# Prescriber Update

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## Goodbye Paper: *Prescriber Update* is Moving to Online Only

*Prescriber Update* will be an online-only journal from March 2019; this December 2018 issue will be the last time that *Prescriber Update* is published in print.

Going online only will reduce *Prescriber Update's* carbon footprint, and it reduces printing and distribution costs. It is also an opportunity to refresh the journal's design.

*Prescriber Update* will continue to be published four times a year on the Medsafe website (**www.medsafe.govt.nz/profs/PUarticles.asp**). You can read individual articles online or download the entire issue as a PDF to read later.

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## Spotlight on Terbinafine

### Key Messages

- ⌘ Ensure use of oral terbinafine is appropriate when prescribing it for fungal infections.
- ⌘ Duration of oral terbinafine treatment depends on the indication and the severity of the fungal infection.
- ⌘ Check for drug interactions before starting a patient on oral terbinafine.

The spotlight series continues with this article on terbinafine. Key information on terbinafine and adverse reaction reporting in New Zealand are described.

Please refer to the medicine data sheets for full prescribing information (**www.medsafe.govt.nz/Medicines/infoSearch.asp**).

### Background information

Terbinafine is an allylamine medicine used to treat fungal infections and is particularly effective against dermatophytes (tinea infections)[1,2].

In New Zealand, terbinafine is available in topical preparations (cream, gel, solution and spray) and oral formulation (tablets)[3]. This article focuses on oral terbinafine.

### Appropriateness of oral treatment

Prescribers should ensure that the presenting infection/condition is caused by susceptible fungal organisms before prescribing oral terbinafine[4], and that the site, severity or extent of the fungal infection warrant the use of a systemic antifungal medicine.

For less extensive or less severe fungal infections, it may be more appropriate to treat with a topical antifungal medicine first.

Use of oral terbinafine is associated with a number of rare but potentially serious adverse reactions[4]. The reactions reported to the Centre for Adverse Reactions Monitoring are summarised later in this article.

### Indications

Oral terbinafine is indicated in New Zealand for the following conditions:[2,5]

- onychomycosis (fungal infection of the nail) caused by dermatophyte fungi
- tinea capitis
- treating tinea pedis, tinea cruris or tinea corporis where oral therapy is appropriate due to the site, severity or extent of the infection
- fungal infections of the skin caused by the genus *Candida* (eg, *Candida albicans*) where oral therapy is appropriate due to the site, severity or extent of the infection.

Unlike topical terbinafine, oral terbinafine is not effective in the treatment of pityriasis versicolor[2,6].

### Recommended dose and duration of oral treatment

The standard adult dose is 250 mg per day[2].

The duration of oral terbinafine treatment differs according to the indication and the severity of the infection (Table 1). Following mycological cure, it may take a further few weeks or months for the signs and symptoms of the infection to resolve[2].

**Table 1: Recommended treatment duration of oral terbinafine according to indication**

| Skin infections | Recommended treatment duration |
|---|---|
| Cutaneous candidiasis | 2–4 weeks |
| Tinea corporis, tinea cruris | 2–4 weeks |
| Tinea pedis (interdigital, plantar/moccasin type) | 2–6 weeks |
| **Hair and scalp infections** | **Recommended treatment duration** |
| Tinea capitis | 4 weeks |
| **Onychomycosis** | **Recommended treatment duration** |
| Fingernail onychomycosis | 6 weeks |
| Toenail onychomycosis | 12 weeks* |

* Longer treatment may be required in patients with poor nail outgrowth.

Source: REX Medical Limited. 2017. *Deolate 250 mg tablets New Zealand Data Sheet* 11 September 2017.
URL: **www.medsafe.govt.nz/profs/Datasheet/d/deolatetab.pdf** (accessed 8 October 2018).

## Considerations in special populations

### Hepatic impairment

Oral terbinafine is not recommended for patients with active or chronic liver disease. Assessment of pre-existing liver disease should be completed before prescribing oral terbinafine[2].

### Renal impairment

Only use oral terbinafine in renally-impaired patients if there is no other alternative. Patients with impaired renal function (eg, creatinine clearance [CrCl] less than 50 mL/min or serum creatinine greater than 300 µmol/L) should take half the normal dose of oral terbinafine. There is no information on use in patients with CrCl less than 20 mL/min[2].

### Pregnancy and lactation

Clinical experience in pregnant women is limited. Oral terbinafine should not be used during pregnancy unless the expected benefits outweigh any expected risks[2].

Oral terbinafine should not be administered to mothers who are breastfeeding as terbinafine is excreted into breast milk[2].

### Elderly patients

Consider the potential for pre-existing kidney or liver impairment in the elderly[2].

### Children

There is no data available on oral terbinafine use in children aged under 2 years who weigh less than 12 kg[2]. See the data sheet for dosing recommendations in children.

## Medicine interactions

Examples of medicines that interact with terbinafine are shown in Table 2.

Terbinafine is metabolised by at least seven CYP450 enzymes, of which CYP1A2, CYP3A4, CYP2C8, CYP2C9 and CYP2C19 are the most important[2,7]. Terbinafine exposure may be altered when co-administered with medicines that inhibit or induce these enzymes.

