Prescriber Update

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Quetiapine — Delivering Hepatic Reactions?

Key Messages

- ⌘ Hepatic adverse effects may occur with the use of quetiapine.
- ⌘ The most commonly reported hepatic adverse reaction is elevated liver enzymes.
- ⌘ Cases of hepatitis and hepatic failure have been reported.
- ⌘ Caution is advised in patients with known hepatic impairment, in patients who are being treated with potentially hepatotoxic medicines or if there are treatment-emergent signs or symptoms of hepatic impairment.

Healthcare professionals are reminded of the potential risk of hepatic adverse effects associated with the use of quetiapine, an atypical antipsychotic.

Quetiapine is extensively metabolised by the liver. Elevations in liver enzyme levels, including aspartate aminotransferase(AST), alanine aminotransferase (ALT) and gamma-GT may occur. Hepatitis has been reported rarely and hepatic failure very rarely during post-market monitoring. The exact mechanism of these hepatic reactions is currently unknown.

Therefore, precautions are recommended when using quetiapine:

- in patients with pre-existing hepatic disorders
- in patients who are also being treated with potentially hepatotoxic medicines
- if signs or symptoms of hepatic impairment develop during treatment.

Dose adjustments or a reduced starting dose of quetiapine may be needed. Data sheets for quetiapine products are in the process of being updated with this information.

The Centre for Adverse Reactions Monitoring (CARM) has received 13 reports of hepatobiliary reactions with the use of quetiapine. The majority of these reports concerned increases in hepatic enzymes (also referred to as 'hepatic function abnormal' in the CARM database). There has also been one case of a hepatic cyst and one case of hepatic failure reported to CARM.

Adverse Reaction Reporting in Older Patients

Reporting suspected adverse reactions to the Centre for Adverse Reactions Monitoring (CARM) is important for all patients independent of age. It is particularly important for older patients who are more likely to be affected by adverse reactions to medicines due to co-morbidities and reduced renal and hepatic function. Reporting these suspected adverse reactions allows Medsafe and CARM to identify possible safety concerns specific to older people.

During the five-year period from 2012 to 2016, 17.3% of all cases reported to CARM were in the 65–79 year age group and 5.8% of all cases were in the 80 years and over age group. These proportions have remained consistent over the last five years (Figure 1). Please note that one report may contain multiple medicines and multiple reactions.

Dabigatran was most commonly associated with a suspected adverse reaction reported to CARM in the last five years in both the 65–79 year age group (6.2% of the 3,729 cases) and the 80 years and over group (13.4% of the 1,265 cases) (Table 1).

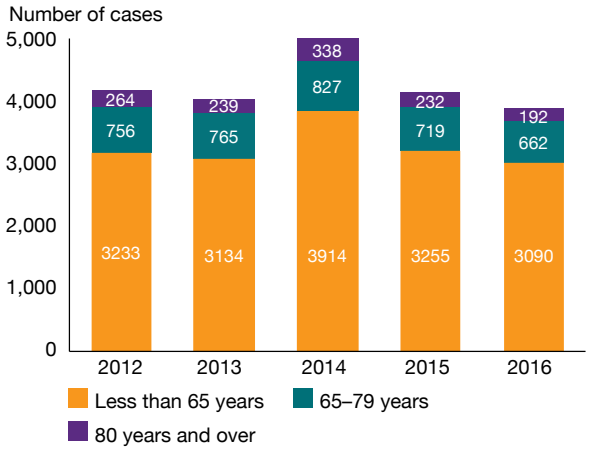

Figure 1: Number of cases of suspected adverse reactions to medicines reported to CARM from 2012 to 2016

Interestingly, no bleeding reactions were in the top five reactions reported. This is likely due to there being multiple bleeding terms available.

Table 1: Top five medicines reported to CARM in older patients in the last five years, 2012–2016

	Age 65–79	Age 80 and over
1	Dabigatran	Dabigatran
2	Iohexol	Zoledronic acid
3	Influenza vaccine	Influenza vaccine
4	Zoledronic acid	Clozapine
5	Clozapine	Omeprazole

The contrast agent, iohexol, was the second most reported medicine associated with a suspected adverse reaction in the 65–79 year age group (4.9% of cases). In the 80 years and over age group, the second most reported medicine was zoledronic acid (5.3% of cases). The influenza vaccine was the third most reported medicine in both age groups (4.9% of cases in the 65–79 year age group and 3.6% of cases in the 80 years and over group).

Clozapine is included in the top five medicines reported in both age groups. This is likely due to the monitoring requirements associated with clozapine.

For the five-year period, the most commonly reported suspected reaction to a medicine taken by patients in both age groups was rash (Table 2). In the 65–79 year age group, rash was reported in 5.5% of the 3,729 cases. In the 80 years and over age group, rash was reported in 5.4% of the 1,265 cases.

