# Prescriber Update

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# Spotlight on Codeine

## Key Messages

- The following patients should not use codeine as the risks of harm outweigh any benefit:
  - children aged under 12 years
  - adolescents aged under 18 years: for pain following surgery to remove tonsils or adenoids, for symptomatic relief of cough, or in patients whose respiratory function might be compromised
  - breastfeeding women.
- Genetic polymorphism in the CYP2D6 gene results in significant variation between individuals in the metabolism of codeine to morphine.
- Ultra-rapid metabolisers are at increased risk of morphine toxicity (including respiratory depression), while poor metabolisers obtain little analgesic benefit from codeine.
- Clinical genotyping to determine CYP2D6 metaboliser status is not widely available. Therefore, any patient prescribed codeine should be advised of the risks of morphine toxicity and to seek immediate medical advice if these occur.

Codeine is a weak opioid analgesic indicated for the relief of mild to moderately severe pain. Codeine also has antitussive properties and is used in some cough and cold medicines to control non-productive cough. Codeine is metabolised in the liver to the active compounds morphine and morphine-6-glucuronide.

### Codeine metabolism

Metabolism of codeine to morphine predominantly involves the cytochrome P450 enzyme CYP2D6. Genetic polymorphism in the CYP2D6 gene results in significant variation in the ability of individuals to metabolise codeine to morphine. Individuals may be classified as a poor, intermediate, extensive or ultra-rapid metabolisers[1].

The extensive metaboliser phenotype represents normal (wild-type) enzyme activity, and most people fall into this category. The frequency of poor metaboliser and ultra-rapid metaboliser phenotypes varies between populations. The relative frequencies of these phenotypes in the New Zealand population are not known.

Poor metabolisers are unable to convert codeine to morphine and receive little if any, analgesic benefit. Extensive metabolisers convert 5–15% of codeine to morphine via the CYP2D6 enzyme. In these patients, a 30 mg dose of codeine phosphate would yield approximately 1.5 mg to 4.5 mg of morphine. Ultra-rapid metabolisers convert codeine to morphine very efficiently, which can lead to morphine toxicity, such as respiratory depression and death.

Both codeine and morphine are excreted into breast milk. This is of particular concern for breastfeeding mothers who are ultra-rapid metabolisers. Exposure of the infant to breast milk containing morphine may lead to opioid toxicity in the infant, with the potential for respiratory depression and death. Furthermore, opioid toxicity in the mother (such as somnolence) may compromise her ability to identify signs of opioid toxicity in her infant.

### Deaths associated with the use of codeine

The United States Food and Drug Administration (FDA) undertook a review of adverse events submitted to the FDA Adverse Event Reporting System from 1969 to 2015. The review identified 64 cases of serious breathing problems, including 24 deaths, associated with codeine-containing medicines in children aged under 18 years[2]. Many of these cases concerned children with obstructive sleep apnoea who received codeine after surgery to remove tonsils or adenoids[3]. Since these children already had underlying breathing problems, they may have been particularly sensitive to morphine-induced respiratory depression.

In New Zealand, 53 deaths were recorded in the National Coronial Information System for the period 1 January 2008 to 31 December 2014 in which codeine was assessed as the primary contributor (JS Fountain, personal communication, April 2018). The median age of death was 48 years (range 18–86 years). In 26.4% of cases, death was considered to be unintentional. Overall, codeine phosphate ranked fourth as the primary contributor to deaths due to pharmaceuticals.

### Pain management in children

Codeine is no longer recommended by the World Health Organization or the Australian and New Zealand College of Anaesthetists for analgesia in children[4,5].

CYP2D6 status is not routinely determined therefore it is not possible to predict whether codeine will provide an analgesic effect or a toxic effect.

### Changes to age restrictions and contraindications for codeine-containing medicines

The Medicines Adverse Reaction Committee (MARC) recently reviewed the benefits and risks of using codeine in children.

The MARC recommended:

- the use of all codeine-containing medicines should be contraindicated in:
  - children aged under 12 years for all indications
  - adolescents aged under 18 years for pain following surgery to remove tonsils and adenoids
  - adolescents aged under 18 years in whom respiratory function might be compromised
  - adolescents aged under 18 years for cough
- the warning to avoid using codeine in breastfeeding mothers should be strengthened to a contraindication.

The MARC noted that codeine-containing cough and cold medicines are already contraindicated in children aged under 12 years[6].

Read more on the recommendations in the minutes of the 173rd meeting **www.medsafe.govt.nz/profs/MARC/Minutes.asp**. Medsafe is working with the New Zealand sponsors of codeine-containing medicines to update the data sheets in line with the MARC's recommendations.

Although the MARC only reviewed the use of codeine in children, health care professionals are advised to inform all patients about the signs and symptoms of morphine toxicity when prescribing codeine.

### References


1. Crews KR, Gaedigk A, Dunnenberger HM, et al. 2014. Clinical Pharmacogenetics Implementation Consortium Guidelines for Cytochrome P450 2D6 Genotype and Codeine Therapy: 2014 Update. *Clinical Pharmacology and Therapeutics* 95(4): 376–82.
2. US Food and Drug Administration. 2017. FDA *Drug Safety Communication: FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women*. URL: **www.fda.gov/Drugs/DrugSafety/ucm549679.htm** (accessed 7 May 2018).
3. US Food and Drug Administration. 2013. *FDA Drug Safety Communication: Safety review update of codeine use in children; new Boxed Warning and Contraindication on use after tonsillectomy and/or adenoidectomy*. URL: **www.fda.gov/downloads/Drugs/DrugSafety/UCM339116.pdf** (accessed 7 May 2018).
4. World Health Organization. 2012. *WHO Guidelines on the Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses*. Switzerland: World Health Organization.
5. Schug SA, Palmer GM, Scott DA, et al (eds). 2015. *Acute Pain Management: Scientific Evidence*. Melbourne: Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine.
6. Medsafe. 2016. Reminder: Using cough and cold medicines in children is inappropriate. *Prescriber Update*. 37(2): 18. URL: **www.medsafe.govt.nz/profs/PUArticles/PDF/Prescriber%20Update%20June%202016.pdf** (accessed 7 May 2018).