Terbinafine is a CYP2D6 inhibitor. Patients receiving concomitant treatment with medication primarily metabolised by this enzyme should be monitored if the interaction is likely to be clinically relevant (eg, some beta-blockers, Class 1C anti-arrhythmics, Type B monoamine oxidase inhibitors, selective serotonin reuptake inhibitors and tricyclic antidepressants)[2].

The extent of the inhibition is such that CYP2D6 extensive metabolisers may find that their response to treatment with dextromethorphan or codeine is similar to that of a poor CYP2D6 metaboliser[2].

**Table 2: Examples of medicine interactions with terbinafine**

| | |
|---|---|
| Medicines that may increase the plasma concentration or the effect of terbinafine | Cimetidine<br>Fluconazole<br>Ketoconazole<br>Amiodarone |
| Medicines that may reduce the plasma concentration or the effect of terbinafine | Rifampicin |
| Terbinafine may increase the plasma concentration or the effect of | Caffeine<br>Medicines metabolised by CYP2D6, including some beta blockers*, Class 1C anti-arrhythmics*, Type B monoamine oxidase inhibitors*, selective serotonin reuptake inhibitors*, tricyclic antidepressants* |
| Terbinafine may reduce the plasma concentration or the effect of | Ciclosporin |

* Monitor patients who are taking these medicines concomitantly with terbinafine.

Source: REX Medical Limited. 2017. *Deolate 250 mg tablets New Zealand Data Sheet* 11 September 2017. URL: **www.medsafe.govt.nz/profs/Datasheet/d/deolatetab.pdf** (accessed 8 October 2018).

## Adverse reactions reported in New Zealand

Between 1 January 2013 and 1 June 2018, the Centre for Adverse Reactions Monitoring (CARM) received 52 case reports where oral terbinafine was considered to be the sole suspect medicine. Some of these reported reactions are listed below.

- Skin reactions: over half of the reports (29) described adverse skin reactions, such as urticaria, pruritus, rash, photosensitivity reaction, skin exfoliation, angioedema, acute generalised exanthematous pustulosis, Stevens-Johnson syndrome.
- Hepatic reactions: six reports, including increased hepatic enzymes, cholestatic hepatitis.
- Taste disturbances: six reports, including metallic taste, dysgeusia, taste loss.
- Blood dyscrasias: three reports, including neutropenia, agranulocytosis.

## References


1. DermNet NZ. 2014. *Terbinafine* URL: **www.dermnetnz.org/topics/terbinafine** (accessed 9 October 2018).
2. REX Medical Limited. 2017. *Deolate 250 mg tablets New Zealand Data Sheet* 11 September 2017. URL: **www.medsafe.govt.nz/profs/Datasheet/d/deolatetab.pdf** (accessed 8 October 2018).
3. Medsafe. 2018. *Product/Application Search*. URL: **www.medsafe.govt.nz/regulatory/DbSearch.asp** (accessed 9 October 2018).
4. Waitemata District Health Board. 2018. *SafeRx: Terbinafine – Safe Prescribing – Nail It!* January 2018. URL: **www.saferx.co.nz/assets/Documents/full/3b835bfc60/Terbinafine.pdf** (accessed 9 October 2018).
5. Dr Reddy's New Zealand Limited. 2017. *Terbinafine-DRLA tablets New Zealand Data Sheet* 2 June 2017. URL: **www.medsafe.govt.nz/profs/Datasheet/t/terbinafine-DRLAtab.pdf** (accessed 8 October 2018).
6. DermNet NZ. 2014. *Pityriasis versicolor*. URL: **www.dermnetnz.org/topics/pityriasis-versicolor** (accessed 9 October 2018).
7. Lexicomp. 2018. Terbinafine (systemic): Drug *information*. In: *UpToDate*. URL: **www.uptodate.com/contents/terbinafine-systemic-drug-information** (accessed 9 October 2018).


## Survey on Adverse Drug Reaction Reporting

Are you a healthcare professional? Complete Medsafe's survey on adverse drug reaction (ADR) reporting now!

Let us know how we can make it easier for you to report ADRs and how we can communicate medicines safety information to you in the best way.

The survey is open until 31 January 2019. **www.surveymonkey.com/r/MedsafeADRSurvey**

## The Dos and Don'ts of Using Hydroxyethyl Starch

### Key Messages

- ⌘ Hydroxyethyl starch is contraindicated in critically ill patients, and in patients with sepsis or renal impairment.
- ⌘ Using hydroxyethyl starch in critically ill patients, including those with severe sepsis, is associated with an increased risk of death or the need for renal replacement therapy.

Hydroxyethyl starch for infusion (Voluven and Volulyte) is indicated for the treatment of hypovolaemia due to acute blood loss when crystalloids alone are not considered sufficient[1,2]. It is contraindicated in critically ill patients, and in patients with sepsis or renal impairment[1,2]. Hydroxyethyl starch is not a substitute for packed red blood cells or fresh frozen plasma[1,2].

European drug utilisation studies have shown that hydroxyethyl starch continues to be used inappropriately in some patients in Europe[3]. Using hydroxyethyl starch in critically ill patients, including those with severe sepsis, has been associated with an increased risk of death and the need for renal replacement therapy[1,2].

