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The Hard Facts on Drug-induced Priapism (Long-lasting Erections)

Key Messages

- ⌘ Priapism is a persistent penile erection not associated with sexual stimulation that lasts more than four hours.
- ⌘ Drug-induced priapism most commonly occurs with antipsychotics and can also occur with a range of medicines.
- ⌘ Priapism or any erection lasting longer than four hours requires immediate medical attention to prevent long-term complications.

What is priapism?

Priapism is a persistent, often painful, penile erection lasting more than four hours that is not associated with sexual interest or stimulation[1]. It can occur in males of any age and occurs when blood in the penis becomes trapped.

At least 95% of all cases of priapism occur by an ischaemic (low-flow or veno-occlusive) mechanism. Ischaemic priapism is a type of compartment syndrome where pressure within the corpora cavernosa severely compromises circulation in the cavernous tissues[1].

What are the causes of priapism?

In the majority of cases, priapism is considered to be idiopathic[1].

The known causes or conditions associated with priapism include[1]:

- medicines (see Table 1 below)
- haematological disorders (eg, sickle cell disease, leukaemia)
- metabolic disorders (eg, amyloidosis, gout)
- recreational drugs (eg, alcohol, cannabis, cocaine).

What medicines can cause priapism?

Drug-induced priapism can occur with a range of medicines; antipsychotics are the most common cause[2].

Are there other medicines that have been reported to cause priapism?

There have only been a few reported cases of priapism with the use of phosphodiesterase type 5 inhibitors, used to treat erectile dysfunction[3].

Priapism has also been associated with methylphenidate treatment, both with dose increases and decreases[4]. The Medicines Adverse Reaction Committee (MARC) recently considered this association and noted the possibility of more than one biological mechanism. This may be demonstrated by reports of priapism associated with both increase in dose and methylphenidate withdrawal.

The MARC also noted that whilst priapism appears to be a very rare reaction, it is likely to be

Table 1: Medicines associated with priapism

Medicine class	Examples
Medicines recognised as increasing the risk of priapism (adapted from Salonia et al)	
Antipsychotics and antidepressants	risperidone, olanzapine, clozapine, chlorpromazine, quetiapine, sertraline, citalopram, escitalopram, lithium, fluoxetine, trifluoperazine, pericyazine
Vasoactive erectile agents	alprostadil, papaverine
α-adrenergic receptor antagonists	doxazosin, tamsulosin, terazosin, prazosin
Antihypertensives	hydralazine, propranolol
Anticoagulants	heparin, warfarin
Hormones	testosterone, gonadotropin-releasing hormone
Medicines that have been reported to cause priapism[3,4]	
Phosphodiesterase type 5 inhibitors	sildenafil, tadalafil
Medicines used for ADHD	methylphenidate, atomoxetine

under-reported and can have serious sequelae if treatment is not sought early enough.

Reports of priapism in New Zealand

The Centre for Adverse Reactions Monitoring (CARM) has received isolated reports of drug-induced priapism, including four reports with chlorpromazine and three reports with citalopram.

Internationally, there have been published case reports of priapism associated with medicines such as risperidone, quetiapine, sildenafil and olanzapine.

What information or advice about priapism should be given to patients?

Although priapism appears to be a very rare reaction, all male patients who are prescribed medicines that may cause priapism should be advised of the signs and symptoms.

Priapism or any erection lasting longer than four hours with or without sexual stimulation requires immediate medical attention to prevent long-term complications.

References

1. Salonia A, Eardley I, Giuliano F, et al. 2014. European Association of Urology Guidelines on Priapism. *European Urology* 65: 480–489.
2. Thompson JW, Ware MR, Blashfield RK. 1990. Psychotropic medication and priapism: a comprehensive review. *Journal of Clinical Psychology* 51(10): 430–433.
3. Broderick GA, Kadioglu A, Bivalacqua TJ, et al. 2010. Priapism: Pathogenesis, epidemiology, and management. *The Journal of Sexual Medicine* 7: 476–500.
4. Food and Drug Administration. 2013. FDA warns of rare risk of long-lasting erections in males taking methylphenidate ADHD medications and has approved label changes. *Drug Safety Communication* 17 December 2013. URL: **www.fda.gov/Drugs/DrugSafety/ucm375796.htm** (accessed 16 July 2014).