## Making Medicines Safer: New e-Learning Module on Reporting Adverse Reactions Launched

Medsafe is pleased to announce the launch of a new e-learning Module, Adverse Drug Reactions: Reporting makes medicines safer, available on the Medsafe website (**www.medsafe.govt.nz/profs/ADR-training/story.html**).

This new online course for health professionals explains why adverse drug reaction (ADR) reporting is important, and how and when to report an ADR.

There is an assessment at the end to check how much you've learned, and you can also download a certificate of completion.

The module is endorsed by the Royal New Zealand College of General Practitioners (RNZCGP) and has been approved for up to 2.0 hours Continuing Medical Education (CME) for General Practice Educational Programme 2/3 (GPEP) and Continuing Professional Development (CPD) purposes.

## Tenofovir Disoproxil – a Salty Tale

### Key Messages

- On 1 June 2018, the funded brand of tenofovir disoproxil changed from Viread (supplied by Gilead) to Tenofovir Disoproxil Teva (supplied by Teva).
- The tenofovir disoproxil brands approved in New Zealand contain the same amount of active ingredient (tenofovir disoproxil 245 mg) but have different salt forms: fumarate, succinate and maleate.
- The brands are clinically equivalent.

Tenofovir disoproxil is indicated in New Zealand for the treatment of chronic hepatitis B and HIV (in combination with other antiretroviral agents) in adults and children aged 12 years and older[1].

On 1 June 2018, PHARMAC switched sole supply from Viread (Gilead) to Tenofovir Disoproxil Teva.

The different brands of tenofovir disoproxil contain different salt forms of the same active chemical substance (Table 1) and the succinate salt form has a different molecular weight to the fumarate. However, the quantity of active ingredient in each of these medicines is the same (tenofovir disoproxil 245 mg). The different brands are clinically equivalent.

Medsafe and PHARMAC have decided to link all products back to the active ingredient (tenofovir disoproxil 245 mg). This will clearly describe the different tenofovir disoproxil medicines, and avoid confusion if alternate salt forms (eg, phosphate) and medicine strengths are introduced to New Zealand in future. Products will either be identified as 245 mg tenofovir disoproxil or have a clear equivalency statement on the label.

From 1 June 2018, please write all prescriptions for the active chemical substance: tenofovir disoproxil 245 mg.

More information about this change is available on the PHARMAC website[2].

### References


1. Teva Pharma (New Zealand) Limited. 2018. *Tenofovir disoproxil tablets (Teva) 245 mg New Zealand Data Sheet* February 2018. URL: **www.medsafe.govt.nz/profs/Datasheet/t/TenofovirDisoproxiltab.pdf** (accessed 20 April 2018).
2. PHARMAC. 2018. *Proposal to widen access and change the funded brand of tenofovir disoproxil and entecavir*. URL: **www.pharmac.govt.nz/news/consultation-2018-03-09-tenofovir-disoproxil-entecavir/** (accessed 20 April 2018).


**Table 1: Tenofovir disoproxil medicines currently approved in New Zealand, their salt forms and content and the tenofovir disproxil content**

| Medicine | Salt form and content (mg) | | Tenofovir disoproxil content (mg) |
|---|---|---|---|
| Viread (Gilead) | tenofovir disoproxil fumarate | 300.0 | 245 |
| Tenofovir Disoproxil Teva | tenofovir disoproxil succinate | 300.6 | 245 |
| Tenofovir Disoproxil Mylan | tenofovir disoproxil maleate | 300.0 | 245 |

## Medicines Interacting with Methadone

### Key Messages

- Pharmacokinetic and pharmacodynamic interactions can both occur between methadone and a number of other medicines.
- Check for medicine interactions when prescribing new medicines for patients currently taking methadone, or when starting a patient on methadone.

Methadone is an opioid analgesic used as an adjunct in the treatment of opioid dependence and for the relief of moderate to severe pain[1,2].

Methadone is extensively metabolised by cytochrome P450 enzymes in the liver, with CYP3A4 and CYP2B6 being major contributors and CYP2C19, CYP2D6 and CYP2C9 being minor contributors[3]. Methadone is also a substrate for P-glycoprotein.

Inducers and inhibitors of these proteins can alter methadone concentrations, potentially

leading to a withdrawal syndrome or an increased risk of respiratory depression, sedation and QT prolongation[4–6]. Concurrent use of other opioids, alcohol or central nervous system (CNS) depressants (eg, benzodiazepines) can also increase the risk of respiratory depression and sedation[6].

Tables 1 and 2 give examples of medicines that interact with methadone. Please refer to the New Zealand data sheets for a full list of interactions with methadone (**www.medsafe.govt.nz/Medicines/infoSearch.asp**).

**Table 1: Examples of methadone pharmacokinetic interactions and their effects[6–8]**

| Medicine Classification | Examples | Mechanism | Effect |
|---|---|---|---|
| Anticonvulsants | carbamazepine, phenobarbitone, phenytoin | Induction of methadone metabolism | Reduced methadone levels |
| Antibiotics | rifampicin | | |
| Non-Nucleoside Reverse -Transcriptase Inhibitors | efavirenz, nevirapine | | |
| Azole antifungals | fluconazole, ketoconazole | Inhibition of methadone metabolism | Increased methadone levels |
| Selective serotonin reuptake inhibitors | fluoxetine | | |
| Protease inhibitors | atazanavir, darunavir, indinavir, ritonavir | Inhibition or induction of methadone metabolism | Increased or decreased methadone levels |

**Table 2: Examples of methadone pharmacodynamic interactions and their effects[6–8]**

| Medicine Classification | Examples | Mechanism | Effect |
|---|---|---|---|
| | alcohol | Additive central nervous system depression | Increased sedation, increased respiratory depression; combination may also increase hepatotoxicity potential |
| Benzodiazepines and hypnotics | clonazepam, diazepam, lorazepam, nitrazepam, oxazepam, temazepam, triazolam, zopiclone | | Enhanced sedative effect; increased respiratory depression |
| Neuroleptics | aripiprazole, clozapine, olanzapine, quetiapine, risperidone | | Enhanced sedative effects; which are dose dependent |
| Other opioids | codeine, fentanyl, morphine, oxycodone | | Enhanced sedative effect; enhanced respiratory depression |
| Sedating antihistamines | cyclizine, promethazine | | Enhanced sedative and psychoactive effect; anecdotal reports of injection of cyclizine with opioids causing hallucinations |
| Opioid antagonists | naloxone, naltrexone | Compete for opioid receptors | Blocks effect of methadone |
| Partial opioid agonist | buprenorphine | Partial agonist of opioid receptors | Antagonistic effect or enhanced sedative effect and respiratory depression |

Up to 31 December 2017, the Centre for Adverse Reactions Monitoring (CARM) had received eight cases describing a medicine interaction with methadone. Three of these cases describe additive CNS depression, where methadone was co-prescribed with a benzodiazepine, another opioid or a neuroleptic. In one case, a patient experienced somnolence when co-prescribed fluconazole.