Drug utilisation studies have not been performed in New Zealand. However, healthcare professionals are reminded that hydroxyethyl starch should not be used if any of the following clinical conditions apply[1,2]:

- critically ill patients (typically admitted to intensive care unit), including those with sepsis
- fluid overload (hyperhydration), especially in cases of pulmonary oedema and congestive cardiac failure
- patients with pre-existing coagulation or bleeding disorders
- renal failure with oliguria or anuria not related to hypovolaemia
- patients receiving dialysis treatment
- intracranial bleeding
- severe hypernatraemia
- severe hyperchloraemia
- severe hyperkalaemia (Volulyte only)
- known hypersensitivity to hydroxyethyl starches
- patients with severe liver disease.

### References


1. Fresenius Kabi New Zealand Limited. 2016. *Voluven 6% Solution for Infusion New Zealand Data Sheet* 29 September 2016. URL: **www.medsafe.govt.nz/profs/Datasheet/v/Voluveninf.pdf** (accessed 1 October 2018).
2. Fresenius Kabi New Zealand Limited. 2016. *Volulyte 6% Solution for Infusion New Zealand Data Sheet* 29 September 2016. URL: **www.medsafe.govt.nz/profs/Datasheet/v/volulytesol.pdf** (accessed 1 October 2018).
3. Fresenius Kabi New Zealand Limited. 2018. *Dear Healthcare Professional Letter: Safety Information Update* 12 September 2018. URL: **www.medsafe.govt.nz/safety/DHCPLetters/Volulyte&Voluven%2012-09-2018.pdf** (accessed 1 October 2018).


## Correction: Some Asthma Inhalers Contain Very Small Amounts of Ethanol

The September 2018 edition of *Prescriber Update* included an article about ethanol in some metered dose inhalers[1]. Table 1 of this article, showing the ethanol content of currently available metered dose inhalers for asthma, omitted the Rexair combination preventer products (fluticasone/salmeterol) and the mast cell stabiliser products, Intal Forte (sodium cromoglycate) and Tilade (nedocromil).

These products have been added to Table 1 in the article on the Medsafe website. Salamol (salbutamol) has been removed from the table as it is not currently available.

### References


1. Medsafe. 2018. Some asthma inhalers contain very small amounts of ethanol. *Prescriber Update* 39(3): 37–8. URL: **www.medsafe.govt.nz/profs/PUArticles/September%202018/AsthmaInhalersEthanol.htm** (accessed 18 September 2018).

# Infusing Iron? Consider Phosphate

## Key Messages

- Ferric carboxymaltose infusion may cause hypophosphatemia.
- The risk of developing hypophosphatemia should be considered before administering ferric carboxymaltose.

### Background

Ferric carboxymaltose is a parenterally-administered iron preparation. Some patients may develop hypophosphatemia following its administration. In many cases the hypophosphatemia is mild, transient and asymptomatic.

More severe or prolonged cases may be associated with muscle weakness, pain, altered mental status and osteomalacia[1,2].

### New Zealand reports

The Centre for Adverse Reactions Monitoring (CARM) has received five case reports of hypophosphatemia in association with parenteral iron treatment, reported between February 2016 and April 2018. All five cases reported ferric carboxymaltose as the suspect medicine, at a dose of 1,000 mg. All patients recovered after treatment with ferric carboxymaltose was stopped. Four of the patients had pre-existing renal disease (Table 1).

### Published cases

Symptomatic hypophosphatemia associated with the use of ferric carboxymaltose has been reported in the literature[3,4]. Symptoms included vertigo, nausea, general weakness, tingling in the hands and depression-like symptoms. The authors highlight the importance of measuring pre-existing serum phosphate levels and renal function to evaluate the risk of developing hypophosphatemia, and continuing to monitor phosphate after the administration of ferric carboxymaltose.

### Suggested mechanism

The mechanism for hypophosphatemia in relation to ferric carboxymaltose is unclear, however, the regulatory protein fibroblast growth factor 23 (FGF23) is believed to be involved[3,4,5]. FGF23 is secreted by osteocytes and acts to increase the loss of phosphate through the kidneys. Administration of ferric carboxymaltose increases the amount of biologically active FGF23, thereby increasing renal phosphate losses[3].

### Product information

Ferinject is the only ferric carboxymaltose product available in New Zealand. Hypophosphatemia is currently listed as a common adverse reaction in the Ferinject data sheet[6]. Medsafe is working with the sponsor to include more information about hypophosphatemia in the data sheet.

Two other parenteral iron products are currently available in New Zealand. The data sheets for Venofer (iron sucrose)[7] and Ferrum H (iron polymaltose)[8] do not list hypophosphatemia as a possible adverse reaction.

**Table 1: Cases of hypophosphatemia associated with ferric carboxymaltose reported to the Centre for Adverse Reactions Monitoring between February 2016 and April 2018**

| CARM ID | Gender/Age | Duration of therapy | Time to onset (days) | Severity |
|---|---|---|---|---|
| 119469 | F 75 | 1 day | 8 days | Severe |
| 120170 | F 39 | 1 day | 7 days | Severe |
| 126269 | F 50 | 1 day | 15 days | Not severe |
| 127938 | M 62 | Every 3 months for 31 months | 18 days | Severe |
| 127939 | F 44 | 1 day | 32 days | Severe |

A higher dose of iron can be administered over a shorter period of time with Ferinject, compared to the other parenteral iron products.

