

# Prescriber Update

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## The Medsafe Files – Episode One: What is Medsafe?

### Key Messages

- ⌘ Medsafe is the medicines and medical devices regulator for New Zealand.
- ⌘ Our role is to administer the New Zealand legislation to help industry and healthcare professionals comply with the law.
- ⌘ The pre-marketing approval process of medicines and the post-marketing surveillance of medicines and medical devices are activities we undertake to manage the risks associated with the use of medicines and medical devices.
- ⌘ Ultimately, the aim is to maintain a favourable balance between the benefits and risks of harm of using a therapeutic product in the intended treatment population.

Responses to consultations and enquiries to Medsafe demonstrate that our role is not always fully understood. Additionally, new legislation is on the way and it is important for you to understand our role so you can contribute to consultation. Welcome to our new series of articles ‘The Medsafe Files’.

Medicines legislation is in place to manage the risks of avoidable harm associated with the use of therapeutic products. Medsafe is the New Zealand Medicines and Medical Devices Safety Authority and, with some exceptions such as pharmacy licensing, is responsible for administering the Medicines Act 1981 and Medicines Regulations 1984.

The role of Medsafe as the regulator is to administer the New Zealand legislation to help industry and healthcare professionals comply with the law. The aim is to maintain a favourable balance between the benefits and risks of harm of using a therapeutic product in the intended treatment population. We undertake activities such as the pre-marketing approval process of medicines and post-marketing surveillance of

medicines and medical devices to manage the risks associated with the use of medicines and medical devices.

Medsafe regulates products that are used for a therapeutic purpose including medicines, related products, medical devices and controlled drugs used as medicines. Definitions for these product types are on the Medsafe website ([www.medsafe.govt.nz/other/about.asp#do](http://www.medsafe.govt.nz/other/about.asp#do)).

Medsafe is accountable to the Ministry of Health and, through the Ministry, to the Minister of Health. Medsafe is largely funded by fees collected from the therapeutics industry. Medsafe is small by international standards, with 56 full-time staff based in both Auckland and Wellington. In comparison, the Therapeutic Goods Administration, the equivalent organisation in Australia, employs around 750 staff.

Medsafe is not involved in funding medicines; this is the responsibility of PHARMAC ([www.pharmac.govt.nz/](http://www.pharmac.govt.nz/)). Medsafe does not regulate healthcare professional practice and Medsafe cannot provide medical advice about an individual’s medical condition. We encourage consumers to talk to their healthcare professional if they have concerns about a medicine they are taking.

Upcoming episodes of The Medsafe Files include the following:

- clinical trials
- pre-market approval
- devices
- pharmacovigilance
- border control
- good manufacturing practice
- classification.

See [www.medsafe.govt.nz/other/about.asp](http://www.medsafe.govt.nz/other/about.asp) for more information about Medsafe.

The Medicines Act 1981 and the Medicines Regulations 1984 is at [www.legislation.govt.nz](http://www.legislation.govt.nz)

## Switching Antidepressants – Careful Management Required

The Centre for Adverse Reactions Monitoring (CARM) recently received a report of a patient who experienced severe withdrawal symptoms within 72 hours of stopping paroxetine<sup>1</sup>. These symptoms, which included dizziness, vertigo, confusion, paraesthesia and excessive dreaming, affected their ability to drive and attend work. The patient had been advised to stop taking paroxetine five days prior to commencing a new antidepressant.

Healthcare professionals are reminded that careful management is required when switching antidepressants to reduce the risk of serotonin syndrome, hypertensive crisis or withdrawal syndrome<sup>2</sup>.

When managing a switch, refer to the New Zealand Formulary table on switching

antidepressants ([http://nzf.org.nz/nzf/resource/Antidepressant\\_Switching\\_Table.pdf](http://nzf.org.nz/nzf/resource/Antidepressant_Switching_Table.pdf)). The table provides general guidance on how to safely and effectively switch between antidepressants<sup>2</sup>. Further information regarding switching antidepressants can be found in individual medicine data sheets, available on the Medsafe website ([www.medsafe.govt.nz/profs/datasheet/DSForm.asp](http://www.medsafe.govt.nz/profs/datasheet/DSForm.asp)).

Please continue to report any adverse reactions to CARM. Reports can be submitted on paper or electronically (<https://nzphvc.otago.ac.nz/>).