Consider potential medicine interactions when prescribing new medicines for patients currently taking methadone, or when starting a patient on methadone.

### References


1. New Zealand Formulary. 2018. *New Zealand Formulary v67: Methadone hydrochloride* 1 January 2018. URL: **http://nzf.org.nz/nzf_2870** (accessed 31 January 2018).
2. Best Practice Advocacy Centre. 2008. *WHO Analgesic Ladder: Methadone — safe and effective use for chronic pain. Best Practice Journal* 18: 21–9 URL: **https://bpac.org.nz/BPJ/2008/December/methadone.aspx** (accessed 31 January 2018).
3. UpToDate. 2018. *Methadone Drug Information* URL: **www.uptodate.com/contents/methadone-drug-information** (accessed 15 May 2018).
4. Medsafe. 2014. Methadone – don't break your heart (QT prolongation). *Prescriber Update* 35(3): 35. URL: **www.medsafe.govt.nz/profs/puarticles/September2014Methadone.htm** (accessed 31 January 2018).
5. Biomed Limited. 2014. *Biodone Data Sheet* 24 June 2014. **www.medsafe.govt.nz/profs/Datasheet/b/Biodoneoralsoln.pdf** (accessed 31 January 2018).
6. Brown R, Kraus C, Fleming M, et al. 2004. Methadone: applied pharmacology and use as adjunctive treatment in chronic pain. *Postgraduate Medical Journal* 80: 654–9.
7. PSM Healthcare Ltd t/a API Consumer Brands Ltd. 2017. *Methatabs Data Sheet* November 2017. URL: **www.medsafe.govt.nz/profs/Datasheet/m/Methatabs.pdf** (accessed 31 January 2018.
8. AFT Pharmaceuticals Ltd. 2017. *Methadone Injection BP Data Sheet* 4 July 2017. URL: **www.medsafe.govt.nz/profs/Datasheet/m/Methadoneinj.pdf** (accessed 31 January 2018).


## Hyoscine Butylbromide Injection and Cardiovascular Adverse Reactions

### Key Messages

- Hyoscine butylbromide injection can lead to cardiovascular adverse reactions, such as hypotension and tachycardia.
- These adverse reactions may be more serious in patients with underlying cardiac disease.
- Monitor patients with underlying cardiac conditions who receive hyoscine butylbromide injection.

Hyoscine butylbromide is an antimuscarinic medicine indicated for muscle spasm of the gastrointestinal tract[1,2].

Hyoscine butylbromide injection can cause serious adverse effects, such as tachycardia hypotension, and anaphylaxis. The risk associated with these adverse effects is greater in patients with underlying cardiac disease.

There have been reports, internationally, of patients who have died after receiving intravenous or intramuscular injection of hyoscine butylbromide[3]. In most of these cases, the fatal adverse event was acute myocardial infarction or cardiac arrest.

In New Zealand, the Centre for Adverse Reaction Monitoring (CARM) received nine reports of suspected cardiovascular adverse reactions to hyoscine butylbromide injection between 1 January 2013 and 31 December 2017. Tachycardia was reported in six of these cases. In one of these reports, the patient was taking cardiovascular medicines indicative of underlying cardiovascular disease.

Use hyoscine butylbromide with caution in patients with underlying cardiovascular disease. These patients require close monitoring in an environment where resuscitation equipment and staff trained to use it are readily available[2].

Parenteral administration of hyoscine butylbromide is contraindicated in patients with tachycardia[2].

### References


1. New Zealand Formulary. 2018. *New Zealand Formulary v70: Hyoscine butylbromide* 1 April 2018. URL: **http://nzf.org.nz/nzf_713** (accessed 16 April 2018).
2. Sanofi-Aventis New Zealand Limited. 2017. *Buscopan and Buscopan Forte Data Sheet* 9 November 2017. URL: **www.medsafe.govt.nz/profs/datasheet/b/Buscopantabinj.pdf** (accessed 16 April 2018).
3. Medicines and Healthcare Products Regulatory Agency. 2017. *Hyoscine butylbromide (Buscopan) injection: risk of serious adverse effects in patients with underlying cardiac disease* 20 February 2017. URL: **www.gov.uk/drug-safety-update/hyoscine-butylbromide-buscopan-injection-risk-of-serious-adverse-effects-in-patients-with-underlying-cardiac-disease** (accessed 16 April 2018).

# Using New Zealand Data to Review the Risk of Venous Thromboembolism with Combined Oral Contraceptives

### Key Messages

- ⌘ Venous thromboembolism (deep vein thrombosis and pulmonary embolism) is a rare side effect of combined oral contraceptive use.
- ⌘ Cases of venous thromboembolism are most frequently reported in the first 12 months of combined oral contraceptive use, but are also reported with longer onset times.
- ⌘ Stay alert for symptoms of deep vein thrombosis and pulmonary embolism in all women taking combined oral contraceptives.

Venous thromboembolism (VTE) is a rare side effect of combined oral contraceptive (COC) use. Other risk factors for the development of VTE include age, family history, prolonged immobility, smoking and being overweight, pregnant or postpartum. The background rate of VTE in women not taking COCs is around two in every 10,000 women. Although COCs are often described as doubling or trebling the risk of VTE, the absolute risk remains small (Table 1).

Numerous studies have investigated the likelihood of a differential risk between COCs. Those containing cyproterone, desogestrel or drospirenone have consistently been associated with a higher risk of VTE than COCs containing levonorgestrel as the progestogen component[1].