## Management

Although mild hypophosphatemia after iron infusion is common and transient, symptomatic hypophosphatemia appears to be rare. Clinicians should remain alert to the possibility of hypophosphatemia after treatment with ferric carboxymaltose, particularly if patients present with symptoms such as weakness, bone pain, or a change in mental state[9]. In such patients, serum phosphate should be measured and hypophosphatemia corrected[9]. Consideration should also be given to the use of alternative parenteral iron products in patients who have risk factors for or a history of hypophosphatemia.

## References


1. Schaefer B, Würtinger P, Finkenstedt A, et al. 2016. Choice of high-dose intravenous iron preparation determines hypophosphatemia risk. *PLoS One* 11(12): e0167146. URL: **www.ncbi.nlm.nih.gov/pmc/articles/PMC5131956/pdf/pone.0167146.pdf** (accessed 9 October 2018).
2. Yu ASL, Stubbs JR. 2018. Signs and symptoms of hyphosphatemia. In: *UpToDate* 9 March 2018. URL: **www.uptodate.com/contents/signs-and-symptoms-of-hypophosphatemia** (accessed 29 October 2018).
3. Anand G, Schmid C. 2017. Severe hypophosphataemia after intravenous iron administration. *BMJ Case Reports* (March 2017): bcr2016219160. URL: **www.ncbi.nlm.nih.gov/pmc/articles/PMC5353490/pdf/bcr-2016-219160.pdf** (accessed 9 October 2018).
4. Blazevic A, Hunze J, Boots JM. 2014. Severe hypophosphatemia after intravenous iron administration. Neth J Med. 72(1): 49–53. URL: **www.njmonline.nl/getpdf.php?id=1406** (accessed 9 October 2018).
5. Zoller H, Schaefer B, Glodny B. 2017. Iron-induced hypophosphatemia: an emerging complication. *Current Opinion in Nephrology and Hypertension* 26(4): 266–75. DOI: 10.1097/MNH.0000000000000329 (accessed 29 October 2018).
6. Pharmacy Retailing (NZ) Ltd. 2016. *Ferinject New Zealand Data Sheet* 6 June 2016. URL: **www.medsafe.govt.nz/profs/Datasheet/f/ferinjectinj.pdf** (accessed 9 October 2018).
7. Pharmacy Retailing (NZ) Ltd. 2016. *Venofer New Zealand Data Sheet* 4 April 2016. URL: **www.medsafe.govt.nz/profs/Datasheet/v/venoferinf.pdf** (accessed 9 October 2018).
8. Pharmacy Retailing (NZ) Ltd. 2014. *Ferrum H New Zealand Data Sheet* February 2014. URL: **www.medsafe.govt.nz/profs/Datasheet/f/FerrumHinj.pdf** (accessed 9 October 2018).
9. BPAC NZ. 2017. *Intravenous ferric carboxymaltose: now available for the treatment of iron deficiency.* URL: **https://bpac.org.nz/2017/docs/iron.pdf** (accessed 23 October 2018).

# The Medsafe Files – Episode Eight: Section 29 Medicines

## Key Messages

- Section 29 of the Medicines Act 1981 allows suppliers located within New Zealand to provide an unapproved medicine to a medical practitioner for the treatment of a particular patient of that practitioner. It is an exemption to the general requirement for product approval.
- Section 29 only applies to supply of medicines to medical practitioners, not to other authorised prescribers.
- Because products supplied this way have not been through the New Zealand approval process, the medical practitioner takes responsibility for balancing the potential risks and benefits for the patient, and must seek informed consent.
- Section 29 requires the supplier to report information about the supply to Medsafe. This information can be used to assist in medicine quality and recall issues.
- Suppliers of unapproved medicines must hold details relating to their supply.

### Medicines Act 1981 provisions for supply of unapproved medicines

The Medicines Act 1981 permits a medical practitioner to administer or arrange for the administration of medicines for the treatment of a patient in his or her care[1]. Section 29 permits a New Zealand supplier to obtain and supply unapproved medicines to any medical practitioner, on the practitioner's request, for the treatment of a particular patient currently under that medical practitioner's care[1].

These provisions in the Medicines Act 1981 allow access to medicines for which there is a clinical need, but where there is no approved product available in New Zealand. This is an exception process and should not be seen as an alternative to seeking approval to distribute these unapproved medicines.

Note that Section 29 specifies only medical practitioners. This means that other authorised prescribers may not procure medicines under the provisions of Section 29.

### Medicines supplied under Section 29

Because these medicines have not been through the usual approval process (formally referred to as gaining 'consent for distribution'), it is not possible to place the same reliance on their quality, safety and efficacy as it is for approved products. Medical practitioners should consider the need to use an unapproved medicine, and whether there is an acceptable benefit-risk balance for use of the medicine in the clinical situation. For instance, some unapproved products may have been approved overseas by a trusted regulator and supplied to New Zealand through the controlled supply chain, whereas others may not have been approved and they may not meet internationally agreed standards with respect to quality, safety and efficacy.

### Responsibilities of the medical practitioner

The medical practitioner should be fully aware that medicines supplied under Section 29 have not been evaluated by Medsafe for quality, safety and efficacy. The prescriber, therefore, takes responsibility for quality, safety and efficacy in these instances. It is the prescriber's responsibility to ensure that they are aware of any safety issues relating to the unapproved medicines that they prescribe. Knowing about the proposed product and the patient's characteristics should allow the practitioner to weigh the risks and benefits and provide credible advice to the patient. Informed consent would be an appropriate way to signal acceptance of the advice.