Table 2: Top five reactions reported to CARM in older patients in the last five years, 2012–2016

	Age 65–79	Age 80 and over
1	Rash	Rash
2	Nausea	Dyspnoea
3	Urticaria	Pruritus
4	Dyspnoea	Nausea
5	Injection site inflammation	Rash pruritic

Healthcare professionals are encouraged to report any suspected adverse reaction(s) to CARM (**https://nzphvc.otago.ac.nz/**). Information about how to submit an adverse reaction report can be found on the Medsafe website (**www.medsafe.govt.nz/profs/adverse.asp**) or on the CARM website (**https://nzphvc.otago.ac.nz/reporting/**).

Spotlight on Levetiracetam

Key Messages

- Levetiracetam is an antiepileptic medicine used as add-on therapy in the treatment of epilepsy.
- The major safety concern with use of levetiracetam is an increase in mood disorders including suicidality.
- Patients, their relatives and friends should be asked to closely monitor for changes in behaviour and to seek immediate medical attention should any changes occur.
- Monitoring renal function and changes in dose may be required in patients with impaired renal function.

The *Prescriber Update* survey ran between 3 March 2016 and 8 April 2016. Feedback from this survey indicated that readers would like to see more reviews about the safety of specific medicines and classes of medicines. The first spotlight article is on levetiracetam.

Levetiracetam is approved as add-on treatment for partial onset seizures with or without secondary generalisation in patients aged six years and older [1,2].

Levetiracetam is an unusual medicine in that almost 100% of the dose is absorbed via the oral route. For this reason, it is generally considered acceptable to change brands without the need for additional monitoring[3]. However, reactions associated with changing the brand of levetiracetam have been reported to the Centre for Adverse Reactions Monitoring (CARM).

Levetiracetam is excreted renally with around 95% of the dose excreted in the urine. A dose adjustment based on the patient's creatinine clearance is necessary in patients with moderate to severe renal impairment[1].

The only contraindication for use is hypersensitivity reactions. Levetiracetam must not be used in patients allergic to levetiracetam, other pyrrolidone derivatives or any of the excipients in the medicine. The 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**).

All patients who are taking levetiracetam should be closely monitored for changes in behaviour. Psychiatric disorders that have been associated with the use of levetiracetam include aggression, abnormal behaviour, suicide and suicidality[1]. Patients, relatives and friends should be encouraged to monitor behaviour and to seek immediate medical advice if changes are noticed. Healthcare professionals are reminded to inform patients and their families and caregivers of the potential risk of suicidality[1].

Further information regarding antiepileptic medicines and suicide can be found in previous *Prescriber Update* articles [4-6].

At 31 December 2016, the Centre for Adverse Reactions Monitoring (CARM) had received 35 reports in which levetiracetam was reported as a suspect medicine. Reaction terms that were reported twice or more include irritability, mood disorder, depression, hyponatraemia, neutropenia, suicidal ideation, vomiting, aggressive reaction and brand switch. All of these potential adverse reactions, excluding brand switch, are listed in the New Zealand data sheet for levetiracetam[1,7].

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

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DRESS: A Pleat for Help

Key Messages

- DRESS is characterised by rash, fever, haematologic abnormalities, lymphadenopathy and internal organ involvement.
- Medicines most commonly associated with DRESS are antiepileptics and allopurinol.
- Olanzapine has recently been associated with DRESS.

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a potentially life-threatening drug-induced hypersensitivity reaction with an estimated mortality of 10%[1]. It is characterised by rash, fever, haematologic abnormalities (eosinophilia, atypical lymphocytosis), lymphadenopathy and internal organ involvement (liver, kidneys, lungs)[1–3].

Healthcare professionals are reminded there are many medicines that have been associated with DRESS (Table 1). Antiepileptics (eg, carbamazepine, lamotrigine, phenytoin) and allopurinol are the medicines most frequently associated with DRESS in the scientific

Table 1: Examples of medicines associated with DRESS[5]

Frequently reported	Allopurinol, carbamazepine, lamotrigine, phenytoin, sulfasalazine, vancomycin, minocycline, dapsone, sulfamethoxazole
Also reported	Beta-lactam antibiotics, nevirapine, olanzapine, oxcarbazepine, strontium ranelate, telaprevir

literature[4]. Sulphonamides, minocycline and vancomycin may also cause DRESS[5].

Most recently, in May 2016, the United States Food and Drug Administration (FDA) warned that olanzapine may cause DRESS[6]. Medsafe is working to ensure that the New Zealand data sheets for all olanzapine-containing products include information on DRESS.

The Centre for Adverse Reactions Monitoring (CARM) has received 39 case reports that included a diagnosis of DRESS from 1 January 2012 to 31 December 2016. The most commonly reported suspected medicines were allopurinol (13 cases), vancomycin (4), piperacillin/tazobactam and sulfasalazine (3 each).

Further information on DRESS is available in a previous edition of *Prescriber Update* (**www.medsafe.govt.nz/profs/PUArticles/DRESSsyndromeJune2011.htm**).

