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New Zealand Government

In memoriam – Stewart Jessamine

Dr Stewart Jessamine suddenly passed away on 7 February 2019.

In honour of his memory and the contribution he made to public health in New Zealand, we include the following tributes from Medsafe and the three medicines expert advisory committees.

Medsafe

It is with great sadness that we write about the passing of Dr Stewart Jessamine.

Stewart joined the Ministry of Health in 1993 in the Therapeutics section. He remained in medicines regulation when Medsafe launched in 1998. Stewart started as a Senior Medical Advisor before progressing to Principal Technical Specialist and then Group Manager of Medsafe in 2008. He moved on at the end of 2014 to undertake the role of acting Director of Public Health and Deputy Director General in the Ministry of Health.

During his time with Medsafe, Stewart was instrumental in leading a number of high profile projects including the world leading regulation of xenotransplantation, improving consumer access to medicines and consumer information, and driving transparency in work Medsafe did and how decisions were made. In more recent times he was also the driving force behind the development of International Health Terminology Standards.

Stewart was an incredibly compassionate leader, always happy to answer questions from staff and members of the public, and had a passion for staff professional development and progression. Even after Stewart moved on to more public health focussed roles within the Ministry, he remained very accessible to Medsafe for advice and knowledge.

Stewart was a very effective communicator, which saw him speak to the media on a wide range of subjects as spokesperson for both Medsafe and the wider Ministry of Health. He had a unique ability to tailor his messages to his audience in a calm and reassuring manner.

His passing is a great loss for both the Medsafe group and all who interacted with him over the years.

Medicines Classification Committee (MCC)

The MCC is deeply saddened to hear about the sudden passing of Stewart Jessamine. Stewart had been a member of the MCC since 1997 and Chair for 20 years. The leadership, knowledge and strategic perspective that Stewart brought to the role greatly benefitted the recommendations made by the MCC. Stewart's chairmanship was conducted with great poise and has contributed to the MCC's reputation as a global leader in reclassification. In this role, Stewart has been a champion for safe consumer access to medicines. Stewart will be deeply missed by the members of the MCC, past and present.

Medicines Assessment Advisory Committee (MAAC)

The MAAC is saddened to hear of Stewart Jessamine's passing. During Stewart's time at Medsafe he made a significant contribution to the pre-market clinical assessment of medicines. The MAAC found Stewart's can-do attitude and risk assessment ability very constructive in resolving regulatory problems. His passing will be a loss for public health in New Zealand.

Medicines Adverse Reaction Committee (MARC)

It was with great sadness that the members of the MARC heard of the passing of Stewart Jessamine. Stewart was well known to the MARC and was a stalwart supporter of our work and for pharmacovigilance in New Zealand. He will be greatly missed, both for his engaging and enthusiastic personality, and also his amazing institutional knowledge. This is a great loss to New Zealand.

Stewart set the direction for pharmacovigilance in New Zealand in the late 1990s and early 2000s. He was instrumental in fashioning the contracts and service deliverables for the Centre for Adverse Reaction Monitoring and the New Zealand Pharmacovigilance Centre, which still apply today. He was amazingly competent and knowledgeable in his role and beyond in the big picture of the Ministry and its interconnections. It was always a pleasure to engage with Stewart collegially for his sharp mind and insights that were often profound.

Members of the MARC also remember Stewart in his clinical roles, as a general practitioner in his early days in New Zealand, and in his interactions outside of Medsafe. He was always jovial and looking to the future. He had such a breadth of perspective that always added another layer to the conversation.

A loss to the sector and certainly to all who knew him well!

Kua hinga te tōtara o Te Waonui a Tāne – moe mai rā e te Rangatira – moe mai rā.

The totara has fallen in the great forest of Tāne – rest peacefully, the esteemed chief, rest peacefully.

Introducing the new look *Prescriber Update*

Welcome to the new look *Prescriber Update*. This is our first online-only issue, and introduces the journal's new design and layout. We hope you like it! Comments are welcome at: **medsafeadrquery@moh.govt.nz**

If you would like to be notified when new issues of *Prescriber Update* are published, you can subscribe at: **www.medsafe.govt.nz/profs/subscribe.asp**

Lithium and pregnancy

Key Messages

- Clinicians prescribing lithium to women of childbearing age should discuss the need for effective contraception to be taken throughout treatment and the potential risks if lithium is taken during pregnancy.
- Studies have shown a small increase in the risk of major congenital malformations when lithium was taken in the first trimester.
- Cardiac malformation, previously identified as a high risk, was found to occur at a rate of around 2–2.5% if lithium was used during the first trimester compared to the background rate of around 1%.

Background

Lithium is a mood stabiliser used in the treatment of bipolar disorder[1]. The use of lithium in pregnancy was recently reviewed by the Medicines Adverse Reactions Committee (MARC) following the publication of new information[2].

Inconsistent results from clinical studies and a lack of studies with sufficient power to confidently describe the level of risk have led to uncertainty about whether women with bipolar disorder should take lithium during pregnancy.

The New Zealand data sheets for lithium strongly recommend that use of lithium be discontinued before a planned pregnancy due to the risk of teratogenicity, particularly during the first trimester[3–5].

Women with bipolar disorder have a significant risk of relapse during pregnancy and post-partum[6]. The risks of lithium during pregnancy therefore need to be weighed against its effectiveness at reducing relapse.

Recent studies

Two recently published studies investigated the risk of congenital cardiac malformations[6,7]. Fetal exposure to lithium during the first trimester of pregnancy had previously been considered a significant risk for congenital cardiac malformations. Both studies aimed to clarify this risk further. The risk of cardiac malformations was lower than previously believed, based on birth registry data from the 1970s[7]. The risk was estimated at around 2–2.5% in both studies. The background rate of congenital cardiac malformations is around 1%[8] (but can vary depending on the data source). The risk of congenital malformations associated with lithium in these studies was still greater than has been reported for antipsychotic medicines[9].

