Prescriber Update

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New Anti-Cancer Therapy – Immune Checkpoint Inhibitors

Key Messages

- Immune checkpoint inhibitors are monoclonal antibodies currently indicated for the treatment of several advanced or metastatic cancers.
- These medicines are associated with a range of immune-mediated adverse reactions.
- Patients should be carefully monitored for signs and symptoms of immune-mediated adverse reactions.
- Immune-mediated adverse reactions can occur weeks to months after the last dose.

Atezolizumab (Tecentriq), ipilimumab (Yervoy), nivolumab (Opdivo) and pembrolizumab (Keytruda) are monoclonal antibodies. These medicines are known as immune checkpoint inhibitors because they block target proteins ('checkpoints') on immune cells. This action enables the immune system to boost its response against cancer cells[1,2].

There are two important immune-checkpoint receptors targeted by these medicines: cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1).

Atezolizumab, ipilimumab, nivolumab and pembrolizumab are used for the treatment of several advanced or metastatic cancers[3–6]. A range of immune-mediated adverse reactions are associated with the use of these medicines. Immune-mediated adverse reactions that are listed in the data sheets include:

- pneumonitis
- colitis
- hepatotoxicity
- nephritis and renal dysfunction
- endocrinopathies
- skin reactions
- gastrointestinal reactions
- neurological reactions
- pancreatitis
- neuropathies[3–6].

All patients taking an immune checkpoint inhibitor should be carefully monitored for signs and symptoms of immune-mediated adverse reactions[3–6]. Healthcare professionals are reminded that these adverse reactions may occur weeks to months after the last dose[3–5]. Further information on specific immune-mediated adverse reactions associated with each immune checkpoint inhibitor can be found in the data sheet for each medicine (**www.medsafe.govt.nz/Medicines/infoSearch.asp**)[3–6].

At 30 June 2017, the Centre for Adverse Reactions Monitoring (CARM) had received 41 cases reporting adverse reactions to immune checkpoint inhibitors. A review of data indicated that a range of reactions have been reported in New Zealand in association with these medicines including two reports of type 1 diabetes.

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

Further information on immune checkpoint inhibitors was presented to the Medicines Adverse Reactions Committee at the 171st meeting. The report is published on the Medsafe website (**www.medsafe.govt.nz/committees/MARC/Reports.asp**).

References

1. American Cancer Society. 2017. *Immune Checkpoint Inhibitors to Treat Cancer* 23 June 2017. URL: **www.cancer.org/treatment/treatments-and-side-effects/treatment-types/immunotherapy/immune-checkpoint-inhibitors.html** (accessed 22 November 2017).
2. National Cancer Institute. 2017. *NCI Dictionary of Cancer Terms* 21 July 2017. URL: **www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=772606** (accessed 22 November 2017).
3. Bristol-Myers Squibb (NZ) Limited. 2017. *Opdivo Data Sheet* 27 July 2017. URL: **www.medsafe.govt.nz/profs/Datasheet/o/opdivoinf.pdf** (accessed 22 November 2017).
4. Bristol-Myers Squibb (NZ) Limited. 2017. *Yervoy Data Sheet* 29 June 2017. URL: www.medsafe.govt.nz/profs/Datasheet/y/yervoyinj.pdf (accessed 22 November 2017).
5. Merck Sharp and Dohme (New Zealand) Limited. 2017. *Keytruda Data Sheet* 16 October 2017. URL: **www.medsafe.govt.nz/profs/Datasheet/k/Keytruda.pdf** (accessed 22 November 2017).
6. Roche Products (New Zealand) Limited. 2017. *Tecentriq Data Sheet* 25 August 2017. URL: **www.medsafe.govt.nz/profs/Datasheet/t/Tecentriqinf.pdf** (accessed 22 November 2017).

Interactions with Donepezil

Key Messages

- ⌘ Donepezil is an acetylcholinesterase inhibitor used in the treatment of Alzheimer's disease and vascular dementia.
- ⌘ Beware of the potential interactions with donepezil when preparing patients taking donepezil for surgery or when prescribing other medicines.

Donepezil is a specific and reversible acetylcholinesterase inhibitor used in the treatment of Alzheimer's disease and vascular dementia[1,2]. Alzheimer's disease is the most common form of dementia and the number of people affected is expected to increase as the population ages.

When patients taking donepezil require treatment with other medicines, consideration should be given to potential interactions. This is particularly important when preparing patients for surgery. For example, donepezil can considerably prolong the depolarising action of suxamethonium and may shorten the duration and diminish the magnitude of neuromuscular blockade with atracurium[3,4].

Medicines that are known to interact with donepezil are shown in Table 1. Check the medicine data sheets (**www.medsafe.govt.nz/Medicines/infoSearch.asp**) or use the interactions search bar in the New Zealand Formulary (**http://nzf.org.nz/nzf_6272**) for more information.

The Centre for Adverse Reactions Monitoring (CARM) has received four reports describing a drug interaction with donepezil. Three of these reports describe an interaction with metoprolol resulting in bradycardia. Please continue to report any adverse reactions, including medicine interactions, with donepezil to CARM. Reports can be submitted on paper or electronically (**https://nzphvc.otago.ac.nz/**).

