

# Prescriber Update

Vol. 34 No.1

March 2013

[www.medsafe.govt.nz](http://www.medsafe.govt.nz)

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

## Contents

<b>Dabigatran</b> — New Contraindication	2
<b>Seasonal Influenza Vaccine</b> Reports in 2012	2
<b>Codeine</b> and Ultra-Rapid Metabolisers	3
<b>Tacrolimus</b> — Check the Brand	4
Adverse Reaction Reminder: <b>Tardive Dyskinesia</b>	4
Osteoporosis Treatments and Atypical Femoral Fracture	5
<b>Adverse Reaction Reporting</b> in New Zealand — 2012	6
Medicines, <b>Dry Mouth</b> and Tooth Decay	7
Generic Medicines and <b>Bioequivalence</b>	8
Complementary Corner: <b>Tea Tree Oil</b>	9
Urogynaecological <b>Surgical Mesh</b> Implants	10
MARC's Remarks: December 2012 Meeting	10
Children and Sedating <b>Antihistamines</b>	11
<b>M<sup>2</sup></b> MEDICINES MONITORING	11

## Dabigatran – New Contraindication

Pradaxa (dabigatran etexilate) is now contraindicated in patients with prosthetic heart valves.

The safety and efficacy of Pradaxa in patients with prosthetic heart valves were evaluated in the European RE-ALIGN trial<sup>1</sup>. This phase II study was terminated early as patients taking Pradaxa experienced significantly more thromboembolic events (valve thrombosis, stroke, and myocardial infarction) and major bleeding events than patients taking warfarin (Table 1). In this study, 160 patients were treated with Pradaxa (dose range: 150mg twice daily to 300mg twice daily) and 89 were treated with warfarin (dose adjusted to therapeutic effect).

To date, CARM have received five adverse reaction reports of dabigatran use in patients with prosthetic heart valves. Of the five reports, there were three thromboembolic events, one possible bleed and one unrelated event.

The New Zealand data sheet has been updated to include this new contraindication<sup>3</sup>. There have been no changes to the approved indications (that is, for use to prevent thrombosis after major orthopaedic surgery and for patients with non-valvular atrial fibrillation).

### References

1. Van de Werf F, Brueckmann M, Connolly SJ, et al. 2012. A comparison of dabigatran etexilate with warfarin in patients with mechanical heart valves: the randomized, phase II study to evaluate the safety and pharmacokinetics of oral dabigatran etexilate in patients after heart valve replacement (RE-ALIGN). *American Heart Journal* 163: 931–7 e1.
2. Food and Drug Administration. 2012. Pradaxa (dabigatran etexilate mesylate) should not be used in patients with mechanical prosthetic heart valves. *FDA Drug Safety Communication* 19 December 2012 (accessed 7 February 2013).
3. Boehringer Ingelheim (NZ) Limited. 2012. *Pradaxa data sheet* 21 December 2012. URL: [www.medsafe.govt.nz/profs/Datasheet/p/Pradaxacap.pdf](http://www.medsafe.govt.nz/profs/Datasheet/p/Pradaxacap.pdf) (accessed 14 February 2013).

**Table 1: Patients in the RE-ALIGN study with thromboembolic and/or bleeding events, as of 10 December 2012<sup>2</sup>**

	Pradaxa (n=160)	Warfarin (n=89)
Death	1 (0.6%)	2 (2.2%)
Stroke	8 (5.0%)	0 (0%)
Systemic embolism event (SEE)	0	0
Transient ischemic attack (TIA)	2 (1.3%)	2 (2.2%)
Valve thrombosis (VT)	4 (2.5%)	0
Myocardial infarction (MI)	3 (1.9%)	0
Composite of events: Death/stroke/SEE/TIA/VT/MI	16 (10.0%)	4 (4.5%)
Major bleeding	6 (3.8%)	1 (1.1%)
Major bleeding in pericardial location	5 (3.1%)	0
Any bleeding	36 (22.5%)	12 (13.5%)

## Seasonal Influenza Vaccine Reports in 2012

In 2012, the Centre for Adverse Reactions Monitoring (CARM) received 193 reports of patients with adverse events suspected to be related to seasonal influenza vaccination (Table 1). Some of the reports contained more than one suspected event.

The most commonly reported events were injection site inflammation (45 reports),

fever (24), arm pain (22), vomiting (20) and headache (20).

### Febrile convulsions

In 2012, CARM received three reports of children having convulsions or fever convulsions. In the United States, surveillance data found the risk of febrile seizures to be highest in children aged

**Table 1: Numbers of reports received by CARM and number of influenza vaccine doses distributed, 2007–2012**

	2007	2008	2009	2010	2011	2012
Reports of adverse events following influenza vaccination	122	122	138	409	207	193
Influenza vaccine doses distributed*	745,600	755,900	960,900	1,046,000	993,500	1,000,600
Estimated reporting rate per 100,000 doses	16.4	16.1	14.4	39.1	20.8	19.3

\* The number of doses distributed is not equal to number administered (eg, some doses may have been destroyed at the end of the influenza season and not used).

six months to four years. Febrile seizures usually occurred on the day of vaccination or the day after. The risk was further increased when the influenza vaccine was given together with the 13-valent pneumococcal vaccine<sup>1</sup>.