International guidelines

In April 2018, the National Institute for Health and Care Excellence (NICE) published updated guidelines on the clinical management and service requirements for antenatal and postnatal mental health in the UK[10]. The guidelines included recommendations concerning the use of lithium during the reproductive years and during pregnancy. The MARC considered that these guidelines are also relevant and useful for New Zealand. The NICE recommendations for using lithium are summarised in Table 1.

Table 1. Treatment decisions, advice and monitoring regarding the use of lithium in women who are planning a pregnancy, pregnant or in the postnatal period – recommendations from NICE

Lithium

Do not offer lithium to women who are planning a pregnancy or pregnant, unless antipsychotic medication has not been effective.

If antipsychotic medication has not been effective and lithium is offered to a woman who is planning a pregnancy or pregnant, ensure:

- the woman knows that there is a risk of fetal heart malformations when lithium is taken in the first trimester, but the size of the risk is uncertain
- the woman knows that lithium levels may be high in breast milk with a risk of toxicity for the baby
- lithium levels are monitored more frequently throughout pregnancy and the postnatal period.

If a woman taking lithium becomes pregnant, consider stopping the medicine gradually over 4 weeks if she is well. Explain to her that:

- stopping medication may not remove the risk of fetal heart malformations
- there is a risk of relapse, particularly in the postnatal period, if she has bipolar disorder.

If a woman taking lithium becomes pregnant and is not well or is at high risk of relapse, consider:

- switching gradually to an antipsychotic or
- stopping lithium and restarting it in the second trimester (if the woman is not planning to breastfeed and her symptoms have responded better to lithium than to other drugs in the past) or
- continuing with lithium if she is at high risk of relapse and an antipsychotic is unlikely to be effective.

If a woman continues taking lithium during pregnancy:

- check plasma lithium levels every 4 weeks, then weekly from the 36th week
- adjust the dose to keep plasma lithium levels in the woman's therapeutic range
- ensure the woman maintains an adequate fluid balance
- ensure the woman gives birth in hospital
- ensure monitoring by the obstetric team when labour starts, including checking plasma lithium levels and fluid balance because of the risk of dehydration and lithium toxicity
- stop lithium during labour and check plasma lithium levels 12 hours after her last dose.

Source: NICE guideline. 2014. *Antenatal and postnatal mental health: clinical management and service guidance* April 2018. URL: www.nice.org.uk/guidance/cg192/chapter/1-recommendations (accessed 14 November 2018).

New Zealand cases

Up to 1 November 2018, four cases of congenital malformations associated with the use of lithium in pregnancy had been reported to the Centre for Adverse Reactions Monitoring (CARM). Three of these cases described cardiac defects (case numbers: 026387, 069446 and 116642).

Data sheet update

It is important for prescribers to discuss the benefits and risks of continuing lithium during pregnancy with women who have bipolar disorder and who are planning to or have become pregnant. Medsafe is working with the New Zealand sponsors of lithium-containing medicines to provide up-to-date information on the risk of fetal abnormalities with lithium use in pregnancy.

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Therapeutic Products Regulatory Scheme consultation

The Ministry of Health is seeking feedback on the draft of the Therapeutic Products Bill. The Therapeutic Products Bill would replace the Medicines Act 1981 and establish a new regulatory scheme for therapeutic products. This includes medicines (including cell and tissue products) and medical devices.

The draft Therapeutic Products Bill and consultation documents are available at: **www.health.govt.nz/publication/therapeutic-products-regulatory-scheme-consultation**

The consultation period ends on 18 April 2019.

Modified-release paracetamol – Unpredictable in overdose

Key Messages

- Overdose of modified-release paracetamol medicines is difficult to treat due to prolonged absorption and unpredictable pharmacokinetics.
- Contact the Poisons Centre for advice if overdose with modified-release paracetamol is suspected.
- Modified-release paracetamol has been reclassified from Pharmacy Only to Restricted (Pharmacist Only) Medicine, in order for pharmacists to provide more information on dosing to patients.

The Medicines Adverse Reaction Committee (MARC) reviewed the safety of modified-release paracetamol at the 172nd meeting on 7 December 2017, following the suspension of these medicines in Europe[1].

Modified-release paracetamol formulation

Modified-release paracetamol tablets are marketed in New Zealand in a formulation containing 665 mg of paracetamol, which is taken up to three times a day[2–4].

The modified-release tablets contain both immediate-release paracetamol (31%) and slow-release paracetamol (69%).

Paracetamol overdose

Products formulated as modified-release paracetamol have acceptable quality, safety and efficacy when taken at the recommended dose.

Paracetamol overdose, whether intentional or accidental, has the potential to cause liver failure. Treatment with N-acetyl cysteine when given early enough can prevent these effects. However, when an overdose involves modified-release paracetamol treatment can be more difficult.

Overdose with modified-release paracetamol results in a prolonged and unpredictable pattern of paracetamol absorption. Serum paracetamol concentration may peak as late as 24 hours after ingestion of modified-release paracetamol. With very large overdoses, the modified-release tablets may form a clump (called a pharmacobezoar) in the gut, which can further delay absorption due to altered disintegration and dissolution properties of the clumped tablets[5].

Standard treatment guidelines for overdose of immediate-release paracetamol are not designed for these extended periods of absorption. The slow absorption and unpredictable pharmacokinetics of modified-release paracetamol following overdose may lead to a delayed peak in serum paracetamol concentration above the nomogram line[5]. The MARC noted that the current paracetamol poisoning guidelines could be improved to deal with overdoses of modified-release paracetamol[1].

