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A Topical Issue — Serious Hypersensitivity and Burning Reactions

Key Messages

- Serious hypersensitivity reactions including anaphylaxis have been reported following the use of topical acne products that contain benzoyl peroxide or salicylic acid.
- There is a risk of chemical skin burns with the use of chlorhexidine solution for skin disinfection in premature neonates.

Topical acne products containing benzoyl peroxide or salicylic acid

Benzoyl peroxide and salicylic acid are used in topical acne products available from pharmacies, supermarkets and other retail stores. These products include gels, creams and face washes.

Local skin irritation reactions such as redness, burning, dryness, itching, peeling, or slight swelling are known to occur particularly with benzoyl peroxide[1]. Serious hypersensitivity reactions including anaphylaxis have also been reported following the use of these topical acne products[2].

The Centre for Adverse Reactions Monitoring (CARM) has received reports of angioedema, periorbital oedema, bronchospasm and syncope with the use of topical acne products that contain benzoyl peroxide or salicylic acid.

Consumers should be advised to stop using these products and to seek emergency medical attention immediately if they experience throat tightness, difficulty breathing, feeling faint, or swelling of the eyes, face, lips or tongue. These are symptoms of a serious hypersensitivity reaction.

Use of chlorhexidine in premature neonates

Chlorhexidine solution is used as a skin disinfectant prior to invasive procedures in neonates. It is available in both alcohol-based and water-based solutions.

There have been reports internationally of chemical skin burns in premature neonates who were treated with chlorhexidine solution before central venous catheterisation[3]. This risk has been associated with both alcohol-based and water-based solutions.

According to these reports and the published literature, the risk appears to be higher in premature neonates, especially those born before 32 weeks of gestation and within the first two weeks of life.

To reduce the risk of chemical skin burns, use the minimum amount of chlorhexidine solution required and do not allow the solution to pool in skin folds or under the patient. Remove any excess solution and any soaked materials from the skin. Monitor patients frequently to ensure that cutaneous side effects are detected and managed at an early stage[3].

There have also been reports of severe allergic reactions including anaphylaxis following chlorhexidine use. Medsafe has previously notified healthcare professionals of this risk (**www.medsafe.govt.nz/profs/PUArticles/June2013Chlorhexidine.htm**).

References

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Atomoxetine and Raynaud's Phenomenon

Key Messages

- Raynaud's phenomenon is a very rare (<0.1%) reaction associated with atomoxetine.
- Patients should be encouraged to seek medical attention if they experience symptoms in their hands including sensations of coldness, burning pain, paraesthesias or intermittent colour changes of one or more digits.
- If Raynaud's phenomenon is diagnosed then atomoxetine treatment may need to be withdrawn.

The Centre for Adverse Reactions Monitoring (CARM) has received a report of Raynaud's phenomenon in a very young patient who was being treated with atomoxetine. The patient exhibited severe Raynaud's phenomenon that resolved as soon as atomoxetine was discontinued. This case report highlights a rare reaction to atomoxetine which can be extremely painful for patients. The association between atomoxetine and Raynaud's phenomenon is listed as very rare (<0.1%) in the data sheet[1].

Atomoxetine is a non-stimulant treatment indicated for Attention-Deficit/Hyperactivity Disorder (ADHD) in adults and children six years of age and older[1]. Raynaud's phenomenon is a reversible vasospasm in parts of the hand in response to cold, emotional stress or vibration[2]. Symptoms of Raynaud's phenomenon include sensations of coldness, burning pain, paraesthesias or intermittent colour changes of one or more digits. If left untreated, Raynaud's phenomenon may result in tissue loss or digital gangrene[2].

The primary treatments for Raynaud's phenomenon are to avoid cold and other triggers. Medical treatment may include calcium channel blockers for vasodilation.

Healthcare professionals should advise patients and caregivers to seek medical attention if they experience symptoms of Raynaud's phenomenon in the first few months after starting atomoxetine.

Please report all suspicions of medicine adverse reactions to CARM.

References

1. Eli Lilly and Company (NZ) Limited. 2013. *Strattera Data Sheet*. 6 August 2013. URL: **www.medsafe.govt.nz/profs/datasheet/s/Stratteracap.pdf** (accessed 12 January 2015).
2. Merck Manual Online. 2014. *Raynaud Syndrome*. URL: **http://www.merckmanuals.com/professional/cardiovascular_disorders/peripheral_arterial_disorders/raynaud_syndrome.html?qt=raynaud&alt=sh** (accessed 12 January 2015).

Check INR after Starting Roxithromycin for Patients on Warfarin

Key message

- Prescribers should monitor the INR three days after (on day three) starting some antibiotics in patients taking warfarin.

Some antibiotics can interact with warfarin which can increase the international normalised ratio (INR) and cause severe bleeding.

Roxithromycin was recently associated with a bleeding episode in a patient taking warfarin for atrial fibrillation. The patient (whose INR had been between 2 and 3) complained of abdominal pain three days after starting roxithromycin. An abdominal bleed was diagnosed and the INR was found to be greater than 7.

