

Prescriber Update

Vol. 38 No. 1

March 2017

www.medsafe.govt.nz

ISSN 1172-5648 (print)
ISSN 1179-075X (online)

Contents

Data Sheets are Changing!	2
Medicines and Hepatitis B Reactivation	2
Tramadol in Children	4
Spontaneous Reports: Seasonal Influenza Vaccination 2016	4
Posterior Reversible (Leuko) Encephalopathy Syndrome (PRES) – Increasingly Linked to Medicines	5
MARC's Remarks: December 2016 Meeting	7
M Medicines Monitoring: Iodinated Contrast Medium and Hypothyroidism	7
Adverse Reaction Reporting in New Zealand – 2016	8
Gathering Knowledge from Adverse Reaction Reports	9
The Medsafe Files – Episode Three: Product Categorisation	9
Medicines and Illicit Drug Interactions	10
Drug-induced Lupus	11
Medicine-induced Vertigo	12
Oxybutynin – Psychiatric Side Effects	13
Appropriate Use of Head Lice Treatments	14
Recent Approvals of Medicines containing a New Active Ingredient	15
Quarterly Summary of Recent Safety Communications	15
Prescriber Update Subscription	16

Data Sheets are Changing!

In March 2016, Medsafe held a consultation on the format of the data sheets. As a result of this consultation, Medsafe has now confirmed that the data sheets should follow the European Summary of Product Characteristics (SmPC) format. This means that the information will be ordered in the same sequence in all data sheets with the clinical information near the beginning. In addition, there will be a summary table at the end of each data sheet outlining the changes from the previous version.

The change-over has already started. Companies have until 28 February 2019 to reformat their existing data sheets.

Find out more on the Medsafe website (www.medsafe.govt.nz/consultations/OutcomeDatasheetFormat.asp).

Data sheets are available on the Medsafe website (www.medsafe.govt.nz/Medicines/infoSearch.asp).

Medicines and Hepatitis B Reactivation

Key messages

- ⌘ Hepatitis B reactivation can occur in patients with a history of hepatitis B infection.
- ⌘ Reactivation can occur spontaneously but is more common in the setting of immune suppression or cancer chemotherapy.
- ⌘ Patients at risk of hepatitis B reactivation requiring immunosuppression should be screened for hepatitis B virus before immunosuppressive therapy is started.

The natural course of hepatitis B virus (HBV) infection depends on the interaction between viral replication and the host's immune response. HBV persists in the body even when there is evidence of serological recovery¹. Therefore, HBV reactivation can occur in patients with a history of HBV infection. Reactivation can occur spontaneously but is more common in the setting of immune suppression or cancer chemotherapy². It can also occur in patients undergoing solid organ or haematopoietic stem cell transplantation¹.

HBV reactivation is a rare but distinctive syndrome defined by a sudden and marked increase in HBV replication. It is usually accompanied by elevations in serum aminotransferase levels and sometimes by jaundice. Reactivation can be severe causing acute liver failure and death².

The prevalence of HBV reactivation reported in the literature ranges widely. This is due to most studies being case reports or small case series that use different definitions of HBV reactivation³.

The exact mechanism of HBV reactivation is unclear but the initiating factor is thought to be loss of immune control over viral replication².

Medicines Implicated in HBV Reactivation

A range of immunosuppressive agents have been implicated in HBV reactivation. Many novel and targeted agents for the treatment of malignant, inflammatory and autoimmune conditions have been associated with clinical evidence of HBV reactivation³.

The risk of HBV reactivation to specific medicine classes has been estimated by the American Gastroenterological Association based on a comprehensive review of the literature (Table 1)^{3,4,5}.

The Medicines Adverse Reactions Committee recently reviewed information on the risk of HBV reactivation with the use of direct-acting antivirals (eg, Viekira Pak, Viekira Pak-RBV, Harvoni) for the treatment of hepatitis C⁶. These data sheets are in the process of being updated to include information on the risk of HBV reactivation.

Prophylaxis of HBV Reactivation

Generally, the outcome is poor when antiviral treatment is started after HBV reactivation is already established³. Therefore, patients at risk of HBV reactivation should be screened for HBV and appropriate antiviral prophylaxis should be considered³.

Cases Reported in New Zealand

The Centre for Adverse Reactions Monitoring (CARM) has received three reports of

suspected hepatitis B reactivation. The suspect medicines reported in these cases were normal immunoglobulin in the first case; rituximab, tacrolimus and prednisone in the second case; and abiraterone in the third case.

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

References

1. Lok AS, Bonis PA. 2016. Hepatitis B virus reactivation associated with immunosuppressive therapy. *UpToDate*. URL: www.uptodate.com/contents/hepatitis-b-virus-reactivation-associated-with-immunosuppressive-therapy (accessed 15 December 2016).
2. Di Bisceglie AM, Lok AS, Martin P, et al. 2015. Recent US Food and Drug Administration warnings on hepatitis B reactivation with immune-suppressing and anticancer drugs: just the tip of the iceberg? *Hepatology* 61(2): 703–11.
3. Pattullo V. 2016. Prevention of Hepatitis B reactivation in the setting of immunosuppression. *Clinical and Molecular Hepatology* 22(2): 219–37.
4. Perrillo R, Gish R, Falck-Ytter Y. 2015. American Gastroenterological Association Institute technical review on prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology* 148(1): 221–44.
5. Reddy KR, Beavers KL, Hammond SP, et al. 2015. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology* 148(1): 215–19.
6. Medsafe. 2016. Safe Prescribing of Direct-Acting Antivirals for Treatment of Hepatitis C - It's Complicated. *Prescriber Update* 37(4): 50–51.

