healthcare Professional Letter	Provisional consent of Neulactil periciazine 2.5 mg and 10 mg tablets (Hong Kong stock) to cover temporary stock shortage

Changes Regarding the Use of Sedating Antihistamines

Key Messages

- There have been some recent changes regarding the use of sedating antihistamines.
- Sedating antihistamines are:
  - contraindicated in children aged under two years
  - not indicated for the treatment of anxiety.

Medsafe sought expert committee advice on sedating antihistamines, resulting in regulatory changes regarding their use.

Medicines Adverse Reactions Committee (MARC)

In June 2016, the MARC reviewed the available information on the indications, contraindications and classifications of sedating antihistamines[1].

The main concerns with using sedating antihistamines in children are the risk of sedation and respiratory depression[2]. The MARC recommended that sedating antihistamines should be contraindicated in children aged under two years[3].

The MARC noted that 'for the treatment of anxiety' is not an approved indication for use[1] and is therefore not necessary in either the Label Statement Database (LSD) or the Classification Database (the LSD is available at **www.medsafe.govt.nz/regulatory/labelling.asp** and the Classification Database at **www.medsafe.govt.nz/profs/class/classintro.asp**).

Medicines Classification Committee (MCC)

In April 2018, the MCC recommended that the statement 'for the treatment of anxiety' should be removed from the pharmacist-only (restricted) medicine classification statements for sedating antihistamines[4].

Label Statements Database (LSD)

The LSD lists the warning and advisory statements that are required on medicine labels under the Medicines Regulations 1984.

The LSD has been updated to include the MARC and MCC recommendations concerning the use of non-sedating antihistamines (Table 1).

References

1. Medsafe. 2016. *Medicines Adverse Reactions Committee: Use of oral sedating antihistamines in children*. Wellington: Medsafe.
2. Medsafe. 2013. Children and sedating antihistamines. *Prescriber Update* 34(1): 11–12. URL: **www.medsafe.govt.nz/profs/PUArticles/PDF/PrescriberUpdate_March2013.pdf** (accessed 25 June 2018).
3. Medsafe. 2016. *Minutes of the 166th Medicines Adverse Reactions Committee Meeting 29 June 2016*. URL: **www.medsafe.govt.nz/profs/adverse/Minutes166.htm** (accessed 25 June 2018).
4. Medsafe. 2018. *Minutes of the 60th meeting of the Medicines Classification Committee held in Wellington on 26 April 2018 at 9:30am*. URL: **www.medsafe.govt.nz/profs/class/Minutes/2016-2020/mccMin26April2018.htm** (accessed 25 June 2018).

Table 1: Label Statements Database entry for sedating antihistamines

Medicine/Group/Class	Conditions	Statements or requirements
Antihistamines, sedating Includes: Alimemazine Brompheniramine Chlorphenamine Cyclizine Dexchlorpheniramine Diphenhydramine Doxylamine Ketotifen Meclozine Mepyramine Pheniramine Promethazine	For oral use	Do not use in children under 2 years old. This medicine may cause drowsiness. Be cautious about driving a vehicle or operating machinery within 8 hours of taking this medicine.
	In cough and cold medicines	Do not use in children under 6 years old. Consult a healthcare professional before using in children aged 6 years and over. Do not use with other antihistamines. Do not use with other medicines intended to treat the symptoms of the common cold except on the advice of a healthcare professional.
	For the treatment of insomnia	Do not use in children under 12 years old. Do not exceed the maximum stated dose. This product is for temporary use only. [or] For short term use only. Consult a doctor if sleeplessness persists.

Source: Medsafe. 2018. Label Statements Database Edition 1.22 (August 2018). URL: **www.medsafe.govt.nz/regulatory/labelling.asp** (accessed 22 August 2018).