References

1. Pfizer New Zealand Ltd. 2012. *Aricept New Zealand Data Sheet* 25 October 2012. URL: **www.medsafe.govt.nz/profs/Datasheet/a/AriceptabAriceptDtab.pdf** (accessed 29 September 2017).
2. REX Medical Limited. 2014. *Donepezil New Zealand Data Sheet* 8 January 2014. URL: **www.medsafe.govt.nz/profs/Datasheet/d/donepeziltab.pdf** (accessed 29 September 2017).
3. AstraZeneca Limited. 2014. *Suxamethonium Chloride BP New Zealand Data Sheet* 9 December 2014. URL: **www.medsafe.govt.nz/profs/Datasheet/s/SuxamethoniumChlorideinj.pdf** (accessed 8 November 2017).
4. GlaxoSmithKline NZ Ltd. 2013. *Tracrium Data Sheet* 20 November 2013. URL: **www.medsafe.govt.nz/profs/Datasheet/t/Tracriuminj.pdf** (assessed 29 November 2017).
5. New Zealand Formulary. 2017. *New Zealand Formulary v64* 1 October 2017. URL: **http://nzf.org.nz/** (accessed 4 October 2017).

Table 1: Summary of medicines that may interact with donepezil[1,2,5]

Interaction Type	Medicine Group	Medicine Examples	Effect
Pharmacodynamic interactions	Non-depolarising neuromuscular blocking agents	pancuronium, rocuronium, vecuronium, atracurium, mivacurium	Donepezil may reduce the effects of these agents.
	Depolarising neuromuscular blocking agents	suxamethonium	Donepezil may prolong the effects of these agents.
	Anticholinesterase agents	neostigmine, pyridostigmine	Synergistic effects with donepezil.
	Beta blockers	atenolol, carvedilol, metoprolol, propranolol	Donepezil may increase the risk of bradycardia.
Pharmacokinetic interactions	CYP3A4 inhibitors CYP2D6 inhibitors	itraconazole, erythromycin, ketoconazole, fluoxetine, quinidine	Could inhibit metabolism of donepezil. Clinical effects not known.
	CYP3A4 inducers CYP2D6 inducers	rifampicin, phenytoin, carbamazepine, dexamethasone	May reduce levels of donepezil.

Adrenal Suppression is Associated with the Use of Topical Corticosteroids

Key Messages

- The use of topical corticosteroids can cause adrenal suppression in both children and adults.
- Diluting a topical corticosteroid in an emollient does not reduce the risk of adverse effects.
- A diluted topical steroid in an emollient can lead to overuse, increasing the risk of adverse effects.
- Remember, patients may be using corticosteroids through more than one route.
- Inappropriate use of topical antibiotics/steroid preparations promotes antimicrobial resistance and should be avoided.

The Centre for Adverse Reactions Monitoring (CARM) has received a case report concerning a patient who experienced adrenal insufficiency after regular use of topical corticosteroids to treat psoriasis. The corticosteroid preparation included clobetasol propionate (Dermol) ointment, betamethasone dipropionate (Daivobet) ointment and mometasone furoate lotion. The patient required treatment with oral steroid supplements for adrenal insufficiency.

Adrenal suppression from topical steroid use can occur in both adults and children, although children are at greater risk due to their high surface area to volume ratio[1].

Medsafe would like to remind healthcare professionals that diluting steroids in an emollient does not reduce the likelihood or severity of an adverse reaction, or alter the efficacy of the medicine[2,3]. Moreover, it may lead to over use of these medicines and increase the risk of experiencing adverse reactions, including adrenal suppression.

The choice of topical corticosteroid should be determined by the severity of the skin condition and the part of the body to which the product will be applied[3,4]. Topical corticosteroid products are available in a range of potencies (Table 1). It is best practice to use the lowest potency corticosteroid needed to control symptoms. A weaker topical corticosteroid should be prescribed if needed, rather than diluting a more potent product in an emollient as this does not actually weaken the effect.

Serious adverse reactions are rarely seen with appropriate use of topical corticosteroids. The risk of adverse effects is increased by:

- use of higher potency corticosteroids
- application of the corticosteroid to a large area of skin and/or application of a large quantity over prolonged periods

Table 1: Potency of topical corticosteroid medicines available on prescription in New Zealand[5]

Potency	Topical corticosteroid preparation
Mild	hydrocortisone 1%
Moderate (2–25 times as potent as hydrocortisone)	clobetasone butyrate 0.05% triamcinolone acetonide 0.02%
Potent (100–150 times as potent as hydrocortisone)	betamethasone dipropionate 0.05% (Diprosone®, Daivobet®†) betamethasone valerate 0.1% diflucotolone valerate 0.1% hydrocortisone butyrate 0.1% methylprednisolone aceponate 0.1% mometasone furoate 0.1%
Very potent (up to 600 times as potent as hydrocortisone)	betamethasone dipropionate 0.05% in propylene glycol base (Diprosone OV®) clobetasol propionate 0.05%

† Daivobet® contains calcipotriol 0.005% and betamethasone dipropionate 0.05%

- application of the corticosteroid under occlusion or to flexural and groin areas, which can increase absorption
- application to striae-prone areas (eg, axillae or groin)
- concomitant use of oral or high-dose inhaled corticosteroids[3].