### Influenza vaccine for 2013

The influenza H3N2 and B vaccine virus strains in the 2013 influenza vaccine are different from those in the 2011–2012 vaccine. The H1N1 strain used in the next season's (2013) vaccine is the same virus that was included in the 2011–2012 vaccine.

In 2013, Fluvax and Fluarix are the funded vaccines. For eligible children under nine years of age, Fluarix continues to be the recommended influenza vaccine.

### References

- Centers for Disease Control and Prevention. 2012. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP)—United States, 2012–13 influenza season. *Morbidity and Mortality Weekly Report* 61(32): 613–8.

## Codeine and Ultra-Rapid Metabolisers

### Key Messages

- ⌘ Patients may respond differently to codeine and some patients may be at increased risk of serious adverse effects.
- ⌘ Symptoms of codeine toxicity or overdose may include somnolence, difficulty waking, confusion, shallow breathing, nausea and vomiting.
- ⌘ Treatment of codeine toxicity is most commonly with the opioid antagonist, naloxone.

Prescribers are reminded that patients may respond differently to codeine treatment and are encouraged to educate parents and caregivers of young patients about possible adverse effects associated with codeine use.

Codeine is a widely used opioid analgesic and is sometimes given post-operatively for pain relief

in children. Codeine has a very low affinity for opioid receptors and is partially metabolised to morphine in the liver via the cytochrome P450 enzyme 2D6 (CYP2D6).

Genetic differences in the expression of the CYP2D6 enzyme results in differences in the extent to which codeine is metabolised. Patients deficient in or lacking this enzyme cannot convert codeine to morphine and therefore may not obtain adequate analgesic pain relief. Conversely, patients who metabolise codeine very rapidly (ultra-rapid metabolisers) are at increased risk of developing adverse effects of opioid toxicity, even at low doses.

Estimates suggest that up to 10% of the Caucasian population may be poor metabolisers and up to 10% may be ultra-rapid metabolisers<sup>1</sup>. The prevalence in Māori and Pacific people is not known. Genetic testing to identify ultra-rapid metabolisers prior to prescribing codeine is not currently available in New Zealand.

Recently, cases of respiratory depression and death following the use of codeine for post-surgery analgesia have been reported in the medical literature<sup>2</sup>. These incidents occurred in children who had evidence of being ultra-rapid metabolisers of codeine. Post-operative codeine use after surgeries such as tonsillectomy or adenoidectomy may increase the risk of breathing difficulties in susceptible children.

Symptoms of codeine toxicity or overdose may include nausea, vomiting, constipation, lack of appetite, somnolence, extreme sleepiness, difficulty waking, confusion, shallow breathing

and coma. Caregivers and patients should be advised to immediately discontinue codeine and seek medical attention if these symptoms occur.

Effects can be reversed with naloxone, a narcotic antagonist. Naloxone acts by competing for the same receptor sites as opioids.

### References

1. de Leon J, Armstrong SC, Cozza KL. 2006. Clinical guidelines for psychiatrists for the use of pharmacogenetic testing for CYP450 2D6 and CYP450 2C19. *Psychosomatics* 47(1): 75–85.
2. Kelly LE, Rieder M, van den Anker J, et al. 2012. More codeine fatalities after tonsillectomy in North American children. *Pediatrics* 129(5): e1343–1347.

## Tacrolimus – Check the Brand

### Key Messages

- ⌘ To reduce the potential for error, tacrolimus should be prescribed with a full description of the drug and the brand.
- ⌘ If the brand, strength and dose frequency are not clearly stated on the prescription, the dispensing pharmacist should check with the prescriber to ensure the appropriate medicine is dispensed.
- ⌘ Switching between brands of tacrolimus requires careful therapeutic monitoring under the supervision of a transplant specialist.

With the introduction of generic versions of tacrolimus in New Zealand, healthcare professionals are reminded that different brands of this medicine are not readily interchangeable.

Tacrolimus is known to have a narrow therapeutic range, meaning small changes in plasma concentration can increase the risk of the patient experiencing a clinically significant event.

Although the two tacrolimus medicines available in New Zealand (Sandoz and Prograf) have been demonstrated to be bioequivalent, switching between brands should only be completed under specialist supervision. Therapeutic monitoring is recommended under specialist supervision to minimise the risk of adverse reactions or graft rejection.