In situations where an overdose involving modified-release paracetamol is suspected, call the National Poisons Centre on 0800 POISON (0800 764 766) for advice.

Modified-release paracetamol is now a Restricted (Pharmacist Only) Medicine

The Medicines Classification Committee (MCC) reviewed the classification of modified-release paracetamol at the 60th meeting in April 2018[6] and at the 61st meeting in November 2018[7]. The MCC recommended that modified-release paracetamol should be reclassified from Pharmacy Only to Restricted (Pharmacist Only) Medicine. The reclassification Gazette notice was published in February 2019 (**https://gazette.govt.nz/notice/id/2019-go841**).

The Restricted Medicine classification maintains over-the-counter access to the medicine while ensuring that consumers receive information from a pharmacist about how to take the medicine correctly, and not taking other paracetamol-containing medicines at the same time.

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Spotlight on rivaroxaban (Xarelto)

Key Messages

- Rivaroxaban (Xarelto) is a direct-acting oral anticoagulant recently funded by PHARMAC.
- The dose of rivaroxaban differs depending on the indication. Patients with reduced renal function may need a dose reduction, depending on the indication.
- Monitoring of anticoagulant effect is not required except in special clinical situations such as overdose.
- There is no anticoagulant reversal agent for rivaroxaban.
- Rivaroxaban is metabolised by both CYP 3A4 and P-gp and is therefore contraindicated in patients taking medicines that strongly inhibit *both* CYP 3A4 and P-gp (eg, ritonavir).
- Care needs to be taken when switching patients to and from rivaroxaban due to the increased risk of bleeding.

Rivaroxaban (Xarelto) was first approved for use in August 2009. It was added to the Pharmaceutical Schedule in August 2018 and is now fully subsidised.

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

What is rivaroxaban and what is it used for?

Rivaroxaban is a direct-acting oral anticoagulant (DOAC), like dabigatran. It acts by inhibiting factor Xa in the coagulation cascade, thereby preventing the conversion of prothrombin to thrombin, and ultimately slowing clot formation[1–3].

In New Zealand, rivaroxaban is indicated for[2]:

- prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery
- prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors
- prevention and treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE).

The dose and duration of rivaroxaban treatment differs depending on the indication and the patient's renal function; full instructions are provided in the data sheet.

Rivaroxaban is contraindicated in patients with creatinine clearance <15 mL/min and in patients with significant hepatic disease[2]. The full list of contraindications is provided in the data sheet.

Take care when switching patients to and from rivaroxaban, due to the increased risk of bleeding[1,2].

In case of haemorrhage

Currently, there is no specific antidote for rivaroxaban[2,4].

Rivaroxaban is not expected to be dialysable as it is highly bound (92–95%) to plasma protein[2].

More information is available in the data sheet. See also the 'Guidelines for management of bleeding with dabigatran or rivaroxaban' available for download from the bpac website (**https://bpac.org.nz/2018/docs/dabigatran-rivaroxaban-bleeding-management.pdf**).

Drug interactions

Table 1: Examples of drugs that interact with rivaroxaban

Example	Effect on rivaroxaban	Comment
Strong CYP 3A4 and P-gp inhibitors: eg, voriconazole, ritonavir	Large increase in plasma concentration	Contraindicated
Strong CYP 3A4 and moderate P-gp inhibitors: eg, fluconazole	Small increase in plasma concentration	No need to change dose – not clinically relevant
Strong 3A4 and P-gp inducers: eg, rifampicin, phenytoin	Reduces plasma concentration by 50%	No need to change dose – not clinically relevant
Anticoagulants: eg, warfarin	Pharmacodynamic interaction	Avoid. See data sheet for switching instructions
NSAIDs	Pharmacodynamic interaction	Caution
Platelet aggregation inhibitors: eg, clopidogrel	Pharmacodynamic interaction	Caution
SSRIs, SNRIs	Pharmacodynamic interaction	Caution

Source: Bayer New Zealand Limited. 2017. *Xarelto 10 mg, 15 mg and 20 mg film-coated tablets New Zealand Data Sheet* 11 December 2017.
URL: www.medsafe.govt.nz/profs/datasheet/x/Xareltotab.pdf (accessed 22 January 2019).

Adverse drug reaction (ADR) reporting in New Zealand

Between 1 January 2014 and 31 December 2018 the Centre for Adverse Reactions Monitoring (CARM) received 49 reports where rivaroxaban was considered to be the suspect medicine.

Of these reports, 19 described events indicative of bleeding. There were also three reports of stroke (CARM ID: 109955, 118725, 130307) and three reports were coded as medicine ineffective (113627, 115065, 130043).

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Adverse reaction reporting in New Zealand – 2018

Thank you to everyone who submitted reports of suspected adverse reactions during 2018. You are making an important contribution to the safety monitoring of medicines in New Zealand.

What is being reported?

In 2018, the Centre for Adverse Reactions Monitoring (CARM) received a total of 4,373 reports of suspected adverse reactions. These included 2,843 reports associated with medicines, 1,473 reports associated with vaccines and 57 reports associated with complementary or alternative medicines (CAMs). This year there was a significant increase in reports for CAMs, partly accounted for by reports of adverse reactions to Arthrem[1]. A significant increase in the number of reports from consumers was also observed this year, this may in part be due to the publication of a consumer reporting portal on the CARM website in November 2017.

Of all reports received in 2018, 20.1% were considered serious. Serious reports accounted for 28.6% of medicine reports, 3.5% of vaccine reports and 24.6% of CAM reports. According to internationally agreed criteria, a serious adverse reaction is defined as any reaction that results in death or is life-threatening, causes or prolongs hospitalisation, results in persistent or significant disability/incapacity, is a congenital abnormality or is a medically important event.

