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Adverse Reaction Reporting in New Zealand – 2015

Medsafe and the Centre for Adverse Reactions Monitoring (CARM) would like to thank all those who have submitted reports of suspected adverse reactions over the past year. Submitting reports provides valuable information for the post-marketing monitoring (pharmacovigilance) of medicines and vaccines in New Zealand.

Types of reports

In 2015, CARM received a total of 4206 suspected adverse reaction reports. Of these, 64.6% were associated with medicines, 34.8% were associated with vaccines, and 0.6% were associated with complementary or alternative medicines (CAMs). This is consistent with previous years, with the exception of 2014 where an increase in reports associated with medicines was received (Figure 1).

In 2015, 27% of all reports were considered serious. A serious adverse reaction is defined, according to internationally agreed criteria, as any drug-related event that results in death, is life-threatening, requires or prolongs inpatient hospitalisation, results in persistent or significant disability or requires intervention to prevent permanent disability, is a congenital abnormality or is a medically important event. Serious reports accounted for 39% of the medicine reports, 5% of the vaccine reports, and 20% of the CAM reports.

Source of reports

In 2015, nurses continued to be the most frequent reporters of suspected adverse reactions (34% of all reports). Doctors followed closely behind submitting 31% of all reports (GPs reported 16% and hospital doctors reported 15%, Figure 2).

Approximately a quarter of all reports come through GP Practice Management Systems (PMS), which can be used by nurses as well as GPs. These systems use an online reporting form linked to the PMS that automatically pre-populates the patient's medical history, medicine history and provides an option to include laboratory results. If the report involves a vaccine, details such as batch number and date of administration are included. The report is then sent directly to CARM via a secure electronic pathway.

How to report

Healthcare professionals are encouraged to report any suspected adverse reaction(s) to a medicine, vaccine or CAM to CARM (**https://nzphvc.otago.ac.nz/**).

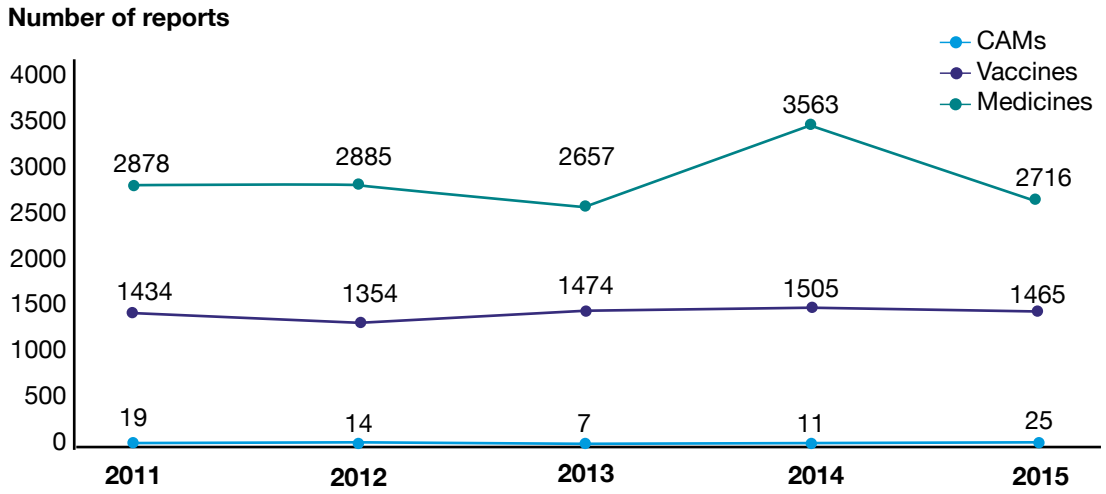

Figure 1: Number of suspected adverse reaction reports received by CARM from 2011 to 2015

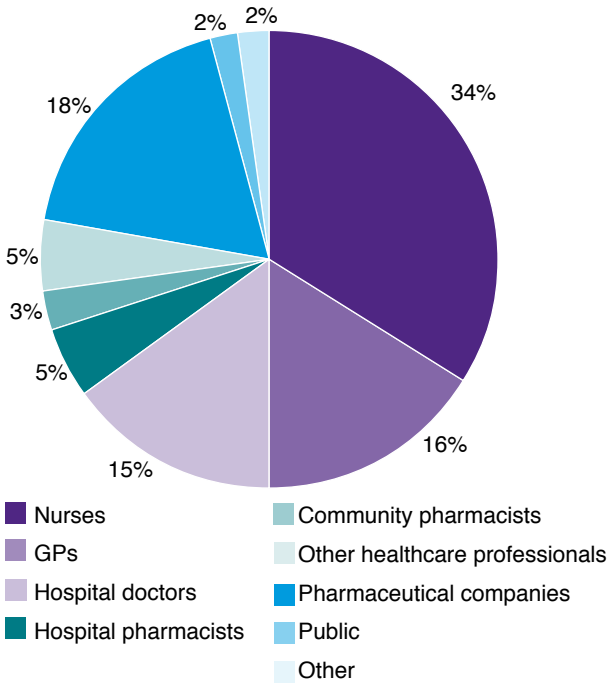

Figure 2: Source of adverse reaction reports in New Zealand in 2015

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/**).