Table 1: Risk estimates of HBV reactivation according to medicine class^{3,4,5}

Risk estimate of hepatitis B reactivation	Medicine class	Medicine examples	Additional information
High (>10%)	B-cell depleting agents	Rituximab	Associated with highest risk due to their potent and durable immunosuppressive effect.
	Corticosteroids	High dose (eg, prednisone ≥20 mg for ≥4 weeks)	Directly affect T-cell function and promote HBV DNA replication. Risk varies according to dose, duration and route of administration.
Moderate (1–10%)	TNFα inhibitors	Infliximab Etanercept Adalimumab	TNFα is a first line of defence in viral infections. Inhibition of TNFα increases the risk of HBV reactivation.
	Cytokine inhibitors and integrin inhibitors	Ustekinumab Natalizumab	Evidence largely based on case reports. The risk may be due to their known relative potency of immunosuppression.
	Tyrosine kinase inhibitors	Imatinib Nilotinib	Moderately immunosuppressive. Risk has been associated with the treatment of conditions including chronic myeloid leukaemia and gastrointestinal stromal tumours.
	Corticosteroids	Moderate dose (eg, prednisone <20 mg for ≥4 weeks)	
Low (<1%)	Traditional immunosuppression	Azathioprine Mercaptopurine Methotrexate	Most cases involve co-administration with corticosteroids or other immunomodulators, thereby increasing the risk.
	Corticosteroids	Low dose (eg, prednisone for <1 week) Intra-articular corticosteroids	

Tramadol in Children

Key messages

- ⌘ Tramadol is contraindicated in children under two years of age due to the limited data on efficacy and safety in this patient group.
- ⌘ The strength of tramadol oral drops funded by PHARMAC in the DHB hospitals is changing. Please take care when prescribing, dispensing and administering tramadol oral drops.

The use of tramadol in children was discussed by the Medicines Adverse Reactions Committee (MARC) in 2016 (www.medsafe.govt.nz/profs/adverse/Minutes166.htm#3.2.3).

Tramadol is indicated for the relief of moderate to severe pain in adults and children. Most of the studies conducted in children investigated the use of tramadol in postoperative pain. The MARC considered that there is a role for the use of tramadol in children. However, as there is very limited data on the efficacy and safety in younger children, the MARC recommended that tramadol should be contraindicated in children aged two years and under. The tramadol data

sheets are in the process of being updated with this contraindication as well as additional information on use following tonsillectomy, adenoidectomy or throat surgery.

Further information on the use of tramadol is available at www.medsafe.govt.nz/profs/PUArticles/December2014Tramadol.htm

Recent Funding Change

PHARMAC has released its decision on the funding of tramadol oral drops in Section H of the Pharmaceutical Schedule (hospital pharmaceuticals). The decision is to:

- list tramadol oral drops 10 mg/mL from 1 January 2017
- delist tramadol oral drops 100 mg/mL from 30 June 2017.

Please take care when prescribing, dispensing and administering tramadol oral drops during this transition period to ensure the correct dose is given to the patient.

Further information on this change in funding is available on the PHARMAC website (www.pharmac.govt.nz/news/notification-2016-12-13-tramadol-hydrochloride/).

Spontaneous Reports: Seasonal Influenza Vaccination 2016

Seasonal influenza has a substantial impact on public health. The annual influenza-related hospitalisation rate in New Zealanders over 80 years of age is 327.8 per 100,000 and under 1 year of age is 244.5 per 100,000¹.

The Southern Hemisphere Influenza Vaccine Effectiveness, Research and Surveillance (SHIVERS) project and the Institute of Environmental Science and Research Limited (ESR) monitors the impact of influenza infection and vaccination in New Zealand. The incidence rate of influenza deaths was calculated at 0.8 per 100,000 in 2015, but this is likely to be an underestimate².

The effectiveness of influenza vaccine is around 50%, when measured by a reduction in hospitalisation due to influenza infection (using a case test-negative design, a type of case-control

study to estimate influenza vaccine effectiveness). However, efficacy is lower in older people^{2,3}.

To reduce hospitalisation and other complications, seasonal influenza vaccine is offered free to those at higher risk of influenza complications (www.influenza.org.nz/eligibility-criteria) and by many employers.

In 2016, the Centre for Adverse Reactions Monitoring (CARM) received 212 reports of 527 adverse events following immunisation (AEFI) with seasonal influenza vaccine (Table 1). Some reports contained more than one AEFI.

The most commonly reported events were injection site inflammation (47 reports), arm pain (25), dizziness (23) and headache (21).

Seven (3%) 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).

In one report, the patient was reported to have died of a myocardial infarction following influenza vaccination. The death was considered unlikely to be due to the vaccination.

The majority of reports were submitted by nurses (80%), followed by GPs (14%) and pharmacists (5%).

Table 1: Number of reports of AEFI received by CARM and number of influenza vaccine doses distributed, 2012–2016

	2012	2013	2014	2015	2016
Reports of adverse events following influenza vaccination	193	290	253	241	212
Influenza vaccine doses distributed*	1,000,600	1,253,600	1,206,573	1,211,152	1,245,934
Estimated reporting rate per 100,000 doses	19.3	23.1	21.0	19.9	17.0

* The number of doses distributed is not equal to number administered.

References

1. Khieu TQ, Piers N, Telfar-Barnard LF, et al. 2015. Estimating the contribution of influenza to hospitalisations in New Zealand from 1994 to 2008. *Vaccine* 33: 4087–92.
2. Institute of Environmental Science and Research Ltd. 2016. *Surveillance report: Influenza surveillance in New Zealand 2015*. URL: https://surv.esr.cri.nz/PDF_surveillance/Virology/FluAnnRpt/InfluenzaAnn2015.pdf (accessed 4 January 2017).
3. Bissielo A, Piers N, Huang Q, et al. 2015. Effectiveness of seasonal influenza vaccine in preventing influenza primary care visits and hospitalisation in Auckland, New Zealand in 2015: interim estimates. *Euro surveillance* 21(1): pii=30101.