Healthcare professionals are also reminded to consider the risk of antimicrobial resistance associated with inappropriate use of topical antibiotic/corticosteroid preparations[6].

New Zealand data sheets for topical corticosteroids include information on the risk of systemic effects, including adrenal suppression (**www.medsafe.govt.nz/Medicines/infoSearch.asp**).

References

1. Mylan New Zealand Ltd. 2017. *Dermol Data Sheet* 4 April 2017. URL: **www.medsafe.govt.nz/profs/Datasheet/d/Dermolcrmoint.pdf** (accessed 30 October 2017).
2. Hoare C, Li Wan Po A, Williams H. 2000. Systematic review of treatments for atopic eczema. *Health Technology Assessment* 4(37): 1–191.
3. Best Practice Advocacy Centre. 2016. Topical corticosteroids for childhood eczema: clearing up the confusion. *Best Practice Journal* December 2016. URL: **www.bpac.org.nz/2016/docs/topical-corticosteroids.pdf** (accessed 30 October 2017).
4. DermNet New Zealand. 2016. *Topical steroids* 4 January 2016. URL: **www.dermnetnz.org/topics/topical-steroids/** (accessed 30 October 2017).
5. New Zealand Formulary. 2017. *Topical corticosteroids* 1 November 2017. URL: **http://nzf.org.nz/nzf_6272** (accessed 31 October 2017).
6. World Health Organization. 2017. *Antibiotic Resistance* October 2017. URL: **www.who.int/mediacentre/factsheets/antibiotic-resistance/en/** (accessed 31 October 2017).

Spotlight on Topiramate: Seize the Day

Key Messages

- ⌘ Topiramate is an antiepileptic medicine used in the treatment of epilepsy and the prevention of migraines.
- ⌘ With hot summer days ahead, remind patients, their families and caregivers to watch for signs of decreased sweating and increased body temperature.
- ⌘ Antiepileptic medicines have been associated with suicidal thoughts and behaviour. Advise patients to seek immediate medical advice if they have concerns about changes in mood and behaviour.

This article on topiramate is the second in the spotlight series where Medsafe reviews the safety information on a specific medicine or class of medicine.

Indications

Topiramate is indicated in adults and children aged two years and over:

- as monotherapy in patients with newly diagnosed epilepsy
- for conversion to monotherapy in patients with epilepsy
- as add-on therapy in partial onset seizures, generalised tonic-clonic seizures or seizures associated with Lennox-Gastaut syndrome[1,2].

Topiramate is also indicated for the prevention of migraine headache in adults[1,2].

Contraindications

The only contraindication for use of topiramate is hypersensitivity to any component of the product[1,2]. Excipients are listed in the data sheet, consumer medicine information (**www.medsafe.govt.nz/Medicines/infoSearch.asp**) and in the product application search on the Medsafe website (**www.medsafe.govt.nz/regulatory/DbSearch.asp**).

Warnings and Precautions

Suicidality, Mood Disturbances, Depression

Antiepileptic medicines have been associated with suicidal thoughts and behaviour, regardless of the indication[3]. In addition, an increased incidence of mood disturbances and depression has been observed during topiramate treatment[1,2].

Inform patients, their families and caregivers of the potential increase in risk of suicidality. Advise patients to seek immediate medical advice if they have any concerns about changes in mood or behaviour.

Oligohydrosis, Hyperthermia

Increases in body temperature resulting from decreased sweating (oligohydrosis) and an inability to sweat normally (anhidrosis) have been reported mostly in children[1,2]. Some

cases have resulted in hospitalisation. With hot summer days ahead, remind patients, their families and caregivers to watch for signs of decreased sweating and increased body temperature. Take care when prescribing other medicines that predispose patients to heat-related disorders[1,2].

Nephrolithiasis

Some patients may be at increased risk for renal stone formation (nephrolithiasis)[1,2]. Signs and symptoms include renal colic, renal pain or flank pain. Advise patients to remain well hydrated to reduce the risk of renal stone formation.

Eye Disorders

A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has been reported[1,2]. Visual field defects independent of elevated intraocular pressure have also been reported[1,2].

Other

Administer topiramate with caution in patients with hepatic impairment as the clearance of topiramate may be decreased[1,2]. Patients with renal impairment may require a longer time to reach steady state so be careful with any dose adjustments[1,2].

Hyperchloremic, non-anion gap, metabolic acidosis is associated with topiramate treatment[1,2].

Hyperammonemia with or without encephalopathy has been reported[1,2]. The risk appears to be dose-related and has been reported more frequently when topiramate is used with sodium valproate. Clinical symptoms often include acute changes in level of consciousness and/or cognitive function with lethargy.

Please refer to the medicine data sheets for further information on topiramate (**www.medsafe.govt.nz/Medicines/infoSearch.asp**).

New Zealand Reports of Adverse Reactions

From January 2012 to 30 September 2017 the Centre for Adverse Reactions Monitoring (CARM) received 24 reports in which topiramate was reported as a suspect medicine. Of the 24 reports, the reported indications for use were migraine or migraine prophylaxis (14), epilepsy (6), an unapproved indication (3) and unknown (1).