Suspected adverse reactions to medicines, vaccines and CAMs can be reported by:

- completing a freepost yellow card
- phoning the CARM line 0800 4 Monitor (0800-466648)
- downloading a form from either the CARM or Medsafe website
- completing an online report available from the CARM website
- electronic reporting through GP Practice Management Systems
- using the iPhone application (ADR Online).

Remember if in doubt, report it.

Launch of a New *Prescriber Update* Search Tool – Making it Easier to Find Important Safety Information

Medsafe recently launched a new *Prescriber Update* article search tool. The new database, which replaces an alphabetical index of articles, allows users to quickly and easily search for articles by keyword.

The new search tool is located on the Medsafe website: **www.medsafe.govt.nz/publications/articlesearch.asp**

The new search tool is designed to improve access to important safety information.

Medsafe *Prescriber Update* Survey – Have your Say!

Medsafe is conducting a short online survey (11 multiple choice questions) to better understand how our readers currently use *Prescriber Update* and how we could improve the publication in the future to better suit you.

The survey is now open and will close on **Friday 8 April 2016**. We value your feedback on this important safety publication and would appreciate it if you could take a few minutes to complete the survey. Respondents will remain anonymous.

To access the survey, go to: **www.surveymonkey.com/r/medsafePUsurvey**

Compliance Packaging of Medicines

Healthcare professionals should carefully consider the properties of each medicine before repacking into compliance packaging as not all medicines are suitable.

Compliance packaging in pharmacies

Compliance packaging is a service offered in many community pharmacies in New Zealand. Although there are many different forms of compliance packaging, they all share the common feature that medicines are repacked into closed, compartmentalised containers specifying administration times.

The aim of compliance packaging is to assist patient adherence to a prescribed medicine regime and to improve the safe administration of medicines.

Key groups that can benefit from compliance packaging include elderly patients, residential care facility residents and patients requiring treatment with a large number of medicines.

Factors to consider

It is important to consider the physical properties of both the active ingredient(s) and excipients as these may determine whether a medicine is suitable for compliance packaging.

When in doubt, a good first point of reference is the Pharmaceutical Precautions section of the medicine data sheet, available on the Medsafe website (**www.medsafe.govt.nz/profs/Datasheet/dsform.asp**). These data sheets are provided by the sponsor of the medicine in New Zealand.

Recent case report

One recent example reported to Medsafe relates to Epilim (sodium valproate) 200mg EC tablets. Sodium valproate is very hygroscopic (readily takes up and retains moisture) and a tablet can lose its integrity and become 'soft' and 'gooey' when deblistered into compliance packaging.

The Sanofi-Aventis data sheet for Epilim states that '*Epilim tablets are hygroscopic and must be kept in protective foil until taken*.'[1] Healthcare professionals need to be aware that if these tablets are placed in compliance packaging, they must be retained in their original foil blister.

Further examples of medicines that should be kept in the original packaging can be found in a previous *Prescriber Update* article 'Medicine Storage — An Uncontained Issue?'[2].

As with all medicines, it is important that all compliance packaging is stored in a cool, dry place, out of reach and sight of children.

References

1. Sanofi-Aventis New Zealand Limited. 2015. *Epilim Data Sheet*. 27 February 2015. URL: **www.medsafe.govt.nz/profs/datasheet/e/Epilimtabsyrliqiv.pdf** (accessed 17 November 2015).
2. Medsafe. 2014. Medicine Storage — An Uncontained Issue? *Prescriber Update* 35(3): 36–37. URL: **www.medsafe.govt.nz/profs/PUArticles/September2014MedicineStorage.htm** (accessed 17 November 2015).

Medicine Expiry Dates – What They Don't Tell You

All medicines have a defined shelf-life or expiry date

One of the most common questions asked by patients is whether a medicine can be used past its expiry date. The short answer is no. Heat, air, light and moisture can impact the effectiveness and safety of a medicine. The shelf-life or expiry date of a medicine is the length of time it has been demonstrated to stay effective and safe when protected from these elements. Use of a medicine past its expiry date may result in a lower dose of active ingredient than that stated on the label (particularly relevant to antibiotics) or an increased risk of microbial contamination (for medicines containing preservatives such as eye drops).

The expiry date is determined from stability studies

As part of the medicine approval process, Medsafe evaluates data from stability studies performed by the manufacturer. The purpose of stability testing is to gain information on the effect of changes in environmental factors such as temperature, humidity and light on the quality of the medicine over time. The data generated in these studies is

used to identify the optimal storage conditions for the medicine in its original container and to assign an expiry date.

The expiry date is specific to the original container

Depending on the medicine, expiry dates may be set for a fixed time after manufacture (unopened) and also during use (opened), but are specific to the container used in the stability studies. Different packaging affords different protection, such as the inclusion of desiccants in containers to trap moisture and enhance stability. Additional studies carried out on the medicine outside its immediate container, or in other packaging materials, are performed at the discretion of the manufacturer. Healthcare professionals are advised to refer to the Pharmaceutical Precautions section of the medicine data sheet, available on the Medsafe website (**www.medsafe.govt.nz/profs/Datasheet/dsform.asp**), for all storage conditions and expiry dates supported by stability data.