Posterior Reversible (Leuko) Encephalopathy Syndrome (PRES) – Increasingly Linked to Medicines

Key messages

- ⌘ Posterior reversible (leuko) encephalopathy syndrome (PRES) describes a disorder of acute onset neurological symptoms due to reversible subcortical vasogenic brain oedema.
- ⌘ The most common symptoms are seizure and headache. The majority of patients have hypertension or an acute increase in blood pressure.
- ⌘ PRES is usually reversible on prompt diagnosis and treatment of underlying conditions.
- ⌘ Medicines linked to PRES are generally used in transplant and cancer patients and include ciclosporin, tacrolimus, sunitinib, immunoglobulin and interferon alpha.

Posterior reversible (leuko) encephalopathy syndrome (PRES) is a clinico-radiological syndrome that is increasingly being recognised as a side effect of medicines^{1,2}. The syndrome refers to a disorder of reversible subcortical vasogenic brain oedema in patients with acute neurological symptoms.

PRES was first described in the 1990s³. The incidence is generally unknown. For patients undergoing organ or stem cell transplant the reported incidence ranges from 1% to 10% in both adults and children⁴. PRES is slightly more common in women¹.

PRES is often associated with conditions such as hypertension (53% of reported cases), kidney disease (45%), malignancy (32%), dialysis dependency (21%), transplantation (24%), autoimmune disorders (11%) and eclampsia (11%)¹.

PRES is also associated with the use of several medicines, particularly immunosuppressants and cancer chemotherapy¹. Medicines implicated in PRES include (this is not an exhaustive list)^{2,4,5,6}:

- tacrolimus (rarely sirolimus)
- ciclosporin
- bevacizumab
- sunitinib
- sorafenib
- interferon alpha
- intravenous immunoglobulins
- cisplatin

- cytarabine
- fludarabine
- rituximab
- infliximab
- alemtuzumab
- corticosteroids
- bortezomib.

The time between starting a medicine and the onset of PRES has not been well described. For medicines used in solid organ transplant, onset times may be over a year and may be associated with episodes of graft versus host disease or infection⁴.

The pathophysiology of PRES is unclear but is thought to be partially due to increased blood pressure².

The most common clinical signs and symptoms are¹:

- seizures (occur in around 85% of cases)
- headache (around 50%)
- amaurosis/hemianopsia (blindness in nearly 50%)
- altered mental status/coma (around 40%)
- nausea and vomiting (around 30%)
- transient motor defects (around 10%).

The onset of symptoms is usually rapid, reaching a peak in 12 to 48 hours⁴.

Diagnosis is difficult, and clinical context and clinical judgement are essential. Differential diagnoses include encephalitis, malignancy, reversible cerebral vasoconstriction syndrome, stroke, progressive multifocal leukoencephalopathy and vasculitis. Although the clinical picture is not specific, an early MRI is usually diagnostic^{1,3}. Brain imaging usually reveals vasogenic oedema in the parieto-occipital regions of both cerebral hemispheres³.

There is no specific treatment, but the disorder usually resolves when the underlying cause is removed². Seizures should be treated in the normal manner^{1,2}, however, the length of treatment is debated². The general consensus is that blood pressure (BP) should be lowered in patients with hypertension. Experts recommend that BP is reduced by 25% in the first few hours^{1,2,4}. Pronounced fluctuations in BP should be avoided

and therefore intravenous (IV) infusion of nitroprusside or nicardapine has generally been used^{1,2,4}. Any medicines suspected of causing PRES should be discontinued².

In most cases of PRES, symptoms typically improve within one week. Neuroimaging resolution normally takes longer⁴.

However, cerebral haemorrhage or ischaemia can occur. Irreversible neurological defects have been reported in 10% to 20% of cases and death in 3% to 6% of cases^{1,2}. PRES may recur in 5% to 10% of cases, more commonly in patients with uncontrolled hypertension.

The Centre for Adverse Reactions Monitoring (CARM) has received three reports of PRES.

- Reported in 2009 in association with ciclosporin, the patient was changed to sirolimus and was recovering⁷.
- Reported in 2011 in association with R-CHOP therapy, the patient was successfully treated with IV labetalol followed with oral felodipine⁸.
- Reported in 2015 in association with ciclosporin, improved with antihypertensive treatment⁹.

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

References

1. Granata G, Greco A, Iannella G, et al. 2015. Posterior reversible encephalopathy syndrome – insight into pathogenesis, clinical variants and treatment approaches. *Autoimmunity Reviews* 14(9): 830–6.
2. Fugate J, Rabinstein A. 2015. Posterior reversible encephalopathy syndrome: clinical and radiological manifestations, pathophysiology, and outstanding questions. *Lancet Neurology* 14(9): 914–25.
3. Hinchey J, Chaves C, Appignani B, et al. 1996. A reversible posterior leukoencephalopathy syndrome. *The New England Journal of Medicine* 334: 494–500.
4. Masetti R, Cordelli D, Zama D, et al. 2015. PRES in children undergoing hematopoietic stem cell or solid organ transplantation. *Pediatrics* 135(5): 890-901.
5. Garg R. 2001. Posterior leukoencephalopathy syndrome. *Postgraduate Medical Journal* 77(903): 24-28.
6. Oshikawa G, Kojima A, Doki N, et al. 2013. Bortezomib-induced posterior reversible encephalopathy syndrome in a patient with newly diagnosed multiple myeloma. *Internal Medicine* 52(1): 111–4.
7. CARM case ID 85779. URL: www.medsafe.govt.nz/Projects/B1/adrsearch.asp
8. CARM case ID 98013. URL: www.medsafe.govt.nz/Projects/B1/adrsearch.asp
9. CARM case ID 115521. URL: www.medsafe.govt.nz/Projects/B1/adrsearch.asp

MARC's Remarks: December 2016 Meeting

The Medicines Adverse Reactions Committee (MARC) met on 1 December 2016 to discuss a number of medicine-related safety issues.