Methadone – Don't Break Your Heart (QT Prolongation)

Key Messages

- ⌘ QT prolongation has been reported in patients receiving doses of methadone greater than 100 mg/day.
- ⌘ ECG monitoring is recommended before dose titration above 100 mg/day and at seven days after titration in patients with no risk factors for QT prolongation.

Methadone is an opioid analgesic for moderate to severe pain used in the treatment of opioid dependence. QT prolongation has been reported in patients receiving doses above 100mg/day with no prior cardiac history.

QT prolongation is used as a surrogate marker for the risk of developing the potentially fatal arrhythmia Torsades de Pointes (TdP).

The risk of QT prolongation with methadone is increased in the presence of other risk factors. These include a genetic predisposition or pre-existing QT prolongation, increasing age, female gender, hypokalaemia or hypomagnesaemia, and medicine interactions[1]. An up-to-date database of medicines with the potential to cause QT prolongation/TdP, including a separate list of medicines to be avoided by patients with congenital long QT syndrome, is available on-line at **www.qtdrugs.org**.

In patients with risk factors for QT prolongation, ECG monitoring is recommended prior to methadone treatment, at dose stabilisation, after dose increases, or after starting any potentially interacting medicine[2].

In patients without risk factors for QT prolongation, ECG monitoring is recommended before dose titration above 100 mg/day and at seven days after titration[2].

The Centre for Adverse Reactions Monitoring (CARM) has received five reports of QT prolongation and/or TdP with the use of methadone at doses between 110 and 160 mg/day. One of these cases reported a cardiac arrest secondary to TdP.

Medsafe is currently working with the relevant sponsors to ensure all methadone data sheets contain these new recommendations.

References

1. Medsafe, 2010. Drug-induced QT prolongation and Torsades de Pointes – the facts. *Prescriber Update* 31(4): 27–29. URL: **www.medsafe.govt.nz/profs/PUArticles/DrugInducedQTProlongation.htm** (accessed 10 July 2014).
2. Thornton & Ross Ltd, 2014. *Methadone 1mg/ml Oral Solution BP – Sugar Free SPC* 12 March 2014. URL: **www.medicines.org.uk/emc/medicine/25339** (accessed 10 July 2014).

Medicine Storage – An Uncontained Issue?

Key Messages

- ⌘ Some medicines cannot be repacked and must be stored in the original container until it is time for the patient to take them. If in doubt, refer to the medicine data sheet.
- ⌘ Heat, air, light and moisture may impact the effectiveness and safety of a medicine. The original container is designed to protect the medicine from these elements.
- ⌘ Medicines such as solid dose cytotoxic preparations, finasteride and chlorpromazine always require special handling precautions.
- ⌘ Unless a medicine requires refrigeration, all medicines should be stored in a cool, dry place, out of the sight and reach of children.

Many medicines are repackaged into monitored dosage systems (blister packs) or plastic compartmentalised containers (pill boxes) to aid medication adherence and safe administration, particularly in residential care facilities. However, healthcare professionals are reminded that removing some medicines from original packaging to repack them into another dosage system may adversely affect the characteristics of the medicine. Repacking medicines can impact the medicine's effectiveness and safety.

The Centre for Adverse Reactions Monitoring (CARM) recently received a report from a patient who experienced haematuria after he began repacking dabigatran (Pradaxa) into a weekly pill box. These symptoms resolved once he stopped repacking dabigatran and kept the capsules in the original container. Dabigatran capsules absorb moisture from surroundings if removed from the original packaging. Moisture absorption may increase the bioavailability of the dabigatran dose, which can in turn increase the risk of adverse effects.

This case highlights that not all medicines are suitable for repacking. In general, the original container protects the medicine from heat, air, light and/or moisture. Exposure to these elements may affect the stability of the formulation and/or the active ingredient, which can alter the effectiveness and safety of the medicine.

The table below gives examples of medicines that should be kept in original packaging (this is not an exhaustive list).