The Medsafe Files – Episode Seven: Medicine Recalls

Key Messages

- A medicine recall is the removal of affected medicinal products from supply or use, when there are issues or deficiencies concerning their safety, quality or efficacy.
- Companies supplying medicines (known as 'Sponsors') are responsible for carrying out recalls. Contact the sponsor for any questions relating to a recall.
- Medicines may be recalled to the wholesale level, hospital/laboratory level, healthcare professional level, pharmacy/retail level or consumer level.
- Those involved in a recall should follow the instructions provided by the sponsor conducting the recall.
- Medsafe publishes a list of medicine recalls on the Medsafe Online Recall Database (MORD).
- All consumer-level recalls are also published on the Ministry of Business, Innovation and Employment's Product Recalls website.

Purpose

A medicine recall is the removal of affected medicinal products from supply or use, when there are issues or deficiencies concerning their safety, quality or efficacy[1].

Sponsors are responsible for carrying out recalls in New Zealand

'Sponsor' is the term used for the person or organisation that is legally responsible for a medicine in New Zealand. This may be a New Zealand manufacturer, supplier or importer [1].

Sponsors are responsible for identifying potential issues with their medicines, assessing the risks of any identified hazards and mitigating those risks. The overall responsibility for medicine recalls lies with the sponsor and any questions relating to a recall should be addressed to the sponsor [1].

Medsafe's role in the recall process is to ensure that the right decisions are made and that appropriate actions are taken. For example, Medsafe approves the sponsor's recall procedure and recall letters, to ensure the potential for patient harm has been minimised.

Levels of recall

Medicines may be recalled to the wholesale level, hospital/laboratory level, healthcare professional level, pharmacy/retail level or consumer level.

The principal factors when determining the level (or depth) of a recall action are the significance of the risk to the consumer, and the medicine's distribution channels. In certain circumstances, where a medicine has only been supplied to a limited number of known customers, a recall may be limited to those customers only[1].

Responsibilities of healthcare professionals

Healthcare professionals have an ethical and professional obligation to safeguard their patients in any recall action. The healthcare professional may delegate these tasks to a competent person but should remain vigilant for clinical repercussions[1].

Carefully read any recall letters and take the appropriate actions in response to the notification. If there is an acknowledgement form included with the recall letter, promptly return it to the sponsor to assist with the stock reconciliation process.

Where an affected medicine has been supplied to another organisation (eg, a nursing home), advise that organisation of the recall action and inform the sponsor conducting the recall[1].

Phases of activity during a recall[1]

Phase 1: Initiation

The sponsor investigates and scopes the issue, conducts a hazard/risk assessment, formulates a recall action plan and consults with Medsafe.

Phase 2: Implementation

The sponsor is responsible for notifying and carrying out the recall action to the agreed level.

Medsafe monitors the recall action process to ensure that it is carried out in an effective and timely manner by reviewing progress reports provided by the sponsor.

Phase 3: Review

The sponsor reviews the effectiveness of the recall action and decides whether a follow-up recall action is necessary.

This phase includes identifying the root cause of the issue and assessing whether the

corrective actions proposed/implemented by the manufacturer/sponsor are likely to manage the risk of the same issue recurring.

Medsafe also reviews corrective actions and determines whether it is appropriate for the medicine to be supplied to the market in the future.

For more information

New Zealand Medicines and Medical Devices Recall Code

This document provides principles and general guidance to sponsors, wholesalers, retailers and healthcare professionals on the effective conduct of recall actions, including an outline of their roles and responsibilities (available at **www.medsafe.govt.nz/safety/RecallCode.pdf**).

Medsafe Online Recall Database (MORD)

MORD provides summary information on all medicine recall actions initiated in New Zealand since 2012 (available at **www.medsafe.govt.nz/hot/recalls/RecallSearch.asp**).

Product Recalls website

The Product Recalls website (**www.recalls.govt.nz**) publishes recalls from the Ministry of Business, Innovation and Employment, the New Zealand Transport Authority and Medsafe (consumer-level recalls for medicines). It also links to the Ministry for Primary Industries for recalled food products.

References

1. Medsafe. 2015. *New Zealand Medicines and Medical Devices Recall Code*. URL: **www.medsafe.govt.nz/safety/RecallCode.pdf** (accessed 17 July 2018).