In the reports received by the Centre for Adverse Reactions Monitoring (CARM), roxithromycin accounted for 44% of the adverse event reports of increased INR in patients taking antibiotics and warfarin. The occurrence of an increased INR in association with the roxithromycin-warfarin combination was noted in a previous article of *Prescriber Update* (**www.medsafe.govt.nz/profs/PUArticles/watchingbriefsMay08.htm#Roxithromycin**).

In a recent observational study, 3.2% of patients taking warfarin and an antibiotic experienced an INR of 5.0 or more[1].

In contrast, rifampicin markedly reduces the anticoagulant effect of warfarin[2].

Prescribers should monitor the INR three days after (on day three)[3] starting the following antibiotics:

- macrolides (erythromycin, azithromycin, clarithromycin, roxithromycin)
- fluoroquinolones (nalidixic acid and ciprofloxacin)
- selected cephalosporins (eg, cefamandole)
- co-trimoxazole.

The mechanism of the interaction is not fully understood but may include inhibition of cytochrome P450, displacement of protein-bound warfarin, interference with platelet function, and the elimination of vitamin-K producing bacteria from the intestine. Fever itself may increase the catabolism of clotting factors and exaggerate a potential antibacterial-warfarin interaction[1, 4].

Please report all suspicions of medicine interactions to CARM.

References

1. Clark NP, Delate T, Riggs CS, et al. Warfarin-Associated Research Projects and Other Endeavors Consortium. 2014. Warfarin interactions with antibiotics in the ambulatory care setting. *JAMA Internal Medicine*. 174(3): 409–16.
2. Stockley IH. 2002. *Stockley's Drug Interactions*. London: Pharmaceutical Press.
3. Bryant L, Fishman T, et al. 2009. Drug interactions that matter and how to manage them. *Journal of Primary Health Care* 1(2).
4. Sweetman SC (ed) 2011. *Martindale: The Complete Drug Reference* (37th Ed). Great Britain: Pharmaceutical Press.

Fruit Interactions with Common Medicines

Key messages

- ⌘ Medicines can interact with whole fruit, fruit pulp or fruit extracts.
- ⌘ Fruit of concern include orange, pomelo, pomegranate, cranberry, red/purple grape, apple and grapefruit.
- ⌘ Patients should be informed about the risk of interactions from consuming fruit.

Medicine interactions with grapefruit juice are well known. Research shows that other fruit juices as well as whole fruit, fruit pulp and fruit extracts have also been associated with altered drug metabolism and subsequent interactions. Variability in fruit strains, environmental conditions, processing procedures and patient factors make it difficult to predict whether a fruit or fruit product will lead to a medicine interaction[1].

Why do these interactions occur?

Some fruits contain flavanoids and furanocoumarins which can interfere with medicine metabolism. The cytochrome p450 isoenzyme, CYP3A4, is inhibited by the flavonoid, naringin, as well the furanocoumarins bergamottin and 6',7'-dihydroxybergamottin[1]. When CYP3A4 is inhibited, it can result in increased concentrations of medicines that are metabolised by this enzyme. Another cytochrome p450 isoenzyme, CYP2C9, may be inhibited by pomegranate and cranberry juices[1].

Furanocoumarins can inhibit P-glycoproteins that are also involved in medicine metabolism (**www.medsafe.govt.nz/profs/PUArticles/P-glycoproteinSept2011.htm**).

Organic anion-transporting polypeptides (OATPs) are membrane transport proteins which facilitate substance uptake[1]. These proteins can be inhibited by orange, apple, and grapefruit juices[1].

Which fruit and fruit products can cause these interactions?

Fruits associated with medicine interactions include orange, pomelo, pomegranate, cranberry, grape, apple and grapefruit. These whole fruit and their products including fruit juices, fruit concentrates, fruit pulp, fruit jams/marmalades, fruit extracts and even cooked products such as sauces (for example apple and cranberry sauce) may have an impact on the clinical effect of affected medicines. It is important to note that apple and orange juices or concentrates are frequently used as bases for fruit drinks that are often advertised as other flavours. The effect of alcohol made from fruit has not been investigated.

Which medicines are affected by these interactions and how should patients be advised?

The table on page 5 lists some of the better established interactions with medicines, it is not a complete list.

Further information about fruit/medicine interactions is available in *Stockley's Drug Interactions*.

Please report any suspected adverse medicine reactions and interactions to the Centre for Adverse Reactions Monitoring (CARM).