You can search for suspected adverse reactions reported in New Zealand on the Medsafe website using the Suspected Medicine Adverse Reaction Search (SMARS) (**www.medsafe.govt.nz/projects/B1/ADRDisclaimer.asp**).

Who is reporting?

Anyone can submit a report. Figure 1 shows the number of reports received from healthcare professionals and consumers during the last five years. Nurses continue to submit the most reports, and the number of reports from consumers is increasing.

Please continue to report any suspected adverse reactions to medicines, vaccines or CAMs to CARM.

How do I report?

Reporting is easiest online: **https://nzphvc.otago.ac.nz/reporting/**

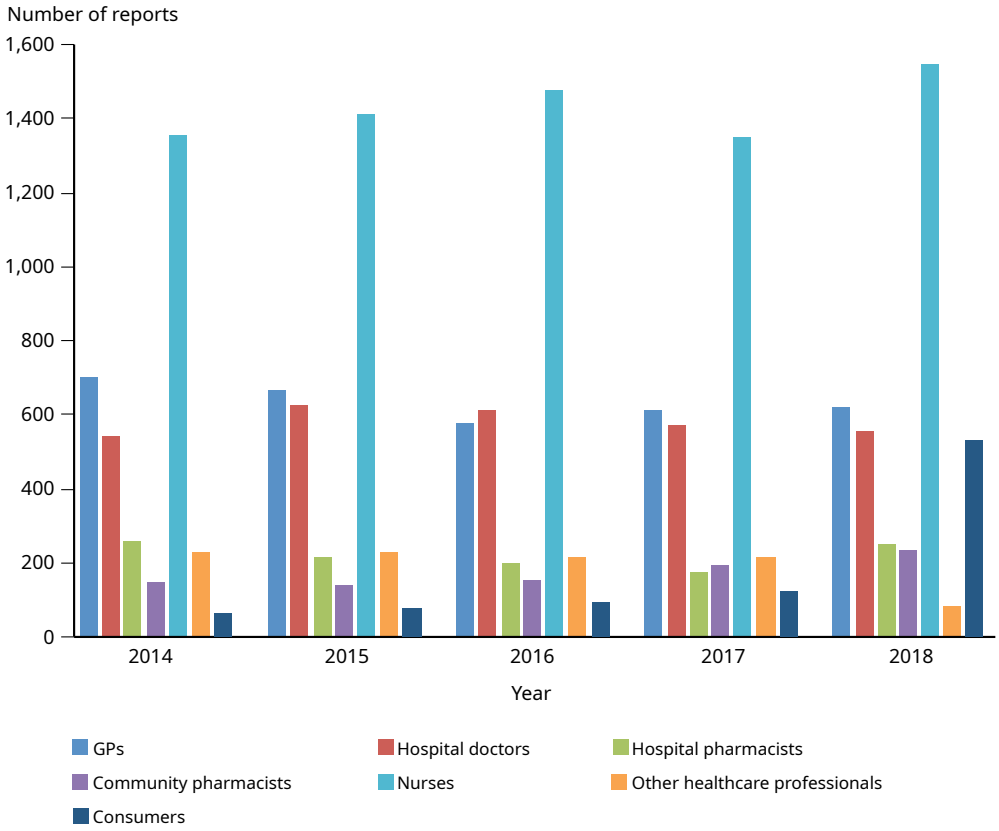
Other ways of reporting include:

- electronic reporting through GP Practice Management Systems
- completing a freepost yellow card
- using the Apple iOS app on your iPhone or iPad (download from **https://nzphvc.otago.ac.nz/app/**)
- contacting CARM by phone on (03) 479 7247 or emailing **carmnz@otago.ac.nz**

Where can I learn more about reporting?

Complete the eLearning module and earn continuing professional development (CPD) points (**www.medsafe.govt.nz/profs/ADR-training/story_html5.html**).

Figure 1: Number of reports received from healthcare professionals and consumers, by year, 2014–2018



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The Medsafe Files – Episode nine: Patients importing medicines for personal use

Key Messages

- Under Section 43 of the Medicines Act 1981, a patient who has imported a prescription medicine requires authorisation from an authorised prescriber before the medicine can be released to them.
- Medicines imported by consumers for personal use have not been evaluated by Medsafe or approved for use in New Zealand. The quality, safety and efficacy of these medicines is unknown to Medsafe.
- The authorised prescriber must be satisfied that the patient's clinical need for the medicine outweighs the risks of taking an unapproved medicine.
- By authorising release, the authorised prescriber takes responsibility for prescribing the unapproved medicine(s) for their patient.

Medsafe frequently receives queries from patients who want to import medicines for personal use. This article is a reminder about the requirements for authorised prescribers when patients request assistance in releasing medicines held at the border.

Background

Medsafe, in conjunction with the New Zealand Customs Service, operates a border programme for imported medicines.

When a prescription medicine is imported for personal use, Medsafe writes to the importer (eg, the consumer) to inform them that authorisation must be obtained from an authorised prescriber before the imported medicine can be released. The letter includes an authorisation form with the details of the imported medicine for the prescriber to sign.

Personal importation

There are two main categories of imported medicines for personal use: those that are purchased over the internet from an overseas website and those that are sent from an overseas family member or medical clinic.

Medicines purchased over the internet

Medicines are frequently purchased over the internet for reasons of cost or confidentiality. Medsafe strongly discourages this practice because the quality of the medicine cannot be assured. These medicines may be of poor quality, sub or super potent, contaminated, adulterated or counterfeit. Even though the medicine may appear to come from a pharmacy in a well-regulated country, this is frequently not the case. The medicine may in fact come from a sophisticated rogue website engaged in fraudulent activity.