The MARC discussed ophthalmological monitoring in patients taking **hydroxychloroquine**. The MARC considered the available evidence and concluded that there is reasonably good support for a first ophthalmologic review within one year of starting hydroxychloroquine and, in the absence of major risk factors, a further review after five years. After five years of use, the MARC considered the frequency of monitoring is dependent on each patient's risk factors however, yearly monitoring should be a minimum. In addition, wherever possible, optical coherence tomography (OCT) and visual field testing are recommended.

The MARC discussed some of the principles and difficulties of decision making and **risk communication** to healthcare professionals and consumers.

The MARC discussed a case concerning an older patient taking **enoxaparin** who had a history of

chronic kidney disease. The patient experienced a fatal cerebral haemorrhage. The MARC noted that caution should be taken around the use of low molecular weight heparin in patients with impaired renal function. The data sheet states that dose adjustment is required for patients with severe renal impairment (www.medsafe.govt.nz/profs/Datasheet/c/Clexaneinj.pdf). This case demonstrates the importance of clinical monitoring when using enoxaparin.

At the 167th MARC meeting held on 8 September 2016, the Committee noted that the data sheets for **aciclovir**-containing products have recently been updated to include 'confusion' as an adverse effect. Aciclovir is used at high doses in the elderly for the treatment of shingles. Healthcare professionals are reminded that use of high-dose aciclovir increases the risk of confusion, and care should be taken.

Further information on the meeting held on 1 December 2016 can be found on the Medsafe website (www.medsafe.govt.nz/profs/adverse/Minutes168.htm).

WE NEED YOUR HELP!

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



MEDICINES
MONITORING

Medicine	Potential Safety Issue	Active Monitoring Ends
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



New Zealand Government



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

Adverse Reaction Reporting in New Zealand – 2016

Medsafe and the Centre for Adverse Reactions Monitoring (CARM) would like to thank all those who have submitted reports of suspected adverse reactions in 2016. These reports make an important contribution to the post-market monitoring of medicines in New Zealand.

Medsafe uses this information to identify possible safety issues and take appropriate actions, such as:

- taking the issue to the Medicines Adverse Reaction Committee (MARC) for advice
- requesting updates to data sheets
- providing information through *Prescriber Update*
- further investigating the issue through the M² scheme.

In 2016, CARM received a total of 3,944 reports of suspected adverse reactions. These reports included 2,522 reports associated with medicines, 1,385 reports associated with vaccines and 37 reports associated with a complementary or alternative medicine (CAM).

Of the reports received, 41% of medicine reports, 32.4% of CAM reports and only 3.6% of vaccine reports were considered serious. A serious adverse reaction is defined, according to internationally agreed criteria, as any reactions that result in death or is life-threatening, causes or prolongs hospitalisation, results in persistent or significant disability/incapacity or is a congenital abnormality.

Additional information about suspected adverse reactions reported in New Zealand can be found on the Medsafe website using the Suspected Medicines Adverse Reaction Search (SMARS) (www.medsafe.govt.nz/Projects/B1/ADRSearch.asp).

Nurses continue to be the most frequent reporter in 2016, followed by hospital doctors and general practitioners (GPs) (Figure 1).

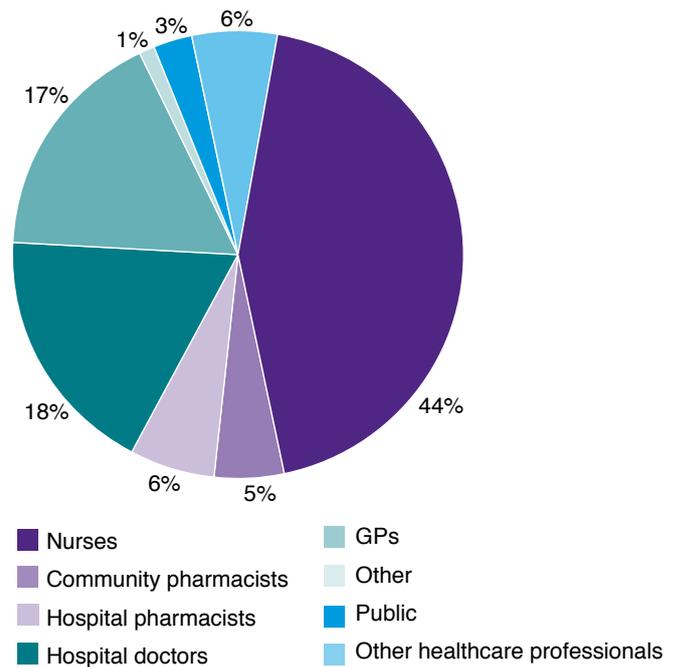


Figure 1: Source of adverse reaction reports in New Zealand in 2016

Healthcare professionals and consumers are encouraged to report any suspected adverse reactions to medicines, vaccines or CAMs to CARM.

Suspected adverse reactions can be reported using one of the following options.

- Online reporting at <https://nzphvc.otago.ac.nz/report/>.
- Freepost Yellow Cards available from CARM.
- Telephone (03) 479 7247, email carmnz@otago.ac.nz or fax (03) 479 7150.
- The electronic adverse reaction reporting tool through GP Practice Management Systems.
- iPhone/iPad application is available for download at <https://nzphvc.otago.ac.nz/app>.

Gathering Knowledge from Adverse Reaction Reports

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

In this new section of *Prescriber Update*, a selection of informative cases from the Centre for Adverse Reactions Monitoring (CARM) database is presented.