### References

1. CARM case ID 119445. URL: [www.medsafe.govt.nz/Projects/B1/adrsearch.asp](http://www.medsafe.govt.nz/Projects/B1/adrsearch.asp)
2. New Zealand Formulary. 2016. Antidepressant drugs. NZF v45. URL: [www.nzf.org.nz/nzf\\_2225](http://www.nzf.org.nz/nzf_2225) (accessed 23 February 2016).

### 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 can be found on the Medsafe website ([www.medsafe.govt.nz/Projects/B2/EWS.asp](http://www.medsafe.govt.nz/Projects/B2/EWS.asp)).

Consumer information leaflets provide information about medicines and medical devices or medical conditions to consumers.

Date	Communication	Topic
6 July 2016	Consumer Information	Can I take St John's wort with other medicines?
21 June 2016	Media Release	Medsafe Warns of the Dangers of Purchasing Medicines Over the Internet
30 May 2016	Consumer Information	The Pros and Cons of Taking Statins
26 May 2016	Monitoring	<sup>M</sup> Rivaroxaban, dabigatran and apixaban and possible risk of hair loss (alopecia) added to the Medicines Monitoring scheme
26 May 2016	Monitoring	Apex e-chamber spacer device - user issues with valve and round mouthpiece

If you would like to receive Medsafe's early warning communications you can subscribe at [www.medsafe.govt.nz/profs/subscribe.asp](http://www.medsafe.govt.nz/profs/subscribe.asp)



## Reminder: Hyperkalaemia caused by Spironolactone and Renin-angiotensin System Medicine Interactions

### Key Messages

- ⌘ The risk of severe hyperkalaemia needs to be considered with the concomitant use of spironolactone and angiotensin-converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs), particularly in patients with renal impairment.
- ⌘ Use the lowest effective doses of spironolactone and ACEis or ARBs if co-administration is required.
- ⌘ Potassium levels and renal function should be regularly monitored.
- ⌘ Treatment should be discontinued or temporarily withheld if hyperkalaemia occurs.

The United Kingdom's medicines regulator (Medicines and Healthcare products Regulatory Agency or MHRA) has recently noted an increase in reports of hyperkalaemia due to the use of spironolactone with angiotensin-converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs)<sup>1</sup>.

In New Zealand, the Centre for Adverse Reactions Monitoring (CARM) has received five cases of hyperkalaemia when an ACEi or an ARB was co-administered with spironolactone in the last 12 years.

Spironolactone is a potassium-sparing diuretic indicated for a number of conditions including essential hypertension and congestive heart

failure<sup>2,3</sup>. ACEis and ARBs can also reduce the loss of potassium via the kidneys and are often used in the management of patients with heart disease and hypertension<sup>3</sup>.

The risk of severe hyperkalaemia needs to be considered with the concomitant use of spironolactone and ACEis or ARBs, particularly in patients with renal impairment. Use the lowest effective doses of spironolactone and ACEis or ARBs if co-administration is required<sup>1</sup>.

Serum potassium levels and renal function should be monitored regularly after initiation of spironolactone, an ACEi or an ARB, and again when increasing the dose<sup>2,3</sup>. Treatment with spironolactone should be discontinued or temporarily withheld in hyperkalaemic patients<sup>2</sup>.

Further information on medicines known to increase serum potassium levels can be found in a previous edition of *Prescriber Update* ([www.medsafe.govt.nz/profs/PUArticles/Sep2015/Medicines&Hyperkalaemia.htm](http://www.medsafe.govt.nz/profs/PUArticles/Sep2015/Medicines&Hyperkalaemia.htm)).

### References

1. Medicines and Healthcare products Regulatory Agency. 2016. *Spironolactone and renin-angiotensin system drugs in heart failure: risk of potentially fatal hyperkalaemia*. 17 February 2016. URL: [www.gov.uk/drug-safety-update/spironolactone-and-renin-angiotensin-system-drugs-in-heart-failure-risk-of-potentially-fatal-hyperkalaemia](http://www.gov.uk/drug-safety-update/spironolactone-and-renin-angiotensin-system-drugs-in-heart-failure-risk-of-potentially-fatal-hyperkalaemia) (accessed 17 June 2016).
2. Mylan New Zealand Limited. 2013. *Spiractin Data Sheet* 26 November 2013. URL: [www.medsafe.govt.nz/profs/datasheet/s/Spirotonetab.pdf](http://www.medsafe.govt.nz/profs/datasheet/s/Spirotonetab.pdf) (accessed 16 June 2016).
3. Best Practice Advocacy Centre. 2013. *Managing patients with heart failure in primary care*. February 2013. URL: [www.bpac.org.nz/BPJ/2013/february/managing-heart-failure.aspx](http://www.bpac.org.nz/BPJ/2013/february/managing-heart-failure.aspx) (accessed 16 June 2016).