Authorisation is required for any imported medicine that contains an ingredient classified as a prescription medicine in New Zealand. Medicine classifications are listed in the Classification Database, available at **https://medsafe.govt.nz/profs/class/classintro.asp**. A medicine may be available in New Zealand in certain strengths without a prescription, but requires a prescription if the strength, recommended daily dose stated on the label, or pack size exceeds a limit specified in the Classification Database. Common examples where this may occur are vitamin D, zinc, and vitamin A. Authorisation is required before these medicines can be released to the importer.

Medicines sent from an overseas family member or medical clinic

People who have moved to New Zealand or are visiting may prefer to source their medicines from their home country. Although these medicines may have been lawfully prescribed and dispensed in their originating country, authorisation from a New Zealand authorised prescriber is required before the medicine can be released.

Authorisation requests

The border pharmacist provides the details of the imported medicine(s) on the authorisation form. To authorise release of an unapproved imported medicine to the patient, the prescriber must be satisfied that it is clinically appropriate to do so. The prescriber must carefully weigh up the benefits and risks of using the unapproved medicine, and discuss this with the patient. The prescriber must comply with all relevant health codes and professional standards, and should also obtain informed consent[1,2].

Further information about unapproved medicines is available on the Medsafe website (**www.medsafe.govt.nz/profs/RIss/unapp.asp**). See also 'The Medsafe Files – Episode Eight: Section 29 Medicines' in the December 2018 issue of *Prescriber Update* (**www.medsafe.govt.nz/profs/PUArticles/December%202018/MedsafeFiles8Section29.htm**).

Medsafe recommends that if the medicine, or a clinically acceptable alternative, is available in New Zealand then it should be used in preference to an unapproved imported medicine.

Providing authorisation

Prescribers choosing to authorise the imported medicine should complete and sign the authorisation form and return it directly to Medsafe. Use of a practitioner's ID stamp will expedite the process. By signing the form the prescriber indicates that they have considered the risks and benefits of the unapproved medicine, and decided that it is appropriate for the medicine to be released to the patient.

Medsafe is not a pharmacy and does not dispense medicines or apply pharmacy labels with dosage instructions. Medsafe cannot divide a pack. If the amount imported exceeds 3 months' supply (or 6 months' supply of oral contraceptives), or the pack size makes the product a prescription medicine, it cannot be supplied directly to the patient. However, with the prescriber's agreement, the medicine can be released to the prescriber to be dispensed in compliance with medicines legislation.

For further information, contact: **medclearance@moh.govt.nz**

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Prescriber Update and Safety Communications

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To subscribe, email **committees@moh.govt.nz** with the words 'classification — subscribe' in the subject line.

The nocebo effect

Key Messages

- The nocebo effect can lead to real adverse reactions.
- Information on treatments should be carefully framed to reduce the risk of initiating nocebo effects.
- Side effects associated with brand changes may be due to the nocebo effect.

What is it?

The nocebo effect is the opposite of the placebo effect. It describes a situation where a negative outcome occurs due to a belief that the intervention will cause harm. It is a sometimes forgotten phenomenon in the world of medicine safety. The term nocebo comes from the Latin 'to harm'.

For adverse reactions to medicines, nocebo implies that patients are more likely to experience an adverse effect if they expect or are worried about the adverse effect. The adverse effects may be physically experienced by the patient and are often clinically diagnosable[1]. An example of the nocebo effect is the severe adverse effects experienced by patients taking a placebo during a clinical trial.

Some experts state that the nocebo effect may have a larger effect on clinical outcomes than the placebo effect as negative perceptions are formed much faster than positive ones[1].

The nocebo effect can be influenced by 'media storms'. Widespread dissemination of concerns about an adverse reaction to a medicine leads to an increase in the number of reports of the adverse reaction. For example, in 2013, British media highlighted the adverse effects, including muscle pains, of statins following an article in the *British Medical Journal*[2]. An estimated 200,000 patients stopped taking statins within six months of the story being published, many due to adverse reactions. There was also an increase in the number of adverse reaction reports of rhabdomyolysis with statins during this time. This incident has since been attributed to the nocebo effect[1].

The nocebo effect can also play a role in patients' experience with generic medicines. Pre-existing scepticism around generic medicines may be a cause of the side effects some patients experience when changing from an innovator 'branded' product to a generic product. A 2015 Finnish report showed that around a quarter of patients discontinued an approved infliximab biosimilar due to a perceived loss of efficacy or an increase in side effects[3]. Other studies have shown that perception of cost (believing that because generics

are cheaper they are less effective) can enhance the nocebo effect[4]. Due to the New Zealand funding situation, there have been numerous instances where the perception of cost may have enhanced the nocebo effect[5].

What can be done about it?

It is important to remember that non-verbal communication may also trigger a nocebo response[6].

Some patients appear to be at higher risk of experiencing nocebo effects. Women, patients with anxiety and depression, those with a pessimistic outlook and strongly influenced by their environment may need more careful counselling to avoid inadvertent initiation of the nocebo effect[6].

The risk of nocebo can be reduced by ensuring a good balance between explaining both the positive and negative effects of the treatment, and ensuring the patient understands the treatment's rationale[1]. Framing the adverse effects of a medicine positively may help to reduce the role of nocebo[6]. For example, *'Most people who take generic brand X notice no difference to innovator brand Y, but a small number of patients may notice a difference'* compared to *'Some patients find that generic brand X is not as effective as innovator brand Y'*.

The nocebo effect can also be reduced by providing information to patients about the adverse effects of a medicine in context, and checking their understanding[1].

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Recent approvals of medicines containing a new active ingredient

For the period 16 October 2018 to 15 January 2019.