<p>CARM ID: 121331 Age: 26 Gender: Female Medicine(s): Cyproterone + ethinylestradiol Reaction(s): Pulmonary embolism</p>	<p>The pulmonary embolism occurred more than five years after starting cyproterone + ethinylestradiol, which was being used for contraception.</p> <hr/> <p>The Ginet data sheet (www.medsafe.govt.nz/profs/Datasheet/g/ginettab.pdf) states that it is not recommended in women solely for contraception. It is indicated as oral contraception in women requiring treatment for androgen-dependent diseases including acne. In general, treatment should be continued over several months. The length of use depends on the severity of the treated condition and the patient's response. It is recommended to take Ginet for at least another three to four cycles after the signs have subsided.</p>
<p>CARM ID: 117663 Age: 63 Gender: Male Medicine(s): Betamethasone + calcipotriol Reaction(s): Hyperglycaemia</p>	<p>The patient experienced an increase in blood sugar levels and a loss of diabetes control after using a betamethasone-containing product (Daivobet). This case highlights the possibility that systemic effects can occur with topical administration of corticosteroids.</p> <hr/> <p>The Daivobet data sheet (www.medsafe.govt.nz/profs/Datasheet/d/daivobetgel.pdf) states that adverse impact on the metabolic control of diabetes mellitus may also occur during topical corticosteroid treatment due to systemic absorption. Be aware of systemic effects in patients using topical corticosteroids.</p>

The Medsafe Files – Episode Three: Product Categorisation

Key messages

- ⌘ Prior to pre-market assessment, products are categorised as a medicine, medical device, dietary supplement, supplemented food, psychoactive substance, cosmetic or related product.
- ⌘ There are a number of factors to consider when categorising a product.
- ⌘ Product categories may differ internationally due to differences in legislation.

What is Product Categorisation?

Product categorisation determines whether a product is a medicine, medical device, dietary supplement, supplemented food, psychoactive substance, cosmetic or related product. Product categorisation also determines the appropriate regulatory framework for the product.

Products with a therapeutic purpose are regulated under the Medicines Act 1981, while dietary supplements are controlled under the Dietary Supplement Regulations 1985. Dietary supplements, supplemented food and cosmetics are not permitted to make a therapeutic claim or contain any ingredients scheduled under the Misuse of Drugs Act 1975.

The current definitions of medicines, medical devices and therapeutic purpose can be found at www.legislation.govt.nz/act/public/1981/0118/latest/DLM53790.html

Factors Influencing Categorisation

The categorisation process is dependent on the product ingredients, purpose of use and the manner in which it is presented in the market (ie, labelling or advertising). A number of factors are considered, such as the:

- indication claim
- mode of action of the product component associated with the indication

- alignment of the product component to the definition of a medicine or medical device
- function of any ingredients in the product.

For example, lubrication eye drops are categorised as a medical device due to its physical action, however, eye drops containing an ingredient with a pharmacological effect are categorised as a medicine. Antibiotic bone cement demonstrates the influence of the primary purpose on categorisation. Although the antibiotic prevents infection, the primary purpose of bone cement is

to provide physical support, hence it is categorised as a medical device.

The same or similar product in New Zealand can be categorised differently overseas due to different legislation and regulatory schemes. Categorisation also depends on the claim the supplier submits to the regulator.

Further information on the categorisation of products in New Zealand is available at www.medsafe.govt.nz/regulatory/categorisation-of-products.asp

Medicines and Illicit Drug Interactions

Key messages

- ⌘ Interactions between prescription medicines and illicit drugs can lead to adverse outcomes.
- ⌘ The possibility of interactions with illicit drugs should be considered when prescribing, and when patients present with suspected adverse reactions.

Patients often fail to inform healthcare professionals about the dietary supplements, complementary medicines or illicit drugs they are taking. However, each of these categories includes substances that can interact with medicines, sometimes with serious, even fatal consequences.

The United Kingdom's medicines regulator (Medicines and Healthcare products Regulatory Agency, [MHRA]) recently received a Coroner's report regarding the death of a man from a subarachnoid haemorrhage after a suspected interaction between citalopram and cocaine¹. The UK's Pharmacovigilance Expert Advisory Group identified plausible mechanisms that could lead to a subarachnoid haemorrhage from this interaction, including hypertension related to cocaine and an increased bleeding risk with citalopram¹.

Interactions between prescription medicines and illicit drugs may result in adverse outcomes, including toxicity or a reduction in therapeutic effect². The potential interactions with any illicit drug should be considered when prescribing

medicines, as well as in patients who present with suspected adverse reactions to medicines¹.

To ensure appropriate prescribing, an adequate patient history should be taken, including the current and recent use of all medicines (including non-prescription, complementary and alternative medicines)³. Open and effective communication is essential and should be encouraged between patients and healthcare professionals⁴.

The New Zealand Formulary includes potential interactions with illicit drugs in its *interaction checker* (http://nzf.org.nz/nzf_1). When using the interaction checker enter the name of the medicine rather than the illicit drug.

References

1. Medicines and Healthcare products Regulatory Agency. 2016. *Citalopram: suspected drug interaction with cocaine; prescribers should consider enquiring about illicit drug use*. URL: www.gov.uk/drug-safety-update/citalopram-suspected-drug-interaction-with-cocaine-prescribers-should-consider-enquiring-about-illicit-drug-use (accessed 19 September 2016).
2. Lindsey WT, Stewart D, and Childress D. 2012. Drug Interactions between Common Illicit Drugs and Prescription Therapies. *The American Journal of Drug and Alcohol Abuse* 38(4): 334–43.
3. Medical Council of New Zealand. 2016. *Good prescribing practice*. URL: www.mcnz.org.nz/assets/News-and-Publications/Statement-on-good-prescribing-practice-June-2016.pdf (accessed 28 September 2016).
4. Medical Council of New Zealand. 2011. *Information, choice of treatment and informed consent*. URL: www.mcnz.org.nz/assets/News-and-Publications/Statements/Information-choice-of-treatment-and-informed-consent.pdf (accessed 28 September 2016).