The Code of Health and Disability Services Consumers' Rights requires that patients have a right to treatment of an appropriate ethical and professional standard, and to be fully informed[2]. Where unapproved medicines are used, the patient should be fully informed of this fact and counselled accordingly. The patient should also be given information in writing if requested.

Further advice on unapproved medicines is available on the Medsafe website (**www.medsafe.govt.nz/profs/RIss/unapp.asp**).

### Responsibilities of the supplier of the unapproved medicine

Suppliers of unapproved medicines under Section 29 must report this supply to Medsafe at the end of each month. The supplier is usually

considered to be the importer or manufacturer of the medicine. The information supplied to Medsafe includes the product name, dose, and pack size, and the number of units supplied. The supplier must also hold information on the medical practitioners that they have supplied the unapproved medicines to, the names of each patient and the date and location of the supply. Medsafe may use this information to identify medicines affected by quality issues and to conduct recalls.

Prescribers should note that if they import a medicine into New Zealand for supply to other medical practitioners, they would be considered a wholesaler of that medicine, and required under Section 29 to report the supply to Medsafe.

### References


1. *Medicines Act 1981*. URL: **www.legislation.govt.nz/act/public/1981/0118/latest/DLM53790.html** (accessed 24 October 2018).
2. *Health and Disability Commissioner (Code of Health and Disability Services Consumers' Rights) Regulations 1996*. URL: **www.hdc.org.nz/your-rights/about-the-code/code-of-health-and-disability-services-consumers-rights/** (accessed 24 October 2018).


## MARC's Remarks: September 2018 Meeting

The Medicines Adverse Reactions Committee (MARC) met on 13 September 2018 to discuss a number of medicines-related safety issues.

The Committee made a number of recommendations based on their review of cases reported to the Centre for Adverse Reactions Monitoring.

- The Committee recommended that Medsafe write an article in *Prescriber Update* on **rivaroxaban** to encourage safe prescribing.
- Ventricular fibrillation and cardiac arrest were suspected to be caused by **droperidol.** The Committee recommended that Medsafe highlight this case to the appropriate colleges and encourage prescribers and pharmacists to closely monitor for potentially fatal cardiac effects of this medicine. (See also the 'Gathering Knowledge' article in this edition of *Prescriber Update*.)
- The Committee recommended that Medsafe monitors opioid adverse effects and withdrawal effects associated with **tramadol** in breastfeeding babies on the M² monitoring scheme.
- Prescribing of biologic medicines (such as **adalimumab** and **methotrexate**) has become more common in primary care, and the Committee recommended that Medsafe writes to organisations, such as the Goodfellow Unit, to request they consider creating educational material on these medicines.
- The Committee recommended that Medsafe updates and republishes the alert communication on **Arthrem** and potential risk of harm to the liver (**www.medsafe.govt.nz/safety/EWS/2018/Arthrem.asp**).

The Committee discussed past and present trends of adverse reaction reporting following brand switches in selected medicines. Potential causes of this phenomenon were discussed. The Committee stated they are confident in the way Medsafe approves generic medicines, which is consistent with international best practice. They are also supportive of the regulator's processes for auditing generic medicine manufacturers against the international standards for Good Manufacturing Practice (GMP).

The Committee discussed **granulocyte-colony stimulating factors (G-CSFs)** and pulmonary haemorrhage/haemoptysis. Medsafe is currently working with sponsors to update the data sheets for **filgrastim**, **pegfilgrastim** and **lipegfilgrastim** products to include this association.

The Committee reviewed the results of the M² monitoring of **dabigatran** and gout. The information gathered was insufficient to support an association. Medsafe will continue to monitor dabigatran and gout as part of regular pharmacovigilance activities.

Further information on this meeting is available on the Medsafe website (**www.medsafe.govt.nz/profs/MARC/Minutes.asp**). The reports presented to the MARC are also available on the Medsafe website (**www.medsafe.govt.nz/committees/MARC/Reports.asp**).

# Gathering Knowledge from Adverse Reaction Reports: December 2018

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

The table below presents a selection of recent informative cases from the Centre for Adverse Reactions Monitoring (CARM) database.