**Table 1: Venous thromboembolism reporting rates versus expected rates**

| Combined oral contraceptive[a] – ethinylestradiol plus: | Number of reports to CARM 2013–2017 | No. of women taking COC[b] | VTE reporting rate per 10,000 women over 5 years | VTE expected rate per 10,000 women years[c,d] |
|---|---|---|---|---|
| norethisterone | 3 | 25,375 | 1.2 | 5–7 |
| levonorgesterol | 14 | 123,340 | 1.1 | 5–7 |
| cyproterone | 8 | 37,070 | 2.2 | 9–12 |
| desogestrel | 0 | 3,297 | N/A | 9–12 |
| drospirenone | 4 | N/A | N/A | 9–12 |

a See Table 2 for the funded brands.

b Based on the average of the number of women dispensed prescriptions per year from DataPharm (beta) between 2013 and 2016[2].

c European Medicines Agency. 2014. *Benefits of combined hormonal contraceptives continue to outweigh risks.* Doc Ref: EMA/35464/2014. URL: **http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Combined_hormonal_contraceptives/European_Commission_final_decision/WC500160277.pdf** (accessed 24 May 2018).

d European Medicines Agency. 2013. *Benefits of Diane 35 and its generics outweigh risks in certain patient groups*. Doc Ref: EMA318380/2013. URL: **http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/cyproterone_ethinylestradiol_107i/European_Commission_final_decision/WC500147176.pdf** (accessed 24 May 2018).

**Table 2: Available and funded combined oral contraceptive brands**

| Active ingredients | Brand names | Funded brand |
|---|---|---|
| ethinylestradiol/norethisterone | Brevinor, Norimin | Brevinor, Norimin |
| ethinylestradiol/levonorgestrel | Ava (20/30/30ED), Levlen ED, Loette, Microgynon (20ED, 30ED, 50ED) Microlut, Monofeme | Microgynon, Levlen |
| ethinylestradiol/cyproterone* | Diane 35, Estelle 35, Ginet | Ginet |
| ethinylestradiol/desogestrel | Marvelon, Mercilon | Marvelon, Mercilon |
| ethinylestradiol/drospirenone | Yasmin, Yaz | Not funded |

* Contraception is a secondary function not an indication for use.

Medsafe reviewed the New Zealand spontaneous reporting data (2013–2017) together with dispensing data for funded medicines (2013–2016). In the last five years, 29 cases of VTE were reported to the Centre for Adverse Reactions Monitoring (CARM) in association with COCs. We used data from Ministry of Health's Pharmaceutical collection, DataPharm (beta)[2], to obtain a frequency estimate (Table 1).

VTE was less likely to be reported with COCs containing levonorgestrel (Ava, Microgynon, Monofeme) and norethisterone (Brevinor, Norimin) than with cyproterone containing products (Diane, Ginet, Estelle). Cyproterone/ethinylestradiol containing products are not primarily indicated for contraception but are included here for completeness. Comparatively few prescriptions for COCs containing desogestrel (Mercilon, Marvelon) were dispensed, and there were no reports of VTE occurring during this time period. We could not estimate the frequency of reports for COCs containing drospirenone (Yasmin, Yaz) as these medicines are not funded. Comparison of the frequency estimate with the expected rate shows that these events are underreported.

Figure 1 shows an analysis of the time from starting the COC to the onset of VTE. Unfortunately, in nearly half of the reported cases, the onset time could not be calculated from the information provided. When this information was provided, in the majority of cases the onset was within the first 12 months of use. However, there were a significant number of cases with longer onset times. Therefore, a high suspicion of VTE should be maintained for all women taking a COC and presenting with symptoms associated with VTE. Women prescribed a COC should be informed about these risks. Medsafe has a consumer leaflet to help with these discussions[3].

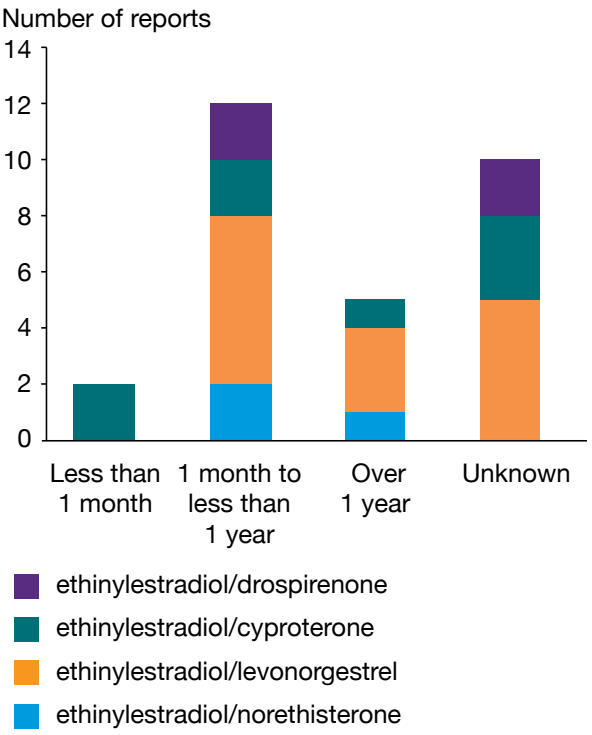


**Figure 1: Time to onset of venous thromboembolism associated with use of combined oral contraceptives**

### References


1. Dragoman M, Tepper N, Fu R, et al. 2018. A systematic review and meta-analysis of venous thrombosis risk among users of combined oral contraception. *Journal of Gynaecology and Obstetrics* 141(3): 287–94. DOI: 10.1002/ijgo.12455.
2. Ministry of Health. 2018. *DataPharm (beta) version 15 March 2018* (data extracted from Pharmaceutical Collection on 18 December 2017). URL: **https://minhealthnz.shinyapps.io/datapharm-beta/** (accessed 16 April 2018).
3. Medsafe. 2014. *Hormonal contraceptives and blood clots*. URL: **www.medsafe.govt.nz/consumers/educational-material/Hormonal%20Contraceptives.pdf** (accessed 16 April 2018).