Medicine	Reason for original packaging
Effervescent, dispersible, buccal, sublingual tablets (eg, Ondansetron orodispersible tablets, Rizatriptan orodispersible tablets, Prochlorperazine buccal tablets)	The foil packaging or tightly closed glass/plastic container protects the product from moisture absorption and thereby prevents product degradation. Use dry hands to prevent the medicine from dissolving prior to administration.
Dabigatran capsules	The original container protects these capsules from moisture absorption. Once the original container is opened, the contents must be used within four months.
Glyceryl trinitrate tablets	The glass amber bottle protects these tablets from both moisture absorption and light. Once opened, the contents need to be discarded within three months.
Nifedipine tablets	The foil packaging protects these tablets from both light and humidity.
Cabergoline tablets	The desiccant in the cap of the bottle should not be removed because it protects the tablets from excess moisture absorption (hygroscopic product).
Sodium valproate tablets	These tablets must be kept in protective foil until taken. This protects the tablet from excess moisture absorption (hygroscopic product).
Levodopa + benserazide dispersible tablets (Madopar)	The packaging protects the tablets from moisture absorption. These tablets should be taken within half an hour of dissolving the tablet due to sedimentation issues.
Ciclosporin capsules	The ethanol (required for solubility of ciclosporin) vaporises out of the soft capsule when removed from the foil packaging.

Some medicines also have special handling requirements. Healthcare professionals who consider repacking or administering medicines need to be aware of these for their own safety. Some examples of medicines that have special handling requirements include:

- solid dose cytotoxic preparations such as methotrexate should not be handled, particularly by women if they are or may potentially be pregnant
- women should not handle crushed or broken finasteride tablets (5α-reductase inhibitor), as this may cause birth defects
- women must avoid contact with broken dutasteride capsules (5α-reductase inhibitor) due to absorption through the skin
- chlorpromazine can cause dermatitis when handled.

It is important that medicines are stored in a cool, dry place, out of the reach and sight of children. If in doubt about the storage conditions of a medicine, refer to the appropriate data sheet (**www.medsafe.govt.nz/profs/datasheet/dsform.asp**) or contact the manufacturer.

Please note that this information is advisory only and it is at the discretion of the healthcare professional to determine if repacking medication is required for patient adherence and safety.

Hyperparathyroidism and Hypercalcaemia with Lithium Treatment

Key Messages

- ⌘ Up to 10% of patients on long-term lithium treatment experience hypercalcaemia.
- ⌘ Serum calcium levels should be measured at least once a year in patients taking lithium.
- ⌘ Parathyroid hormone levels should be measured in patients with raised calcium levels.
- ⌘ Patients with raised calcium and parathyroid hormone levels should be referred for specialist treatment.
- ⌘ Patients with raised calcium levels only, should be monitored more closely unless the level exceeds 11mg/dl in which case lithium treatment should be stopped.

Lithium-associated hyperparathyroidism (LAH) was first described in 1973[1]. However it is unclear if lithium causes the disease or reveals an underlying hyperparathyroidism (HPT)[1]. There is a wide spectrum of abnormalities in calcium homeostasis in patients taking lithium which range from overt hyperparathyroidism to hypercalcaemia with normal parathyroid hormone levels[1].

In patients taking lithium the prevalence of lithium-associated hyperparathyroidism is estimated at 4.3–6.3%, which is higher than the prevalence of HPT in the general population (1–4 in every 1000 people)[1]. Up to 10% of patients on long-term lithium treatment develop hypercalcaemia[2].

Patients with LAH are often asymptomatic. However, when symptoms are reported these include: fatigue, constipation, nephrolithiasis, bone pain and abdominal pain[3]. Patients with LAH often present with serum calcium levels ranging from slightly above normal (normal range 8.5–10.2 mg/L, depending on the laboratory) to over 15 mg/dl. The PTH levels in these patients range from high normal to several times the upper limit of normal (normal range 10–55 pg/ml, depending on the laboratory)[3]. Multiglandular disease is more often reported in LAH compared to sporadic cases of HPT[1].

Hypercalcaemia has been reported after one day of lithium treatment. Overt HPT has been reported after one to two months of lithium treatment. Cases of HPT have also been reported after discontinuation of lithium treatment[1].

Patients taking lithium should have their serum calcium levels measured at least once per year[2]. The frequency of monitoring should be increased in patients with an abnormal result or those with risk factors for HPT such as a family history[2]. If raised calcium levels are detected then the serum parathyroid level should be measured; if this is also raised the patient should be referred for specialist treatment[3].