How a medicine is stored will affect its expiry date

Many medicines are repackaged into individualised dosage systems, such as blister packs, to aid medication adherence and safe administration. When a medicine is repackaged, its characteristics may change in ways that have not been evaluated during the approval process (further information can be found in this edition and in a previous edition of *Prescriber Update*[1]). Consequently, the manufacturer's expiry date no longer applies and a pharmacist may affix a new expiry date that is shorter than that originally set, to account for these variables.

The stability of some medicines will be further influenced by where they are stored at home. In New Zealand this is commonly bathrooms and kitchens, which can suffer extremes of temperature and humidity. Patients should always be advised to store their medicines as recommended on the label, and to discard the medicine after the expiry date.

Reference

1. Medsafe. 2014. Medicine Storage – An Uncontained Issue? *Prescriber Update* 35(3): 36–37. URL: **www.medsafe.govt.nz/profs/PUArticles/September2014MedicineStorage.htm** (accessed 21 January 2016).

Serotonin Syndrome: Short Time to Onset, even with the First Dose

Key Messages

- Serotonin syndrome may very rarely occur after only one dose of a serotonergic medicine.
- Serotonin syndrome may also occur when the dose of a serotonergic medicine is increased, with the addition of another serotonergic medicine, or in overdose.
- The majority of cases occur within 24 hours of taking the suspect medicine.

A recent report to the Centre for Adverse Reactions Monitoring (CARM) described a patient who experienced serotonin syndrome after taking one dose of the selective serotonin reuptake inhibitor (SSRI), escitalopram. Within 24 hours of taking the SSRI, the patient developed tachycardia, hyperreflexia, restlessness and diaphoresis (profuse sweating), consistent with a diagnosis of serotonin syndrome. This case highlights that symptoms may occur within hours of ingesting only one dose of a serotonergic medicine.

Medicine classes associated with serotonin syndrome include antidepressants (eg, SSRIs, serotonin-norepinephrine reuptake inhibitors, monoamine oxidase inhibitors and tricyclic antidepressants), opioid analgesics (eg, tramadol, pethidine), central nervous system stimulants (eg, amphetamines, 'Ecstasy'), herbal products (eg, St John's wort) and other miscellaneous agents (eg, methylene blue, dextromethorphan, linezolid). Further information on medicines linked to serotonin syndrome can be found in the '*Advice about Serotonin Syndrome*' Alert Communication on the Medsafe website (**www.medsafe.govt.nz/safety/EWS/2015/SerotoninSyndrome.asp**).

Serotonin syndrome is a clinical diagnosis: the classic triad of clinical features includes neuromuscular excitation, autonomic nervous

system dysfunction and altered mental state (Table 1)[1–5]. Mild cases may be easily missed, but the diagnosis should be suspected if any of these symptoms or signs are manifest after starting or increasing the dose of a potent serotonergic drug or shortly after a second serotonergic drug is added.

Table 1: Signs and symptoms of serotonin syndrome[1–5]

Altered mental state	Agitation or restlessness Confusion Anxiety
Autonomic dysfunction (effects on functioning of internal organs)	Hypertension Tachycardia Hyperthermia Mydriasis Sweating Flushing Shivering Diarrhoea
Neuromuscular excitation (effects on nerves that control voluntary muscle movement)	Tremor Clonus (spontaneous, inducible or ocular) Myoclonus Hyperreflexia Hypertonia

Of the 19 reports of serotonin syndrome received by CARM in which time to onset was known, the majority (14 reports) occurred within one week of starting the suspect agent. In a case-series of 39 cases of serotonin syndrome reported in the literature from 1995 to 2000, approximately 75% presented within 24 hours of treatment initiation, a change in dose or overdose of the serotonergic agent[6]. Treatment involves stopping the serotonergic medicine and providing supportive care. Symptoms usually resolve within 24 hours with treatment.

Healthcare professionals are encouraged to continue reporting serotonin syndrome type reactions to CARM and to include as much information as possible (**https://nzphvc.otago.ac.nz/**).

References

1. Boyer EW, Shannon M. 2005. The Serotonin Syndrome. *New England Journal of Medicine* 352:1112–1120.
2. Isbister GK, Buckley, NA, Whyte IM. 2007. Serotonin toxicity: a practical approach to diagnosis and treatment. *Medical Journal of Australia* 187(6): 361–365.
3. Ables A, Nagubilli R. 2010. Prevention, Diagnosis, and Management of Serotonin Syndrome. *American Family Physician* 81: 1139–1142.
4. Buckley NA, Dawson AH, Isbister GK. 2014. Serotonin syndrome. *British Medical Journal* 348: g1626.
5. Dunkley EJ, Isbister GK, Sibbritt D, et al. 2003. The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity. *Queensland Journal of Medicine* 96: 635–642.
6. Mason PJ, Morris VA, Balcezak TJ. 2000. Serotonin syndrome. Presentation of 2 cases and review of the literature. *Medicine (Baltimore)* 79: 201–209.