Patients can play their part in reducing potential problems also. To prevent confusion, patients should take note of the name of their tacrolimus medicine and if unsure, check this with their doctor or pharmacist. If it is necessary to change the tacrolimus medicine a patient is taking, this should be fully discussed with the patient.

## Adverse Reaction Reminder: Tardive Dyskinesia

Tardive dyskinesia is a serious adverse effect, characterised by repetitive, involuntary, painless movements. Features of tardive dyskinesia typically appear after months or years of antipsychotic use. Importantly, this condition is often non-reversible and difficult to treat.

The lower face is primarily affected, with symptoms such as facial grimacing, repetitive chewing, tongue protrusion, and lip smacking<sup>1</sup>. Less commonly, muscles of the eyelids, neck, torso and extremities are affected.

Tardive dyskinesia has mainly been associated with antipsychotics. Other medicines also associated with tardive dyskinesia include antiemetics (eg, metoclopramide), antihistamines (eg, promethazine), and antidepressants (eg, selective serotonin reuptake inhibitors and tricyclic antidepressants).

The exact mechanism is not fully understood. However, tardive dyskinesia is generally believed to be a result of long-term blockade of dopamine D2 receptors in the nigrostriatal

pathway. This blockade results in increased sensitivity and an abundance of dopamine receptors, producing altered movements.

It has been estimated that 15–30% of people on long-term antipsychotics may be affected by tardive dyskinesia<sup>1</sup>. The incidence is much higher with the use of first generation ('typical') antipsychotics, than second generation ('atypical') antipsychotics. However, the use of atypical antipsychotics does not exclude the possibility of developing tardive dyskinesia.

Severity of tardive dyskinesia ranges from isolated dyskinesias that are not noticed by the patient, through to disabling effects which interfere with day-to-day activities such as walking and talking.

Diagnosis follows physical and neuropsychiatric evaluation, while other movement disorders must be excluded. Reducing the dose or withdrawing the causative agent where possible may be beneficial. Alternatively, switching to another medicine with a lower risk of tardive dyskinesia could be considered.

Other risk factors for the development of tardive dyskinesia include increasing age, a history of alcohol or substance abuse, developmental

disabilities, and extra-pyramidal symptoms at initiation of therapy. The risk is also higher in post-menopausal women.

In New Zealand, 17 cases of tardive dyskinesia were reported to the Centre for Adverse Reactions Monitoring (CARM) between January 2000 and December 2012. The majority of cases were associated with risperidone (8 reports). A total of 13 cases were associated with the use of an atypical antipsychotic, either alone or in combination with another medicine known to be associated with the development of tardive dyskinesia.

The increased reporting of tardive dyskinesia with atypical antipsychotics over typical antipsychotics is likely due to the increased use of atypical antipsychotics and the increased awareness of this possible adverse effect.

Healthcare professionals are encouraged to report these reactions to CARM and to include as much information as possible to help identify other medications or risk factors that may be associated with this serious adverse effect.

## References

1. Brasic JR. 2012. Tardive Dyskinesia. *Medscape*. URL: <http://emedicine.medscape.com/article/1151826-overview#showall> (accessed 5 February 2013).

## Osteoporosis Treatments and Atypical Femoral Fracture

### Key Messages

- ⌘ Atypical subtrochanteric and diaphyseal fractures have been associated with long-term bisphosphonate treatment.
- ⌘ Atypical subtrochanteric and diaphyseal fractures have also been associated with denosumab treatment.
- ⌘ These fractures are rare and the benefits of bisphosphonate treatment clearly outweigh the risk.
- ⌘ Interruption of bisphosphonate therapy may be necessary in patients with atypical femoral fractures.

In November 2009, Medsafe highlighted an association between alendronate and low-energy femoral shaft fracture<sup>1</sup>.

Since then, similar cases have been published involving other bisphosphonates as well as denosumab (Prolia). Denosumab is a new

treatment for osteoporosis that is approved but not currently available in New Zealand. Information on this risk is included in the data sheets for Fosamax (alendronate), Zometa (zoledronate) and Pamisol (pamidronate).

To date, there has been no confirmed association between strontium, teriparatide, raloxifene or hormone replacement therapy and atypical fractures of the femur.

Features associated with subtrochanteric and diaphyseal fractures include<sup>2</sup>:

- minimal to no trauma
- transverse fracture line on radiography
- prodromal pain
- unilateral cortical beaking and bilateral thickened diaphyseal cortices on radiography
- poor fracture healing.

The Centre for Adverse Reactions Monitoring (CARM) has received two reports of fractures describing some of the features outlined

above. In both cases, the patient was taking alendronate.

Atypical subtrochanteric fractures are rare, less than 0.1% of total fractures in a New Zealand study<sup>3</sup>. For a population of 10,000 patients at high risk of fracture, bisphosphonate treatment might be expected to prevent 108 hip fractures (and around 750 other fractures) per year and result in three subtrochanteric fractures<sup>2</sup>. Therefore, the benefit risk ratio for bisphosphonate treatment remains favourable.