If serum calcium levels are raised above 11mg/dl with normal parathyroid hormone levels lithium treatment should be stopped[3]. Calcium

levels should be measured weekly to ensure that they return to within the normal range[3].

Re-treatment with lithium may be considered if no effective alternatives are available, however the patient's calcium levels must be closely monitored. For full details of the monitoring recommendations see the data sheets for lithium on the Medsafe website (**www.medsafe.govt.nz/profs/datasheet/dsform.asp**).

References

1. Szalat A, Mazeh H and Freund HR. 2009. Lithium-associated hyperparathyroidism: report of four cases and review of the literature. *European Journal of Endocrinology* 160: 317-323.
2. McKnight R, Adida M, Budge K. 2012. Lithium toxicity: a systematic review and meta-analysis. *The Lancet* 379: 721-728.
3. Lehmann SW, Lee J. 2013. Lithium-associated hypercalcaemia and hyperparathyroidism in the elderly: what do we know? *Journal of Affective Disorders* 146: 151-157.

What are Medicine Quality Complaints?

Medicine quality complaints can encompass a wide range of issues identified after medicines have been released for distribution. These issues can affect the identity, quality, durability, reliability, safety or effectiveness of a medicine, which may make it unsafe or unfit for purpose.

Quality complaints can include:

- suspected mislabelled medicines
- abnormal odour or taste
- inaccurate or unreadable product labels/ labelling (including the package insert)
- capsule leakage
- packaging that is torn or punctured
- chipped, cracked, or splitting tablets
- sterile containers or vials that are punctured or leaking
- tablet or capsule discolorations
- packaging or product mix-ups
- broken, cracked, or chipped syringes
- suspected product contamination
- sterile products with floating objects or growth
- inconsistent tablet sizes
- leaking vials.

Some examples of complaints reported to Medsafe include:

- illegible writing on container labels for tablets. This complaint was resolved by the manufacturer changing the font size and colour for the labelling text
- foreign particles found in solution for injection. This complaint led to a product recall
- inconsistent sizing of tablets which could potentially lead to an overdose or under dose. This complaint led to a product recall.

Who can make a medicines quality complaint to Medsafe?

Complaints relating to the quality of medicines are reported to Medsafe by consumers, pharmacists, wholesalers, prescribers and the pharmaceutical industry.

Medsafe complaint investigation process

Medsafe assesses all complaints received and assigns a priority for review and action based on the perceived degree of risk to New Zealand public. For example, a serious issue with widely used prescription medicine will be investigated as a high priority, while a minor issue with website advertising may be treated as a low priority.

Medsafe may request additional information from the relevant parties such as manufacturers, sponsors and reporters if required to proceed with the investigation. They may also seek assistance and/or information from other specialists at Medsafe in relation to good manufacturing practice, pre-market medicines assessment and/or clinical risk assessment to help formulate a decision.

A health risk analysis is performed to assess the potential health impact in New Zealand and to determine the most appropriate action.

Reporting a problem

When an issue related to the quality of a medicine is identified, it should be reported promptly. This ensures the issue can be investigated and any corrective action, if necessary, can be taken quickly.

Issues related to the quality of specific products can sometimes be an indicator of a larger problem which needs to be addressed immediately. Where applicable, complaint

samples should be quarantined and stored in a safe place as these may be required for further testing.

Complaints should be reported to either the Compliance Management Branch at Medsafe, or to the company that distributes the product in New Zealand, or to both.

Questions about the quality complaints process should be directed to the Compliance Management Branch. Phone: 04-819-6800 or email recall@moh.govt.nz.

Reports of adverse drug reactions should be reported to the Centre for Adverse Reactions Monitoring (CARM): **https://nzphvc.otago.ac.nz/reporting/**

Febuxostat – An Additional Xanthine Oxidase Inhibitor

Febuxostat is approved in New Zealand for the treatment of chronic hyperuricaemia in patients with gout (including a history, or presence of, tophus and/or gouty arthritis)[1]. Febuxostat (Adenuric) has been funded by PHARMAC in New Zealand since 1 June 2014, subject to Special Authority criteria[2].

Febuxostat provides an alternative xanthine oxidase inhibitor option in patients who are treatment resistant or intolerant of allopurinol. Febuxostat can be used in patients with mild or moderate renal impairment.