## Hypocalcaemia – a Risk with Zoledronic Acid

### Key Messages

- ⌘ Hypocalcaemia is a common adverse reaction of zoledronic acid.
- ⌘ Measure serum calcium levels and treat pre-existing hypocalcaemia before administering zoledronic acid.
- ⌘ Give adequate calcium and vitamin D to all patients receiving zoledronic acid.
- ⌘ Monitor serum calcium levels and related metabolic parameters after starting zoledronic acid therapy.
- ⌘ Be cautious when administering zoledronic acid with medicines known to cause hypocalcaemia.

Zoledronic acid (zoledronate), is a bisphosphonate used for prevention of skeletal-related events in patients with advanced malignancies involving bone, and treatment of tumour-induced hypercalcaemia, Paget's disease and osteoporosis[1].

### Hypocalcaemia

Hypocalcaemia has been reported in 5–10% of patients treated with zoledronic acid infusion[2]. Because zoledronic acid rapidly reduces bone turnover, transient hypocalcaemia may develop after administration, due to reduced bone contribution to the calcium pool. Transient hypocalcaemia is usually seen after the first infusion of zoledronic acid[3].

Although most cases are mild and asymptomatic, severe hypocalcaemia presenting with cardiac arrhythmias and neurologic events (seizures, tetany, and numbness) has been reported. In some instances, the hypocalcaemia may be life-threatening[4]. Severe hypocalcaemia can occur within one day to several months after starting therapy[2].

Between May 2009 and December 2017, the Centre for Adverse Reactions Monitoring (CARM) received 10 reports of hypocalcaemia with zoledronic acid. One case was fatal. Zoledronic acid was the sole suspect medicine in nine of the cases. Baseline serum calcium level was reported to be normal in five of the cases while it was not reported in the remaining five cases.

### Risk factors

Patients with low pre-treatment calcium level, co-administration of corticosteroids[5], inadequate calcium intake, Paget's disease[2], low parathyroid reserve, vitamin D deficiency[3], and concomitant use of aminoglycosides, calcitonin or loop diuretics[4] are at increased risk of developing severe hypocalcaemia following zoledronic acid infusion.

### Reducing the risk of hypocalcaemia

The risk of hypocalcaemia can be reduced by:

- measuring serum calcium and correcting pre-existing hypocalcaemia before starting therapy[3, 4]
- adequately supplementing patients with calcium and vitamin D during therapy[3, 4]
- monitoring serum calcium (albumin-corrected) levels and related metabolic parameters such as phosphate, magnesium and serum creatinine, after initiating zoledronic acid infusion[3, 4].

### References


1. New Zealand Formulary. 2018. *New Zealand Formulary v71: Zoledronic acid* 1 May 2018 URL: **http://nzf.org.nz/nzf_4035** (accessed 1 May 2018).
2. UpToDate. 2018. *Zoledronic acid: Drug information*. URL: **www.uptodate.com/contents/zoledronic-acid-drug-information** (accessed 30 April 2018).
3. Novartis. 2016. *Aclasta New Zealand Data Sheet* 13 December 2016. URL: **www.medsafe.govt.nz/profs/Datasheet/a/Aclastainf.pdf** (accessed 10 May 2018).
4. Novartis New Zealand Limited. 2016. *Zometa New Zealand Data Sheet* 23 May 2016. URL: **www.medsafe.govt.nz/profs/Datasheet/z/Zometaconcinf.pdf** (accessed 30 April 2018).
5. Hanamura M, Iwamoto T, Soga N, et al. 2010. Risk factors contributing to the development of hypocalcemia after zoledronic acid administration in patients with bone metastases of solid tumor. *Biol Pharm Bull* 33(4): 721–4.


## Pharmacogenomics – Helps Reduce Rash Decisions

### Key Messages

- ⌘ Severe Cutaneous Adverse Reactions (SCAR) are potentially life-threatening skin reactions associated with many medicines.
- ⌘ Genetic screening before prescribing certain medicines (abacavir, allopurinol and carbamazepine) can significantly reduce the risk of SCAR.

### Introduction

Pharmacogenomics is the study of how genes influence an individual's response to medicines.

### Human leukocyte antigen (HLA) alleles

Severe cutaneous adverse reactions (SCAR) are rare but potentially lethal. SCAR is an umbrella term that includes Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reactions with eosinophilia and systemic symptoms (DRESS).

Variant human leukocyte antigen (HLA) alleles put some individuals at higher risk of developing SCAR. (An allele is variant form of a given gene that is located at a specific position on a specific chromosome.) The prevalence of these HLA variant alleles varies widely between individuals but may be related to their geographical origin[1].

**Table 1: Abacavir, allopurinol and carbamazepine, their associated human leukocyte antigen alleles and at-risk populations**

| Medicine | HLA type(s) | At-risk populations (HLA frequency, where known) |
|---|---|---|
| Abacavir[2,3] | HLA-B*57:01 | All populations (UK prevalence 4.5%) |
| Allopurinol[4,5] | HLA-B*58:01 | Han Chinese, Korean, Thai (5–20%) European (1–2%) |
| Carbamazepine[6–8] | HLA-B*15:02 | Han Chinese, South-East Asian |
| | HLA-A*31:01 | European, Japanese |

Three medicines have a well-established genetic HLA association (Table 1). Other HLA-drug associations have also been reported, including dapsone, phenytoin, sulfamethoxazole, lamotrigine, nevirapine and methzolamide.

## Polymorphisms of drug metabolising enzymes

Genetic polymorphisms of drug cytochrome P450 drug metabolising status or other enzymes involved in metabolism can have an effect on drug metabolism and lead to toxicity or lack of response.

Examples of polymorphic drug metabolising enzymes include:

- CYP2D6: important for codeine, tamoxifen, some antipsychotics[9]
- CYP2C9: important for phenytoin[1], warfarin (the Clinical Pharmacogenetics Implementation Consortium recommends the algorithm at **www.warfarindosing.org** to predict optimal starting doses of warfarin[10])
- thiopurine methyltransferase (TPMT): azathioprine, mercaptopurine
- UDP-glucuronosyltransferase 1-1 (UGT1A1): irinotecan.

## Clinical implications

The risk of adverse reactions to medicines can be reduced by screening patients and avoiding prescribing medicines to those with these HLA types or enzyme polymorphisms.