In patients with atypical femoral fractures, bisphosphonate treatment should be considered as a possible cause. Interruption of bisphosphonate therapy may be necessary

for fracture healing. Re-treatment should be considered if bone density again begins to fall and after a discussion of the benefits and risks with the patient.

## References

1. Medsafe. 2009. Alendronate — risk of low-energy femoral shaft fracture. *Prescriber Update* 30(4): 25.
2. Rizzoli R, Akesson K, Bouxsein M, et al. 2011. Subtrochanteric fractures after long-term treatment with bisphosphonates: a European Society on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis, and International Osteoporosis Foundation Working Group Report. *Osteoporosis International* 22(2): 373–390.
3. Warren C, Gilchrist N, Coates M, et al. 2012. Atypical subtrochanteric fractures, bisphosphonates, blinded radiological review. *ANZ Journal of Surgery* 82: 908–912.

---

## Adverse Reaction Reporting in New Zealand — 2012

Reporting of adverse reactions provides valuable information about the use of medicines in clinical practice and is an important contribution to pharmacovigilance in New Zealand.

Before a medicine is approved in New Zealand, safety and efficacy experience is usually limited to its use in clinical trials. However, clinical trials do not always reflect the actual use of a medicine or vaccine in real life. In addition, some important reactions are rare and may not be observed until a large number of people have received the medicine or have taken the medicine for a long period. Therefore, it is very important to monitor all the medicines after they have been approved.

In New Zealand, the monitoring of adverse reactions through spontaneous reporting is coordinated by Medsafe and the Centre for Adverse Reactions Monitoring (CARM). CARM is contracted by Medsafe to collect and analyse adverse reactions reports submitted in New Zealand. This information is then provided to Medsafe and the two organisations work together to identify possible safety issues with medicines. If after further investigation, the safety issue is confirmed, Medsafe takes appropriate action to ensure the safety of these medicines is improved.

If further information on potential safety issues is required, the medicine and potential safety issue can be placed on Medsafe's **M** scheme. The aim of **M** is to highlight potential safety concerns identified to health care professionals

to stimulate further reporting. Information about medicines currently on **M** and the outcome of monitoring can be found on the Medsafe website [www.medsafe.govt.nz/profs/M2MedicinesMonitoring.asp](http://www.medsafe.govt.nz/profs/M2MedicinesMonitoring.asp)

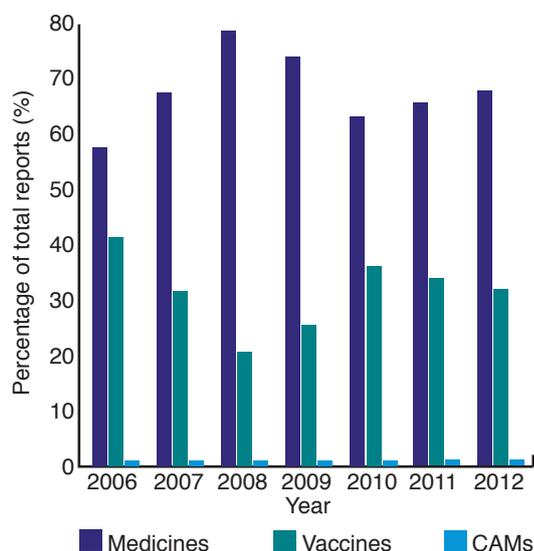
### Adverse Reaction Reports in 2012

In 2012, CARM received a total of 4253 *suspected* adverse reaction reports. The number of reports submitted in New Zealand has remained consistent since 2008.

Adverse reaction reports to medicines made up the majority of the reports received by CARM (67.8%) (Figure 1). The remainder of the suspected adverse reaction reports were associated with vaccines (31.8%) and complementary therapies (CAMs) (0.3%).

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

Of the medicine and CAM reports received, approximately one third were considered serious. In comparison, only 4.3% of the vaccines reports were considered serious. A serious adverse reaction is determined by CARM according to internationally agreed criteria (ie, resulting in hospitalisation, is life-threatening, fatal, results in a disability or requires intervention to prevent permanent disability, or results in a congenital abnormality).