Treatment with febuxostat is not recommended in patients with ischaemic heart disease or congestive heart failure. Hypersensitivity reactions, including life-threatening Stevens-Johnson Syndrome, have been reported. Prescribers are advised to check the datasheet for full details of precautions.

All suspected adverse reactions associated with febuxostat should be reported to the Centre for Adverse Reactions Monitoring (CARM).

References

1. Te Arai BioFarma Ltd. 2014. Adenuric Data Sheet. 29 April 2014. URL: **www.medsafe.govt.nz/profs/datasheet/** (accessed 24 July 2014).
2. PHARMAC. Decision to fund febuxostat (Adenuric) for treatment-resistant gout. 14 May 2014. URL: **www.pharmac.health.nz/news/notification-2014-05-14-febuxostat/** (accessed 24 July 2014).

Dermal Fillers – Blinded for Beauty

Key Messages

- ⌘ Dermal fillers used for cosmetic purposes have been associated with a small risk of reversible and irreversible vision disorders, including blindness.
- ⌘ Practitioners are advised to discuss this potential risk with patients prior to administration.
- ⌘ Dermal fillers are now categorised as medical devices, not medicines.
- ⌘ Dermal fillers should not be used on certain areas of the face.

Dermal fillers including collagen, hyaluronic acid and autologous adipose tissue are injected into the face for cosmetic purposes. Reports from overseas, dating back to 1988, highlighted both temporary and permanent visual disorders that occurred following dermal injection of these substances during aesthetic procedures[1]. Visual disorders included both partial and total visual losses, including cases of temporary and permanent blindness.

Practitioners are advised to discuss this risk with patients who are considering having dermal fillers injected. Complications affecting patients' vision have occurred both during administration and more than a year following the procedure[1]. Patients should be advised to seek medical advice immediately if any visual disturbances occur.

Dermal fillers should not be injected into certain areas of the face[2]. Complications may occur due to the technique applied and the vulnerability of the facial vasculature to blockage from injected substances[1]. Treatment to restore normal vision requires early recognition, identification and removal of blockages to recover perfusion[1].

Since 1 July 2014, dermal fillers have been re-categorised from medicines to medical devices. It is important to note that there is no pre-market approval process for medical devices in New Zealand under the Medicines Act 1981. Clinicians who use or would consider using dermal fillers should ensure the product has been approved by a regulatory authority for the intended purpose.

Summary of data sheet information for hyaluronate sodium/hyaluronic acid dermal fillers prior to re-categorisation as medical devices

- Not all products are suitable for injection into the periorbital area, check with the manufacturer first.
- Do not overcorrect.
- Do not inject into blood vessels (intravascular). Inadvertent injection into blood vessels could potentially lead to vascular occlusion, ischaemia and necrosis.
- Must not be used in patients who are known to be hypersensitive to the contents of the filler or who have a history of severe allergic reactions.
- Simultaneous use with laser therapy, chemical peeling or dermabrasion may cause inflammation at the injection site.
- Safety has not been established in women who are pregnant or breast feeding, or in children or those with autoimmune deficiency.
- Must not be used in areas showing skin problems such as inflammation and/or infections (eg, acne, herpes, etc).
- Special caution should be exercised when treating areas with limited collateral circulation, due to increased risk of ischaemia.
- Injection procedures can lead to reactivation of latent or subclinical herpes viral infections.
- Patients who are using substances that affect platelet function, such as aspirin and non-steroidal anti-inflammatory drugs may, as with any injection, experience increased bruising or bleeding at injection sites.
- It is recommended that patients avoid make up for 12 hours after injection and sunlight/UV light and temperature extremes for 2 weeks after injection.
- May not be suitable in patients with a tendency to develop hypertrophic scars.

References

1. Lazzeri D, Agostini T, Figus M, Nardi M, Pantaloni M, Lazzeri S. 2012. Blindness following Cosmetic Injections of the Face. *Plastic and Reconstructive Surgery* 129(4): 995-1012.
2. Carle MV, Roe R, Novack R, Boyer DS. 2014. Cosmetic Facial Fillers and Severe Vision Loss. *Journal of the American Medical Association Ophthalmology* 132(5): 637-639.

MARC's Remarks: June 2014 Meeting

The Medicines Adverse Reactions Committee (MARC) met on 12 June 2014 to review a number of medicine related safety issues.