There are differences internationally in the use of these tests. For example, all patients requiring medicines such as allopurinol are screened at some centres in Thailand. In other countries, testing is only performed for patients belonging to certain population groups. For example, the American College of Rheumatology recommends genetic screening before prescribing allopurinol in Koreans with stage 3 or worse chronic kidney disease, and all those of Han Chinese and Thai descent regardless of kidney function[11]. HLA testing before starting abacavir is universal.

## New Zealand reports

Table 2 shows all reports received by the Centre for Adverse Reactions Monitoring (CARM) of SCAR associated with carbamazepine and allopurinol up to 31 December 2017. To date, none of the reports have included information on whether genetic testing had been performed. There are no reports for abacavir.

**Table 2: All reports of severe cutaneous adverse reactions[a] for carbamazepine and allopurinol received by the Centre for Adverse Reactions Monitoring to 31 December 2017**

| | Allopurinol | Carbamazepine | Total |
|---|---|---|---|
| **Total reports** | 46 | 39 | 85 |
| **Deaths** | 5 | 1 | 6 |
| **Reported ethnicity[b]** | | | |
| European | 15 | 20 | 35 |
| Māori | 10 | 5 | 15 |
| Pacific | 3 | 4 | 7 |
| Other | 13 | 7 | 20 |
| Unknown | 5 | 3 | 8 |

a Includes reports for Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reactions with eosinophilia and systemic symptoms (DRESS).

b Ethnicity is a cultural affiliation and does not necessarily reflect ancestry[12].

### Current and future work

Pharmacogenomics is likely to become more widespread in the future. In New Zealand, UDRUGS (Understanding Adverse Drug Reactions Using Genomic Sequencing) has been established with two major goals: to establish a DNA bank linked to clinical information of patients who have experienced severe adverse drug reactions or exhibited aberrant response to pharmacological treatment, and to explore the range of variations in known pharmacogenes that may contribute to the observed phenotypes[13].

### References


1. Su S-C, Hung S-I, Fan W-L, et al. 2016. Severe cutaneous adverse reactions: The pharmacogenomics from research to clinical implementation. *International Journal of Molecular Sciences* 17(11): 1890.
2. Mallal S, Phillips E, Carosi G, et al. 2008. HLA-B*5701 screening for hypersensitivity to abacavir. *The New England Journal of Medicine* 358(6): 568–79.
3. Orkin C, Sadqu ST, Rice L, et al. 2010. Prospective epidemiological study of the prevalence of human leukocyte antigen (HLA)-B*5701 in HIV-1-infected UK subjects. *HIV Med* 11(3): 187–92. DOI: 10.1111/j.1468-1293.2009.00762.x (accessed 16 May 2018).
4. Somkrua R, Eickman EE, Saokaew S, et al. 2011. Association of HLA-B* 5801 allele and allopurinol-induced Stevens Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. *BMC Medical Genetics* 12(1): 118.
5. Ko T-M, Tsai C-Y, Chen S-Y, et al. 2015. Use of HLA-B* 58: 01 genotyping to prevent allopurinol induced severe cutaneous adverse reactions in Taiwan: national prospective cohort study. *BMJ* 351: h4848.
6. Chen P, Lin J-J, Lu C-S, et al. 2011. Carbamazepine-induced toxic effects and HLA-B* 1502 screening in Taiwan. *New England Journal of Medicine* 364(12): 1126–33.
7. McCormack M, Alfirevic A, Bourgeois S, et al. 2011. HLA-A* 3101 and carbamazepine-induced hypersensitivity reactions in Europeans. *New England Journal of Medicine* 364(12): 1134–43.
8. Ozeki T, Mushiroda T, Yowang A, et al. 2010. Genome-wide association study identifies HLA-A* 3101 allele as a genetic risk factor for carbamazepine-induced cutaneous adverse drug reactions in Japanese population. *Human Molecular Genetics* 20(5): 1034–41.
9. Drozda K, Müller D, Bishop J. 2014. Pharmacogenic testing for neuropsychiatric drugs: current status of drug labeling, guidelines for using genetic information, and test options. *Pharmacotherapy* 34(2): 166–84. URL: **www.ncbi.nlm.nih.gov/pmc/articles/PMC3939793/** (accessed 16 May 2018).
10. Johnson JA, Gong L, Whirl-Carrillo M, et al. 2011. Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C9 and VKORC1 genotypes and warfarin dosing. *Clinical Pharmacology & Therapeutics* 90(4): 625–9.
11. Khanna D, Fitzgerald JD, Khanna PP, et al. 2012. American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care & Research* 64(10): 1431–46.
12. Stats NZ. 2018. *Ethnicity*. URL: **www.stats.govt.nz/topics/ethnicity** (accessed 15 May 2018).
13. Maggo SD, Chua EW, Chin P, Cree S, Pearson J, Doogue M, et al. 2017. A New Zealand platform to enable genetic investigation of adverse drug reactions. *New Zealand Medical Journal* 130(1466): 62–9.


## MARC's Remarks: March 2018 Meeting

The Medicines Adverse Reactions Committee (MARC) met on 8 March 2018 to discuss a number of medicine-related safety issues.

The MARC noted a case reported to the Centre for Adverse Reactions Monitoring (CARM) regarding the effects of stopping smoking on **theophylline**. Interactions between medicines and smoking have been described in a previous edition of *Prescriber Update*[1] and a Consumer Information Leaflet[2].

The MARC also noted a case of hypocalcaemia following a **zoledronic acid** infusion. Further information is available in this edition of *Prescriber Update*[3].

The MARC discussed the latest evidence for **levonorgestrel** and its weight-based efficacy. The current information was insufficient for MARC to make a recommendation on the benefit of using an unapproved dose (3 mg) of levonorgestrel in women over 70 kg or a body mass index greater than 26 kg/m$^2$. The MARC and Medsafe remind health professionals that patients must give informed consent before using this unapproved dose.

The MARC discussed the safety of **codeine** in children. Further information on the recommendations made by the MARC is available in this edition of *Prescriber Update*[4].