References

1. Jones S, Preston CL, Sandhu H. 2014. How fruit juice interacts with common medicines. *Pharmaceutical Journal* 293 (7831): 369–372.
2. Stockley IH. 2002. *Stockley's Drug Interactions*. London: Pharmaceutical Press.
3. New Zealand Formulary – Interactions Stockleys. **http://nzf.org.nz/interactions/stockleys/between/29589391000116109?t=1421114287611**

Table 1: Possible fruit, juice and supplement interactions with commonly prescribed drugs[2,3]

Fruit/juice/supplement	Drug	Recommended actions
Cranberry	Warfarin	Avoid drinking cranberry juice or taking cranberry capsules/ concentrates where possible
Grapefruit	Amiodarone	Avoid grapefruit juice
	Atorvastatin	Avoid large quantities (more than 1.2 litres daily) of grapefruit juice
	Carbamazepine	Avoid grapefruit juice and the whole fruit
	Felodipine	Avoid grapefruit juice and the whole fruit
	Simvastatin	Avoid grapefruit juice and the whole fruit
	Tacrolimus	Avoid grapefruit juice and the whole fruit

Adapted from New Zealand Formulary – Interactions

Sexual Dysfunction Associated with Antidepressants and Antipsychotics

Key Messages

- ⌘ Sexual dysfunction is a common, often unrecognised side effect of treatment with antidepressants and antipsychotics.
- ⌘ Sexual dysfunction is the most common reason for patients stopping antidepressant or antipsychotic medicines, often without telling their prescriber.
- ⌘ Prescribers can help to support medication adherence by actively discussing sexual function.
- ⌘ Management strategies include dose reduction, switching medicines, augmenting treatment or adding a reversal agent. However these strategies are variably successful in different patients and all are associated with risks of treatment failure and/or additional side effects.
- ⌘ Patients should be reassured that the problem is usually manageable.

The Centre for Adverse Reactions Monitoring (CARM) continues to receive reports of sexual dysfunction associated with the use of antidepressants and antipsychotics. Since 1965, the most frequently reported medicines have been fluoxetine (17 reports), citalopram (12), paroxetine (7), venlafaxine (5), risperidone (12) and clozapine (7).

Disorders of sexual functioning can be classified into four categories.

- Sexual desire disorders, including partial or total lack of libido.
- Sexual arousal disorders including erectile dysfunction and lack of vaginal lubrication.
- Orgasm disorders, including premature, delayed or absent orgasm (anorgasmia); also failure of ejaculation.
- Sexual pain disorders including dyspareunia and vaginismus[1].

Sexual dysfunction in depression

Recent reviews indicate that the prevalence of sexual dysfunction in major depression may

be up to 70% of patients. Most often this takes the form of lack of libido. Sexual desire tends to improve with treatment of depression; however, successful antidepressant treatment often causes other detrimental effects on sexual function[1].

Reported rates of sexual dysfunction associated with antidepressants in clinical studies vary by assessment method. Studies using specific instruments (questionnaires) to assess sexual dysfunction identify more cases than those relying on spontaneous reporting (both in clinical trials and to pharmacovigilance agencies such as CARM)[2]. Many patients do not volunteer to discuss problems with sexual function with their prescriber and may simply stop taking the medicine without mentioning it.

Antidepressant-associated sexual dysfunction may also result from inadequate treatment of depression, comorbid alcohol abuse, comorbid physical illness, relationship problems, or a combination of these factors[1].

Results of a meta-analysis found that up to 80% of patients reported sexual dysfunction that emerged with antidepressant treatment[2]. The meta-analysis showed that the medicines with the greatest risk included: sertraline, venlafaxine, citalopram and paroxetine. No difference from placebo was found for bupropion, moclobemide and mirtazapine. Other antidepressants such as escitalopram and imipramine had an intermediate effect.

Men taking an antidepressant tended to have higher rates of desire and orgasm dysfunction whereas women had greater arousal dysfunction[2]. Sexual dysfunction associated with antidepressants may also be dose-dependent[1].

Management of sexual dysfunction during treatment with antidepressants can be difficult, in part due to often multifactorial aetiology (see above). Therefore, prior to treatment, it is important to ascertain existing sexual dysfunction and the likely cause. The possibility of treatment-emergent sexual dysfunction should be discussed and the importance of sexual function to the patient should be taken into consideration when choosing an antidepressant[3].

Patients are often hesitant to discuss sexual dysfunction with their doctor. Patients taking antidepressants should be sensitively questioned regarding sexual dysfunction. Doctors may be surprised by how willing (and sometimes relieved) patients are to discuss sexual function once the issue has been broached. Close monitoring helps to optimise quality of life and support treatment adherence. It is also important to provide reassurance that the problem is common and usually manageable.

There are several options for patients experiencing problems (Table 1).

Antidepressant associated sexual dysfunction is generally reversible on discontinuation of treatment.

Sexual dysfunction in schizophrenia

Rates of sexual dysfunction are higher in patients with schizophrenia than the general population or patients with other psychiatric disorders[5,6]. There is a correlation between the severity of psychotic symptoms and the reported severity of sexual dysfunction.