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Prescribing Cannabis-based Products

The use of cannabis-based products for medicinal purposes is attracting considerable public interest in New Zealand and internationally. In New Zealand, over the past few years, there has been increasing public pressure on prescribers, the Ministry of Health and Government to enable greater access to products derived from the cannabis plant. Cannabinoid products can also be manufactured synthetically and have been available in the United States and some other countries for several years. However, most advocates of the medical benefits of cannabis believe that products derived from plant material are more effective.

The Government prefers to refer to '*cannabis-based products*' rather than '*medicinal cannabis*' because the majority of the products available do not meet the criteria normally associated with a medicine. That is, the products are not manufactured to international good manufacturing practice (GMP) standards for pharmaceutical-grade products. Evidence of the composition of these products, the reproducibility of the composition from batch to batch and the stability of the products in use is not available. Evidence of the safety and efficacy of most of the individual products from clinical trials is lacking. Nonetheless, an evidence base for the use of cannabis for medicinal purposes is developing.

Evidence

There are now a large number of clinical trials of cannabis-based medicines reported and several systematic reviews[1–3]. The majority of trials have used synthetically produced medicines. Evidence of the efficacy of cannabis-based medicines in certain conditions is now emerging and there is good agreement across the systematic reviews as to the benefits of cannabis-based products and also the potential harms.

The most recent and comprehensive review is *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*[1].

Information for Healthcare Professionals

Health Canada has a comprehensive publication *Information for Health Care Professionals: Cannabis (marihuana, marijuana) and the cannabinoids* (**www.hc-sc.gc.ca/dhp-mps/marihuana/med/infoprof-eng.php**). It was published in February 2013 and an update is due later in 2017.

This publication provides comprehensive information on pharmacology and potential therapeutic uses. Please note that in Canada, cannabis is available for smoking from federally licensed producers and since the publication of this document patients have again been allowed to grow their own cannabis pursuant to a medical document.

The Therapeutic Goods Administration (TGA) in Australia is undertaking a systematic review with the aim to develop clinical guidelines to educate and assist prescribing choices. They aim to complete this review in 2017. In the interim, the Queensland Department of Health has developed the first clinical guidelines for Australia (**www.health.qld.gov.au/__data/assets/pdf_file/0023/634163/med-cannabis-clinical-guide.pdf**).

The Queensland Department of Health notes that this guide will be replaced by the national document when completed. The information is mostly transferable to the New Zealand situation. One principal difference is that Sativex is available in New Zealand, whereas it is imported on an individual patient approval basis in Australia.

Products

At the time of writing, Sativex is the only cannabis-based medicine with consent (approval) for distribution in New Zealand. Sativex is indicated as add-on treatment for symptom improvement in patients with moderate to severe spasticity due to multiple sclerosis who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity-related symptoms during an initial trial of therapy. Sativex for other indications is unapproved.

All other cannabis-based products are unapproved in New Zealand. Prescribers need to be clear on their responsibilities under the *Code of Health and Disability Services Consumers' Rights* to ensure that the patient is fully informed and that written consent is obtained. Please see the Medsafe Guidelines for Use of Unapproved Medicines (**www.medsafe.govt.nz/profs/RIss/unapp.asp**).

Other products that the Ministry of Health believes are of pharmaceutical grade or are GMP certified for at least part of the manufacturing process are Tilray and Bedrocan.

Tilray products are manufactured by a Canadian company. Tilray has oil and capsule products that have been produced to GMP standards for the cultivation and extraction of the active ingredients, but the Ministry of Health does not consider that the products are pharmaceutical grade.

Bedrocan products are obtained from certified sites in the Netherlands. Bedrocan has a range of standardised plant (cannabis flowers, often called flos, and granulated plant material) products with different standardised concentrations of THC and CBD. The recommended method of administration for Bedrocan is via a medical vaporisation device.

Other cannabinoid-based medications include Marinol containing dronabinol (a synthetic THC), Cesamet containing nabilone (a synthetic analogue of THC) and Syndros, a liquid formulation of dronabinol. These are medicines based on cannabinoids but have been manufactured synthetically rather than derived from cannabis plant material. They are all pharmaceutical grade, FDA approved and can legally be exported from the United States.

All other available cannabis-based products produced in the United States that the Ministry of Health is aware of are not pharmaceutical grade. Cannabis-based products derived from plant material are also classified as Schedule 1 substances, which means that they cannot be legally exported from the United States.

To date, the Ministry of Health has only received applications to prescribe and import one particular Tilray product. The Ministry of Health has not tested the availability of the other products listed above.

Application Process

Cannabis-based products are Class B1 or C1 controlled drugs and Ministerial approval is required before these can be prescribed, supplied or administered, in accordance with Regulation 22 of the Misuse of Drugs Regulations 1977.

Ministerial approval is now delegated to the Ministry of Health for all types of cannabis-based products.