Antiepileptic Medicines and Suicide

Antiepileptic medicines have been associated with suicide and suicidality when used to treat epilepsy and other conditions. All patients who are taking antiepileptic medicines should be closely monitored for changes in behaviour that could indicate suicidality.

Patients, their families and caregivers should seek immediate medical advice if they have any concerns about changes in mood or behaviour.

Medicines with an indication for use in the treatment of epilepsy in New Zealand include: carbamazepine, oxcarbazepine, ethosuximide, gabapentin, pregabalin, lacosamide, lamotrigine, levetiracetam, phenobarbital, primidone, phenytoin, topiramate, sodium valproate, vigabatrin, clobazam and clonazepam.

The Centre for Adverse Reactions Monitoring (CARM) has received 31 reports of suicide, suicide attempt, suicidal tendency, suicidal ideation or thoughts of self-harm in patients taking antiepileptic medicines up until 30 September 2015 (Table 1).

Suicidality can occur at any point during treatment. When time to onset was reported (25 of the 31 cases reported to CARM), it varied between less than 12 hours to over five years.

In 27 reports, the indication for use was provided. These medicines were used to treat epilepsy or convulsions in seven cases, pain related indications in 11 cases, mood disorders in seven cases and obesity in one case.

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

Table 1: Reports to CARM of suicidality associated with use of an antiepileptic medication up until 30 September 2015 (n=total number of reports received for medicine)

	Clonazepam (n=66)	Valproate (n=359)	Lamotrigine (n=144)	Topiramate (n=90)	Gabapentin (n=182)	Pregabalin (n=15)
Thoughts of self-harm			2	2		
Suicidal ideation				1		
Suicidal tendency	1		2	5	5	
Suicidal attempt	5	2	1		2	1
Suicide	3	1	1		1	1
Total reports of suicidality*	**6**	**3**	**5**	**7**	**8**	**2**

* Reports may contain more than one relevant reaction term.

Idiopathic Intracranial Hypertension

Key Messages

- ⌘ The incidence of idiopathic intracranial hypertension is increasing.
- ⌘ Idiopathic intracranial hypertension is associated with a range of medicines, in particular vitamin A derivatives, contraceptives and tetracyclines.

Idiopathic intracranial hypertension (IIH, previously known as pseudotumor cerebri) is a disorder of increased cerebrospinal fluid pressure in which patients maintain an alert and oriented mental state. Signs and symptoms include headache, pulsatile tinnitus, diplopia, papilloedema and visual loss[1,2].

IIH occurs more often in women than men and most commonly occurs in obese women of childbearing age. More than 90% of patients with IIH are obese and the incidence is rising in parallel with the increasing prevalence of obesity[2].

Other risk factors for IIH include hyperaldosteronism, Cushing's syndrome, hypervitaminosis A, use of recombinant growth factor and some medicines.

Medicines known to be associated with IIH include[1–4]:

- antibiotics including tetracyclines (eg, minocycline, doxycycline), naldixic acid and nitrofurantoin
- steroids (on withdrawal)
- contraceptives
- vitamin A derivatives such as isotretinoin
- indomethacin or ketoprofen in patients with Bartter's syndrome
- amiodarone
- thyroid replacement therapy in hypothyroid children.

Because of the risk of IIH, concomitant use of tetracyclines and vitamin A or retinoids is contraindicated.

Prompt discontinuation of the causative medicine leads to resolution of the disorder, usually over two to four weeks[3]. Weight loss is associated with improvement of IIH in overweight patients[4].

Of the reports of IIH received by the Centre for Adverse Reactions Monitoring (CARM), 84% occurred in females and 69% of reports in females were associated with a tetracycline or a contraceptive medicine.

Any suspected or confirmed case of IIH in association with medicines should be reported to CARM (**https://nzphvc.otago.ac.nz/**).

References

1. Ko MW, Liu GT. 2010. Pediatric Idiopathic Intracranial Hypertension (Pseudotumor Cerebri). *Hormone Research in Paediatrics* 74: 381–389.
2. Wall M. 2010. Idiopathic Intracranial Hypertension. *Neurologic Clinics* 28(3): 593–617.
3. Lochhead J, Elston JS. 2003. Doxycycline induced intracranial hypertension. *BMJ* 326: 641–642.
4. Andrews LE, Liu GT, Ko MW. 2014. Idiopathic Intracranial Hypertension and Obesity. *Hormone Research in Paediatrics* 81: 217–225.

Venlafaxine and Photosensitivity

Key Messages

Patients taking medicines that can cause photosensitivity reactions should:

- ⌘ Cover up with dark and closely-woven clothing
- ⌘ Wear a wide-brimmed hat, long-sleeved shirts and trousers
- ⌘ Use topical sunscreen agents with a very high Sun Protection Factor (SPF 50+), that are water resistant and broad spectrum.