Table 1: Options for patients experiencing sexual dysfunction associated with antidepressants

Option	Caveats
Reduce dose	May increase risk of relapse[1,4]
Drug holidays	May jeopardise compliance with treatment Does not allow for spontaneity[1] Withdrawal symptoms may be experienced in patients using antidepressants with short half-lives[4]
Switch antidepressant	May increase risk of relapse May result in different side effects
Continuing treatment ('wait and see')	Relatively few patients experience resolution of symptoms; this may take several months
Addition of an reversal agent (eg, phosphodiesterase inhibitor)	Additional side effects are possible

Sexual dysfunction is rated as one of the most distressing side effects of antipsychotics and a major cause of poor quality of life. Sexual dysfunction is associated with a negative attitude towards therapy and, as with antidepressants, often results in non-adherence to treatment[5].

Risperidone, haloperidol and olanzapine have been reported to be associated with the greatest risk of sexual dysfunction. These medicines are most often associated with erectile and ejaculatory dysfunction in men, menstrual irregularities, amenorrhea and decreased vaginal lubrication in women, as well as more general effects impairing libido and orgasm[5,6].

Clozapine is associated with generally low rates of sexual dysfunction, except for erectile and ejaculatory problems. Quetiaptine has been reported to have a lower impact on sexual function in terms of number of patients affected and the severity of the dysfunction[7]. Aripiprazole appears to be associated with the lowest risk of sexual dysfunction, based on current evidence. More research is needed in this area[6].

Other factors contributing to sexual dysfunction include the disease itself, psychosocial factors (including performance anxiety), comorbid diseases (especially cardiovascular) and concomitant medication[7].

There is limited information on the management of sexual dysfunction in patients taking antipsychotics. Active discussion of the risks of sexual dysfunction prior to and on treatment is recommended to help support patient adherence to treatment. Potential strategies to help manage sexual dysfunction are outlined in Table 2.

Table 2: Options for patients experiencing sexual dysfunction associated with antipsychotics[7]

Option	Caveats
Reduce dose	May increase risk of relapse
Switch antipsychotic	May increase risk of relapse May result in different side effects
Augmentation of treatment	Aripiprazole has been recommended
Addition of an reversal agent (eg, dopamine agonist)	May aggravate psychosis Additional side effects are possible

References

1. Schweitzer I, Maguire K, Ng Chee. 2009. Sexual side-effects of contemporary antidepressants: review. *Australian and New Zealand Journal of Psychiatry.* 43: 795–808.
2. Serretti A, Chiesa A. 2009. Treatment-emergent sexual dysfunction related to antidepressants a meta-analysis. *Journal of Clinical Psychopharmacology* 29: 259–266.
3. Kennedy SH, Rizvi S. 2009. Sexual dysfunction, depression and the impact of antidepressants. *Journal of Clinical Psychopharmacology* 29: 157–164.
4. Clayton AH, Croft HA, Handiwala L. 2014. Antidepressants and sexual dysfunction: mechanisms and clinical implications. *Postgraduate Medicine* 126: 91–99.
5. Bella AJ, Shamloul R. 2013. Psychotropics and sexual dysfunction. *Central European Journal of Urology* 66: 466–471.
6. Serretti A, Chiesa A. 2011. Sexual side effects of pharmacological treatment of psychiatric diseases. *Clinical Pharmacology and Therapeutics* 89: 142–147.
7. De Hert M, Detraux J, Peuskens J. 2014. Second-generation and newly approved antipsychotics, serum prolactin levels and sexual dysfunctions: a critical literature review. *Expert Opinion in Drug Safety* 13: 605–624.

Rotavirus Vaccination – Summary of Adverse Event Reports Received in the First Six Months of Funding

The Centre for Adverse Reactions Monitoring (CARM) has been closely monitoring reports of adverse events associated with vaccination with rotavirus vaccine.

The RotaTeq brand of rotavirus vaccine was funded from 1 July 2014. As of 31 December 2014 CARM had received 112 reports describing 236 adverse events associated with RotaTeq. The majority of reports were submitted by nurses (81.3%) and described events after the first dose (81%).

The most frequently reported adverse events were gastrointestinal (110/236 reports) and the three most common reactions were diarrhoea (36), vomiting (27) and abdominal pain (14). In addition there has been one report describing blood in the stool; a known adverse effect[1].

The most serious adverse effect associated with rotavirus vaccination is intussusception. To date the Ministry of Health has been made aware of one case where a child showed symptoms consistent with intussusception following RotaTeq vaccination. Vaccinators are reminded that parents need to be informed of this risk and what to do if their child displays signs of intussusception.

More information can be found on the Ministry of Health website (**www.health.govt.nz/your-health/conditions-and-treatments/diseases-and-illnesses/rotavirus**) and the Medsafe website (**www.medsafe.govt.nz/consumers/educational-material/rotavirusQandA.asp**).

Other events frequently reported with rotavirus vaccination included irritability (14), fever (14) and persistent crying (8) with 19 reports of crying – various. More information on events reported with rotavirus vaccination can be found on the Medsafe website (**www.medsafe.govt.nz/Projects/B1/ADRDisclaimer.asp**).