To prescribe cannabis-based products:

1. an application to the Ministry of Health is required in most cases. The **exception** is when prescribing Sativex for the consented condition of multiple sclerosis. In this case, a general ministerial approval has been gazetted to allow medical practitioners with a vocational scope of practice of Internal Medicine (specialising in neurology), or a general practitioner on the recommendation of a neurologist, to prescribe Sativex for multiple sclerosis without an application to the Ministry.
2. a specialist needs to be involved in the application process in all instances, and needs to make the application to the Ministry of Health, except for applications for off-label uses of Sativex when a GP can apply following the recommendation of a specialist.

Further information and application forms can be found on the Ministry of Health website (**www.health.govt.nz/our-work/regulation-health-and-disability-system/medicines-control/prescribing-cannabis-based-products**).

If you have any questions relating to an application, or potential application, for a cannabis-based product please email **medicinescontrol@moh.govt.nz**

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Fluoride Content in Toothpaste for Children

Key Messages

- ⌘ Reduction of dental caries by fluoride toothpaste is balanced against the increased risk for dental fluorosis due to toothpaste ingestion by young children.
- ⌘ Toothpastes containing less than 1,000 ppm fluoride are not recommended for use at any age in New Zealand.
- ⌘ To minimise the risk of ingestion of toothpaste, children should be supervised when brushing their teeth, a smear of toothpaste (five years and under) or a pea-sized amount (six years and over) should be used and children should be taught to spit out any excess.
- ⌘ Toothpaste should be kept out of reach of children.

The use of fluoride toothpaste is an important public health measure to both prevent and reduce the severity of dental caries in all age groups. The protective effect of fluoride against caries is well recognised.

Fluoride works topically primarily by reducing demineralisation and enhancing remineralisation of enamel, reducing the susceptibility of the teeth to caries progression. A sustained level of fluoride in plaque and on the enamel surface is desirable and one important source is fluoride toothpaste. Fluoride in toothpaste is usually in the form of sodium fluoride (NaF) or sodium monofluorophosphate (MFP).

Commercially available fluoride toothpastes for general sale in New Zealand have differing levels of fluoride content ranging from approximately 500 parts per million (ppm) to 1,450 ppm fluoride. The 500 ppm formulations are labelled for children under six years by manufacturers, leading to confusion for consumers, as these low fluoride toothpastes are not recommended at any age in New Zealand[1].

The *New Zealand Guidelines for the Use of Fluoride* recommends that 1,000 ppm fluoride toothpaste is used for children of all ages[2]. A recent Cochrane review found limited evidence of any caries preventive effect following use of toothpaste with less than 1,000 ppm fluoride[3]. Commencing tooth brushing with fluoride toothpaste before two

years of age is associated with enhanced caries prevention.

The beneficial effects of fluoride toothpaste must be counterbalanced against the risk of dental fluorosis from its ingestion. The risk of dental fluorosis is of aesthetic concern and relates to ingestion of excess fluoride in children under age five years.

New Zealand studies show that the prevalence of diffuse enamel opacities that may be fluoride-related has not increased over time and that all cases recorded were either mild or very mild[4–6]. The evidence regarding the role of fluoride toothpaste in contributing to the risk of fluorosis is conflicting and may be related to the amount used, the concentration used and commencing use before age 12–14 months[7].

New Zealand recommendations for toothpaste use in young children balance the issue of caries prevention and avoidance of moderate or severe dental fluorosis. The recommendation to use toothpaste of at least 1,000 ppm fluoride addresses the lack of evidence of a caries preventive effect for toothpaste below this concentration.

The recommendation to use a smear of toothpaste for children five years and under controls the amount of toothpaste that should be used. The recommendation to commence use of toothpaste as soon as teeth begin to emerge (approximately six months) recognises that teeth are at risk of dental caries from that time, the high levels of early childhood dental caries in New Zealand children and the lack of evidence of moderate or severe dental fluorosis in New Zealand children[8].

Pharmacies and dental practices can also supply a 5,000 ppm fluoride toothpaste, which is not suitable for general use, but may be recommended in specific cases mainly in adults and in older children with high levels of dental caries. This toothpaste should be limited to use on the recommendation of an oral health professional.

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MARC's Remarks: March 2017 Meeting

The Medicines Adverse Reactions Committee (MARC) met on 9 March 2017 to discuss a number of medicine-related safety issues.

The MARC discussed the concomitant use of **opioids, benzodiazepines and other CNS depressants** and the risk of serious side effects. Usage trends, deaths, over-the-counter (OTC) availability of codeine and other opioids, the amount funded by PHARMAC on prescription, prescribing practices in primary and secondary care, and information included in data sheets were discussed. Further information on the MARC's discussion on this topic can be found on the Medsafe website (**www.medsafe.govt.nz/profs/adverse/Minutes169.htm**).