The MARC reviewed information from a statutory benefit risk review of **hydroxyethyl starch**. The MARC noted that action had already been taken to restrict the use of these medicines and considered that no further regulatory action is required at this time[1].

The MARC reviewed the benefits and risks of treatment with **strontium ranelate**. The MARC noted that action had already been taken to restrict the use of this medicine and considered that no further regulatory action is required to improve the balance of benefits and risks of strontium ranelate at this time[2].

The benefits and risks of **domperidone** were also reviewed by the MARC. Medsafe is currently working with the relevant sponsors to update these data sheets. An update will be provided in a future edition of *Prescriber Update*.

The MARC discussed the risk of long-lasting erections (priapism) with the use of **methylphenidate**. Further information can be found in this edition of *Prescriber Update*[3].

Finally, the MARC discussed **levonorgestrel** emergency contraception and weight-based efficacy.

The MARC noted that the two randomised controlled trials used in the meta-analysis were not initially designed to examine the effect of body weight on the effectiveness of emergency contraception.

The MARC suggested that data sheets and consumer medicine information for emergency contraceptives containing levonorgestrel should include information on weight-based efficacy.

The MARC recommended that these medicines remain a suitable treatment option for women requiring emergency contraception. The MARC noted that women should use emergency

contraception as soon as possible after intercourse as efficacy declines over time.

Further information on these issues can be found on the Medsafe website (**www.medsafe.govt.nz/profs/adverse/Minutes158.htm**).

References

1. Medsafe. 2014. Hydroxyethyl starch (Voluven and Volulyte 6%) – review of benefits and risks of harm. *Trans-Tasman Early Warning System – Alert Communication*. URL: **www.medsafe.govt.nz/safety/EWS/2014/Hydroxyethyl-starch-solutions.asp** (accessed 25 July 2014).
2. Servier Laboratories (New Zealand) Limited. 2014. *Protos data sheet*. 2 April 2014. URL: **www.medsafe.govt.nz/profs/datasheet/p/Protossusp.pdf** (accessed 25 July 2014).
3. Medsafe. 2014. The Hard Facts on Drug-Induced Priapism (Long-lasting Erections). *Prescriber Update* 35(3): 34

Vancomycin and Severe Cutaneous Adverse Reactions (SCARs)

Key Messages

- ⌘ Vancomycin is associated with a risk of serious skin reactions.
- ⌘ Patients should be advised to seek medical advice immediately if signs or symptoms such as a skin rash, conjunctivitis, skin peeling or mouth ulcers occur, as these are associated with the development of serious skin reactions.
- ⌘ Vancomycin should be discontinued immediately in the event of a serious skin reaction.

Vancomycin is indicated for potentially life-threatening infections caused by susceptible organisms that cannot be treated with another effective, less toxic antimicrobial drug. The use of vancomycin is limited by its poor oral absorption and potential for nephro- and ototoxicity[1,2].

Vancomycin is associated with a risk of Severe Cutaneous Adverse Reactions (SCARs), which includes Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN) and Acute Generalized Exanthematous Pustulosis (AGEP). In addition, literature reports have associated vancomycin with Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)[3].

The Centre for Adverse Reactions Monitoring (CARM) has received seven cases of severe cutaneous adverse reactions associated with vancomycin treatment. In 2014, CARM received a report that described a fatal case of TEN.

Prompt recognition of SCARs and immediate cessation of the causative agent is essential to minimise both morbidity and mortality. Patients should be advised to seek immediate medical attention at the first appearance of a skin rash, conjunctivitis, skin peeling, mouth ulcers, or any sign of hypersensitivity. If serious skin reactions occur, the causative agent such as vancomycin should be discontinued immediately and appropriate treatment commenced.

References

1. Mylan New Zealand Ltd. 2011. *Vancomycin Data Sheet*. 25 May 2011. URL: **www.medsafe.govt.nz/profs/datasheet/v/VancomycinMylaninf.pdf** (accessed 31 July 2014).
2. Hospira NZ Limited. 2011 DBL. *Vancomycin Hydrochloride Data Sheet*. 15 December 2011. URL: **www.medsafe.govt.nz/profs/datasheet/v/Vancomycininf.pdf** (accessed 31 July 2014).
3. DermNet NZ. 2013. Drug hypersensitivity syndrome. URL: **www.dermnetnz.org/reactions/drug-hypersensitivity-syndrome.html** (accessed 4 August 2014).