The Centre for Adverse Reactions Monitoring (CARM) has received four reports of a photosensitivity reaction in association with venlafaxine. In the most recent case, the photosensitivity reaction started after the dose was increased. In all cases, the photosensitivity reaction was reported to have started either in the same month or in the month after the patient started venlafaxine treatment.

Photosensitivity reactions typically appear as unexpected sunburn or a dry or blistering rash on sun-exposed skin, which may or may not be itchy. The most commonly affected areas are the face, neck, arms, backs of hands, lower legs and feet[1].

Photosensitivity reactions are an expected uncommon adverse effect of the anti-depressant venlafaxine (estimated to occur at frequencies of ≥0.1% and <1%)[2].

The New Zealand Dermatological Society recommends patients taking medicines that can cause photosensitivity reactions[1].

- Cover up with dark and closely-woven clothing.
- Wear a wide-brimmed hat, long-sleeved shirts and trousers.
- Use topical sunscreen agents with a very high Sun Protection Factor (SPF 50+), that are water resistant and broad spectrum.

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

References

1. New Zealand Dermatological Society. *Drug-induced photosensitivity*. URL: **www.dermnetnz.org/reactions/drug-photosensitivity.html** (accessed 18 December 2015).
2. Pfizer. 2015. *Efexor-XR Data Sheet*. 2 October 2015. URL: **www.medsafe.govt.nz/profs/datasheet/e/Efexorxrcap.pdf** (accessed 18 December 2015).

Post-Finasteride Syndrome

Key Messages

- ⌘ Post-Finasteride Syndrome is a recently recognised condition that occurs in some men who have taken finasteride.
- ⌘ Symptoms (sexual, physical, and mental and neurological) often persist after the patient has stopped taking finasteride.
- ⌘ Patients should be informed of the risks of taking finasteride prior to treatment initiation.
- ⌘ The symptoms associated with Post-Finasteride Syndrome should be discussed with patients prior to treatment.

Post-Finasteride Syndrome (PFS) is a recently recognised condition that can occur in patients who have taken finasteride[1]. Finasteride is a 5-alpha reductase type II enzyme inhibitor used to treat hair loss (eg, Propecia, Profal and ReGen) or enlarged prostate (eg, Proscar, Finasteride Rex and Fintral).

PFS includes sexual, physical, and mental and neurological symptoms in patients who have taken finasteride (Table 1). Symptoms often persist after the patient has stopped taking finasteride.

Importantly, some patients can experience suicidal ideation and depression after stopping finasteride treatment. Patients and their families should be advised about these symptoms and to seek medical advice as soon as possible if they occur.

Unfortunately, PFS is a condition with no known cure and few, if any, effective treatments.

Further information about PFS can be found on the Post-Finasteride Syndrome Foundation website (**www.pfsfoundation.org/**).

To date, the Centre for Adverse Reactions Monitoring (CARM) has received 10 reports associating finasteride use with at least one of the symptoms of PFS listed in Table 1. Age, when reported, ranged from 22 to 81 years of age. Only three patients reported that they had recovered at the time of the report.

Please report any adverse events, including those associated with PFS, to CARM (**https://nzphvc.otago.ac.nz/**).

Reference

1. Post-Finasteride Syndrome Foundation. 2015. *Global Public Health Advisory – US National Institutes of Health Recognises Post-Finasteride Syndrome*. URL: **us5.campaign-archive2.com/?u=644fb8b633594fee188a85091&id=9cea0753a4&e=5459eb9419** (accessed 6 October 2015).

Table 1: Reported symptoms of Post-Finasteride Syndrome[1]

Sexual Symptoms	Physical Symptoms	Mental and Neurological Symptoms
Decreased or complete loss of sex drive	Female-like breast development and enlargement	Severe memory/recall impairment
Erectile dysfunction, impotence	Chronic fatigue, listlessness	Slowed thought processes
Loss of morning and spontaneous erections	Muscle atrophy, weakness	Impaired problem solving, decreased comprehension
Sexual anhedonia, loss of pleasurable orgasm	Decreased oil and sebum production	Depression
Decreased semen volume and force	Chronically dry, thinning of skin	Anxiety
Penile shrinkage and numbness	Melasma	Suicidal ideation
Peyronie's disease	Tinnitus	Emotional flatness and anhedonia
Scrotal shrinkage and numbness	Increased fat deposition, obesity and elevated body mass index	Insomnia
	Decrease in body temperature	
	Reduced HDL cholesterol, raised fasting glucose and triglycerides	
	Attempted suicide	
	Completed suicide	

Spontaneous Reports: Seasonal Influenza Vaccination 2015

In 2015, the Centre for Adverse Reactions Monitoring (CARM) received 241 reports of adverse events following seasonal influenza vaccination (Table 1). A total of 596 adverse events were described; many reports contained more than one suspected event.

The most commonly reported events were injection site inflammation (57 reports), arm pain (33), headache (25), injection site pain (17) and pruritus (17).

At the beginning of the 2015 vaccination season, an increased proportion of reports of hypersensitivity and local reactions with the seasonal influenza vaccination were reported to CARM as compared with previous years (**www.medsafe.govt.nz/safety/EWS/monitoring-communications.asp#22June2015**). However by vaccination season end, the reported number of these reactions were comparable to previous years.