The MARC discussed Medsafe's proposed monitoring for the National Immunisation Schedule change for **varicella vaccine** (Varilrix) against chickenpox and considered this to be adequate. Healthcare professionals are encouraged to report any suspected adverse reactions to varicella vaccines to the Centre for Adverse Reactions Monitoring (CARM).

It is also important to note that Varilrix and Varivax are varicella vaccines used to vaccinate against chickenpox and can be used in children, whereas Zostavax is a zoster vaccine used for the prevention of shingles in individuals 50 years of age and above. Further information on the

differences between these vaccines can be found in a previous edition of *Prescriber Update*[1].

The MARC discussed the use of **anaesthetic and sedative agents** in young children. Clinical studies conducted in humans are predominantly observational and have shown conflicting results for neurotoxicity and effects on brain development. It is not clear if the association is a true effect of anaesthetic agents, the surgery or underlying condition requiring surgical intervention, or due to uncontrolled confounding of other factors.

Overall, the MARC considered that the evidence for an association between the use of anaesthetics in young children and risk of neurotoxicity was equivocal, but that parents should be informed about this safety concern. Further information is available from the United States Food and Drug Administration (**www.fda.gov/Drugs/DrugSafety/ucm532356.htm**).

The MARC noted the revised dosing recommendations for use of **etoricoxib** for rheumatoid arthritis and ankylosing spondylitis. Healthcare professionals are reminded that the recommended dose listed in the data sheet for these indications is now 60 mg or 90 mg once daily. The minimum effective daily dose is 60 mg once daily and dose escalation to 90 mg should be considered on an individual patient basis.

Further information on this meeting can be found on the Medsafe website (**www.medsafe.govt.nz/profs/adverse/Minutes169.htm**).

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Dopamine Agonists and Impulse Control Disorders

Key Messages

- ⌘ Impulse control disorders are a recognised adverse effect associated with the use of dopaminergic medicines.
- ⌘ Impulse control disorders include compulsive shopping, problem gambling, binge-eating and hypersexuality.
- ⌘ Prescribers are reminded to enquire about symptoms of impulse control disorders when reviewing patients on dopamine agonists or levodopa.

Impulse control disorders are a recognised adverse effect associated with the use of dopaminergic medicines, including dopamine receptor agonists and levodopa. Currently approved dopamine receptor agonists include ropinirole, pramipexole, bromocriptine, pergolide, apomorphine and cabergoline. Levodopa is approved in combination products containing either benserazide or carbidopa.

Impulse control disorders include compulsive shopping, problem gambling, binge-eating and hypersexuality. Patients and their family/caregiver should be alerted to the possibility of these adverse reactions, which can have disastrous personal and financial consequences. Patients may be embarrassed about their behaviour and may not volunteer that they are unable to control, for example, their spending or gambling.

The Centre for Adverse Reactions Monitoring (CARM) has received two reports of compulsive gambling associated with the use of dopamine agonists.

1. 2007: problem gambling reported in a 55-year-old female in association with ropinirole and paroxetine. Ropinirole was stopped, but the outcome was unknown.
2. 2008: problem gambling reported in a 74-year-old male in association with ropinirole, levodopa, clonazepam, selegiline and doxazosin. The patient recovered following withdrawal of ropinirole.

Prescribers are reminded to enquire about symptoms of impulse control disorders when reviewing patients on dopamine agonists or levodopa. Reduction in the dose or tapered discontinuation of the dopaminergic medicine should be considered if symptoms of an impulse control disorder develop during treatment with these medicines.

Gathering Knowledge from Adverse Reaction Reports: June 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: 123194 **Age:** 29 **Gender:** Female **Medicine(s):** Jadelle**,** Rifampicin **Reaction(s):** Unintended pregnancy	The unintended pregnancy occurred approximately one year after Jadelle insertion and about six months after starting rifampicin.
	The Jadelle data sheet (**www.medsafe.govt.nz/profs/Datasheet/j/Jadelleimplant.pdf**) states that rifampicin diminishes the efficacy of Jadelle by enzyme induction. Enzyme induction can be observed within a few days of treatment and may be sustained for about four weeks after cessation of the inducer.
CARM ID: 123149 **Age:** 15 **Gender:** Male **Medicine(s):** Sodium valproate **Reaction(s):** Hyperammonaemia	The patient experienced hyperammonaemia encephalopathy. On review, the patient was found to have an elevated sodium valproate level and five times normal range of ammonia in blood.
	The sodium valproate data sheet (**www.medsafe.govt.nz/profs/Datasheet/e/Epilimtabsyrliqiv.pdf**) notes hyperammonaemic encephalopathy, sometimes fatal, has been reported following initiation of valproate therapy in patients with urea cycle disorders, a group of uncommon genetic abnormalities, particularly ornithine transcarbamylase deficiency. Patients who develop symptoms of unexplained hyperammonaemic encephalopathy while receiving valproate therapy should be evaluated for underlying urea cycle disorders.
CARM ID: 123120 **Age:** 78 **Gender:** Female **Medicine(s):** Venlafaxine **Reaction(s):** Hyponatraemia	Five days after starting venlafaxine the patient's serum sodium had dropped to below 120 mmol/L. A week after discontinuing venlafaxine, the patient's serum sodium levels had returned to baseline.
	The data sheet for venlafaxine (**www.medsafe.govt.nz/profs/Datasheet/e/Efexorxrcap.pdf**) states cases of hyponatraemia may occur with venlafaxine. Older patients, patients taking diuretics and patients who are otherwise volume depleted, may be at greater risk for this event. These have resolved on discontinuation of the drug.
CARM ID: 120887 **Age:** 12 **Gender:** Male **Medicine(s):** Prednisone, Methylprednisolone, Hydrocortisone **Reaction(s):** Bilateral cataracts	The patient's severe eczema was treated with topical and systemic steroids. The patient developed bilateral cataracts with vision reduced to light perception.
	The prednisone data sheet (**www.medsafe.govt.nz/profs/Datasheet/a/Apoprednisonetab.pdf**) states that prolonged use of corticosteroids may produce subcapsular cataracts and nuclear cataracts (particularly in children).