The MARC was presented with a case report where a woman experienced discontinuation symptoms upon stopping her three-monthly **medroxyprogesterone** depot injection (brand name Depo-Provera). The MARC noted that while there is limited information on this issue in the medical literature, there are many reports on social media platforms where women discuss problems upon stopping Depo-Provera. The MARC determined that the evidence was too weak to require data sheet updates, however health professionals should always discuss the potential risks and discontinuation effects that women may experience from this medicine.

The MARC was asked to comment on a request by the sponsor to change the contraindications and precautions in the **celecoxib** data sheet regarding use in patients with cardiovascular conditions. The MARC asked Medsafe to request further information from the manufacturer before recommendations can be made.

The MARC was presented with the Risk Management Plan (RMP) for **nusinersen**, which is a novel, antisense oligonucleotide medication for the management of spinal muscular atrophy. The RMP was considered to be thorough, appropriate and complete.

The MARC discussed a potential association between **ulipristal acetate** and drug-induced liver injury. The MARC discussed individual cases and agreed that there was an association between the medicine and the adverse drug reaction. The MARC recommended that Medsafe conducts a risk-benefit review of ulipristal acetate under section 36 of the Medicines Act 1981.

Further information on this meeting is available on the Medsafe website (**www.medsafe.govt.nz/profs/adverse/Minutes173.htm**). The reports presented to the MARC are also available (**www.medsafe.govt.nz/committees/MARC/Reports.asp**).

### References


1. Medsafe. 2013. Smoking can interact with medicines. *Prescriber Update* 34(4): 41–2. URL: **www.medsafe.govt.nz/profs/PUArticles/PDF/PrescriberUpdate_December2013.pdf** (accessed 19 April 2018).
2. Medsafe. 2016. *Quitting smoking can affect the medicines you are taking*. URL: **www.medsafe.govt.nz/consumers/educational-material/QuittingSmokingCanAffectYourMedicines.pdf** (accessed 19 April 2018).
3. Medsafe. 2018. Hypocalcaemia – a risk with zoledronic acid. *Prescriber Update* 39(2): 24–5.
4. Medsafe. 2018. Spotlight on Codeine. *Prescriber Update* 39(2): 18–9.


## Gathering Knowledge from Adverse Reaction Reports: June 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 is a selection of recent informative cases from the Centre for Adverse Reactions Monitoring (CARM) database.

| | |
|---|---|
| **CARM ID:** 126558<br>**Age:** 39<br>**Gender:** Female<br>**Medicine(s):** Carbamazepine<br>**Reaction(s):** Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) | Six weeks after starting carbamazepine, a 39-year-old female experienced a fine pimply rash which spread over the whole body and was associated with fever. Blood test results showed increased eosinophils and deranged LFTs. |
| | The Tegretol data sheet (**www.medsafe.govt.nz/profs/Datasheet/t/Tegretoltabsyrup.pdf**) lists two different HLA alleles associated with severe cutaneous adverse reactions, including DRESS.<br>Also refer to the article on Pharmacogenomics in this edition of *Prescriber Update*. |
| **CARM ID:** 126816<br>**Age:** 64<br>**Gender:** Male<br>**Medicine(s):** Olanzapine<br>**Reaction(s):** Diabetic ketoacidosis | A 64-year-old male patient was given Zyprexa Relprevv (olanzapine). His condition deteriorated over the next few weeks. On admission to hospital he had a severe diabetic ketoacidosis. He had not been diagnosed as diabetic prior to this event. |
| | The Zyprexa Reprevv data sheet (**www.medsafe.govt.nz/profs/Datasheet/z/zyprexarelprevvinj.pdf**) states that hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including Zyprexa Relprevv. |
| **CARM ID:** 127173<br>**Age:** 46<br>**Gender:** Male<br>**Medicine(s):** Atorvastatin and amiodarone<br>**Reaction(s):** Rhabdomyolysis | A patient taking 80 mg atorvastatin required an amiodarone infusion. A few days later the patient experienced a rise in CK, associated with rhabdomyolysis. |
| | The Cordarone infusion data sheet (**www.medsafe.govt.nz/profs/Datasheet/c/CordaroneXtabinj.pdf**) states that the risk of muscular toxicity is increased by concomitant administration of amiodarone with statins metabolised by CYP3A4 such as simvastatin, atorvastatin and lovastatin. Medsafe recommends using a statin that is not metabolised by CYP3A4, if a patient requires amiodarone. |

## WE NEED YOUR HELP!

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

MEDICINES MONITORING

| Medicine | Potential Safety Issue | Active Monitoring Ends |
|---|---|---|
| Dabigatran | Gout or gout-like symptoms | 31 July 2018 |

- 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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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.

# Recent Approvals of Medicines Containing a New Active Ingredient

For the period 16 January 2018 to 15 April 2018.

| Trade Name (active ingredient) | Dose Form and Strength | Therapeutic Area |
|---|---|---|
| Movantik (naloxegol oxalate) | Film coated tablet 12.5 mg and 25 mg | Opioid-induced constipation |
| Zurampic (lesinurad) | Film coated tablet 200 mg | Gout |

See the Medsafe website for data sheets of currently marketed medicines (**www.medsafe.govt.nz/Medicines/infoSearch.asp**).

# The Medsafe Files – Episode Six: Global Pharmacovigilance

### Key Messages

- New Zealand is a member of the World Health Organization Programme for International Drug Monitoring (PIDM).
- The PIDM was set up in 1968 following the thalidomide tragedy of the late 1950s to early 1960s to serve as an early warning system for possible harm caused by medicines.
- The PIDM is a global network of national pharmacovigilance centres that contribute anonymised case reports of suspected adverse drug reactions to a central database, called VigiBase.
- VigiBase is a valuable resource for investigating emerging safety signals.

### Introduction

Before a medicine is marketed, experience of its safety and efficacy is limited to use in clinical trials. Typically, these trials involve a few hundred to a few thousand carefully selected individuals.

Some adverse reactions occur only rarely and do not become apparent until the medicine has been used by a much larger and more diverse population. A single country such as New Zealand may not have sufficient use of a medicine to be able to detect rare adverse drug reactions or reactions that occur only in certain risk groups. By pooling adverse reaction reports from many countries in a single database, it is possible to identify emerging safety signals relatively quickly.