The reports included a total of 56 reaction terms. The top three System Organ Classes with the most reaction terms were psychiatric disorders (14), nervous system disorders (10) and special senses (7). The most frequently reported reaction terms were paraesthesia distal (3), numbness localised (2), dysgeusia (2), and weight decrease (2).

References

1. Janssen-Cilag (New Zealand) Ltd. 2016. *Topamax New Zealand Data Sheet* 23 August 2016. URL: **www.medsafe.govt.nz/profs/Datasheet/t/topamaxtabcap.pdf** (accessed 5 October 2017).
2. Teva Pharma (New Zealand) Limited. 2017. *Topiramate Actavis New Zealand Data Sheet* 30 May 2017. URL: **www.medsafe.govt.nz/profs/Datasheet/t/topiramateactavistab.pdf** (accessed 5 October 2017).
3. Medsafe. 2016. Antiepileptic medicines and suicide. *Prescriber Update*. 37(1): p. 6–7. URL: **www.medsafe.govt.nz/profs/PUArticles/March2016/AntilepilepticMedicinesAndSuicide.htm** (accessed 22 November 2017).

Recent Approvals of Medicines Containing a New Active Ingredient

For period 16 July 2017 to 15 October 2017.

Trade Name (active ingredient)*	Dose Form and Strength	Therapeutic Area
Afluria Quad (**influenza vaccine polyvalent**)†	Suspension for injection 60 µg/0.5mL	Influenza A & B immunisation
Elelyso (**taliglucerase alfa**)†	Powder for injection 200 U	Type 1 Gaucher disease
Jaqinus (**tofacitinib**)†	Film coated tablet 5 mg	Rheumatoid arthritis
Tagrisso (**osimertinib**)	Film coated tablet 40 mg and 80 mg	EGFR T790M mutation-positive non-small cell lung cancer

* 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/Medicines/infoSearch.asp**).

MARC's Remarks: September 2017 Meeting

The Medicines Adverse Reactions Committee (MARC) met on 14 September 2017 to discuss a number of medicine-related safety issues.

The MARC discussed the use of **sodium valproate** (Epilim) in pregnancy. The MARC considered that there are women with epilepsy for whom sodium valproate is the only effective medicine. However, when considering the use of sodium valproate in bipolar disorder the MARC considered there are alternatives that can be used. The MARC considered that it would be appropriate to restrict the indication for use in bipolar disorder to when other treatments have failed. In women of childbearing potential effective contraception must also be prescribed.

The MARC noted that the Accident Compensation Corporation (ACC) together with the Ministry of Health, the Health Quality & Safety Commission and Foetal Anti-Convulsant Syndrome New Zealand (FACS NZ) have worked with 15 clinicians and consumer advocates to create and distribute booklets on the benefits and risks of taking antiepileptic medicines for females. These booklets are available online and copies can be ordered for free on ACC's website (**www.acc.co.nz/for-providers/treatment-safety/**).

The MARC discussed the use of **immune checkpoint inhibitors** in the New Zealand context. The MARC considered it important that knowledge about immune-mediated adverse effects with these medicines was widely disseminated to healthcare professionals likely to be involved in the care of these patients. Further information on these medicines is available in this edition of *Prescriber Update*[1].

The MARC discussed the risks of severe depression, anxiety and suicidal ideation with **hormonal contraceptives**. The MARC noted that there have been reports of altered mood with the use of hormonal contraceptives. However, the available information on the risks of severe depression, anxiety and suicidal ideation with the use of hormonal contraceptives is conflicting. It is important for patients presenting with these symptoms to be referred to mental health service providers for support and an alternative method of contraception to be provided if necessary.

Further information on this meeting can be found on the Medsafe website (**www.medsafe.govt.nz/profs/adverse/Minutes171.htm**). Papers presented to the MARC are also published on the Medsafe website (**www.medsafe.govt.nz/committees/marc/Reports.asp**).