Please continue to report adverse events and medication errors associated with rotavirus vaccination to CARM. Your reports help CARM and Medsafe monitor the safety of RotaTeq and helps us understand the profile of this medicine in New Zealand.

References

1. Merck Sharp & Dohme NZ Ltd. 2013. *RotaTeq Data Sheet* 3 July 2013 URL: **www.medsafe.govt.nz/profs/Datasheet/r/RotaTeqsusp.pdf** (accessed 16 January 2015).

MARC's Remarks: December 2014 Meeting

The Medicines Adverse Reactions Committee (MARC) met on 4 December 2014 to consider a number of medicine-related safety issues.

The MARC reviewed the risk of fatal lactic acidosis associated with **metformin** use, in particular in patients with impaired renal function. The MARC was satisfied that metformin can induce lactic acidosis and this reaction is clinically important. An article on this topic will be published in a future edition of *Prescriber Update*.

The MARC reviewed the available information on the benefits and risks of cough and cold medicines that contain either **bromhexine** or **codeine** for use in children. The MARC recommended that the use of these medicines for cough and cold be restricted to adults and children over six years of age for medicines that contain bromhexine and to adults and children over 12 years of age for medicines that contain codeine.

The MARC reviewed the utility of the **trans-Tasman early warning system** (EWS). The MARC advised on further methods that may be useful for this type of investigation and recommended that additional communications via the EWS are needed before the system can be fully reviewed.

Further information on these issues can be found on the Medsafe website (**www.medsafe.govt.nz/profs/adverse/Minutes160.htm**).

Risk of Stroke with Ranibizumab (Lucentis), Bevacizumab (Avastin) and Aflibercept (Eylea), Administered by Intravitreal Injection

Key Messages

- Intravitreal administration of VEGF-A inhibitors can result in stroke.
- There may be a greater risk of stroke associated with bevacizumab than ranibizumab.
- Patients should be assessed for stroke risk prior to treatment to ensure that the expected benefits outweigh the risk of harm.
- Patients should be monitored after each administration and instructed to seek immediate medical attention if they develop any symptoms associated with stroke.

The Centre for Adverse Reactions Monitoring (CARM) has received two reports of systemic arterial thromboembolic events (ATE) after intravitreal injection of bevacizumab. In the first case a transient ischaemic attack was reported by a female patient. In the second case, a male patient over 70 years old experienced a stroke four days after treatment.

Bevacizumab is a recombinant humanised monoclonal antibody that binds to and inactivates vascular endothelial growth factor (VEGF-A). Ranibizumab is a fragment derived from the same antibody. Aflibercept is a fusion protein with acts as a VEGF-A decoy receptor. Only ranibizumab and aflibercept are approved for the treatment of age-related macular degeneration (AMD). However, bevacizumab has been used off-label for this indication[1].

VEGF-A inhibitors can be detected in the plasma after intravitreal administration and can result in systemic effects. The risk of arterial thrombotic effects such as stroke, transient ischaemic attack and myocardial infarction are of particular concern. There is some evidence that ranibizumab is associated with ATE, but this association requires further research[2,3].

Bevacizumab may be associated with a higher risk of ATE than ranibizumab since it remains in the systemic circulation for longer. Meta-analysis of trials comparing bevacizumab with ranibizumab did not show a statistically significant difference in ATE, although there was an imbalance in the number of events (higher in the bevacizumab treated patients)[4]. A recent observational study found a significantly higher number of ATE in patients treated with bevacizumab compared to ranibizumab[5].

Patients who require treatment for AMD should be assessed for their risk of stroke and treatment should only be initiated if the benefits are considered to outweigh the risk of harm. Patients should be monitored after each intravitreal administration and instructed to seek immediate medical attention if they develop any symptoms associated with stroke.

References

1. Tridente G. 2014. *Adverse events with Biomedicines*. Milan: Springer.
2. Bressler NM, Boyer DS, Williams DF et al. 2012. Cerebrovascular accidents in patients treated for choroidal neovascularization with ranibizumab in randomized controlled trials. *Retina* 32: 1821–1828.
3. Pratt NL, Ramsay EN, Kemp A et al. 2014. Ranibizumab and risk of hospitalisation for ischaemic stroke and myocardial infarction in patients with age-related macular degeneration: a self-controlled case-series analysis. *Drug Safety* 37: 1021–1027.
4. Wang W, Zhang X. 2014. Systemic adverse events after intravitreal bevacizumab versus ranibizumab for age-related macular degeneration: a meta-analysis. *PLoS ONE* 9(10) e 109744.
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Medicine Labels – Rubbing Salt into the Wound

Key messages

- The salt form of an active ingredient can significantly influence the pharmaceutical properties of a medicine.
- Some medicines have multiple salt forms of the same active ingredient.
- The strength of the active ingredient stated on a medicine label is typically based on the active moiety (strength = active) but can also be expressed as the salt form of the active ingredient (strength = active + salt).

Prescribers are reminded that different salt forms have different doses.