MARC's Remarks: July 2018 Meeting

The Medicines Adverse Reactions Committee (MARC) met on 3 July 2018 to discuss a number of medicine-related safety issues.

The MARC discussed benefits and risks of harm of **ulipristal acetate** (Esmya) under section 36 of the Medicines Act 1981. Ulipristal acetate is indicated for treatment of uterine fibroids in adult women. The MARC considered the risk-benefit balance of ulipristal acetate is favourable only for women where surgery is not an appropriate treatment option.

The MARC reviewed the Risk Management Plan (RMP) for the **recombinant meningococcal B vaccine** (Bexsero) and considered the RMP to be thorough, appropriate and complete at this time.

The MARC discussed the association between **atypical antipsychotics** and sleepwalking/sleep-related eating disorder. Given the available evidence, the MARC agreed the association is likely due an individual drug effect rather than a class effect. The Committee recommended the New Zealand data sheets for **aripiprazole, olanzapine, paliperidone**, **quetiapine, risperidone** and **ziprasidone** should include information about these adverse reactions.

A potential drug-drug interaction between **nefopam** (Acupan) and **tramadol** was also considered. The MARC recommended a precaution is added to the New Zealand nefopam data sheet. The warning should highlight the potential for serotonin syndrome when nefopam is used concomitantly with any medicine(s) that can increase serotonin availability, including tramadol.

The MARC reviewed two topics relating to **isotretinoin**.

- Pregnancy prevention measures: The MARC considered increased use of the *bestpractice* isotretinoin module would help to manage the teratogenic risk of isotretinoin as it includes information about pregnancy prevention. The MARC also recommended pharmacists dispense isotretinoin for women of childbearing potential in the original manufacturer's pack.
- Obsessive Compulsive Disorder (OCD): The MARC recommended that this possible association is further investigated through Medsafe's Medicines Monitoring (M^2) system[1].

See the Medsafe website for the MARC meeting minutes **(www.medsafe.govt.nz/profs/MARC/Minutes.asp)** and the reports presented to the MARC **(www.medsafe.govt.nz/committees/MARC/Reports.asp).**

References

1. Medsafe. 2018. Isotretinoin and Obsessive Compulsive Disorder. URL: **www.medsafe.govt.nz/safety/EWS/2018/Isotretinoin.asp** (accessed 15 August 2018).

Gathering Knowledge from Adverse Reaction Reports: September 2018

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

The table below presents a selection of recent informative cases from the Centre for Adverse Reactions Monitoring (CARM) database.

CARM ID: 125366 **Age:** 58 **Gender:** Male **Medicine(s):** Cisplatin **Reaction(s):** Cerebral atrophy, memory loss	A 58-year-old man was treated with cyclical neoadjuvant cisplatin and doxorubicin for osteosarcoma of the femur. He subsequently experienced memory decline.
	The DBL Cisplatin (**www.medsafe.govt.nz/profs/Datasheet/d/DBLCisplatininj.pdf)** and Cisplatin Ebewe (**www.medsafe.govt.nz/profs/Datasheet/c/CisplatinEbeweinj.pdf**) data sheets contain information on neurotoxicity, and state that neurological examinations should be performed regularly.
CARM ID: 127529 **Age:** 55 **Gender:** Female **Medicine(s):** Zoledronic acid **Reaction(s):** Uveitis	Three days after infusion of zoledronic acid, a 55-year-old woman developed uveitis, with sore eyes, photosensitivity, vision disturbance, eye redness and lacrimation.
	The Aclasta data sheet (**www.medsafe.govt.nz/profs/Datasheet/a/Aclastainf.pdf**) lists uveitis as an uncommon or rare adverse reaction, according to data from individual and clinical studies.
CARM ID: 128440 **Age:** 71 **Gender:** Female **Medicine(s):** Mirtazapine **Reaction(s):** Anger, aggression	A 71-year-old woman with bipolar disorder and benzodiazepine dependency was admitted to hospital for re-initiation of lithium therapy. She was also switched from dothiepin to mirtazapine for treatment of depression, after which she developed physically aggressive behaviour.
	The Apo-Mirtazapine data sheet (**www.medsafe.govt.nz/profs/Datasheet/a/ApoMirtazapinetab.pdf**) lists aggression as a rare adverse reaction.
CARM ID: 128445 **Age:** 28 **Gender:** Female **Medicine(s):** Erythromycin, methadone, quetiapine, paroxetine, zopiclone **Reaction(s):** Drug interaction, cyanosis, depressed level of consciousness	A 28-year-old woman being treated with methadone, paroxetine, quetiapine and zopiclone was started on erythromycin for strep throat. The next day she was found unresponsive and cyanosed.
	The E-Mycin data sheet (**www.medsafe.govt.nz/profs/Datasheet/e/E-Mycintabsus.pdf**) states that serum levels of medicines metabolised by the cytochrome P450 system may be elevated when erythromycin is used concurrently. Also refer to the 'Medicines interacting with methadone' article in the June 2018 edition of *Prescriber Update*.