The Medsafe Files — Episode Four: New Medicines Assessment (Part 1)

Key Messages

- ⌘ Before medicines and related products can be sold in New Zealand, a New Medicine Application must be submitted to Medsafe to seek the Minister's consent to distribute a medicine.
- ⌘ Consent to distribute a medicine may be attained via a full evaluation process or an abbreviated evaluation process.
- ⌘ Provisional consent may be granted when it is desirable for a medicine to be sold, supplied or used on a restricted basis for the treatment of a limited number of patients.
- ⌘ The Medicines Assessment Advisory Committee provides advice to the Minister of Health on the benefits and risks of new medicines.

New Medicine Applications (NMAs)

Medicines and related products (see Section 2 of the Medicines Act 1981 [the Act] for definitions) need consent from the Minister of Health before being marketed in New Zealand. When seeking consent to distribute a new medicine, a New Medicine Application (NMA) must be submitted to Medsafe by the New Zealand sponsor. A new medicine is a medicine for which consent for distribution in New Zealand has not been granted or the approval has lapsed.

Medsafe also has an abbreviated evaluation procedure, which is based on a medicine's approval by another recognised regulatory agency (eg, European Medicines Agency, Therapeutic Goods Administration of Australia, Health Canada). A review of overseas regulatory reports does not mean that the originator approval will be adopted in full by Medsafe. This evaluation process is not applicable to all medicine applications.

Applications can also be made for provisional consent (under Section 23 of the Act). Provisional consent is defined mainly by the clinical need. It is ideally suited to medicines still undergoing clinical development but where it is desirable that patients have early access. It is anticipated that the medicine will be used on a restricted basis for the treatment of a limited number of patients. Provisional consent is only granted for a period not exceeding two years and will then expire, unless the sponsor applies for a renewal.

Clinical Assessment

Supporting data must be included in an application to demonstrate the safety, efficacy and quality of the ingredients and the final product. The regulatory assessment of new medicines ideally follows pharmaceutical product development. Medsafe evaluators carry out pharmaceutical chemistry and clinical assessments.

If a pharmaceutical company wishes to sell or distribute a medicine in New Zealand, data from preclinical studies must be submitted as part of the application. Data includes:

- toxicity studies
- mutagenicity studies
- carcinogenicity studies
- single and repeated dose toxicity (in two species)
- first in human studies
- dose-ranging studies
- pivotal trials.

Parts 2 and 3 of *Episode Four: New Medicines Assessment* will cover pharmaceutical chemistry assessment and pharmaceutical Good Manufacturing Practice and will be included in upcoming editions of *Prescriber Update*.

Medicines Assessment Advisory Committee (MAAC)

After the evaluation of a NMA, Medsafe evaluators will make a recommendation on whether or not consent should be granted.

In instances when Medsafe is not able to recommend that consent is granted, applications can be referred to the Medicines Assessment Advisory Committee (MAAC). The MAAC has expertise in the safety, quality and efficacy of medicines and provides advice to the Minister of Health on the benefits and risks of new medicines.

Applications are referred to the MAAC in situations such as when:

- it is for a new vaccine indicated in children
- it is a novel technology such as medicines derived from stem cells and nanotech
- it is for a medicine that has been withdrawn or refused consent by a recognised regulator
- other regulators differ in their approvals
- it is a world first new chemical entity
- Medsafe is unsure whether to recommend consent.

Change Medicine Notifications (CMNs)

The sponsor of a product must notify the Director-General of Health of planned changes to an approved product. This type of application is called a Change Medicine Notification (CMN) and includes data sheet updates and package labelling updates for over-the-counter medicines.

CMNs are assessed to ensure the change does not adversely affect the quality or benefit/risk balance of the medicine.