Medsafe ensures that the strength of the active ingredient is clearly stated on labels as this is crucial to the safe and effective use of medicines. There is potential for confusion when the same active ingredient is present as different salts in different products with similar indications.

The selection of an appropriate salt form for an active ingredient is a critical step in pharmaceutical development. The salt form of the active ingredient is used to alter the physical or chemical properties of the medicine, such as solubility, pH, stability and shelf life, and bioavailability. This in turn can influence the dose form of the medicine.

An example of an active ingredient with different salt forms is metoprolol, a selective ß1 receptor blocker indicated for the treatment of hypertension, angina and hyperthyroidism. There are two salt forms of metoprolol currently available in New Zealand; metoprolol tartrate (eg, Lopresor tablets) and metoprolol succinate (eg, Betaloc CR tablets). Metoprolol tartrate is formulated as an immediate-release tablet and the succinate salt form is an extended-release tablet. Both dose forms have slightly different indications and different dosing requirements. A fumarate salt form of metoprolol is also approved but not currently available in this country.

The strength of the active ingredient specified on a medicine label is typically based on the active moiety but can also be expressed as the salt form of the active ingredient. This is particularly relevant if a patient's prescription is changed to different dose form of the same active ingredient because different salts can require different dosages. For example, 95 mg of metoprolol succinate is equivalent to 100 mg metoprolol tartrate.

If in doubt, prescribers should refer to the product data sheet on the Medsafe website for full dosing instructions.

Domperidone – At the Heart of the Matter

Key Messages

- Domperidone may be associated with an increased risk of QT interval prolongation, serious ventricular arrhythmia or sudden cardiac death.
- The risk may be higher in patients older than 60 years or at total daily doses of more than 30mg.
- The maximum recommended dose of domperidone has been reduced from 80mg per day to 40mg per day. Use the lowest effective dose for the shortest duration.
- Prescribers should exercise caution when prescribing domperidone to patients who are taking CYP3A4 inhibitors, have existing prolongation of cardiac conduction intervals, significant electrolyte disturbances or underlying cardiac diseases such as congestive heart failure.

Domperidone is a peripheral dopamine (D_2) receptor antagonist. It acts as a gastroprokinetic agent by blocking gastrointestinal (GI) tract D_2-receptors and as an antiemetic by blocking D_2-receptors at the chemo-receptor trigger zone[1,2]. Domperidone is used to treat dyspeptic symptoms that may be associated with delayed

gastric emptying and acute symptoms of nausea and vomiting.

Recent population-based studies and subsequent reviews have associated domperidone use with an increased risk of adverse cardiac effects such as QT interval prolongation, ventricular arrhythmias and sudden cardiac death[1,3,4]. The Medicines Adverse Reactions Committee (MARC) reviewed the efficacy and safety data for domperidone due to these concerns (**www.medsafe.govt.nz/profs/adverse/Minutes158.htm**).

The MARC concluded that there is a small increased risk of adverse cardiac effects. However, the balance of benefits and potential harms for domperidone remains favourable. The available data suggests that this small increased risk may be higher in patients older than 60 years or at total daily doses of more than 30mg.

As a result of the MARC review, several changes have been made to the domperidone data sheets (**www.medsafe.govt.nz/profs/datasheet/dsform.asp**). The key changes are highlighted below.

Indications

Domperidone is indicated for the symptomatic treatment of the dyspeptic symptom complex that may be associated with delayed gastric emptying such as epigastric sense of fullness, abdominal distension or swelling, or epigastric pain or discomfort. Domperidone may also be used for the acute symptoms of nausea and vomiting.

The MARC considered that there was insufficient evidence to support the use of domperidone in childhood gastro-oesophageal reflux disease. It may not be suitable for chemotherapy- or radiotherapy-induced nausea and vomiting or post-operative nausea and vomiting.

Dosage and administration

Janssen (manufacturer of the Motilium brand of domperidone) has concluded that the maximum recommended dose should be reduced from 80mg to 40mg daily. The dose of domperidone should be the lowest effective dose for the individual situation for the shortest possible duration. For children weighing ≥ 35kg, the dose is 0.25 mg/kg three or four times a day, up to a maximum daily dose of 1.0 mg/kg. The use in children under 2 years of age is contraindicated[5].

Contraindications

Domperidone is predominantly metabolised by the cytochrome P450 enzyme 3A4 (CYP3A4)[2]. When domperidone is co-administered with potent CYP3A4 inhibitors, domperidone plasma concentrations can increase. The risk of QT prolongation is increased when domperidone plasma concentrations are increased. Examples of potent CYP3A4 inhibitors include (but are not limited to) clarithromycin, diltiazem, erythromycin, itraconazole, verapamil and ritonavir[6]. Medicines that prolong the QTc interval are also contraindicated with concomitant domperidone use.