## Can I Take St John's Wort with Other Medicines?

Medsafe recently published an information leaflet to help consumers understand whether they can take other medicines with St John's wort.

The leaflet provides information about St John's wort including:

- how St John's wort affects medicines

- which medicines can be affected
- what to look out for if taking St John's wort.

The leaflet is available on the Medsafe website ([www.medsafe.govt.nz/Consumers/educational-material/St%20John's%20Wort%20July%202016.pdf](http://www.medsafe.govt.nz/Consumers/educational-material/St%20John's%20Wort%20July%202016.pdf)).

## Drug-induced Gynaecomastia

### Key Messages

- ⌘ Medicines cause 10% to 25% of all cases of gynaecomastia.
- ⌘ Consider the possibility of a medicine-related cause in male patients who develop gynaecomastia, even if the medicine has been taken for some time.
- ⌘ Gynaecomastia may persist after the causal medicine has been discontinued.

A recent report to the Centre for Adverse Reactions Monitoring (CARM) described a male patient who developed bilateral gynaecomastia after taking omeprazole (20 mg twice a day) for 10 years<sup>1</sup>.

Gynaecomastia is a benign proliferation of male breast glandular tissue caused by an imbalance between the actions of oestrogens relative to the actions of androgens on breast tissue<sup>2-6</sup>.

Medicines have been estimated to cause 10% to 25% of all cases of gynaecomastia<sup>2,4,5</sup>.

### Diagnosis

In male patients proliferation of breast tissue may be due to gynaecomastia, pseudo-gynaecomastia or breast cancer. A physical examination is necessary to distinguish the cause<sup>2-5</sup>. Breast imaging and ultrasonography may be considered if breast cancer is suspected<sup>2,3,5</sup>.

Once gynaecomastia is confirmed, consider reversible causes including medicines and over-the-counter products (see Causal Medicines)<sup>2-6</sup>.

In patients with no apparent cause of gynaecomastia, laboratory tests may be useful. Tests may include liver, renal and thyroid

function<sup>2-5</sup>. A limited hormonal work-up (eg, testosterone, oestradiol, LH, FSH, hCG, and prolactin) may be useful to detect hormonal imbalances<sup>2-5</sup>.

### Causal Medicines

Medicines may cause gynaecomastia through a number of mechanisms including:<sup>4,5</sup>

- increased serum oestrogen levels or oestrogen-like activity
- decreased testosterone levels
- hypogonadism
- anti-androgenic effects
- increased prolactin levels.

Many commonly prescribed medicines have been reported to cause gynaecomastia<sup>5</sup>. Table 1 provides examples of medicines that have been associated with gynaecomastia<sup>2,3</sup>.

Other reported non-medicine causes of gynaecomastia include alcohol, amphetamines, heroin, marijuana (cannabis) and phytoestrogens (in some herbal medicines)<sup>2,3,4,7</sup>.

### New Zealand Cases

Up to 30 June 2016, 124 reports of gynaecomastia suspected to be caused by medicines have been reported to CARM (4.8% of reports were in women). These reports involved 135 suspected medicines as more than one medicine was described in some reports. The average age in these reports was 58 years.