WE NEED YOUR HELP!

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

M2 MEDICINES MONITORING

Medicine	Potential safety issue	Active monitoring ends
Allopurinol	Lichenoid-type skin reactions	31 October 2014
Doxazosin	Nightmare	31 October 2014
Alendronate, Pamidronate, Zoledronate	Optic neuritis	31 December 2014

Interaction Between Omeprazole and Citalopram/Escitalopram

Key Messages

- There is the potential for a pharmacokinetic and/or pharmacodynamic interaction between omeprazole and citalopram/escitalopram.
- To reduce the risk of a patient experiencing an adverse event due to an interaction, the maximum recommended dose for citalopram is 20 mg daily when omeprazole is being taken concurrently.

Interactions between medicines can occur through pharmacokinetic and pharmacodynamic mechanisms.

Omeprazole and citalopram/escitalopram are metabolised by cytochrome P450 (CYP) 2C19. Co-administration of omeprazole and citalopram doubled exposure to the S-isomer of citalopram[1]. Co-administration of omeprazole and escitalopram resulted in a 50% increase in plasma levels of escitalopram[1].

The pharmacokinetic interaction between omeprazole and citalopram/escitalopram increases the risk of QT prolongation, as this effect is associated with higher doses of citalopram[2]. The recommended maximum dose of citalopram is 20 mg daily in patients who are also taking omeprazole[3]. Similarly a dose reduction of escitalopram may be needed in some patients also taking omeprazole[4].

Omeprazole and citalopram/escitalopram can each individually cause hyponatraemia. Therefore co-administration may increase the risk of hyponatraemia.

The Centre for Adverse Reactions Monitoring (CARM) has received six reports of hyponatraemia in patients taking both omeprazole and citalopram/escitalopram. In four cases the patient's sodium level was close to the lower limit of normal on long term medicines including omeprazole, and experienced rapid falls within a week of adding citalopram/escitalopram. In one case severe hyponatraemia occurred within one week when omeprazole was added to long-term citalopram, with recovery when citalopram was discontinued. One patient experienced convulsions and two patients experienced confusion as a consequence of hyponatraemia. The majority of the patients were elderly, which is a known risk factor for developing hyponatraemia.

Caution is therefore advised when treating patients with omeprazole and citalopram/escitalopram concomitantly.

Please report any suspicions of drug interactions to CARM.

References

1. AstraZeneca Ltd. *Losec Modified Release Capsule Data Sheet*. 13 January 2014. URL: **www.medsafe.govt.nz/profs/datasheet/l/Loseccap.pdf** (accessed 28 July 2014)
2. Medsafe. 2012. Citalopram and Escitalopram – Similar Risk of QT Prolongation? *Prescriber Update* 33 (1): 3–4.
3. Healthcare Logistics. *Cipramil Data Sheet*. 29 July 2013. URL: **www.medsafe.govt.nz/profs/datasheet/c/cipramiltab.pdf** (accessed 28 July 2014)
4. Mylan New Zealand Ltd. *Loxalate Data Sheet*. 3 April 2014. URL: **www.medsafe.govt.nz/profs/datasheet/l/loxalatetab.pdf** (accessed 28 July 2014)

Intrauterine Devices and Uterine Perforation

Key Message

- There is an increased risk of uterine perforation in women who have an IUD inserted in the post-partum period while breastfeeding.

There is a higher risk of uterine perforation with the use of intrauterine contraceptive devices (IUDs) in women who are breastfeeding and also who are up to 36 weeks post-partum at the time of insertion. This risk is associated with both levonorgestrel and copper IUDs and is based on a recent report of the European Active Surveillance Study for Intrauterine Devices (EURAS-IUD)[1].

The EURAS-IUD study is a large cohort study of over 61,000 women who received either levonorgestrel or copper IUDs. Interim results from this study demonstrate that breastfeeding at the time of insertion led to a sixfold increase in the risk of perforation (RR 6.1, 95% CI 3.6–10.1). This association was consistent for both the

levonorgestrel and copper IUDs. There is also a higher risk for women who are up to 36 weeks post-partum at the time of insertion (see table).