Fifteen (6%) of the influenza vaccine-related reports in 2015 were considered serious. A serious adverse reaction is defined, according to internationally agreed criteria, as any drug-related event that results in death, is life-threatening,

requires or prolongs inpatient hospitalisation, results in persistent or significant disability or requires intervention to prevent permanent disability, is a congenital abnormality or is a medically important event.

Two deaths with a temporal association to the 2015 influenza vaccination were reported to CARM. One patient had a terminal condition and the reporter did not consider the vaccine to be a causal factor. The second patient, with a history of myocardial ischaemia and congestive cardiac failure, died of a sudden cardiac event.

In 2015, the majority of reports were submitted by nurses (71%), followed by GPs (18%) and pharmacists (5%). This reporter pattern is similar to previous years.

Table 1: Number of reports received by CARM and number of influenza vaccine doses distributed, 2011-2015

	2011	2012	2013	2014	2015
Reports of adverse events following influenza vaccination	207	193	290	253	241
Influenza vaccine doses distributed*	993,500	1,000,600	1,253,600	1,206,573	1,211,152
Estimated reporting rate per 100,000 doses	20.8	19.3	23.1	21.0	19.9

*The number of doses distributed is not equal to number administered (eg, some doses may have been destroyed at the end of the influenza season and not used)

Reminder: Immunomodulatory Medicines and Risk of Progressive Multifocal Leukoencephalopathy

Key Messages

- Immunomodulatory medicines are associated with the development of progressive multifocal leukoencephalopathy (PML).
- PML is a demyelinating disease of the CNS caused by the JC virus.
- A diagnosis of PML should be considered in patients taking immunomodulatory medicines who present with progressive neurological symptoms.

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system. PML is caused by the human polyomavirus John Cunningham (JC) virus and may be fatal or result in severe disability.

A compromised immune system due to either disease or immunomodulatory medicines is the major risk factor for development of PML[1]. Cases of PML have been reported in individuals with HIV, lymphoproliferative disorders and malignancies[1].

Medicines associated with an increased risk of PML, either alone or with other immunomodulatory medicines, include:

- fingolimod
- azathioprine
- natalizumab
- rituximab
- dimethyl fumarate
- alemtuzumab
- mycophenolate mofetil
- cyclophosphamide
- tacrolimus.

PML should be considered in patients with compromised immune systems that present with progressive neurological signs or symptoms including cognitive dysfunction, and motor and sensory disturbance[1].

More detailed information on PML can be found in the 2012 *Prescriber Update* article 'PML: A rare but serious disease'[1].

Reference

1. Medsafe. 2012. PML: A Rare but Serious Disease. *Prescriber Update* 33(3): 21–23. URL: **www.medsafe.govt.nz/profs/PUArticles/PMLSept2012.htm** (accessed 3 November 2015).

Delayed Skin Reactions Commonly Reported with Penicillins

Skin reactions are commonly reported in association with penicillins. Between 1 January 2010 and 31 December 2014, the Centre for Adverse Reactions Monitoring (CARM) received a total of 471 reports of skin reactions associated with penicillin treatment. Time to onset was reported in 81% of reports.

Rapidly developing (IgE-mediated) immediate type hypersensitivity often occurs within the first hour after starting penicillin-containing antibiotics. Of the 471 reports, skin reactions occurred within the first hour after penicillin administration in 18% of reports and within 24 hours of treatment initiation in 46% of reports (Figure 1). These skin reactions typically included rash, urticaria and angioedema.

Other skin reactions may take longer to manifest and may even occur after the treatment course is completed. Eight percent of all penicillin-related skin reactions were reported to have occurred between 8 and 30 days following the start of treatment.

Delayed skin reactions are often T cell-mediated and typically take days to weeks to manifest. The most serious of these are toxic epidermal necrolysis and Stevens-Johnson syndrome. More common delayed skin reactions include maculopapular and morbilliform rashes.

Should a skin reaction occur, treatment with the penicillin should be discontinued and appropriate supportive and alternative therapy instituted.

Please continue to report suspected allergic reactions to medicines, including time to onset, to CARM (**https://nzphvc.otago.ac.nz/**). Reporting of suspected allergies is particularly important to enable the medical warning system to be updated for the patient involved.