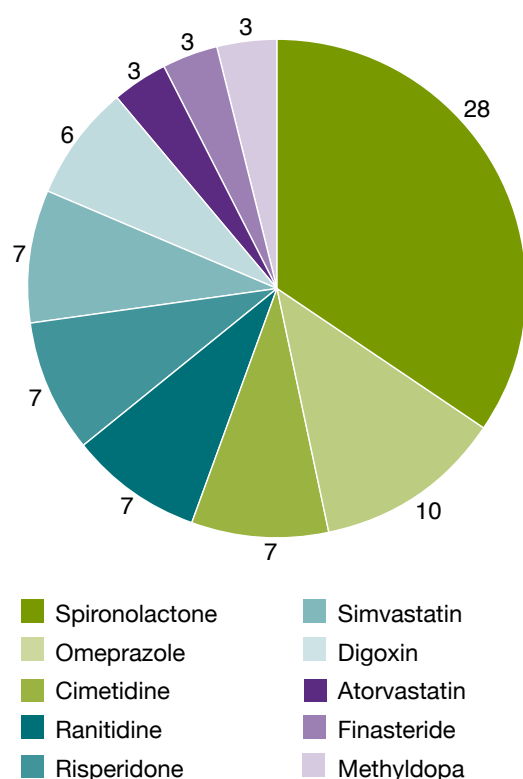
The 10 most frequently reported medicines are summarised in Figure 1. These medicines comprise 65% of total reports. Of these (n=81), time to onset was reported in 67 reports. In six reports, the onset was reported to have occurred

**Table 1: Medicines reported to be associated with gynaecomastia [this is not an exhaustive list]<sup>2-7</sup>**

Quality of Evidence*	Examples of Medicines and/or Medicine Classes
Good	Bicalutamide, cyproterone, dutasteride, finasteride, flutamide, goserelin, ketoconazole, leuprorelin, oestrogens, spironolactone
Fair	Alkylating agents, anabolic steroids, efavirenz, nifedipine, omeprazole, opioids, risperidone, verapamil

\*Classification of quality of evidence for strength of medicine associations with gynaecomastia. Good: Systematic review of randomised controlled trials, randomised placebo controlled trial, or prospective cohort studies with or without concurrent controls plus good pathophysiological explanation. Fair: Retrospective studies, case-control studies or case series with good pathophysiological explanation.

within one month and in 61 reports, the onset was reported to be one year or longer.



**Figure 1: Top 10 medicines associated with gynecomastia in the CARM database (number of reports)**

## Management

If medicine-induced gynecomastia is suspected, the medicine should be withdrawn or discontinued if possible<sup>2,4</sup>. Switching to a medicine of the same class, but with a lower association with gynecomastia may prevent re-emergence of gynecomastia<sup>2</sup>.

Within one month of discontinuing the causal medicine, a reduction in tenderness and softening of the glandular breast tissue should occur. However, if the gynecomastia has been present for more than one year, the presence of fibrosis may mean that surgery is required<sup>2-6</sup>.

Please continue to report any adverse reactions to CARM. Reports can be submitted on paper or electronically (<https://nzphvc.otago.ac.nz/>).

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1. CARM case ID 119664. URL: [www.medsafe.govt.nz/Projects/B1/adrsearch.asp](http://www.medsafe.govt.nz/Projects/B1/adrsearch.asp)
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5. Narula HS, Carlson HE. 2014. Gynecomastia – pathophysiology, diagnosis and treatment. *Nature Reviews Endocrinology* 10: 684–698.
6. Carlson HE. 2011. Approach to the Patient with Gynecomastia. *The Journal of Clinical Endocrinology & Metabolism* 96: 15–21.
7. Bowman JD, Kim H, Bustamante JJ. 2012. Drug-Induced Gynecomastia. *Pharmacotherapy* 32(12): 1123–1140.

## Posaconazole (Noxafil) – Tablets and Suspension are not Interchangeable

Posaconazole (Noxafil) is a broad-spectrum triazole antifungal, available as both a modified release tablet and oral suspension.

Healthcare professionals are reminded that the two formulations are not interchangeable due to a difference in dosing of each formulation<sup>1</sup>.

Medication errors have resulted from substitutions of the tablets and oral suspension. The European Medicine Agency (EMA) recently reported that some patients have mistakenly received oral suspension instead of tablets, leading to underdosing<sup>2</sup>. The EMA also reports that patients have received tablets instead of the suspension, leading to overdose and side effects<sup>2</sup>.

Further information is available on the medicine data sheet ([www.medsafe.govt.nz/profs/datasheet/n/Noxafil susp.pdf](http://www.medsafe.govt.nz/profs/datasheet/n/Noxafil susp.pdf)).