**Figure 1: Types of adverse reaction reports received by CARM from 2006 to 2012**

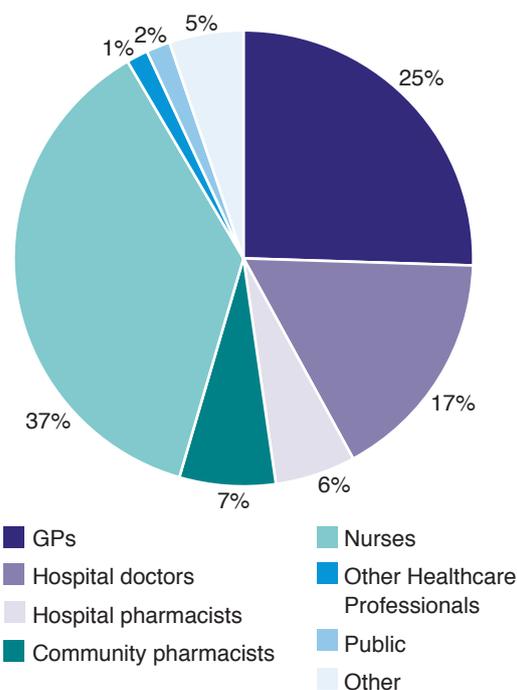
### Source of Reports

In 2012, nurses continued to submit the most adverse reaction reports by healthcare professionals, followed by GPs and hospital doctors (Figure 2).

### How to Report

Healthcare professionals (and consumers) are encouraged to report any suspected adverse reaction to a medicine, vaccine or CAM to CARM.

Information about how to submit an adverse reaction report can be found on the Medsafe website [www.medsafe.govt.nz/profs/adverse.asp](http://www.medsafe.govt.nz/profs/adverse.asp) or on the CARM website <https://nzphvc-01.otago.ac.nz/carm-adr/reporting.php>



**Figure 2: Source of adverse reaction reports from healthcare professionals in New Zealand in 2012**

Suspected adverse reactions to medicines, vaccines and CAMs can be reported by:

- completing a yellow card sent via freepost to CARM
- downloading a form from either the CARM or Medsafe websites
- completing an online report available from either the CARM or Medsafe websites
- electronic reporting through GP software
- iPhone app.

Medsafe and CARM would like to thank all those who have submitted suspected adverse reaction reports and contributed to pharmacovigilance in New Zealand.

## Medicines, Dry Mouth and Tooth Decay

### Key messages

- ⌘ Many different medicines can cause a dry mouth.
- ⌘ Simple techniques can be advised to minimise the discomfort of a dry mouth.
- ⌘ Patients should be advised of the risk of tooth decay and how to prevent this occurring.

Dry mouth (or xerostomia) is a known side effect of many different types of medicines, particularly those with antimuscarinic (anticholinergic) properties.

Healthcare professionals are encouraged to check known adverse effects in medicines data sheets or in the New Zealand Formulary (NZF) as numerous medicines have been associated with dry mouth. Medicine data sheets are available on the Medsafe website [www.medsafe.govt.nz/profs/Datasheet/dsform.asp](http://www.medsafe.govt.nz/profs/Datasheet/dsform.asp)

A persistently dry mouth increases the risk of tooth decay, gum disease, oral infections and ulceration (particularly among denture wearers). Therefore, maintenance of good oral hygiene is very important.

Dry mouth can also cause a sticky feeling in the mouth, bad breath, mouth or throat pain, cracked lips, dry tongue, burning sensation in the mouth, angular stomatitis, and difficulties with tasting, chewing, swallowing and speaking.

Since 2000, the Centre for Adverse Reactions Monitoring (CARM) has received 227 reports of dry mouth involving 236 suspected medicines. In seven cases, associated effects of a dry mouth such as tongue or lip ulceration or toothache were reported. Of the 227 reports of dry mouth, approximately 75% were in female patients.

**Table 1: Top 10 medicines associated with dry mouth as reported to CARM**

Medicine	Number of reports
Levothyroxine	29
Omeprazole	21
Bupropion	10
Influenza vaccine	9
Paroxetine	9
Simvastatin	7
Amitriptyline	6
Venlafaxine	6
Sibutramine	5
Varenicline	5

Levothyroxine and omeprazole were the medicines most commonly reported to CARM associated with dry mouth (Table 1).

### Management of dry mouth

If the causative medicine(s) cannot be stopped, patients should be advised to<sup>1,2</sup>:

- take frequent sips of water (or sugarless drinks) particularly with meals to assist with chewing, swallowing and tasting
- chew sugar-free chewing gum or suck on sugar-free lollies
- avoid caffeinated drinks, alcohol or tobacco
- use a humidifier at night
- be aware that spicy or salty foods may cause pain
- consider the use of saliva substitutes
- consider the use of a salt and bicarbonate mouth rinse<sup>2</sup>.

Healthcare professionals should remind patients to maintain excellent oral hygiene including the use of a soft toothbrush with fluoride toothpaste, flossing their teeth every day and having regular dental check-ups.