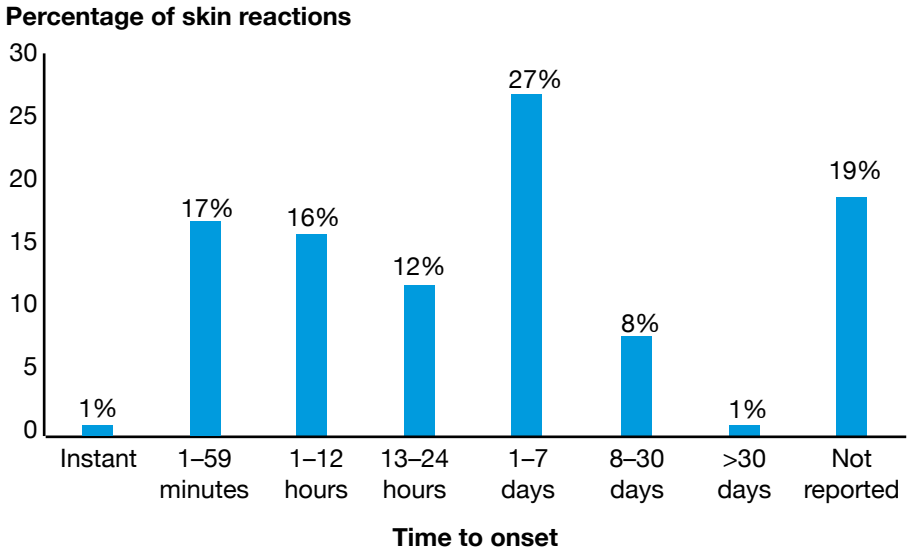

Figure 1: Percentage of penicillin-related skin reactions by time to onset

Amlodipine and Gingival Hyperplasia

The Centre for Adverse Reactions Monitoring (CARM) has received three reports of gingival hyperplasia (gum enlargement) associated with the use of amlodipine. In one case, the patient was switched to another antihypertensive agent after 15 months due to progressive gingival hyperplasia.

Gingival hyperplasia is a known adverse reaction associated with several calcium channel blockers, including amlodipine[1]. It is also associated with other medicines, including ciclosporin and some anticonvulsants[2,3] .

Management of gingival hyperplasia includes good oral hygiene and regular dental examinations to monitor whether the hyperplasia is progressive[4].

If medicine-induced gingival hyperplasia is intolerable or progressive, the patient should consult their doctor about suitable alternatives.

Healthcare professionals are reminded to report any suspected adverse reactions to medicines to CARM (**https://nzphvc.otago.ac.nz/**).

References

1. Pfizer New Zealand Ltd. 2014. *Norvasc Data Sheet*. 8 October 2014. URL: **www.medsafe.govt.nz/profs/datasheet/n/Norvasctab.pdf** (accessed 12 January 2016).
2. Novartis New Zealand Limited. 2014. *Neoral Data Sheet*. 29 October 2014. URL: **www.medsafe.govt.nz/profs/datasheet/n/Neoralsolcap.pdf** (accessed 12 January 2016).
3. Pfizer New Zealand Ltd. 2013. *Dilantin Data Sheet*. 29 May 2013. URL: **www.medsafe.govt.nz/profs/datasheet/d/Dilantincapsusptab.pdf** (accessed 12 January 2016).
4. New Zealand Dental Association. 2016. *Your Oral Health: Gum Disease*. URL: **www.healthysmiles.org.nz/default,284,gum-disease.sm** (accessed 12 January 2016).

Risk of Hyponatraemia with the Use of Glucose 4% Sodium Chloride 0.18% Infusion Solution ('Bart's Solution') in Children

Key Messages

- Glucose 4% sodium chloride 0.18% infusion solution should not normally be used for fluid replacement in children because of the risk of hyponatraemia.
- Consult a physician experienced in intravenous fluid therapy if low sodium fluids are required in children.

Healthcare professionals are reminded that glucose 4% sodium chloride 0.18% infusion solution should not normally be used for fluid replacement in children because of the risk of hyponatraemia[1].

The availability of glucose 4% sodium chloride 0.18% infusion solution should be restricted to critical care and specialist wards such as renal, liver and cardiac units[1]. It is important to consult a physician experienced in intravenous fluid therapy if low sodium fluids are required in children[2].

Infants and children may have an impaired ability to regulate fluid and electrolytes compared to adults. Fluid replacement therapy should be closely monitored in these populations as fluid and electrolyte disturbances such as hyponatraemia may occur[2].

Hyponatraemia can lead to headache, nausea, seizures, lethargy, coma and cerebral oedema[2]. Prompt action must be taken if children (or adults) develop these signs and symptoms as fatalities have been reported.

References

1. New Zealand Formulary for Children. 2016. *Parenteral preparations for fluid and electrolyte imbalance*. NZFC v43. URL: **www.nzfchildren.org.nz/nzf_5043** (accessed 13 January 2016).
2. Baxter Healthcare Ltd. 2015. *Glucose and sodium chloride data sheet*. 26 October 2015. URL: **www.medsafe.govt.nz/profs/datasheet/GlucoseAndDextroseInSodiumChlorideinf.pdf** (accessed 13 January 2016).

MARC's Remarks: December 2015 Meeting

The Medicines Adverse Reactions Committee (MARC) met on 3 December 2015 to discuss a number of medicine-related safety issues.

The MARC discussed a number of safety concerns recently associated with **Gardasil** (HPV) vaccination. The MARC concluded that there is no safety concern relating to the development of complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS) after Gardasil vaccination.

The MARC reviewed the available information on the risk of pneumonia with **inhaled corticosteroids**. The MARC considered that there appears to be an association between inhaled corticosteroids and pneumonia and that this was likely a class effect. The Committee noted that information on the management of patients with chronic obstructive pulmonary disease can be found in a recently published article by the Best Practice Advocacy Centre (**www.bpac.org.nz/BPJ/2015/February/copd-part1.aspx**).