| | |
|---|---|
| **CARM ID:** 127096<br>**Age:** 75<br>**Gender:** Female<br>**Medicine(s):** Zoledronic acid<br>**Reaction(s):** Renal failure resulting in death | A 75-year-old woman was given an infusuion of zoledronic acid following a fracture. Several days later it was noted that her kidneys were failing. Despite treatment she did not recover and died. The report noted that the lack of hydration prior to treatment may have had an effect on the patient's outcome. |
| | The Aclasta data sheet (**www.medsafe.govt.nz/profs/Datasheet/a/Aclastainf.pdf**) states that patients must be appropriately hydrated prior to administration. This is especially important in the elderly and for patients receiving diuretic therapy. |
| **CARM ID:** 128298<br>**Age:** 12<br>**Gender:** Male<br>**Medicine(s):** Clonidine, methylphenidate<br>**Reaction(s):** Reduced facial expression, epistaxis | A 12-year-old boy taking methylphenidate was prescribed clonidine for behavioural issues. He then developed a 'blank face' and nose bleeds. |
| | The Catapres (**www.medsafe.govt.nz/profs/Datasheet/c/Cataprestabinj.pdf**) data sheet states that there is little supporting evidence for use and safety of clonidine in children and adolescents. Use of clonidine in these populations therefore cannot be recommended. In particular, when clonidine is used off-label concomitantly with methylphenidate in children, serious adverse reactions, including death, have been observed. Therefore, clonidine in this combination is not recommended. |
| **CARM ID:** 129124<br>**Age:** 17<br>**Gender:** Male<br>**Medicine(s):** Isotretinoin<br>**Reaction(s):** Proteinuria | A 17-year-old male with normal renal function experienced fatigue some months after starting isotretinoin. Testing revealed proteinuria, which was thought to be a side effect of the isotretinoin. |
| | Proteinuria is listed as a rare adverse effect in the Isotane (**www.medsafe.govt.nz/profs/Datasheet/i/isotanecap.pdf**) and Oratane (**www.medsafe.govt.nz/profs/Datasheet/o/oratanecap.pdf**) data sheets. |
| **CARM ID:** 129288<br>**Age:** 36<br>**Gender:** Male<br>**Medicine(s):** Felodipine<br>**Reaction(s):** Gingival hyperplasia | A 36-year-old man experienced gingival hyperplasia while on felodipine. The problem resolved once the medicine was discontinued. |
| | Gingival hyperplasia is listed as a very rare adverse effect in the Felo ER (**www.medsafe.govt.nz/profs/Datasheet/f/felotab.pdf**) and Plendil ER (**www.medsafe.govt.nz/profs/Datasheet/p/PlendilERtab.pdf**) data sheets. |
| **CARM ID:** 129199<br>**Age:** Unknown<br>**Gender:** Male<br>**Medicine(s):** Atorvastatin<br>**Reaction(s):** Erectile dysfunction | A male patient taking atorvastatin experienced erectile dysfunction, which resolved after atorvastatin was stopped. |
| | The Lorstat data sheet (**www.medsafe.govt.nz/profs/Datasheet/l/lorstattab.pdf**) states that erectile dysfunction has been reported as an uncommon adverse effect in clinical trials. |
| **CARM ID:** 128224<br>**Age:** 17<br>**Gender:** Female<br>**Medicine(s):** Droperidol<br>**Reaction(s):** Cardiac arrest | A 17-year-old patient was administered IV droperidol for prevention of post-operative nausea and vomiting. She subsequently experienced ventricular fibrillation and cardiac arrest. |
| | The Droperidol Panpharma (**www.medsafe.govt.nz/profs/Datasheet/d/droperidolPanpharmainj.pdf**) and Droleptan (**www.medsafe.govt.nz/profs/Datasheet/d/droleptaninj.pdf**) data sheets say cases of QT interval prolongation, ventricular arrhythmias and sudden death have been reported rarely. |

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

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

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

# Influenza Immunisation in Pregnant Women

### Key Messages

- ⌘ Influenza immunisation is strongly recommended for pregnant women.
- ⌘ The influenza vaccine can be given during any trimester of pregnancy.

### Background

Influenza is an acute respiratory infection caused by influenza viruses. Vaccines are the most effective way to prevent infection and severe outcomes caused by these viruses[1]. The influenza ('flu') vaccine is especially important for people at risk of serious complications from influenza, including people aged 65 years and older, individuals with certain medical conditions, and pregnant women. For these people, influenza immunisation in New Zealand is free[2].

### Immunisation during pregnancy

Influenza immunisation is strongly recommended for women who will be (or intend to be) pregnant during autumn and winter. New Zealand research shows that pregnant women are nearly five times more likely to be hospitalised with influenza than women who are not pregnant[3].

Influenza immunisation during pregnancy offers protection to the neonate through maternal antibody transfer[4]. Influenza vaccines are not approved for infants aged under 6 months, so vaccination during pregnancy offers protection to newborns and infants who are too young to have been vaccinated at the time of exposure to the virus[4]. Influenza vaccination during pregnancy has been shown to significantly decrease influenza infection in infants up to 6 months of age[4].

The influenza vaccine is safe to administer during any trimester of pregnancy or while breastfeeding[4].

Pregnant women can receive free influenza vaccine at their general practice or from some community pharmacies.

### Influenza vaccines for 2019

The recommended composition of influenza virus vaccines for use in New Zealand for the 2019 influenza season is now available[5]. The proposed trivalent and quadrivalent vaccines introduce a new A (H3N2)-like virus strain and a new strain for the B Victoria lineage when compared to the composition of the influenza vaccines used in New Zealand in 2018.

Medsafe will work with suppliers of the influenza vaccines for the 2019 season to ensure the data sheets contain clear guidance around the use of the influenza vaccine during pregnancy and/or breastfeeding.

Note that, from approximately December 2018 to February 2019, there may be two data sheets published on the Medsafe website for each influenza vaccine: one for the 2018 influenza season and one for the 2019 season (**www.medsafe.govt.nz/Medicines/infoSearch.asp**).