### References

1. Food and Drug Administration. 2011. Dry Mouth? Don't delay treatment. *Consumer Updates*. URL: [www.fda.gov/ForConsumers/ConsumerUpdates/ucm254273.htm](http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm254273.htm) (accessed 12 February 2013).
2. New Zealand Dental Association. 2010. *Healthy Mouth, Healthy Ageing: Oral Health Guide for Caregivers of Older People*. Auckland: New Zealand Dental Association. URL: [www.health.govt.nz/publication/healthy-mouth-healthy-ageing](http://www.health.govt.nz/publication/healthy-mouth-healthy-ageing) (accessed 19 February 2013).

## Generic Medicines and Bioequivalence

A generic medicine contains the same active ingredient (including different salts), in the same quantity as an innovator medicine (original brand). Generic medicines enable wider access to beneficial medicines.

Generic medicines can only enter the market following the expiration of the patent for the innovator medicine. They are manufactured to the same international quality standards and Good Manufacturing Practice requirements as those required for innovators.

As clinical trial data on the safety and efficacy of the active ingredient is already available from the innovator, these expensive, lengthy studies are not required for a generic. Instead, bioequivalence studies, performed to strict internationally agreed standards, are accepted by Medsafe and regulatory authorities worldwide<sup>1</sup>.

Bioequivalence is the absence of a significant difference in the rate and extent of absorption of the active ingredient that reaches the systemic circulation (bioavailability). If products have

equivalent bioavailability, it is considered they will have the same clinical effects. This is based on the premise that the concentration of the active ingredient in plasma is directly related to its clinical effect.

Bioequivalence studies follow well-defined procedures and are performed:

- in healthy volunteers
- in a randomised, cross-over design
- where all subjects receive both test medicines separated by a washout period (inter-subject variability is eliminated)
- to measure the rate and extent of absorption of the active ingredient in plasma
- to compare the plasma concentration time curves.

The two pharmacokinetic parameters used to determine bioequivalence are:

1. the maximum plasma concentration ( $C_{max}$ )
2. the area under the plasma concentration time curve (AUC), which represents the extent of systemic exposure.

The products are considered bioequivalent if the 90% confidence intervals for the ratio (generic/innovator) of the means of  $C_{max}$  and AUC are within the range 0.80–1.25<sup>1</sup>. The 0.80–1.25 acceptance range accounts for statistical error and is internationally considered to be clinically insignificant<sup>2,3</sup>.

The actual difference in exposure to the active ingredient between generics and innovators is typically less than 5%. A compilation of the results from 2070 bioequivalence studies assessed by the US Food and Drug Administration during 1996–2007 showed the mean difference between generic and innovator products was 3.56% for AUC and 4.35% for  $C_{max}$ <sup>4</sup>.

A tighter bioequivalence acceptance range of 0.90–1.11 is applied for medicines with a narrow therapeutic range (eg, tacrolimus) due to the smaller difference between therapeutic and

toxic plasma concentrations<sup>5</sup>. However, it is still advisable to closely monitor patients when switching between brands.

Some medicines, although they may have shown bioequivalence, cannot be freely changed due to the nature of the active ingredient (eg, levothyroxine due to its incomplete and variable absorption). For others, a bioequivalence study is not suitable because the oral bioavailability of the drug is not directly related to its clinical effect (eg, warfarin). Medsafe require the datasheets for such products to contain a warning that they cannot be freely changed. In these cases, extra clinical consideration is required on an individual patient basis.

For the majority of patients, changing between bioequivalent medicines should not be an issue. However, it is possible for patients to experience higher or lower exposure to an active ingredient following a change due to inter-patient variability. In this case, the patient may need to have the dose of the medicine reassessed.

## References

1. European Medicines Agency. 2010. *Guideline on the Investigation of Bioequivalence*. Doc Ref: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr \*\*. URL: [www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2010/01/WC500070039.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf)
2. Food and Drug Administration. 2001. *Guidance for Industry: Statistical Approaches to Establishing Bioequivalence*. URL: [www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070244.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070244.pdf)
3. BPAC. 2009. What is bioavailability and bioequivalence? *Best Practice Journal: Special Edition Generics* 4–8. URL: [www.bpac.org.nz/magazine/2009/generics/docs/bpjse\\_generics\\_2009.pdf](http://www.bpac.org.nz/magazine/2009/generics/docs/bpjse_generics_2009.pdf)
4. Davit BM, Nwakama PE, Buehler GJ, et al. 2009. Comparing generic and innovator drugs: a review of 12 years of bioequivalence data from the United States Food and Drug Administration. *Annals of Pharmacotherapy* 43(10): 1583–1597.
5. European Medicines Agency. 2012. *Questions and Answers: Positions on specific questions addressed to the pharmacokinetics working party*. Doc Ref: EMA/618604/2008 Rev. 6. URL: [www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500002963.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002963.pdf)

## Complementary Corner: Tea Tree Oil

Medsafe has recently been advised of a young patient who suffered a severe systemic reaction to 15% tea tree oil applied topically to a cut.