Warnings and precautions

Studies suggest that the increased risk of arrhythmia and sudden cardiac death may be higher in patients older than 60 years or at total daily doses of more than 30mg. Caution should also be exercised in patients who have existing prolongation of cardiac conduction intervals, significant electrolyte disturbances or underlying cardiac diseases such as congestive heart failure. Other risk factors for sudden cardiac arrest include a family history of coronary artery disease, high blood pressure, high blood cholesterol, obesity, diabetes, smoking and excessive alcohol consumption.

Further information on the data reviewed is published in Medsafe's alert communication (**www.medsafe.govt.nz/safety/EWS/2014/Domperidone.asp**).

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Adverse Reaction Reporting in New Zealand – 2014

Key messages

- ⌘ If in doubt – report it!
- ⌘ You don't need to be certain – just suspicious!

Medsafe and the Centre for Adverse Reactions Monitoring (CARM) would like to thank everyone who submitted reports of suspected adverse reactions to medicines in 2014. These reports make an important contribution to medicine safety in New Zealand. Issues identified from your reports may be:

- further investigated through the M² scheme
- taken to the Medicines Adverse Reactions Committee (MARC) for advice
- highlighted in *Prescriber Update*
- used to update the data sheet
- the subject of an early warning system communication.

In 2014 CARM received a total of 5079 reports of suspected adverse reactions. These reports included 3563 associated with medicines, 1505 associated with vaccines and 11 associated with complementary or alternative medicines (CAM). A summary of these reports is published in the suspected medicines adverse reactions search (SMARS) on the Medsafe website (**www.medsafe.govt.nz/projects/B1/ADRDisclaimer.asp**).

Overall, 27% reports were considered to be serious. The serious reports included 37% of the medicine reports, 4% of the vaccine reports and 73% of the CAM reports.

Nurses continue to be the most frequent reporters (Figure 1).

We encourage you to report any suspected adverse reaction to any medicines in one of the methods listed below:

- using the online report form (**https://nzphvc.otago.ac.nz/report/**)
- completing a yellow card
- phoning 0800 4 Monitor (0800 466648)
- emailing **carmnz@otago.ac.nz**
- through your GP software
- using your iPhone or iPad (ADR Online application).

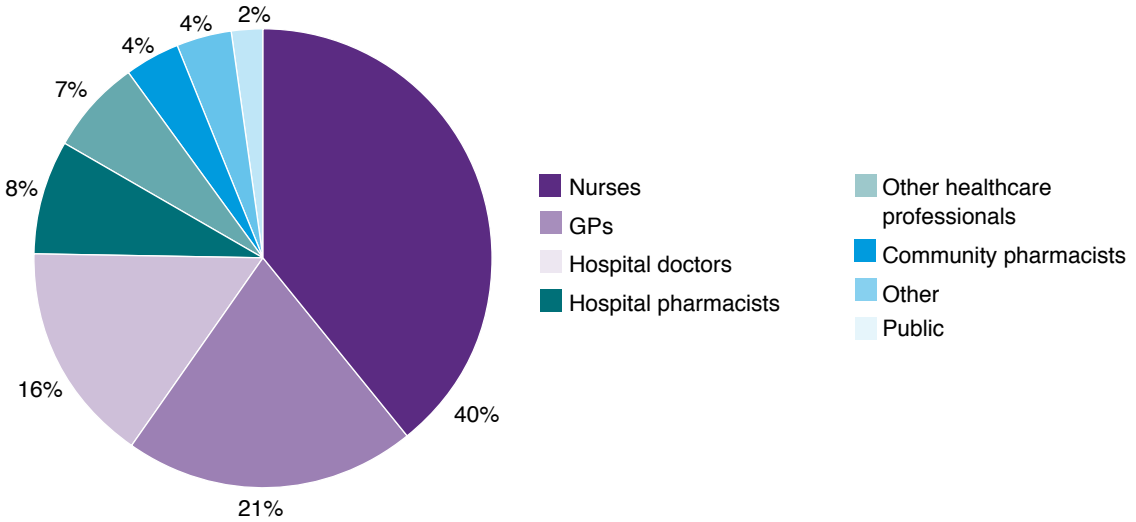

Figure 1: Source of adverse reaction reports from healthcare professionals and consumers in New Zealand in 2014

Spontaneous Reports: Seasonal Influenza Vaccination 2014

In 2014, the Centre for Adverse Reactions Monitoring (CARM) received 253 reports of adverse events following seasonal influenza vaccination (Table 1). Some reports contained more than one suspected event.

The most commonly reported events were injection site inflammation (50 reports), headache (35), arm pain (30) and nausea (26).

In 2014, eight (3.2%) of the influenza vaccine-related reports were considered serious.

A serious adverse reaction is determined by CARM according to internationally agreed criteria (ie, resulting in hospitalisation, is life-threatening, fatal, results in a disability or requires intervention to prevent permanent disability, or results in a congenital abnormality).

There was one death report of an older male who went into cardiac arrest a few minutes after his vaccination and died following resuscitation treatment. He had previously received the influenza vaccine multiple times in the past decade. His post mortem revealed pre-existing damage which indicated susceptibility to cardiac death.