References

1. Medsafe. 2017. Spotlight on New Anti-Cancer Therapy – Immune Checkpoint Inhibitors. *Prescriber Update* 38(4): 50.

Gathering Knowledge from Adverse Reaction Reports: Dec 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: 120222 **Age:** 8 **Gender:** Male **Medicine(s):** Omeprazole **Reaction(s):** Depression	An 8-year-old boy taking omeprazole daily experienced symptoms of depression within a week of starting treatment. A similar effect had been noted when he had previously used omeprazole.
	The Losec data sheet (**www.medsafe.govt.nz/profs/Datasheet/l/Loseccap.pdf**) lists depression as a rare adverse reaction.
CARM ID: 122712 **Age:** 86 **Gender:** Male **Medicine(s):** Amiodarone, Metoprolol, Atorvastatin **Reaction(s):** Liver function test increased, hepatic cirrhosis	The patient's liver function tests were monitored after starting amiodarone. Two years after treatment initiation there was a mild elevation in the transaminases that persisted for another four years. In the subsequent year there was a further rise in transaminases. Approximately two years later a liver CT scan identified cirrhosis. The patient subsequently died.
	The Cordarone X data sheet (**www.medsafe.govt.nz/profs/Datasheet/c/CordaroneXtabinj.pdf**) recommends regular monitoring of liver function tests during treatment. Elevation of liver enzyme levels occurs quite commonly. These changes appear to be dose dependent. The data sheet recommends reducing or discontinuing treatment if transaminase increase exceeds three times the normal range. These effects are usually reversible on stopping the medicine. However, fatal cases have been reported.
CARM ID: 119850 **Age:** 67 **Gender:** Female **Medicine(s):** Simvastatin **Reaction(s):** Acute kidney injury, CK level consistent with rhabdomyolysis	After taking simvastatin 80 mg per day for an unknown length of time the patient experienced acute kidney injury and an elevated CK level consistent with rhabdomyolysis.
	The Arrow Simva data sheet (**www.medsafe.govt.nz/profs/Datasheet/a/ArrowSimvatab.pdf**) states that in a clinical trial of patients treated with simvastatin 80 mg/day, patients 65 years and above had an increased risk of myopathy compared to patients under 65 years of age.
CARM ID: 124734 **Age:** 8 months **Gender:** Male **Medicine(s):** Chloramphenicol **Reaction(s):** Neutropenia	An eight month old baby had been given chloramphenicol recurrently for an eye infection and developed neutropenia.
	The data sheet for Chlorafast eye drops (**www.medsafe.govt.nz/profs/Datasheet/c/chlorafasteyedrops.pdf)** states that bone marrow hypoplasia has been rarely reported following local application. Chloramphenicol is absorbed systemically from the eye.

The Medsafe Files — Episode Four: New Medicines Assessment (Part 3): GMP

Key Messages

- Medicines that are approved for supply in New Zealand must be manufactured in accordance with Good Manufacturing Practice (GMP).
- GMP helps to ensure that medicines are of high quality and are fit for use.
- Unapproved products may not have been manufactured under GMP.
- Medsafe performs site audits to verify compliance with GMP.

Good Manufacturing Practice (GMP) is the part of Quality Assurance which ensures medicines are consistently produced to appropriate standards.

GMP helps to ensure medicines are fit for their intended use, comply with the conditions of their consent, and do not place patients at risk due to inadequate safety, quality, or efficacy. Manufacturing in accordance with GMP ensures that:

- manufacturing, packing, testing, and storage facilities are adequate
- equipment is suitable for use
- processes are well defined, validated, and under control
- appropriate quality control testing is completed
- materials used in manufacture are traceable and of acceptable quality
- staff are suitably qualified and trained
- systems are in place to manage excursions from the defined processes
- issues which may pose a risk to product quality are investigated and managed appropriately
- product complaints are investigated and systems are in place to execute a product recall.

Medicine manufacturing and packing sites are audited and licenced by Medsafe.

Medsafe conducts on-site audits of medicine manufacturers in New Zealand against the New Zealand Code of GMP. Auditors observe manufacturing and packing processes and associated records, and evaluate the supporting quality systems. Where a manufacturer is operating in compliance, Medsafe will issue a Licence to Manufacture Medicines and/or a Licence to Pack Medicines.

Medsafe uses a risk-based approach to determine the audit duration and frequency. This takes into account factors such as the inherent risk of the medicines manufactured on-site (eg, sterile medicines are higher risk) and the compliance history of the manufacturer.

Medsafe recognises GMP Certification from other medicine regulators.

Medsafe is a member of the Pharmaceutical Inspection Co-operation Scheme (PIC/S). PIC/S is an international community of medicine regulators that includes the United States Food and Drug Administration and many European Union regulators. One of the aims of PIC/S is to harmonise the inspection procedures of its members. The New Zealand Code of GMP is aligned with internationally accepted standards.

Medsafe recognises GMP certification issued by a number of other medicine regulators, and Medsafe GMP certification is widely recognised. Mutual recognition enables Medsafe to verify that overseas manufacturers of medicines approved for the New Zealand market meet the requirements of GMP.

Methotrexate – Once Weekly Dosing

Key Messages

- ⌘ Patients can find the dose schedule for methotrexate taken for rheumatoid arthritis and psoriasis confusing.
- ⌘ Check regularly that your patients understand how to take methotrexate correctly.
- ⌘ Specify on every prescription, and the dispensed medicine label, the day of the week the dose is to be taken.
- ⌘ It is important to regularly monitor renal and liver function tests, full blood count and respiratory symptoms in all patients taking methotrexate.

Methotrexate is used to treat cancer and, in lower doses, to treat rheumatoid arthritis and psoriasis. Methotrexate interferes with folic acid metabolism and folic acid tablets are used to reduce adverse effect such as nausea or stomatitis[1].

Dosing

When methotrexate is used for rheumatoid arthritis, it is taken either once a week or in three divided doses over 36 hours once a week. Folic acid is normally prescribed to be taken on a different day to methotrexate. Treatment of psoriasis with methotrexate is also prescribed intermittently over a week. Additional dose

information is included in the data sheets for methotrexate[2].

These are unusual dose regimens that may confuse some patients. It is important to clearly explain the dosing schedule to each patient and make sure they have understood the information. Specify on every prescription, and the dispensed medicine label, the day of the week (written in full) the dose is to be taken.