Some product changes such as additional indications, new sites of drug substance manufacture, failure to respond to requests for information or extensions to the current indication or dosing regimen require additional assessment by Medsafe. These applications may be referred to the Minister of Health under Section 24(5) of the Act when the proposed changes are of such a character or degree that the medicine should not be distributed without the consent of the Minister of Health. Consequently, CMNs referred under Section 24(5) typically have a longer processing time frame than a CMN.

Further information on application processes and the MAAC is outlined in Part 2 of the Guideline on the Regulation of Therapeutic Products in New Zealand (GRTPNZ) (**www.medsafe.govt.nz/regulatory/Guideline/GRTPNZ/Part2.pdf**).

Recent Approvals of Medicines Containing a New Active Ingredient

For period 16 January 2017 to 15 April 2017

Trade Name (active ingredient)*	Dose form and strength	Therapeutic area
Descovy (emtricitabine/**tenofovir**)†	Tablet 200 mg/10 mg and 200 mg/25 mg	HIV-1 infection
Eliriduc/Golyra/Praluent (**alirocumab**)§	Solution for injection 75 mg/mL and 150 mg/mL	Hypercholesterolaemia
Ilevro (**nepafenac**)	Eye drops, suspension 0.3%	Postoperative pain and inflammation associated with cataract surgery
Perjeta (**pertuzumab**)	Concentrate for infusion 420 mg/14 mL	HER2-positive breast cancer
Tecentriq (**atezolizumab**)#	Concentrate for infusion 1,200 mg/20 mL	Metastatic non-small cell lung cancer (NSCLC) or urothelial carcinoma

* New active ingredient shown in bold type

† The new active ingredient in Descovy is tenofovir alafenamide fumarate (TAF), which replaces tenofovir disoproxil fumarate (TDF) in the related product Truvada

§ Not available

Provisional consent

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

Mitochondrial Disorders: Medicines to Avoid

Key Messages

- Medicines can affect a variety of mitochondrial functions.
- Medicines that are toxic to mitochondrial functions should be avoided in patients with mitochondrial disorders.
- Due to the great diversity in mitochondrial disease manifestations differing outcomes can be reported in different patients for the same medicine.

Mitochondrial disorder (disease) is a collective term for a group of disorders that can affect many different organs. There is no specific treatment for these disorders although the symptoms they cause may be managed with medicines, surgery or diet. One of the important aims of managing patients with mitochondrial disorders is to avoid medicines that are toxic to mitochondrial functions[1,2].

Mitochondria are thought originally to be free-living aerobic bacteria that were captured into non-bacterial cells. Mitochondria have their own DNA that replicates independently of nuclear DNA under the control of enzymes similar to those in bacteria. Mitochondria are responsible for energy production via the respiratory chain and oxidative phosphorylation. Other functions include beta-oxidation, iron metabolism, copper metabolism, heat production, apoptosis, calcium signalling, haem synthesis, steroid synthesis and amino acid metabolism[2–4].

Genetic mitochondrial diseases are due either to mutations in the mitochondrial DNA (mtDNA) or the nuclear DNA (nDNA). Mitochondrial disease can affect the brain, heart, liver, skeletal muscles, kidney, endocrine system and respiratory systems. The symptoms within these systems are diverse and may be due to a number of different defects within the mitochondria[1,5].

Medicines can affect many of the different functions within the mitochondria. The mitochondrial respiratory chain (MRC) is composed of five enzyme complexes: I-V and uses cytochrome c and coenzyme Q10, which act as electron carriers. Pharmacotherapy induced MRC dysfunction may result from the direct inhibition of one or more of the enzyme complexes or uncoupling of oxidative phosphorylation. As the enzyme complexes are susceptible to free radical-induced oxidative damage, medicines that cause oxidative stress may also result in MRC toxicity. The replication of mtDNA and protein synthesis may also be affected by medicines[2,4].

High quality evidence of the effects of medicines in people with mitochondrial disease is sparse. Much of the available information is derived from *in vitro* or animal studies. Additionally, due to the great diversity in mitochondrial disease manifestations, conflicting outcomes can be reported in different patients for the same medicine. Consensus appears to be lacking on which medicines should be completely avoided and which may be used with close monitoring[1–5]. A summary of the available data is provided in Table 1.

Table 1: Medicines to avoid in patients with mitochondrial disease[1–5]*

Medicine	Proposed mechanism	Adverse effects related to mitochondrial toxicity
Amiodarone	Inhibits MRC I and III and beta oxidation	Pulmonary toxicity, microvesicular steatosis and liver failure
Antibiotics: gentamicin, chloramphenicol, tetracycline	Reduces mt protein synthesis	Deafness, renal failure, myopathy
Anti-cancer medicines: doxorubicin, cisplatin	mtDNA mutation	Cardiomyopathy
Antipsychotics: haloperidol, risperidone, clozapine	Inhibits MRC I, increases reactive oxygen species, inhibits oxidative phosphorylation	Extrapyramidal symptoms, metabolic syndrome
Aspirin	Inhibits oxidative phosphorylation and beta oxidation	Causes a Reye-like syndrome