Drug-induced Lupus

Key messages

- ⌘ Drug-induced lupus is a rare, mild to moderately severe, lupus-like syndrome.
- ⌘ Patients generally present with lupus-like symptoms such as fever, malaise, weight loss, arthralgia and myalgia.
- ⌘ The onset time between starting the causal medicine and the first symptoms appearing ranges from one month to more than 10 years.

The Centre for Adverse Reactions Monitoring (CARM) recently received a report of probable drug-induced lupus (DIL) in a patient taking mesalazine¹. Anti-histone antibodies were detected. The dose of mesalazine was gradually reduced and subsequently stopped, with improvement of symptoms.

What is Drug-induced Lupus?

DIL is a rare, mild to moderately severe, lupus-like syndrome². It occurs due to continuous exposure to a specific medicine and resolves after the triggering medicine is stopped².

Drug-mediated disruption of immune tolerance is believed to be involved in the development of DIL, but the pathogenesis is not fully understood³.

DIL is a separate diagnosis to drug-induced flares of pre-existing or latent systemic lupus erythematosus (SLE)². However, it can be difficult to distinguish idiopathic SLE from DIL in a patient taking a medicine associated with DIL.

Differences Between Drug-induced Lupus and Systemic Lupus Erythematosus

Patients with DIL usually experience mild or few lupus-like symptoms initially. These symptoms include fever, malaise, weight loss, arthritis, arthralgia and myalgia³. Symptoms generally worsen the longer the patient is maintained on the suspect medicine³. Some symptoms such as malar or discoid rash, photosensitivity, oral ulcers, hair loss and renal or neurological disorders are common in SLE, but are uncommon in DIL³.

The latent period between starting the medicine and first symptoms appearing ranges from one month to more than 10 years².

Certain types of antinuclear antibodies, such as anti-histone antibodies, can help to confirm a diagnosis of DIL³. Although these autoantibodies are also common in SLE, patients with SLE usually have additional autoantibodies such as antibodies against double stranded DNA³. Therefore, when a diagnosis of SLE or DIL cannot be clearly distinguished on clinical grounds, the presence of double stranded DNA antibodies should be considered as evidence against a diagnosis of DIL³.

Medicines Associated with Drug-induced Lupus

Medicines associated with DIL are classified as high, moderate, low or very low risk³. There are up to 58 medicines that have been reported to induce autoimmunity and, less frequently, lupus-like disease³. Examples of medicines reported in association with DIL are summarised in Table 1.

Medicines that are associated with DIL should be avoided in patients with SLE³.

Table 1: Examples of medicines reported in association with DIL (this is not an exhaustive list)^{2,3}

Medicine	Risk
Procainamide*	High
Hydralazine	High
Quinidine*	Moderate
Isoniazid	Low
Minocycline	Low
Methyldopa	Low
Chlorpromazine	Low
TNF α inhibitors (eg, adalimumab)	Low/very low
Mesalazine	Very low

* These medicines are no longer available in New Zealand

Management

The suspect medicine should be stopped². Symptoms generally improve within one to two weeks of stopping the medicine³. Autoantibodies eventually normalise but can take as long as one to two years to disappear³.

No specific treatment is usually required². However, the use of non-steroidal anti-inflammatory drugs (NSAIDs) and oral corticosteroids (eg, prednisone) may be useful if severe manifestations such

as pericarditis with tamponade, debilitating polyarthritis or glomerulonephritis develop³.

New Zealand Cases

Procainamide is the most common medicine reported to CARM in association with DIL reactions. However, procainamide is no longer available and the last report received for this medicine was in 1978. Other medicines reported include adalimumab (13 reports), infliximab (five reports), mesalazine and methyldopa (three reports each).

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

References

1. CARM case ID 115326. URL: www.medsafe.govt.nz/Projects/B1/adrsearch.asp
2. DermNet New Zealand. 2016. *Drug-induced lupus erythematosus*. URL: www.dermnetnz.org/topics/drug-induced-lupus-erythematosus/ (accessed 13 July 2016).
3. Rubin RL. 2015. Drug-induced lupus. *Expert Opinion on Drug Safety* 14(3): 361–78.

Medicine-induced Vertigo

Key messages

- ⌘ Consider the possibility of a medicine-related cause in patients presenting with vertigo.
- ⌘ Many different types of medicines may cause vertigo.
- ⌘ Some medicines that cause vertigo are also ototoxic.
- ⌘ When reporting cases of ‘vertigo’ to CARM, it is helpful to differentiate between true vertigo and other sensations of ‘dizziness’.

Vertigo has a number of possible causes, most commonly vestibular neuritis, benign paroxysmal positional vertigo (BPPV) or vestibular migraine, but it can also be caused by medicines^{1,2}.

Vertigo is a sensation of motion either of the body or the surrounding environment. It occurs when the brain receives conflicting visual, proprioceptive and vestibular information about one’s position in space³.

Vertigo is often described by patients as ‘dizziness’, a non-specific term used to express a variety of sensations that may also include light-headedness, faintness and imbalance, all of which have many possible causes. It is important to distinguish between these symptoms as the cause and management may differ.

Medicines Known to Cause Vertigo

A variety of medicines have been associated with vertigo (Table 1).

Some medicines that cause vertigo are also ototoxic (eg, aminoglycosides, anti-inflammatory

medicines, phosphodiesterase type-5 inhibitors, furosemide). When a patient who is taking a medicine known to be ototoxic presents with vertigo, dose reduction or discontinuation of the medicine may need to be considered to prevent irreversible hearing loss.