Healthcare professionals should also check that the patient is taking methotrexate correctly.

Serious and sometimes life-threatening or fatal adverse effects can be caused from incorrect methotrexate dosing[2].

Guidance on prescribing methotrexate safely has been published elsewhere[1,3].

Monitoring

It is imperative that monitoring of renal and liver function tests, full blood count and chest radiography occur before and during treatment. The Best Practice Advocacy Centre (BPAC) recommendations for monitoring methotrexate and management of methotrexate toxicity are outlined in Tables 1 and 2[3]. Please note that local guidelines may vary.

Adverse effects

The risk of serious adverse effects is greater with higher doses and with prolonged methotrexate treatment. Hepatotoxicity may occur without previous signs of gastrointestinal or haematological toxicity. Pulmonary toxicity including pneumonitis and pulmonary fibrosis can also occur at any time during therapy. Methotrexate is usually contraindicated in patients with impaired renal function[3].

Table 1: Methotrexate monitoring recommendations[3]

Laboratory monitoring	Frequency	What to do if outside limits
Full blood count (FBC)	Baseline Every two to four weeks initially, then every month to three months if results have been normal on a stable dose.	Discuss with specialist team immediately.
Liver function tests (LFTs)	Baseline Every two to four weeks initially, then every month to three months if results have been normal on a stable dose.	Withhold until discussed with specialist team. Other factors to consider: • Check alcohol intake. • Review medicines which may cause liver dysfunction (eg, NSAIDs).
Serum creatinine	Baseline Often performed at same time as LFTs and FBC monitoring during dosing changes. Every three months for patients on stable treatment.	Reduce dose.
Chest x-ray	Baseline	Repeat if respiratory symptoms occur (see below).

Table 2: Management of methotrexate toxicity[3]

Symptoms	What to do
Rash or oral ulceration	Withhold methotrexate until discussed with specialist team. Folic acid mouth wash may help with mucositis.
Nausea and vomiting, diarrhoea	Dividing the dose over the day or giving methotrexate by subcutaneous injection is often a good way of avoiding nausea.
New or increasing dyspnoea or dry cough (pneumonitis)	Withhold and discuss URGENTLY with specialist team. Arrange chest x-ray and respiratory function tests.
Severe sore throat, abnormal bruising	Request immediate FBC and withhold until results available. Discuss any unusual results with specialist team.

At 30 September 2017, the Centre for Adverse Reactions Monitoring (CARM) had received eight cases in which a medication error was identified and methotrexate was assessed as a causal medicine. These cases included patients who had taken methotrexate in the prescribed dose every day of the week instead of once a week, patients who got the wrong strength of methotrexate tablets and a patient who had taken methotrexate without adequate monitoring.

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

References

1. Waitemata District Health Board. 2017. Methotrexate — Safe Prescribing — Once A Week! *Safer Use of High Risk Medicines* May 2017. URL: **www.saferx.co.nz/full/methotrexate.pdf** (accessed 22 November 2017).
2. Pfizer New Zealand Limited. 2017. *Methotrexate DBL Data Sheet* 25 August 2017. URL: **www.medsafe.govt.nz/profs/Datasheet/d/dblMethotrexateinjmayne.pdf** (accessed 22 November 2017).
3. Best Practice Advocacy Centre. 2014. Safer prescribing of high-risk medicines — Methotrexate: potentially fatal in overdose. *Best Practice Journal* 64: 48–52. URL: **www.bpac.org.nz/BPJ/2014/October/docs/BPJ64-safer-prescribing.pdf** (accessed 22 November 2017).

Update: Varenicline and Neuropsychiatric Adverse Reactions

Key Messages

- Healthcare professionals should discuss the benefits and risks of harm of using varenicline for smoking cessation with patients.
- Patients and their families should be advised to stop taking varenicline and contact their doctor or emergency services immediately if they notice any changes in their mood, behaviour or thinking.
- Healthcare professionals should encourage patients to discuss any history of psychiatric illness before prescribing varenicline.

Recently, the US Food and Drug Administration (FDA) announced they would be removing the black box warning for serious neuropsychiatric adverse reactions from the varenicline (Champix) data sheet[1]. This decision is based on the results of a large clinical trial that evaluated the neuropsychiatric safety of varenicline for smoking cessation in patients with and without a history of psychiatric disorders[2].

In the group of patients without a history of psychiatric disorder, 1.3% of the participants in the varenicline group reported moderate and severe neuropsychiatric adverse events, compared to 2.4% in the placebo group and 2.5% in the nicotine patch group[2].

In the group of patients with a clinically stable psychiatric disorder, moderate and severe neuropsychiatric adverse events were reported in 6.5% of the varenicline group, compared with 4.9% in the placebo group and 5.2% in the nicotine patch group[2].

Varenicline, bupropion, and nicotine replacement patches were all more effective for helping people quit smoking than placebo regardless of whether or not they had a history of mental illness[2].

The data sheet for Champix notes that there have been reports of neuropsychiatric symptoms, as well as worsening of pre-existing psychiatric illness in patient's attempting to quit smoking by taking Champix[3].