Trade name (Active ingredient)	Dose form and strength(s)	Therapeutic area
Adynovate (rurioctocog alfa pegol)	Powder for injection 250 IU 500 IU 1000 IU 2000 IU	Haemophilia A (congenital factor VIII deficiency)
Kyprolis (carfilzomib)	Powder for infusion 30 mg 60 mg	Multiple myeloma

See the Medsafe website for more information about these medicines (**www.medsafe.govt.nz/regulatory/DbSearch.asp**). Data sheets of currently marketed medicines are also available (**www.medsafe.govt.nz/Medicines/infoSearch.asp**).

Influenza vaccine: Healthcare worker vaccination, and adverse reaction reports 2018

Key Messages

- One out of four New Zealanders is infected with influenza each year, and around 80 percent of those infected are asymptomatic but still contagious.
- The Ministry of Health's goal is for 80 percent of all healthcare workers to be immunised annually against influenza.
- The most commonly reported suspected adverse reactions to influenza vaccine in 2018 were injection site inflammation, arm pain, nausea, headache and pruritus.
- Nurses submitted the majority of influenza vaccine adverse reaction reports in 2018, followed by GPs and pharmacists.

Influenza is a significant public health issue in New Zealand, with up to a quarter of the population infected each year.

Annual influenza vaccination of healthcare workers

Healthcare workers are at increased risk of exposure to influenza[1] and may transmit infection without knowing they are infected[2]. A recent serosurvey showed that 1 out of 4 New Zealanders is infected with influenza each year, and that around 80 percent of those infected are asymptomatic[3]. An asymptomatic carrier can unknowingly expose their family, co-workers and patients to the influenza virus.

In 2018, the Ministry of Health introduced a goal of 80 percent of all healthcare workers to be immunised annually against influenza[2]. Achieving influenza immunisation coverage of 80 percent of the population is sufficient to establish herd immunity against most influenza viruses[4]. Annual influenza vaccination of healthcare workers is likely to reduce illness among the patients they care for[1,5,6].

National district health board (DHB) healthcare worker influenza coverage in 2018 was 68 percent, with individual DHBs ranging from 57 percent to 88 percent[7]. (Note that this coverage figure only includes healthcare workers employed by DHBs.)

Influenza vaccine adverse reaction reports

Quadrivalent influenza vaccines were funded for the first time in 2018 (Influvac Tetra for individuals aged 3 years and older; Fluarix Tetra for children aged under 3 years). The vaccines contained two influenza A strains and two influenza B strains.

The Centre for Adverse Reactions Monitoring (CARM) received 232 reports of adverse reactions to influenza vaccine in 2018 (Table 1); as expected, based on the higher usage, the majority (73%) were associated with Influvac Tetra. There were a total of 582 suspected adverse reactions to the vaccines described in these reports.

Table 1: Number of reports of adverse events following influenza vaccination received by CARM and number of influenza vaccine doses distributed, 2013–2018

	2013	2014	2015	2016	2017	2018
Number of adverse event reports following influenza vaccination	290	253	241	212	191	232
Influenza vaccine doses distributed[a]	1,253,600	1,206,573	1,211,152	1,245,934	1,217,169[b]	1,317,197
Estimated reporting rate per 100,000 doses	23.1	21.0	19.9	17.0	15.7	17.6

a. The number of doses distributed is not equal to the number of people who received the vaccine.

b. The 2017 influenza vaccine distribution figures were updated in 2018 and differ slightly from those previously published in *Prescriber Update* (www.medsafe.govt.nz/profs/PUArticles/March2018/seasonal-flu-vaccine-spontaneous-reports.htm). The estimated reporting rate is unchanged.

The most commonly reported suspected adverse reactions were injection site inflammation, arm pain, nausea, headache and pruritus (Table 2).

Table 2: Top five reported suspected adverse reactions for the seasonal influenza vaccines, 2018

Adverse reaction	Number	Percentage of total reactions (n=582)	Percentage of total reports (n=232)
Injection site inflammation	42	7.2	18.1
Arm pain	23	3.9	9.9
Nausea	23	3.9	9.9
Headache	21	3.6	9.1
Pruritus	19	3.3	8.2

Six of the influenza vaccine-related reports were considered serious. A serious adverse event is determined by CARM according to internationally agreed criteria (ie, results in death or is life-threatening, causes or prolongs hospitalisation, results in persistent or significant disability/incapacity or is a congenital abnormality).

One death with a temporal association to the 2018 influenza vaccine was reported to CARM. A patient with a history of severe coronary artery disease and underlying flu-like illness was reported to have died after receiving influenza and zoster vaccines. The death was considered to be due to cardiac arrest and the patient's associated background history, and not related to the vaccines.

The majority of reports in 2018 were submitted by nurses (72.4%), followed by GPs (16.8%) and pharmacists (3.9%). This reporter pattern is similar to previous years.

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MARC's remarks: December 2018 meeting

The Medicines Adverse Reactions Committee (MARC) met on 6 December 2018 to discuss a number of medicine-related safety issues.

Based on their review of cases reported to the Centre for Adverse Reactions Monitoring (CARM), the Committee recommended that the Chair of the MARC communicates with:

- District Health Boards (DHBs) to highlight considerations around frailty and analgesia selection in elderly patients
- Starship Hospital regarding the considerations of quality and period of observation after administration of **chloral hydrate**
- various organisations about the possibility of producing consumer information and increasing public awareness of the safety issues around **paracetamol** use in children.