A search of Australia and New Zealand's joint adverse event notification system database

(JAENS) identified eight reports of adverse events associated with the use of tea tree oil since 2000. These reactions included application site reaction, pain and burn, as well as dermatitis, pruritus, urticaria, blister, and oedema.

Tea tree oil is extracted from the leaves of the *Melaleuca alternifolia* and is marketed as a natural topical antimicrobial and anti-inflammatory to treat a wide range of conditions<sup>1</sup>. The preparations vary from very dilute to 100%<sup>1</sup>.

The first case report of a systemic hypersensitivity reaction to topical application of tea tree oil was published in 2003<sup>2</sup>. The patient experienced anaphylaxis after applying tea tree oil to psoriatic lesions on his legs, resulting in admission to hospital<sup>2</sup>.

Oxidation of the oil upon exposure to light, moisture, heat and air increases the sensitisation potential of tea tree oil<sup>1</sup>. Therefore, a bottle which has been opened intermittently over a

prolonged period would be more likely to cause skin reactions than a new bottle.

Healthcare professionals should be aware that adverse reactions to tea tree oil can occur and advise patients of this potential risk if recommending tea tree oil products.

### References

1. Rutherford T, Nixon R, Tam M, et al. 2007. Allergy to tea tree oil: retrospective review of 41 cases with positive patch tests over 4.5 years. *Australasian Journal of Dermatology* 48(2): 83–87.
2. Mozelsio NB, Harris KE, McGrath KG, et al. 2003. Immediate systemic hypersensitivity reaction associated with topical application of Australian tea tree oil. *Allergy and Asthma Proceedings* 24(1): 73–5.

---

## Urogynaecological Surgical Mesh Implants

Medsafe recommends that healthcare professionals who are implanting or following patients with urogynaecological surgical mesh implants should familiarise themselves with the Royal Australia and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) advice.

Information regarding urogynaecological surgical mesh, including RANZCOG advice, is available on Medsafe's website [www.medsafe.govt.nz/Consumers/devices/UrogynaecologicalSurgicalMeshImplants.asp](http://www.medsafe.govt.nz/Consumers/devices/UrogynaecologicalSurgicalMeshImplants.asp)

Links to information from various regulators and professional bodies are also published on Medsafe's website. These regulators include the Australian Therapeutic Goods Administration (TGA), Health Canada, US Food and Drug Administration (FDA) and the UK Medicines

and Healthcare products Regulatory Agency (MHRA).

In 2008, Medsafe investigated a number of adverse event reports relating to urogynaecological surgical mesh. Medsafe concluded that surgical mesh is safe when used in accordance with the manufacturers' instructions by an appropriately trained surgeon. This finding was supported by an independent panel of healthcare professionals and is consistent with that of other medical device regulators and professional bodies. Medsafe continues to monitor adverse event reports relating to surgical mesh.

Healthcare professionals and patients who wish to lodge an adverse event report with Medsafe relating to any medical device, including surgical mesh implants, should use the reporting form available for download from the Medsafe website [www.medsafe.govt.nz/downloads/device.doc](http://www.medsafe.govt.nz/downloads/device.doc)

---

## MARC's Remarks: December 2012 Meeting

The Medicines Adverse Reactions Committee (MARC) held their 152<sup>nd</sup> meeting on 6 December 2012.

The MARC reviewed the current use of **codeine** in children in New Zealand. The MARC noted that the use of codeine in children in New Zealand is relatively low. However, as up to 10% of the population may be ultra-rapid metabolisers, the MARC agreed that this information be highlighted to healthcare professionals<sup>1</sup>.

The MARC also reviewed the potential safety signal of the use of **proton pump inhibitors** (PPIs) and an increased risk of pneumonia. The MARC agreed that the available data was insufficient to confirm a causal effect but the issue should continue to be monitored by Medsafe.

### References

1. Medsafe. 2013. Codeine, ultra-rapid metabolisers and post-surgery pain relief in children. *Prescriber Update* 34(1): 3–4.

## Children and Sedating Antihistamines

### Key Messages

- ⌘ Sedating antihistamines are contraindicated in children less than two years of age for all indications.
- ⌘ Sedating antihistamines are contraindicated in children less than six years of age for cough and cold symptoms.
- ⌘ Adverse effects of sedating antihistamines include sedation, dizziness and incoordination, and in overdose can cause respiratory depression, coma and death.
- ⌘ Children with coughs and colds should be given plenty of fluids and rest.

Prescribers are reminded that 'first generation' or 'sedating' antihistamines are contraindicated for use:

- in children aged less than two years of age for all indications
- in children aged less than six years of age for coughs and colds.

The Cough and Cold Review Group in conjunction with Medsafe has previously found no evidence to support the use of sedating antihistamines in treating the symptoms of the common cold in children<sup>1</sup>.