Cases of Vertigo Reported to CARM

The Centre for Adverse Reactions Monitoring (CARM) received 98 case reports of vertigo from 1 January 2006 to 31 December 2015.

The most frequently reported medicine was influenza trivalent vaccine (11 reports). However, only three of the reports gave a clear description of vertigo. In one of these cases, vertigo was associated with severe headache and weakness on one side. In the remaining eight cases, the term vertigo was used, but it is not clear from the case description whether it was true vertigo or dizziness.

The second most frequently reported medicine was thyroxine (eight reports). The majority of these cases appear to be related to a change in formulation that was introduced in September 2007.

The next most frequently reported medicines are simvastatin (five reports), venlafaxine (five) and omeprazole (four).

As is often the case for medicines with an established safety profile, cases of vertigo associated with medicines that are well known to cause vertigo (eg, aminoglycosides), are rarely reported to CARM.

Vertigo is not listed as an adverse effect in the data sheets of the majority of medicines in the cases

Table 1. Examples of medicines that may cause vertigo (this is not an exhaustive list)

Medicine Class	Examples
Analgesics	codeine
Antibiotics	aminoglycosides, macrolides, minocycline, nitrofurantoin, sulfamethoxazole
Anticonvulsants	levetiracetam, phenytoin, pregabalin
Anti-inflammatories	celecoxib, parecoxib, naproxen, prednisone
Antimalarials	mefloquine, quinine, hydroxychloroquine
Antivirals	oseltamivir, raltegravir
Anti-Parkinson's drugs	lisuride
Cardiovascular drugs	nifedipine, furosemide, indapamide, prazosin, terazosin, glyceryl trinitrate, isosorbide mononitrate, sotalol, timolol
Gastroenterology drugs	omeprazole, lansoprazole, sucralfate
Rheumatology drugs	zoledronic acid, alendronate
Phosphodiesterase type-5 inhibitors	sildenafil, vardenafil
Other medicines	lithium, haloperidol, benzodiazepines, desmopressin, melatonin

reported to CARM. However, it is worth noting, 'dizziness' is listed as an adverse effect.

When reporting cases of 'vertigo' to CARM, it is helpful to differentiate between true vertigo and other forms of 'dizziness'. A description of the patient's symptoms is useful, particularly whether or not the patient experienced a sense of motion (eg, 'felt that the room was spinning'). This helps CARM and Medsafe to identify whether any update to the medicine's data sheet is necessary and any further communication is required.

References

1. Drug-induced true vertigo and balance disorders. 2015. *Prescribe International* 24(156): 18.
2. Best Practice Advocacy Centre (BPAC). 2012. *A delicate balance: managing vertigo in general practice*. URL: www.bpac.org.nz/BPJ/2012/september/vertigo.aspx (accessed 22 October 2016).
3. Walker B, Colledge N, Ralston S, et al. 2014. *Davidson's Principles and Practice of Medicine 22nd edition*. Edinburgh: Churchill Livingstone.

Oxybutynin – Psychiatric Side Effects

Oxybutynin is an anticholinergic medicine indicated for urinary frequency and urgency. It is available as tablets, syrup and patches^{1,2}. Oxybutynin, like all anticholinergic medicines, can cause psychiatric side effects such as confusion, agitation, anxiety, hallucinations, nightmares, paranoia, symptoms of depression and dependence (in patients with a history of drug or substance abuse). Although the patch reduces patient exposure to oxybutynin, psychiatric side effects have also been reported with this formulation.

Patients should be warned about these side effects as they can affect driving ability. If patients experience these effects, a dose reduction or an alternative treatment may be required.

References

1. Apotex New Zealand Limited. 2016. *Apo-oxybutynin data sheet* 14 March 2016. URL: www.medsafe.govt.nz/profs/Datasheet/a/Apoxybutynintabsyrup.pdf (accessed 23 September 2016).
2. Actavis New Zealand Limited. 2013. *Oxytrol Transdermal patch data sheet* 1 July 2013. URL: www.medsafe.govt.nz/profs/Datasheet/o/Oxytroltransdermal.pdf (accessed 23 September 2016).

Appropriate Use of Head Lice Treatments

Key messages

- ⌘ Head lice treatments should only be used if the presence of live lice are confirmed.
- ⌘ Serious side effects are rare with head lice treatments but are more common when treatment is applied more frequently or in higher doses than recommended.
- ⌘ Healthcare professionals should advise consumers that Para Plus is potentially flammable and should not be applied close to a naked flame (eg, cigarette or candle) or an external heat source (eg, heater or hairdryer).

Head lice treatments are widely used in New Zealand. Products with a range of active ingredients, including insecticides and essential oils, are available (Table 1). PHARMAC currently funds Para Plus aerosol spray and Parasidose shampoo.

Despite the high use of head lice treatments, adverse drug reactions (ADRs) are rarely reported in New Zealand. Since 2006, the Centre for Adverse Reactions Monitoring (CARM) has received a total of 12 ADR reports associated with head lice treatments.

The majority of these cases were non-serious and included reactions such as pruritus, rash, dermatitis and application site reaction, consistent with the known safety profile of head

lice treatments^{1,2}. However, three of the reports were serious.

One of the serious reports concerned a child who suffered burns to the face when Para Plus ignited during application (although no source of ignition was identified). The report noted that Para Plus was being used frequently. No other reports of ignition of Para Plus were identified in New Zealand or internationally, which suggests that this is an extremely rare adverse effect. The product packaging of Para Plus includes a warning not to use near a naked flame (eg, cigarette or candle) or an external heat source (eg, heater or hairdryer) due to presence of flammable hydrocarbons (butane and propane) in the aerosol.