The Committee also discussed the **venlafaxine** brand switch reports received by CARM. This discussion is summarised in the media release published on the Medsafe website (**www.medsafe.govt.nz/publications/media/2018/venlafaxine-monitoring.asp**). The Committee concluded that the rise in adverse reaction reporting of venlafaxine is not caused by medicine safety or quality issues. The Committee recommended that Medsafe continue to monitor *Enlafax XR* closely, and publish information of public interest about this topic on the Medsafe website.

The Committee discussed **hydrochlorothiazide** and non-melanoma skin cancer (NMSC) and recommended data sheet updates for all hydrochlorothiazide-containing products. The Committee also recommended that an alert communication on this topic is published on the Medsafe website.

The Committee discussed **Viekira Pak/Viekira Pak-RBV** and hallucinations and psychotic disorders. The Committee concluded that there was insufficient evidence of an association.

The Committee considered dose reduction of **dabigatran** for certain subpopulations in the treatment and prevention of deep vein thrombosis (DVT)/pulmonary embolism (PE). The Committee recommended that the dosage recommendations for the DVT/PE indications are harmonised with those for stroke prevention in atrial fibrillation (SPAF).

The Committee discussed fetal exposure to **lithium** during pregnancy and recommended that the data sheets of lithium-containing products are updated to include additional information about use in pregnancy. Further information on this topic, including the prescribing guidelines from the National Institute for Health and Care Excellence (NICE), is provided in this edition of *Prescriber Update* (see pages 4–6).

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**).

Quarterly summary of recent safety communications

The table below is a summary of recent safety communications to healthcare professionals and consumers, published on the Medsafe website (**www.medsafe.govt.nz**).

Date	Communication	Topic
4 February 2019	Alert Communication	Recall and Hazard Alert: Medtronic Adapta Dual Chamber Pacemaker
21 December 2018	Dear Healthcare Professional Letter	Epilim – Updated educational materials for use in women of child-bearing potential (PDF 68 KB, 1 page)
19 December 2018	Monitoring Communication	M² Tramadol and opioid effects in breastfeeding babies
5 December 2018	Safety Alert	Tecentriq – Revision of indication for treatment of locally advanced or metastatic urothelial carcinoma (PDF 502 KB, 2 pages)
5 December 2018	Safety Alert	Tecentriq – New important identified risk: Nephritis (PDF 645 KB, 2 pages)

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/**).

Bullous pemphigoid – A blistering problem

Key Messages

- Bullous pemphigoid is an autoimmune blistering skin disease that mainly affects the elderly.
- Some medicines have been associated with bullous pemphigoid, including dipeptidyl peptidase-4 (DPP-4) inhibitors, such as the newly funded vildagliptin.
- Treatment usually consists of stopping the medicine and using corticosteroids.

Introduction

Dipeptidyl peptidase-4 (DPP-4) inhibitors (also known as 'gliptins'), used to treat type 2 diabetes mellitus, have recently been associated with bullous pemphigoid[1].

What is bullous pemphigoid?

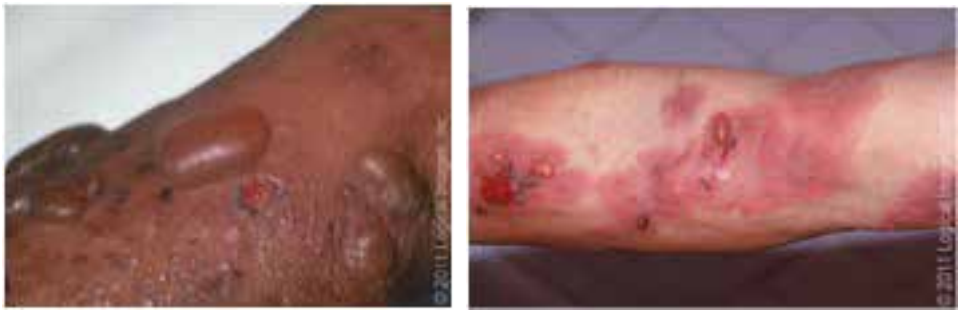
Bullous pemphigoid is an autoimmune disease that results in subepidermal blistering[1]. Autoantibodies and activated T lymphocytes target proteins in the basement membrane of the epidermis, triggering the inflammatory process, which leads to blister formation[2].

Most cases of bullous pemphigoid occur in individuals aged over 60 years[3]. It usually presents with severe itching and large (1–3 cm) fluid-filled blisters, called bullae (Figure 1).

The bullae eventually burst leaving moist erosions and crusts that resolve without scarring. Mucous membranes may also be involved[2,4,5].

Bullous pemphigoid is usually a self-limiting disease with a clinical course that may last from months to years[4]. However, it can be a serious and potentially fatal disease, particularly when lesions are widespread or resistant to treatment[2,6].

Figure 1: Bullous pemphigoid images



a: Multiple tense bullae on skin with one eroded blister base

b: Arm skin with tense bullae arising on urticarial plaques and eroded blister bases

Source: Leiferman KM. 2018. Clinical features and diagnosis of bullous pemphigoid and mucous membrane pemphigoid. In: *UpToDate*. 30 November 2018. URL: www.uptodate.com/contents/clinical-features-and-diagnosis-of-bullous-pemphigoid-and-mucous-membrane-pemphigoid (accessed 18 January 2019). Reproduced with permission from visualdx.com.

What are the causes of bullous pemphigoid?

The risk of bullous pemphigoid is increased with[2,4]:

- advanced age
- certain HLA associations, indicating a genetic predisposition
- exposure to some medicines (see the following section)
- comorbidities such as neurological disease (eg, stroke, dementia, Parkinson's disease), psoriasis, cancer, skin infection.

What medicines are associated with bullous pemphigoid?

Penicillamine and furosemide are most frequently implicated from case reports of drug-induced bullous pemphigoid[7]. Cases associated with captopril, penicillin and its derivatives, sulfasalazine, and topical fluorouracil have also been reported internationally. Case-control studies have found a significant association between bullous pemphigoid and neuroleptics, loop diuretics, and spironolactone[7].