Beta-blockers: metoprolol, propranolol	Inhibits MRC I	Case report of muscle wasting
Ciprofibrate	Inhibits MRC I, weak peroxisome proliferator activated receptor ligand	Myopathy and rhabdomyolysis
Corticosteroids	Inhibit mt membrane potential, generate reactive oxygen species	Myopathy
Fluoxetine	Inhibits MRC I and V, interferes with cytochrome c	Gastrointestinal damage
Isoflurane	Inhibits MRC I	Hepatotoxicity
Isoflurane / halothane / sevoflurane	Inhibits MRC I	Hepatotoxicity, neurotoxicity cardiac effects
Linezolid	Inhibits mt protein synthesis	Polyneuropathy and lactic acidosis
Local anaesthetics: bupivicane, lidocaine	Inhibtis MRC V, increases reactive oxygen species, inhibits oxidative phosphorylation	Myopathy
Metformin	Inhibits MRC I	Causes lactic acidosis
Nicotine	Inhibits respiratory chain	
Non-steroidal anti-inflammatory drugs: ibuprofen, diclofenac, naproxen	Inhibits oxidative phosphorylation and beta oxidation	Hepatotoxicity
Nucleoside reverse transcriptase inhibitors: zidovudine, didanosine, lamivudine, abacavir	mtDNA depletion which then affects all functions	Encephalomyopathy, anaemia, polyneuropathy, pancreatitis and lactic acidosis
Paracetamol (overdose)	MRC I	Hepatotoxicity
Phenytoin	Inhibits mt ATPase	Case report of intestinal pseudo obstruction, may cause hepatotoxicity
Pioglitazone	Inhibits MRC I, weak, peroxisome proliferator activated receptor ligand	Increases anaerobic glycolysis
Propofol (particularly > 4 mg/kg/h for > 48 hours)	Inhibition of free fatty acid entry to mt, beta oxidation	Propofol infusion syndrome: metabolic acidosis, rhabdomyolysis, heart failure, hepatomegaly, asystole
Sertraline	Inhibits MRC I and V, inhibits oxidative phosphorylation	Hepatotoxicity
Simvastatin (other statins have weaker effects)	Inhibits MRC I, reduces coenzyme Q10 levels, weak peroxisome proliferator activated receptor ligand	Causes myopathy, rhabdomyolysis
Sodium valproate	Inhibits oxidative phosphorylation, beta-oxidation	Liver failure, hyperammoninaemia, hypoglycaemia, steatosis and encephalopathy
Tricyclic antidepressants: amitriptyline, clomipramine	Inhibits MRC	Extrapyramidal symptoms, memory impairment

* Table in alphabetical order, which is not the same as order of importance of the medicines.
mt = mitochondria

References

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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
24 March 2017	Monitoring Communication	Animas Vibe Insulin Pump and Blood Glucose Analyser — ongoing issues with screen fade, cracked battery casing and other issues
24 March 2017	Alert Communication	*Andrographis paniculata* — potential risk for allergic reactions
20 March 2017	Media release	Primodos
13 March 2017	Monitoring Communication	M² Viekira Pak and Viekira Pak-RBV — Possible effects on blood glucose control when used in patients with type 2 diabetes
2 March 2017	Monitoring Communication	M² Possible risk of hypothyroidism in infants exposed to iodine-containing contrast agents added to the medicines monitoring scheme
2 March 2017	Consumer information leaflet	Hydroxychloroquine — what you can expect when starting treatment
8 February 2017	Consumer information leaflet	Medicines for Gout

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

WE NEED YOUR HELP!

M² MEDICINES MONITORING

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

Medicine	Potential Safety Issue	Active Monitoring Ends
Viekira Pak, Viekira Pak-RBV	Blood Glucose Control in Type 2 Diabetes	31 December 2017
Iodinated Contrast Medium (Iodixanol, Iohexol, Ioversol, Iopamidol, Iodised oil, Diatrizoate sodium, Diatrizoate meglumine with sodium amidotrizoate)	Hypothyroidism	30 September 2017

- M² is a Medsafe scheme designed to collect more information on potential safety signals for specific medicines.
- Safety signals are identified from reports of adverse medicine reactions sent to the Centre for Adverse Reactions Monitoring (CARM). For further information see the Medsafe website.
- The M² scheme does not replace routine adverse reaction reporting. Find out how to report at: **www.otago.ac.nz/carm** or **www.medsafe.govt.nz**

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New Zealand Government

CARM CENTRE FOR ADVERSE REACTIONS MONITORING

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

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Medsafe
New Zealand Medicines and Medical Devices Safety Authority

A business unit of the Ministry of Health

Editor
Dr Amanda Taylor
Medsafe, PO Box 5013,
Wellington, New Zealand
Ph: (04) 819 6800
E-mail: medsafeadrquery@moh.govt.nz

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