Febuxostat – Interaction with Azathioprine or Mercaptopurine

Key Messages

- Febuxostat is used for the treatment of chronic hyperuricaemia in patients with gout.
- Febuxostat is not recommended in patients concomitantly treated with azathioprine or mercaptopurine.
- Where the combination cannot be avoided, closely monitor patients and reduce the dose of azathioprine or mercaptopurine to avoid adverse haematological effects.

Indications and use in New Zealand

Febuxostat (Adenuric) is a potent, non-purine, selective inhibitor of xanthine oxidase that reduces the formation of uric acid[1].

Febuxostat is approved in New Zealand for the treatment of chronic hyperuricaemia in patients with gout. It is also approved for the prevention and treatment of hyperuricaemia in patients undergoing chemotherapy for haematological malignancy at intermediate- to high-risk of Tumour Lysis Syndrome[1].

The use of febuxostat has increased significantly[2] in New Zealand since it was funded by PHARMAC on 1 June 2014, subject to Special Authority criteria[3].

Interactions with azathioprine and its metabolite – 6-mercaptopurine

Azathioprine is an immunosuppressive agent. It is first metabolised to 6-mercaptopurine, which in turn is converted to inactive products by xanthine oxidase[4]. Inhibition of xanthine oxidase by febuxostat may cause increased plasma concentrations of azathioprine or mercaptopurine, leading to toxicity[1].

There are no drug interaction studies for febuxostat co-administered with medicines metabolised by xanthine oxidase. A number of post-marketing and literature cases of interaction with azathioprine have been reported globally[1,5].

As at 30 June 2018 there had been no reports from New Zealand.

Febuxostat is not recommended in patients concomitantly treated with azathioprine or mercaptopurine[1]. Where the combination cannot be avoided, closely monitor patients and reduce the dose of azathioprine or mercaptopurine to avoid possible haematological effects[1].

References

1. A.Menarini New Zealand Pty Ltd. 2016. *Adenuric New Zealand Data Sheet* 18 May 2016. URL: **www.medsafe.govt.nz/profs/Datasheet/a/adenurictab.pdf** (accessed 23 July 2018).
2. Ministry of Health. 2018. DataPharm (beta) version 15 March 2018 (data extracted from Pharmaceutical Collection on 18 December 2017). URL: **https://minhealthnz.shinyapps.io/datapharm-beta/** (accessed 23 July 2018).
3. Medsafe. 2014. Febuxostat - an additional xanthine oxidase inhibitor. *Prescriber Update* 35(3): 39. URL: **www.medsafe.govt.nz/profs/PUArticles/September2014Febuxostat.htm** (accessed 23 July 2018).
4. Medsafe. 1998. Azathioprine-allopurinol interaction: Danger! *Prescriber Update* 17: 16–17. URL: **www.medsafe.govt.nz/profs/puarticles/azathioprine.htm** (accessed 23 July 2018).
5. Jordan A and Gresser U. 2018. Side effects and interactions of the xanthine oxidase inhibitor febuxostat. *Pharmaceuticals* 11(2): 51. DOI: 10.3390/ph11020051 (accessed 23 July 2018).

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