Recently, DPP-4 inhibitors have been associated with bullous pemphigoid[1,8]. Evidence for this association was initially based on case reports and national pharmacovigilance database analyses, and now includes controlled observational studies[8]. The pathomechanism underlying the association between DPP-4 inhibitors and bullous pemphigoid is not yet fully understood.

Vildagliptin, sitagliptin, and saxagliptin are the approved DPP-4 inhibitors in New Zealand. Bullous pemphigoid is listed as an adverse event derived from post-marketing experience in the vildagliptin[9,10] and sitagliptin data sheets[11,12].

New Zealand case reports

In New Zealand, between 1965 and 2018, the Centre for Adverse Reactions Monitoring (CARM) received 20 reports of pemphigoid reactions suspected to be caused by a medicine. One of these reports was associated with D-penicillamine (CARM ID number: 012003), one with furosemide (001113) and three with penicillin derivatives (000929, 098771, 114683). There were no reports of pemphigoid reactions associated with DPP-4 inhibitors.

What is the treatment for bullous pemphigoid?

If a medicine is suspected to be causing the bullous pemphigoid, discontinue the medicine and consider referral to a dermatologist. First-line treatment of bullous pemphigoid usually involves topical or systemic corticosteroids and supportive care. However, immunosuppressant therapy may be required[6].

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Gathering knowledge from adverse reaction reports: March 2019

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: 129817 **Age:** 64 **Gender:** Female **Medicine(s):** Tramadol, venlafaxine **Reaction(s):** Serotonin syndrome, drug interaction	A 64-year-old female patient experienced serotonin syndrome whilst taking venlafaxine and after her regular dose of tramadol increased from 50 mg to 100 mg.
	Venlafaxine and tramadol are medicines with serotonergic effects. The Enlafax (**www.medsafe.govt.nz/profs/datasheet/e/enlafaxXRcap.pdf**) and Arrow Tramadol (**www.medsafe.govt.nz/profs/Datasheet/a/arrowtramadolcap.pdf**) data sheets state serotonin syndrome may occur with concomitant use of serotonergic medicines. See also the September 2015 *Prescriber Update* article 'Reminder: Interactions resulting in serotonin syndrome' (**www.medsafe.govt.nz/profs/PUArticles/Sep2015/InteractionsSerotoninSyndrome.htm**).
CARM ID: 129881 **Age:** 67 **Gender:** Male **Medicine(s):** Aripiprazole **Reaction(s):** Neuroleptic malignant syndrome	A 67-year-old male who had previously experienced neuroleptic malignant syndrome (NMS) with clozapine developed NMS following a single dose of aripiprazole. The patient subsequently died.
	The Aripiprazole Sandoz data sheet states that a potentially fatal symptom complex sometimes referred to as neuroleptic malignant syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including aripiprazole (**www.medsafe.govt.nz/profs/datasheet/a/aripiprazolesandoztab.pdf**). See also the December 2012 *Prescriber Update* article 'Neuroleptic malignant syndrome or serotonin syndrome?' (**www.medsafe.govt.nz/profs/PUArticles/Dec2012Neuroleptic.htm**).
CARM ID: 130055 **Age:** 35 **Gender:** Male **Medicine(s):** Gabapentin **Reaction(s):** Myoclonic jerks	A 35-year-old male patient taking gabapentin experienced myoclonic jerks, which resolved upon discontinuation.
	Myoclonus is listed as an adverse effect identified during post-marketing in the Apo-Gabapentin data sheet (**www.medsafe.govt.nz/profs/Datasheet/a/ApoGabapentincaptab.pdf**).

CARM ID: 130104 **Age:** 30 **Gender:** Female **Medicine(s):** Gabapentin **Reaction(s):** Eosinophilia, abnormal hepatic function, malaise, pruritic rash	A 30-year-old female taking gabapentin developed a severe itchy rash and malaise, and was noted to have liver test dysfunction and eosinophilia.
	These symptoms are suggestive of DRESS (drug rash with eosinophilia and systemic symptoms), which is listed in the Apo-Gabapentin data sheet (**www.medsafe.govt.nz/profs/Datasheet/a/ApoGabapentincaptab.pdf**).
CARM ID: 130571 **Age:** 58 **Gender:** Female **Medicine(s):** Cilazapril **Reaction(s):** Photosensitivity	A 58-year-old female patient who recently started cilazapril developed a severe sunburn reaction after a brief exposure to the sun (in October).
	Photosensitivity is listed in the Apo-Cilazapril (**www.medsafe.govt.nz/profs/Datasheet/a/apocilazapriltab.pdf**) and Zapril data sheets (**www.medsafe.govt.nz/profs/Datasheet/z/zapriltab.pdf**).

Information about suspected adverse reactions reported to CARM is available on the Medsafe website using the Suspected Medicines Adverse Reaction Search (SMARS) (**www.medsafe.govt.nz/Projects/B1/ADRSearch.asp**).

By selecting the ingredient of a medicine you can find out:

- the number of reports and suspected adverse reactions for that ingredient. The suspected reactions are grouped by body system or organs (summary report)
- single case reports, listing the medicines involved that contain the ingredient and the suspected adverse reactions (detail report).

We need your help!

MEDICINES MONITORING

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

Medicine	Potential Safety Issue	Active Monitoring Ends
Tramadol	Opioid effects in breastfeeding babies	30 June 2019
Zoster (shingles) vaccine or Influenza vaccine	Lichen planus	31 July 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.

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New Zealand Government

CARM CENTRE FOR ADVERSE REACTIONS MONITORING

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