This information helps to build a more complete safety profile of the medicine, enabling healthcare professionals and consumers to make well-informed therapeutic choices.

### History of the WHO PIDM

Following the thalidomide disaster of the late 1950s to early 1960s, the World Health Organization (WHO) initiated a global monitoring system to detect early signs of possible harms caused by medicines after their release for general use[1].

A three-year pilot project was set up in 1968 to determine the feasibility of a global adverse drug reaction (ADR) reporting programme. After a successful pilot phase, the WHO formally established the WHO Programme for International Drug Monitoring (PIDM)[2,3].

In 1978, the Uppsala Monitoring Centre (UMC) was established in Sweden to maintain the international database of Individual Case Safety Reports (ICSRs) Vigibase on behalf of WHO.

Now in its 50th year, the WHO PIDM comprises 131 full member countries, with a further 26 countries registered as associate members. As at May 2018, VigiBase contains over 17 million ICSRs. More information on the WHO PIDM is available on the WHO website (**www.who-umc.org/**).

### How the WHO PIDM works

National pharmacovigilance centres from participating countries, including New Zealand's Centre for Adverse Reactions Monitoring (CARM), collect and assess reports of adverse drug reactions, and submit the anonymised reports to VigiBase.

National medicines regulatory authorities and/or pharmacovigilance centres of participating countries can use VigiBase to support their investigation of local medicine safety issues.

UMC periodically screens VigiBase for emerging signals. Signals are often detected earlier in Vigibase than smaller local databases. These signals are communicated to the national pharmacovigilance centres of participating countries for local review.

Signals identified in VigiBase are published in the *WHO Pharmaceutical Newsletter* (**www.who.int/medicines/publications/newsletter/en/**). This newsletter also contains information on safety issues and regulatory action taken by countries participating in the WHO PIDM.

VigiBase data is also publicly available (**www.vigiaccess.org/**).

### How does New Zealand benefit?

Membership of the WHO PIDM enables New Zealand to participate in a global pharmacovigilance network that facilitates information sharing about emerging medicine safety issues.

A key benefit is access to VigiBase, a valuable resource used by CARM and Medsafe for investigating medicine safety issues.

Membership enables New Zealand to contribute to the annual work programme and priority setting of the WHO PIDM and provides a platform for sharing new initiatives and learning from other countries' experiences.

New Zealand's participation in the WHO PIDM helps Medsafe to respond rapidly to emerging medicine safety issues, to ensure that the benefit-risk balance of medicines approved for use in New Zealand remains favourable.

### References


1. World Health Organization. 1963. *16th World Health Assembly, Part 1: Resolutions and Decisions*. Geneva: World Health Organization.
2. Venulet J, Helling-Borda M. 2010. WHO's international drug monitoring – the formative years, 1968–1975: Preparatory, pilot and early operational phases. *Drug Safety* 33(7): e1–e23.
3. Kunac DL, Harrison-Woolrych M, Tatley MV. 2008. Pharmacovigilance in New Zealand: the role of the New Zealand Pharmacovigilance Centre in facilitating safer medicines use. *New Zealand Medical Journal* 121(1283): 76–89.


## Correction: Adverse Reaction Reporting in New Zealand – 2017

The March 2018 edition of *Prescriber Update* included an article about adverse reaction reporting in New Zealand in 2017[1]. The numbers of adverse reaction reports included in the article were incorrect. The online article on the Medsafe website has been updated with the correct numbers.

In 2017, the Centre for Adverse Reactions Monitoring (CARM) received 3,815 suspected adverse reaction reports. This included 2,553 reports associated with medicines, 1,236 reports associated with vaccines and 26 reports associated with complementary or alternative medicines.

### References


1. Medsafe. 2018. Adverse Reaction Reporting in New Zealand – 2017. Prescriber Update 39(1): 4. URL: **www.medsafe.govt.nz/profs/PUArticles/March2018/adverse-reaction-reporting-2017.htm** (accessed 23 March 2018).

## Medicine Classification Update – November 2017

There were a number of medicine classification changes recommended at the 59th meeting of the Medicines Classification Committee (MCC), held on 7 November 2017.

The following substances were reclassified.

- **Hydrocortisone** 1% w/w is now a pharmacist-only medicine when combined with aciclovir 5% w/w in packs of not more than 2 g for dermal use in adults or children aged 12 years and older for the treatment of herpes labialis (cold sores).
- **Penciclovir** is now a general sale medicine but only in preparations containing 1% or less for the treatment of herpes labialis in packs containing 10 g or less.
- **Patent blue V** is now classified as a prescription medicine for injection when used in diagnostic procedures.

The MCC considered a proposal to amend the classification statement for **influenza vaccine** to include registered nurses. A valid objection was received following the meeting, and the proposal has been withdrawn.

The MCC made a recommendation to reclassify medicines containing codeine as the only active ingredient to a restricted medicine (with conditions) and to reclassify medicines containing codeine with other ingredients to prescription.

The current classification of codeine will remain unchanged until a notice is published in the New Zealand Gazette. All products containing codeine as the sole active ingredient will remain a prescription medicine and controlled drug until the gazette notice is published.

Any updates on the reclassification of codeine will be published on the Medsafe website (**www.medsafe.govt.nz/profs/class/ReclassificationOfCodeine.asp**).

See the Medsafe website for further information on the classification process and the minutes of MCC meetings (**www.medsafe.govt.nz/committees/mcc.asp**).

Check the classification of an ingredient using the classification database (**www.medsafe.govt.nz/profs/class/classintro.asp**).

### Quarterly Summary of Recent Safety Communications

The early warning system provides current and historical information on safety concerns for medicines and medical devices. These warnings are intended to help consumers and healthcare professionals make informed decisions about their use of medicines and medical devices.

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

| Date | Communication | Topic |
|---|---|---|
| 18 April 2018 | Alert Communication | Consumer Level Recall – Apo-Primidone 250 mg tablets |
| 30 April 2018 | Monitoring Communication | Beware turmeric/curcumin containing products can interact with warfarin |
| 9 May 2018 | Monitoring Communication | Life-threatening severe allergic reaction (anaphylaxis) to Calocurb dietary supplement |

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

## 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 (**http://nzphvc.otago.ac.nz/report/**).

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