This reminder follows a report received by the Centre for Adverse Reactions Monitoring (CARM) concerning a three-year-old child who was given chlorphenamine for a lower respiratory tract infection and experienced a serious neurological disorder. Fortunately, the child eventually recovered without any ongoing ill-effects.

Sedating antihistamines have the ability to cross the blood-brain barrier, to bind to non-histamine receptors and have less selectivity for peripheral or central H1-receptors<sup>2</sup>. Therefore, sedating antihistamines tend to cause more adverse reactions than 'second generation' or 'non-sedating' antihistamines<sup>2</sup>.

The most common adverse effects with sedating antihistamines are sedation, dizziness and incoordination. However, paradoxical stimulation ranging from excitation through to

### 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
Ibuprofen	Hypokalaemia/Renal tubular acidosis	31 March 2013
Ondansetron	Serotonin Syndrome (Toxicity)	30 June 2013

- **M<sup>2</sup>** 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 **M<sup>2</sup>** scheme does not replace routine adverse reaction reporting. Find out how to report at: [www.otago.ac.nz/carm](http://www.otago.ac.nz/carm) or [www.medsafe.govt.nz](http://www.medsafe.govt.nz)



New Zealand Government

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

tremors, hallucinations and convulsions may occur. Excessive doses in children have led to respiratory depression, coma and death<sup>3,4</sup>.

With winter approaching, it is important to note that coughs and colds are often self-limiting conditions and may not require pharmacological intervention<sup>5</sup>. Symptomatic measures, such as increasing fluids, making sure children get enough rest and reducing the spread of the virus (including regular hand washing) should be practiced. For children requiring antihistamines for allergies, a non-sedating antihistamine such as loratadine or cetirizine is preferred.

## References

1. Medsafe. 2009. *Use of cough and cold medicines in children – New Advice*. URL: [www.medsafe.govt.nz/hot/alerts/coughandcold/infooct2009.asp](http://www.medsafe.govt.nz/hot/alerts/coughandcold/infooct2009.asp) (accessed 5 February 2013).
2. Ten Eick AP, Blumer JL, Reed MD. 2001. Safety of antihistamines in children. *Drug Safety* 24(2): 119–47.
3. Sanofi-Aventis NZ Limited. 2009. *Promethazine Winthrop data sheet* 31 January 2013. URL: [www.medsafe.govt.nz/profs/Datasheet/p/PromethazineWinthropElixir.pdf](http://www.medsafe.govt.nz/profs/Datasheet/p/PromethazineWinthropElixir.pdf) (accessed 31 January 2013).
4. Douglas Pharmaceuticals Ltd. 2009. *Histafen data sheet*. 8 September 2009. URL: [www.medsafe.govt.nz/profs/Datasheet/h/Histafenelixir.pdf](http://www.medsafe.govt.nz/profs/Datasheet/h/Histafenelixir.pdf) (accessed 31 January 2013).
5. BPAC. 2010. Do cough & cold preparations work in children? *Best Practice Journal* 29: 32–39.

### Medsafe

New Zealand Medicines and Medical Devices Safety Authority  
A business unit of the Ministry of Health

### Editor

Dr Amanda Taylor, PhD  
Medsafe, PO Box 5013,  
Wellington 6145, New Zealand  
Ph: (04) 819 6800, Fax: (04) 819 680  
Email: [Amanda\\_Taylor@moh.govt.nz](mailto:Amanda_Taylor@moh.govt.nz)

### Editorial Team

Chris James, Clinical Risk Manager  
Frances Greer, Senior Advisor Science  
Jan Carey, Advisor Science  
Dr Martin Bonne, Medical Advisor  
Dr Richard Jaine, Senior Medical Advisor  
Robert Jelas, Senior Advisor Medical Devices  
Rowan Pollock, Advisor Pharmacovigilance  
Dr Sharon Sime, Senior Medical Advisor  
Dr Susan Kenyon PhD, Principal Technical Specialist

### Principal Clinical Advisor

Dr Enver Yousuf

### Group Manager

Dr Stewart Jessamine

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

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

An electronic version of *Prescriber Update* is available at [www.medsafe.govt.nz/profs/PUarticles.asp](http://www.medsafe.govt.nz/profs/PUarticles.asp)

To receive *Prescriber Update* electronically, please register at [www.medsafe.govt.nz/profs/profs.asp](http://www.medsafe.govt.nz/profs/profs.asp)

Data sheets, consumer medicine information, media releases, medicine classification issues and adverse reaction forms can be found at [www.medsafe.govt.nz](http://www.medsafe.govt.nz)

Published with the permission of the Director-General of Health

The copyright owner of this publication is the Ministry of Health, which is part of the New Zealand Crown. Information about copyright requirements available at [www.moh.govt.nz/copyright](http://www.moh.govt.nz/copyright)

Prescriber Update is a  
member of the



New Zealand Government