Healthcare professionals should advise consumers on the appropriate use of head lice treatments, including the frequency of use and amount to be applied. Insecticide-based head lice treatments should only be used if live lice are present. Head lice treatments are not recommended as preventatives. Do not use medicated treatments more frequently than recommended by the manufacturer's instructions. If head lice persists, alternative treatment is required.

References

1. Hartley M. 2010. *Insecticides and the skin*. URL: www.dermnetnz.org/topics/insecticides-and-the-skin/ (accessed 01 February 2017).
2. Goldstein A, Goldstein B. 2015. *Pediculosis capitis*. *UpToDate*. URL: www.uptodate.com/contents/pediculosis-capitis?source=search_result&search=Pediculosis%20capitis&selectedTitle=1~37#H9 (accessed 01 February 2017).

Table 1: Examples of head lice treatments available in New Zealand (this is not an exhaustive list)

Active Ingredient(s)	Type of product	Brand/Product	Sponsor
Permethrin	Insecticide	Lice Clear Scalp lotion	AFT Pharmaceuticals Ltd
		Quedella Head Lice Treatment Scalp lotion	Orion Laboratories (NZ) Ltd
Phenothrin/ pyrethrin/pyrethrum	Insecticide	Parasidose Shampoo, Extra strength	Multichem NZ Limited
Malathion/permethrin/ piperonyl butoxide	Insecticide	Para Plus aerosol spray	Orion laboratories
Eucalyptus oil Lemon tree oil	Suffocant	Moov head lice solutions	Douglas Pharmaceuticals Ltd
Benzyl alcohol	Suffocant	Neutralice	Wilson Consumer Products

Recent Approvals of Medicines containing a New Active Ingredient

For period 16 October 2016 to 15 January 2017

Trade Name (active ingredient)*	Dose form and strength	Therapeutic area
Brimica Genuair (aclidinium) /formoterol	Powder for inhalation 340 mcg/12 mcg	Chronic obstructive pulmonary disease (COPD)
Entresto 24/26 (sacubitril) /valsartan	Film coated tablet 24.3 mg/25.7 mg	Chronic heart failure
Epclusa (sofosbuvir) /velpatasvir	Tablet 400 mg/100 mg	Chronic hepatitis C virus infection
Genvoya (cobicistat/elvitegravir/emtricitabine/ tenofovir)†	Tablet 150 mg/150 mg/200 mg/10 mg	HIV-1 infection
Lynparza (olaparib)	Capsule 50 mg	Ovarian, fallopian tube or primary peritoneal cancer
Otezla (apremilast)	Film coated tablet, titration pack 10 mg, 20 mg, 30 mg	Plaque psoriasis
Zepatier (elbasvir) /grazoprevir	Film coated tablet 50 mg/100 mg	Chronic hepatitis C virus infection (genotypes 1, 3, or 4)

* New active ingredient shown in bold type

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

The data sheets for currently marketed prescription medicines are published on the Medsafe website www.medsafe.govt.nz/Medicines/infoSearch.asp

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

Date	Communication	Topic
2 February 2017	Educational material	Gardasil 9 Questions and Answers
31 January 2017	Link to Ministry of Health website	Clarification on the Classification of Cannabidiol
11 January 2017	Publications	Medicines Classification – Oral Contraception Recommendation made
20 December 2016	Medical devices	Reporting Adverse Events Associated With Medical Devices
1 December 2016	Safety information	Guidance for Pharmacists Dispensing Prescriptions for Span-K

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

Subscribe to Printed Editions of *Prescriber Update*

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

Print editions of *Prescriber Update* will continue to be supplied to organisations such as pharmacies and general practices, and will also be available to individuals who subscribe.

If you would like to continue to receive a print edition of *Prescriber Update*, you must re-subscribe by emailing prescriberupdate@atlantishealthcare.com with your name and postal address with the word 'subscribe' as the subject.

Subscription to electronic copy of *Prescriber Update* can be found on the Medsafe website (www.medsafe.govt.nz/profs/subscribe.asp).

Medsafe

New Zealand Medicines and Medical Devices
Safety Authority

A business unit of the Ministry of Health

Editor

Minhao Zhan

Medsafe, PO Box 5013,

Wellington, New Zealand

Ph: (04) 819 6800, Fax: (04) 819 6806

E-mail: medsafeadrquery@moh.govt.nz

Editorial Team

Rowan Pollock, Acting Manager,
Clinical Risk Management

Dr Susan Kenyon, PhD, Principal Technical
Specialist, Pharmacovigilance

Lily Chan, Senior Advisor
Pharmacovigilance

Jo Pranker, Advisor Pharmacovigilance

Dr Sharon Sime, Senior Advisor
Pharmacovigilance

Dr Geraldine Hill, Senior Medical Advisor

Kathy Daly, Team Leader, Product Safety,
Compliance Management

Acknowledgements

Dr Nikki Turner

Associate Professor David Menkes,
University of Auckland

Clinical Advisor

Dr Geraldine Hill

Group Manager

Chris James

Prescriber Update is published and distributed by Medsafe in the interests of safer, more effective use of medicines and medical devices.

Medsafe also acknowledges the contribution of the New Zealand Pharmacovigilance Centre in providing data and advice for articles.

An electronic version of *Prescriber Update* is available at www.medsafe.govt.nz/profs/PUarticles.asp

To receive *Prescriber Update* electronically, please register at www.medsafe.govt.nz/profs/subscribe.asp

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

Published with the permission of the Director-General of Health.



This work is licensed under the Creative Commons Attribution 4.0 International

licence. In essence, you are free to: share, ie, copy and redistribute the material in any medium or format; adapt, ie, remix, transform and build upon the material. You must give appropriate credit, provide a link to the licence and indicate if changes were made.