The MARC discussed the association between the use of **hormone replacement therapy** by post-menopausal women and the risk of ovarian cancer. The MARC considered that the risks are well articulated in the data sheets and women should be able to make an informed choice about the use of these medicines.

The MARC reviewed the available information on a safety concern of retinopathy in preterm infants associated with the use of **epoetin beta**. The MARC concluded that the evidence was insufficient to support an association.

The MARC discussed the use of oral contraceptives containing **drospirenone** and **dienogest** and the risk of venous thromboembolism. The MARC considered that the data sheets and consumer medicine information accurately reflect the available information. Further information relating to the use of hormonal contraceptives can be found in the Consumer Educational Material on the Medsafe website (**www.medsafe.govt.nz/consumers/educational-material.asp**).

Following the 163rd meeting held on 10 September 2015, Medsafe obtained further information relating to **cross-reactivity** with **beta-lactam** antibiotics. The MARC reviewed this new information and discussed the availability of skin testing in the community. The MARC recommended that the data sheets for **cephalosporin**-containing products should be updated to harmonise the contraindications and warnings and precautions. An article on this topic will be published in a future edition of *Prescriber Update*.

Review of CARM's Quarterly Report indicated that some of the serious and fatal adverse reactions may have resulted from medication errors. A number of different themes were identified.

- Failure to note MedicAlert or patient history about serious adverse drug reactions leading to re-administration of the same medicine (**www.medsafe.govt.nz/profs/PUArticles/March2014MedicineInducedAnaphylaxis.htm**).
- Use of a non-steroidal anti-inflammatory drug (NSAID) with anticoagulants leading to haemorrhage (**www.medsafe.govt.nz/profs/PUArticles/June2015/June2015OralAnticoagulants.htm**).
- Administration of an NSAID to a very elderly patient without gastroprotection (**www.medsafe.govt.nz/profs/PUArticles/ReducingGIReactionRiskwith%20NSAIDsAndCox2.htm**).
- Prescribing NSAIDs to patients already taking an ACE inhibitor and a diuretic causing acute renal failure (**www.medsafe.govt.nz/profs/PUArticles/DangTrio.htm**).
- Prescribing medicines excreted via the kidney to patients with severe renal failure (check data sheet contraindication **www.medsafe.govt.nz/profs/datasheet/DSForm.asp**).

Further information on this meeting can be found on the Medsafe website (**www.medsafe.govt.nz/profs/adverse/Minutes164.htm**).

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**).

Dear Healthcare Professional (DHCP) Letters are intended to inform healthcare professionals about important new or updated safety information regarding a medicine. Dear Healthcare Professional Letters are prepared by the medicine sponsor and are published on the Medsafe website with the sponsor's agreement.

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

Date	Communication	Topic
1 December 2015	DHCP Letter	Tarceva: Indication restricted to EGFR-activating mutations only
8 December 2015	DHCP Letter	Cellcept: New restrictions on use due to teratogenic risk
December 2015	Consumer Information	Severe Allergic Reactions (Anaphylaxis) to Medicines (English and Te Reo versions available)
11 January 2016	Consumer Information	How to safely give medicines to children
11 January 2016	Consumer Information	Medicines and breastfeeding
11 January 2016	Consumer Information	Serotonin Syndrome

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 reports for the potential safety issue* listed below to the Centre for Adverse Reactions Monitoring (CARM)

Medicine	Potential safety issue	Active monitoring ends
Ticagrelor	Depression Suicidality	30 September 2016

- 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 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**

MEDSAFE
NEW ZEALAND MEDICINES AND MEDICAL DEVICES SAFETY AUTHORITY
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www.medsafe.govt.nz

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.

CARM
CENTRE FOR ADVERSE REACTIONS MONITORING

Adverse Reactions to Medicines, Vaccines and Devices

CARM fax: (03) 479 7150
CARM phone: (03) 479 7247
www.otago.ac.nz/carm

Patient Details

Surname: First name/s:	NHI No:	
	Date of birth:	Sex:
Address:	Ethnicity:	

All medicines in use *asterisk suspect medicine/s* Include over-the-counter (OTC) and alternative medicines

Medicine or Vaccine+batch no.	Daily Dose	Route	Date Started	Date Stopped	Reason for Use

Description of Adverse Reaction or Event

Date of onset:

Recovered Not yet recovered but improved Not yet recovered Unknown Fatal – Date of Death:

Severe? – Yes No Rechallenged? – No Yes Result

Other Factors – Please tick or specify as appropriate

Renal disease Allergy : Other Medical Conditions :

Hepatic disease Nutritional Suppl or OTC use : Industrial Chemicals :

Reporter - Please tick as appropriate Doctor Pharmacist Dentist Other

Name:
Address: Signature:

Phone: Date:

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Data sheets, consumer medicine information, media releases, medicine classification issues and adverse reaction forms can be found at **www.medsafe.govt.nz**

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