The Centre for Adverse Reactions Monitoring (CARM) has received 31 reports of uterine perforation with IUDs in the last 25 years. Two of these women were breastfeeding and a further four women were ≤ 36 weeks after delivery.

Reference

1. Heinemann K, Westhoff CL, Grimes DA, Moehner S. 2014. Intrauterine Devices and the Risk of Uterine Perforations: Final Results From the EURAS-IUD Study. *Obstetrics and Gynecology* 123 Supplement 1:3S.

Table 1: Incidence of perforation per 1000 insertions for the entire study cohort, stratified by breastfeeding and time since delivery at insertion (parous women)

	Breastfeeding at time of insertion	Not breastfeeding at time of insertion
Insertion ≤ 36 weeks after delivery	5.6 per 1000 (95% CI: 3.9-7.9) n=6,047 insertions	1.7 per 1000 (95% CI: 0.8-3.1) n=5,927 insertions
Insertion > 36 weeks after delivery	1.6 per 1000 (95% CI: 0.0-9.1) n=608 insertions	0.7 per 1000 (95% CI: 0.5-1.1) n=41,910 insertions

Table modified from Bayer Healthcare communication. *Updates on risk of uterine perforation with intrauterine devices*. 14 May 2014.

Quarterly Summary of Medsafe's Early Warning System Communications

More information about the early warning system can be found on the Medsafe website (**www.medsafe.govt.nz/Projects/B2/EWS.asp**).

4 August 2014	Monitoring	Statins (atorvastatin, simvastatin, pravastatin, rosuvastatin) and acute kidney injury without rhabdomyolysis
21 July 2014	Monitoring	Provive MCT – LCT 1% Emulsion for Injection (10mg/mL) and Provive 1% Emulsion for Injection (10mg/mL) – investigation of infection in Australia
17 July 2014	Alert	Consumer Level Recall – Amoxicillin Actavis Powder for oral suspension; glass fragments found in two bottles

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

Fake and Adulterated Medicines on the Internet – Operation PANGEA VII

The internet can be misused by criminals to sell fake and adulterated medicines. Each year, enforcement agencies from over 100 countries work together in Operation PANGEA to target these criminals.

Operation PANGEA VII took place in May 2014. Over 10,600 websites worldwide were shut down, 237 arrests were made and nearly USD$36 million worth of potentially dangerous medicines were seized. Customs agencies from around the world inspected approximately 543,000 packages, of which nearly 20,000 were seized. Among the 9.4 million fake and illicit medicines seized were slimming pills, cancer medication, erectile dysfunction pills, cough and cold medication, anti-malarials, cholesterol medication and nutritional products.

In New Zealand, authorities held 248 packages for further investigation. These parcels originated from 32 different countries around the world. The parcels were stopped because they were found to contain prescription medicines, did not have labels or were known to contain undeclared or hidden ingredients.

Most of the parcels seized contained lifestyle type medicines such as those for erectile dysfunction, weight loss, and performance and image enhancing drugs. The accuracy of the

labels on these medicines cannot be guaranteed and other products may contain undeclared ingredients. For example, a consumer may be led to believe they have purchased a 'safe herbal product', which in fact contains a prescription medicine.

Healthcare professionals can help reduce the number of fake and adulterated medicines that enter New Zealand by doing the following:

1. Be wary if a patient requests a prescription for medicine purchased over the internet. Criminals go to great lengths to make their websites appear genuine. It is common for online businesses to purport to be reputable online pharmacies when they are not. Some pretend to be located in New Zealand.
2. Consider the following questions before providing a prescription for a medicine obtained from an online business:
   - Is the patient under your care?
   - Is the medicine, dose and quantity appropriate for the patient?
   - Is the patient aware of the risks of using medicines purchased over the internet?
   - Are you willing to take responsibility for prescribing your patient an unapproved medicine that is likely to be of unknown quality and origin?
   - Are you satisfied that your actions will meet ethical standards?
3. If a patient presents with unexplained symptoms, consider that the patient may have used a medicine or dietary supplement purchased over the internet.
4. Report adverse reactions to the Centre for Adverse Reactions Monitoring (CARM).

Please note that by writing a prescription for one of these medicines, the prescriber assumes the risks. This includes the risks associated with the medicine being unapproved or counterfeit, as well as the risks that the product is of unknown quality and origin.

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