### References


1. World Health Organization. *Influenza*. URL: **www.who.int/influenza/en/** (accessed 23 October 2018).
2. Immunisation Advisory Centre. 2018. *Eligbility criteria*. URL: **www.influenza.org.nz/eligibility-criteria** (accessed 23 October 2018).
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4. Ministry of Health. 2018. *Immunisation Handbook 2017* (2nd ed, March 2018). URL: **www.health.govt.nz/publication/immunisation-handbook-2017** (accessed 23 October 2018).
5. Medsafe. 2018. *Influenza vaccine composition*. URL: **www.medsafe.govt.nz/regulatory/flu.asp** (accessed 23 October 2018).

# Erythropoietin and Pure Red Cell Aplasia

## Key Messages

- Pure red cell aplasia has been reported after treatment with erythropoietin.
- Most cases have occurred in patients with chronic kidney disease who had received the treatment subcutaneously.
- If pure red cell aplasia is diagnosed, discontinue treatment immediately and consider testing for erythropoietin antibodies.

## Background

Pure red cell aplasia (PRCA) has been reported after treatment with recombinant human erythropoietin (r-HuEPO)[1], particularly with Eprex[2]. Most cases occurred in patients with chronic kidney disease who had received Eprex subcutaneously[2]. Eprex is an erythropoiesis-stimulating agent used to treat or prevent anaemia of varying origins.

## Pure red cell aplasia

PRCA is a rare condition of severe anaemia characterised by a very low reticulocyte count and the virtual absence of red cell precursors in the bone marrow[2]. All other cell lines are present and seem quantitatively and morphologically normal. Iron studies may show elevated ferritin and high transferrin saturation due to the arrested erythropoiesis and build-up of iron stores[3].

PRCA results from the induction of neutralising immunoglobulin G antibodies directed against the protein component of the recombinant erythropoietin[2]. These neutralising antibodies cross-react with endogenous erythropoietin, inhibiting the growth of red cell precursors in the bone marrow.

## Management

If PRCA is diagnosed, r-HuEPO treatment must be discontinued immediately, and testing for erythropoietin antibodies should be considered[1]. If antibodies to erythropoietin are detected, patients should not be switched to another erythropoiesis-stimulating agent, as anti-erythropoietin antibodies cross-react with other erythropoiesis-stimulating agents[1]. Other causes of PRCA, such as viral infection (particularly parvovirus B19), malignancy, haemolytic syndromes, autoimmune disease, and seropositive arthritides may need to be excluded[3].

## New Zealand reports

Up to September 2018, the Centre for Adverse Reactions Monitoring (CARM) had received 11 case reports of pure red cell aplasia after treatment with erythropoietin. The time to onset was known for 10 reports, and ranged from 1 week to 26 months (median 8.4 months).

## References


1. Janssen-Cilag (New Zealand) Ltd. 2017. *Eprex solution for injection New Zealand Data Sheet* 24 November 2017. URL: **www.medsafe.govt.nz/profs/Datasheet/e/eprexinj.pdf** (accessed 9 October 2018).
2. Berns JS. 2017. Pure red cell aplasia due to anti-erythropoietin antibodies. In: *UpToDate* 7 August 2017. URL: **www.uptodate.com/contents/pure-red-cell-aplasia-due-to-anti-erythropoietin-antibodies** (accessed 9 October 2018).
3. Mohd Slim MA, Shaik R. 2013. Pure red cell aplasia associated with recombinant erythropoietin: a case report and brief review of the literature. *New Zealand Medical Journal* 126(1386): 106–10. URL: **www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2013/vol-126-no-1386/cc-slim** (accessed 30 October 2018).


CARM
CENTRE FOR ADVERSE REACTIONS MONITORING

**Report Adverse Drug Reactions**

Reporting adverse reactions contributes to the safety of medicines in New Zealand.

If you think your patient has had an adverse reaction to a medicine, report it to CARM.

Online reporting is easiest (**https://nzphvc.otago.ac.nz/report/**).

# Parasomnias – A Medicine Nightmare

## Key Messages

- Medicines such as beta-blockers, statins, selective serotonin re-uptake inhibitors and nicotine replacement therapies have been associated with various parasomnias.
- More recently, parasomnias have been reported in association with atypical antipsychotics.

## Background

Parasomnia is an umbrella term for complex movements or behaviours during sleep. These can include abnormal dreaming, nightmares (paroniria), sleepwalking (somnambulism) and sleep-related eating disorder[1]. Some medicines are known to interfere with non-rapid eye movement (NREM) and/or rapid eye movement (REM) sleep, resulting in parasomnias. These include widely used medicines such as beta-blockers, statins, selective serotonin re-uptake inhibitors (SSRIs) and nicotine replacement therapies[2].

## Antipsychotics

At their 174th meeting, the Medicines Adverse Reactions Committee (MARC) reviewed a safety signal of somnambulism and sleep-related eating disorder induced by atypical antipsychotics. Based on the evidence provided, the Committee concluded that there is an association between these events and quetiapine, olanzapine, and ziprasidone. The data sheets for these medicines are currently being updated to include somnambulism and related sleep disorders as adverse effects. Other antipsychotics will continue to be monitored as part of regular pharmacovigilance activities[3].

## New Zealand reports

The Centre for Adverse Reactions Monitoring (CARM) has received over 70 reports of various parasomnias over the past 5 years. Although arousal-associated parasomnias typically affect children[1], CARM has received reports of parasomnias from all age groups, associated with various medicines. The most frequently reported terms are:

- abnormal dreams (n=21)
- paroniria (n=42)
- sleep disorder (n=11).