Despite the recent study results, healthcare professionals are reminded to discuss with patients the benefits and risks of using varenicline as an aid to quit smoking. Patients and their families should also be advised to stop taking varenicline and contact their doctor or emergency services immediately if they notice changes in their mood, behaviour or thinking.

In the last five years (1 September 2012 to 31 August 2017), the Centre for Adverse Reactions Monitoring (CARM) has received 413 reports of suspected adverse reactions to varenicline, containing 762 reactions in total. The most frequently reported reaction was nausea (124). Of the 413 reports, 221 contained at least one neuropsychiatric reaction (361 neuropsychiatric reactions in total).

The most frequently reported neuropsychiatric reactions are shown in Table 1. There were 136 reports in females (61.5%) and 85 reports in males (38.5%). The majority of the reports were classified as not serious (90.5%). The most frequently reported age-group was 40–49 years (31.2%) (Figure 1).

Information on how to report suspected adverse reactions to medicines 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/**).

Table 1: Most frequently reported suspected neuropsychiatric reactions during the period 1 September 2012 to 31 August 2017

Neuropsychiatric reaction	Frequency (Percentage of total reports)
Dreaming abnormal	46 (6.04%)
Depression	41 (5.38%)
Insomnia	30 (3.94%)
Nightmares	25 (3.28%)
Sleep disturbed	17 (2.23%)
Anxiety	16 (2.1%)
Suicidal ideation	15 (1.97%)
Aggressive reaction	14 (1.84%)
Anger	12 (1.57%)
Emotional lability	12 (1.57%)
Irritability	12 (1.57%)

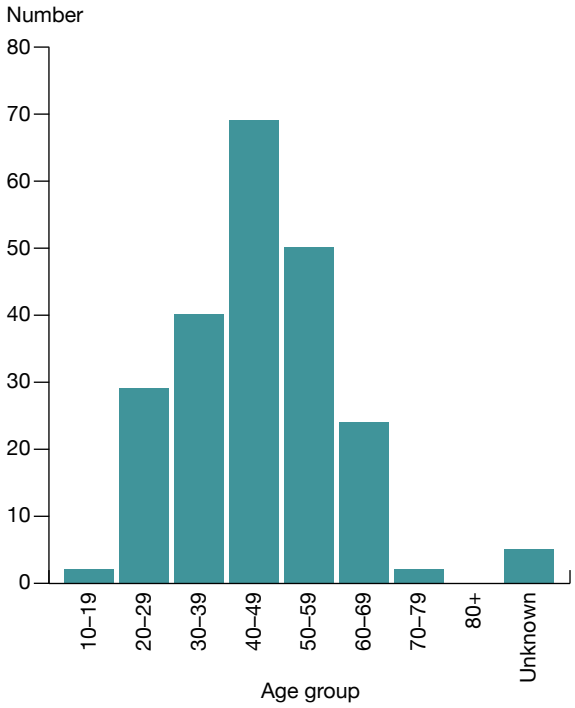

Figure 1: Suspected adverse reaction reports to varenicline containing neuropsychiatric reactions submitted to CARM during the period 1 September 2012 to 31 August 2017, by age group

References

1. Food and Drug Administration. 2016. FDA revises description of mental health side effects of the stop-smoking medicines Chantix (varenicline) and Zyban (bupropion) to reflect clinical trial findings. *Drug Safety Communications* 16 December 2016.
2. Anthenelli RM, Benowitz NL, West R, et al. 2016. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. *Lancet* 387: 2507–20.
3. Pfizer New Zealand Limited. 2017. *Champix Data Sheet* 15 March 2017. URL: **www.medsafe.govt.nz/profs/Datasheet/c/Champixtab.pdf** (accessed 15 November 2017).

Subscribe to Medicine Classification Emails

The Medicines Classification Committee (MCC) makes recommendations to the Minister of Health on the classification of medicines. Your comments are valuable to the MCC decision making process.

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NSAIDs and Heart Disease

Key Messages

- All non-steroidal anti-inflammatory drugs (NSAIDs) are associated with a small increased risk of serious cardiac events.
- The highest risk of cardiac events occurs when NSAIDs are used at the highest recommended daily doses.
- The lowest effective dose of NSAIDs should be used for the shortest possible duration.
- Patients should be advised of the risk of harm and the warning signs of cardiac problems.
- The overall benefits of using NSAIDS continue to outweigh the risk of harm when they are used according to the instructions in the data sheet.

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used to treat pain and inflammation. These medicines are available on prescription and over the counter.

Safety Concern

Research has shown that all NSAIDs are associated with an increased risk of serious cardiac events. The effect of dose and treatment duration have been extensively investigated. Currently, the frequency of these events appears to be similar for all NSAIDs.

Recent Meta-analysis

In a meta-analysis published in 2017, the risk of acute myocardial infarction in patients taking NSAIDs was analysed using real world data[1]. The analysis investigated the effects of ibuprofen, diclofenac, naproxen, celecoxib and rofecoxib. The risk of acute myocardial infarction in NSAID users was compared with non-users.

The analysis indicated that all NSAIDs were associated with an increased risk of acute myocardial infarction. The risk of myocardial infarction with celecoxib was comparable to that of traditional NSAIDs. The authors noted that the risk increased from the first week of use.