In 2014, most reports were submitted by nurses (68%), followed by GPs (10.7%), hospital doctors (2.8%) and pharmacists (2.0%).

Table 1: Numbers of reports received by CARM and number of influenza vaccine doses distributed, 2010–2014.

	2010	2011	2012	2013	2014
Reports of adverse events following influenza vaccination	409	207	193	290	253
Influenza vaccine doses distributed*	1,046,000	993,500	1,000,600	1,253,600	1,206,573
Estimated reporting rate per 100,000 doses	39.1	20.8	19.3	23.1	21.0

* 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).

WE NEED YOUR HELP!

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

M² MEDICINES MONITORING

Medicine	Safety concern	Active monitoring ends
Zoledronic acid	Tendon injury/Tendinitis	30 April 2015

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

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NEW ZEALAND MEDICINES AND MEDICAL DEVICES SAFETY AUTHORITY
A BUSINESS UNIT OF THE MINISTRY OF HEALTH
www.medsafe.govt.nz

New Zealand Government

CARM
CENTRE FOR ADVERSE REACTIONS MONITORING

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

Preventing Paediatric Medication Errors

Key Messages

- ⌘ Many medication errors and subsequent adverse reactions that occur in children are preventable.
- ⌘ Healthcare professionals and parents/carers have the opportunity to help reduce paediatric medication administration errors.
- ⌘ Measuring devices such as oral syringes, droppers and medicine measuring cups can improve accurate and consistent doses at the time of administration.

Medication errors are considered adverse events which can lead to adverse drug reactions. These errors can occur at any stage from prescription to dispensing to administration. Paediatric patients are an especially vulnerable group as these adverse events can result in more serious and severe outcomes than would occur with the same error in adults.

There are numerous factors that contribute to the risk of medication errors in paediatric patients. The nature of paediatric dosing lends itself to an increased risk of errors due to individualised dosing and varied strengths in available formulations. For example, different children in the same family are likely to require different doses with different strengths of the same drug. All healthcare professionals have the opportunity to reduce medication administration errors in paediatric population as errors can be detected and corrected at various stages before administration.

There are many points at which errors occur and can be prevented. The most vital stage is the point of administration as those who administer the medicines are the final barrier to protect a child from a medication error. Measuring devices such as oral syringes, droppers and medicine measuring cups can improve accurate and consistent doses at the time of administration. If those administrating medicines are well-informed and possess the correct tools, they are empowered to reduce the risk of an error.

Reducing errors is an ongoing process and particular vigilance is required with paediatric patients as they may not always be able to communicate symptoms which would indicate an adverse reaction.

These points to consider may be helpful in reducing medication errors in children.

Points to consider for paediatric medicines

All healthcare professionals

- Allergy status.
- History of adverse reactions.
- Other medications currently being administered/prescribed to prevent accidental additional doses.
- Current weight of the child at the time of drug administration. Weigh the child if uncertain.
- Correct mg/kg basis of dose and calculation with child's current weight – it may be helpful to provide a written copy of the dose, calculation (and volume for liquid formulations) to be administered for the parent/carer who will administer the medication to the child.
- For children who weigh 40kg or more, check that the dose does not exceed an adult dose.
- Check if those who will administer the medicine have access to droppers/oral syringes or other measuring devices to facilitate accurate dose administration of liquid formulations.
- Check that parents/carers are clear on how to administer medicines and feel comfortable/confident with the procedure. Encourage them to discuss any concerns or uncertainty around administering medicines. Ask them to explain it to you (as they would explain to another carer such as a grandparent or babysitter).
- Report medication errors so measures can be taken to reduce the risk of these occurring in the future and to help prevent others from making similar mistakes.

Prescribers

- Provide specific instructions in the prescription on how to give each dose – avoid vague phrases such as 'take as directed' or 'when required'.
- Include the maximum dose (or number of doses) in 24 hours .
- Ask about other medications currently being administered/prescribed to the child.
- Confirm current weight of the child. Weigh the child if uncertain.

Pharmacists

- Provide specific instructions on how to give each dose – avoid vague phrases such as 'take as directed' or 'when required'.
- Double check the strength of formulation to be administered and double check the dose calculation.
- Include the volume to be administered for liquid formulations.
- Include the maximum dose (or number of doses) in 24 hours.
- Ask about other medications currently being administered/prescribed to the child.
- Confirm current weight of the child. Weigh the child if uncertain.
- Encourage those administering the medicine to use oral syringes or other measuring devices to facilitate accurate dose administration of liquid formulations.

At time of administration

- Check when the last/previous/most recent dose was administered and how many doses have been given in the previous 24 hours.
- Check the strength of the formulation.
- Check that the dose calculation of mg/kg x weight of child matches the volume to be administered (compare to written information provided).
- Check the measuring device to ensure the units match the volume to be administered.
- Monitor for adverse effects following administration of a medicine.

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