Medicines commonly reported in association with parasomnias include:

- statins (n=6)
- varenicline (n=17)
- montelukast (n=5).

## References


1. Vaughn B. 2018. Approach to abnormal movements and behaviors during sleep. In: *UpToDate* 6 June 2018. URL: **www.uptodate.com/contents/approach-to-abnormal-movements-and-behaviors-during-sleep** (accessed 4 October 2018).
2. Harvard Health Publishing. 2010. *Medications that can affect sleep.* URL: **www.health.harvard.edu/newsletter_article/medications-that-can-affect-sleep/** (accessed 4 October 2018).
3. Medsafe. 2018. *Minutes of the 174th Medicines Adverse Reactions Committee 3 July 2018.* URL: **www.medsafe.govt.nz/profs/adverse/Minutes174.htm** (accessed 4 October 2018).


## Quarterly Summary of Recent Safety Communications

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

| Date | Communication | Topic |
|---|---|---|
| 26 October 2018 | Medicines Monitoring | Possible risk of lichen planus or lichenoid drug eruption with zoster (shingles) vaccine or influenza vaccine |
| 27 September 2018 | Recall | Coaguchek |
| 25 September 2018 | Safety Alert | Volulyte and Voluven |
| 5 September 2018 | Alert Communication | The USFDA Warns Against Use of Energy-Based Devices to Perform Vaginal 'Rejuvenation' or Vaginal Cosmetic Procedures: FDA Safety Communication |

## Test Your Knowledge

**Have you been reading *Prescriber Update* in 2018?**

Test your knowledge with the end-of-year *Prescriber Update* quiz.

Answers to the quiz are at the bottom of page 63 or at **www.medsafe.govt.nz/profs/PUPDF.asp**

1. **How many puffs of Respigen (salbutamol) would you need to take to be exposed to the amount of alcohol that is present in 100 g of ripe banana?**
   a) 1
   b) 10
   c) 100
   d) 1000

2. **In which of the following patient groups is codeine a suitable option for pain relief?**
   a) Breastfeeding mothers following Caesarean section.
   b) Children aged under 6 years following orthopaedic surgery.
   c) Children aged under 12 years following bowel surgery.
   d) Adolescents aged under 18 years following removal of tonsils or adenoids.
   e) None of the above.

3. **As a CYP2D6 inhibitor, terbinafine may [increase/decrease] the plasma concentration (ie, the effect) of metoprolol.**

4. **What is the amount of active ingredient in the approved brands of tenofovir disoproxil in New Zealand?**

5. **Opioid concentrations disappear immediately from the body after removal of a transdermal opioid patch.**
   True False

6. **Which products are currently being monitored by Medsafe because of a possible risk of neural tube defects when taken early in pregnancy?**

7. **How do you reduce the risk of hypocalcaemia associated with zoledronic acid?**
   a) Measure baseline serum calcium levels and treat pre-existing hypocalcaemia before administering zoledronic acid.
   b) Give adequate calcium and vitamin D to all patients receiving zoledronic acid.
   c) Monitor serum calcium levels and related metabolic parameters after starting zoledronic acid therapy.
   d) Be cautious when administering zoledronic acid with medicines known to cause hypocalcaemia.
   e) All of the above.

8. **Febuxostat is not recommended in patients concomitantly treated with azathioprine or mercaptopurine.**

   True False

9. **What must a medical practitioner consider when arranging to administer a Section 29 medicine?**

   a) The medicine must only be administered to a patient under their care.

   b) The medicine has not been evaluated by Medsafe for quality, safety and efficacy.

   c) They must seek informed consent from the patient.

   d) The supplier of the Section 29 medicine must hold information on the name of each patient who receives the unapproved medicine.

   e) All of the above.

10. **A second dose of which medication may be needed to reverse the effects of dabigatran?**

## Subscribe to Medsafe Updates and Alerts

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To subscribe: **www.medsafe.govt.nz/profs/subscribe.asp**

### Regulatory Web Update emails

These emails outline new and updated data sheets and consumer medicine information, changes to the Regulatory Guidelines, publication dates of Gazette Notices and other regulatory-related changes published on the Medsafe website.

To subscribe: **www.medsafe.govt.nz/regulatory/subscribe.asp**

### Medicine Classification emails

The Medicines Classification Committee (MCC) makes recommendations to the Minister of Health on the classification of medicines. Your comments are valuable to the MCC decision-making process.

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

**Quiz Answers**

1. 10 2. e) 3. Increase 4. 245 mg 5. False 6. Tivicay and Triumeq 7. e) 8. True 9. e) 10. idarucizumab (Praxbind)

## Recent Approvals of Medicines Containing a New Active Ingredient

For the period 16 July 2018 to 15 October 2018.

| Trade Name (Active ingredient) | Dose form and strength | Therapeutic area |
|---|---|---|
| Hemlibra (emicizumab) | Solution for injection<br>30 mg/1 mL 60 mg/0.4 mL<br>105 mg/0.7 mL 150 mg/1 mL | Haemophilia A (congenital factor VIII deficiency) |
| Spinraza (nusinersen) | Solution for injection<br>12 mg/5 mL | Spinal muscular atrophy |

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


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