What this Study Tells Us

The recent meta-analysis indicates that there is no difference between NSAIDs or celecoxib regarding the risk of myocardial infarction.

Consistent with previous analyses, high doses were associated with greater risk of cardiac events. For example, no risk of cardiac events was found with low dose (over the counter dose) of ibuprofen[2].

Although there is small increased risk of cardiac events associated with NSAID use, the benefit outweighs the risk of harm when used according to the instructions in the data sheet.

The MARC has previously recommended that the lowest possible dose of NSAID for the shortest period of time should be used and long-term treatment with NSAIDs should be reviewed regularly[3].

Individual risk factors should be taken into account before prescribing a NSAID and the patient should be advised of the risk of harm.

Cases in New Zealand

Between January 2005 and 30 September 2017, the Centre for Adverse Reactions Monitoring (CARM) received 11 reports of myocardial infarction or cardiac arrest.

Table 1: Cases of myocardial infarction and cardiac arrest reported to CARM January 2005 to September 2017

Medicine	Myocardial infarction	Number of cardiac arrests
Celecoxib	0	0
Diclofenac	3	2
Ibuprofen	3	1
Naproxen	1	1

References

1. Bally M, Dendukuri N, Rich B, et al. 2017. Risk of acute myocardial infarction with NSAIDs in real world use: bayesian meta-analysis of individual patient data. *BMJ* 357: j1909.
2. Medsafe. 2015. Ibuprofen and Cardiovascular Risk. *Prescriber Update* 36(3): 42. URL: **www.medsafe.govt.nz/profs/PUArticles/Sep2015/Ibuprofen&Cardiovascular.htm** (accessed 17 November 2017).
3. Medsafe. 2008. Non-Selective NSAIDS – Cardiovascular, Skin and Gastrointestinal Risks. *Prescriber Update* 29(1): 15–16. URL: **www.medsafe.govt.nz/profs/PUArticles/NSAIDSRisks.htm** (accessed 17 November 2017).

Test Your Knowledge

Have you read your copies of *Prescriber Update* in 2017?

Have you kept up to date with emerging safety signals?

Test your knowledge with the end-of-year *Prescriber Update* quiz.

Answers to the quiz are at the bottom of page 63 or at **www.medsafe.govt.nz/profs/PUPDF.asp**.

1. **The major safety concern with the use of levetiracetam is an increase in mood disorders, including suicidality, and patients should be monitored for changes in behaviour.**

   True False

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

   a) If a pharmaceutical company wishes to sell or distribute a medicine in New Zealand, data from pre-clinical studies is not needed.

   b) Before a medicine can be sold in New Zealand, an application must be submitted to Medsafe to seek the Minister's consent to distribute the medicine.

   c) Applications can be made for provisional consent where there is a clinical need for the medicine and use is expected to be in a limited number of patients.

   d) The Medicines Assessment Advisory Committee can provide advice to the Minister of Health in instances where Medsafe is not able to recommend that consent to distribute a medicine in New Zealand is granted.

3. **It is safe to give Zostavax vaccine to patients who are immunosuppressed or immunodeficient.**

   True False

4. **What medicine is currently on Medsafe's M² scheme associated with a possible effect on blood glucose control when used in patients with type 2 diabetes?**

5. **Which of these medicine classes are associated with a high (>10%) risk of hepatitis B reactivation?**

   a) TNF-α inhibitors

   b) Tyrosine kinase inhibitors

   c) B-cell depleting agents

   d) Cytokine inhibitors and integrin inhibitors

6. **Olanzapine has not been associated with DRESS.**

   True False

7. **Which of the following is not a consequence of JC virus reactivation?**

   a) Progressive Multifocal Leukoencephalopathy

   b) Granule Cell Neuronopathy

   c) Guillain Barre Syndrome

   d) Encephalopathy

8. It is important to regularly monitor which of the following in all patients taking methotrexate.

a) Renal function b) Liver function c) Respiratory symptoms

d) Full blood count e) All of the above

9. Tramadol is contraindicated in children under two years of age.

True False

10. Which of the following topical corticosteroids is the most potent?

a) Hydrocortisone 1%

b) Betamethasone dipropionate 0.05% in propylene glycol base

c) Betamethasone dipropionate 0.05%

d) Clobetasone butyrate 0.05%

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
16 October 2017	Consumer Information Leaflet	Taking metformin for gestational diabetes (PDF 255 KB, 2 pages)
29 September 2017	Media Release	Medsafe highlights the dangers of purchasing medicines over the internet
22 September 2017	Alert Communication	Consumer Level Recall - Maxiclear Sinus & Pain Relief and Maxiclear Cold & Flu Relief
25 August 2017	Monitoring Communication	Watch out for INR changes when direct-acting antivirals (DAAs) are used concomitantly with warfarin
21 August 2017	Alert Communication	Gadolinium based contrast agents for MRI and retention of gadolinium in the brain

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

Quiz Answers

1. True 2. a) 3. False 4. Viekira Pak, Viekira Pak-RBV 5. c) 6. False 7. c) 8. e) 9. True 10. b)

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In response to the *Prescriber Update* survey in March 2016, *Prescriber Update* will gradually move towards a predominantly online publication.

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