## References

1. Merck Sharp & Dohme New Zealand Limited. 2015. *Noxafil Data Sheet* 16 October 2015. URL: [www.medsafe.govt.nz/profs/datasheet/n/Noxafil susp.pdf](http://www.medsafe.govt.nz/profs/datasheet/n/Noxafil susp.pdf) (accessed 20 July 2016).
2. European Medicines Agency (EMA). 2016. *EMA warns that Noxafil tablets and oral suspension have different doses and are not interchangeable* 24 June 2016. URL: [www.ema.europa.eu/ema/index.jsp?curl=pages/news\\_and\\_events/news/2016/06/news\\_detail\\_002557.jsp&mid=WC0b01ac058004d5c1](http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/06/news_detail_002557.jsp&mid=WC0b01ac058004d5c1) (accessed 20 July 2016).



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## Prescriber Update Survey — The Results are In!

The *Prescriber Update* survey ran between 3 March and 8 April 2016. This was your chance to give your feedback and help us improve *Prescriber Update*.

Three-hundred and fifty-two readers participated in the survey. We estimate that this is 8.5% of individuals subscribed to receive *Prescriber Update* through electronic subscription or 2.3% of the total number of recipients.

Participants included pharmacists (34.1%), doctors (25.3%) and nurses (19.9%).

*Prescriber Update* was rated as relevant (54.3%) or somewhat relevant (37.7%) to the work of the respondents.

*Prescriber Update* is read from cover-to-cover by one-third (33.1%) of respondents. Twenty percent of respondents only read the key messages. Around half (52.7%) of respondents like the current publication frequency (three monthly). Most respondents (70%) were satisfied or very satisfied with the current format of *Prescriber Update*.

Some changes to *Prescriber Update* were proposed in the survey.

- Inclusion of a short summary (one to two sentences) of each article on the cover page was rated useful by 44% of respondents.
- The use of pictures and/or photos where relevant was endorsed by 25% of respondents.

Articles that readers would like to see more of include the following.

- Reviews about the safety of a specific medicine or class of medicine.
- Safety briefings reporting on a specific medicine and adverse reaction.
- Occasional spotlight on a particular therapeutic class or class of medicine.
- Information on new medicines.

Medsafe would like to thank everyone who took the time to participate in the survey. We are taking your feedback into consideration; look out for some changes in the near future!

Read the summary report on the survey at [www.medsafe.govt.nz/profs/PUArticles/ReaderSatisfactionSurveyOutcomeReportJuly2016.pdf](http://www.medsafe.govt.nz/profs/PUArticles/ReaderSatisfactionSurveyOutcomeReportJuly2016.pdf)

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## Dangers of Purchasing Online Medicines (Operation PANGEA IX)

Medsafe recently participated with New Zealand Customs in the annual international initiative known as Operation PANGEA, to highlight the illicit trade in medicines around the world. The results highlight the continuing importation of potentially substandard medicines into New Zealand.

Operation PANGEA IX was an International Internet Week of Action led by INTERPOL (30 May to 7 June 2016) involving 103 countries. It feeds data from the ongoing New Zealand border control programme into the worldwide effort aimed at disrupting criminal networks trading in illegal counterfeit and poor quality medicines.

As a result of Operation PANGEA IX, 173 packages were held requiring further investigation, slightly less than last year.

These parcels originated from 31 countries around the world and were stopped because

they contained prescription medicines, were not labelled or were known to contain undeclared or hidden ingredients. The most common sources of these products were India (84), China (14) and the United Kingdom (14).

Medicines for erectile dysfunction were the most common products examined by Medsafe (3652 individual tablets). Medicines for the treatment of infections, heart disease and pain were the next most prevalent.

Medicines purchased online present a risk to consumers because their quality, safety and effectiveness cannot be guaranteed and they may not be appropriate for the intended recipient.

It is important to stress that although a website may seem to be legitimate and established in a well-regulated country, this may not always be the case.

Medsafe routinely receives packages from New Zealand Customs that are suspected to contain medicines, with thousands of interceptions each year being referred for assessment.

Prescription medicines are referred to Medsafe by New Zealand Customs to ensure compliance with New Zealand law. Most prescription medicines Medsafe detains are held until the person importing them provides a valid authorisation from their doctor indicating that it is acceptable for them to use the medicine. If this does not occur the medicines are destroyed.

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

1. Be wary if a patient requests a prescription for a medicine purchased over the internet. Criminals go to great lengths to make their websites appear genuine. It is common for online businesses to purport to be reputable online pharmacies when they are not. Some pretend to be located in New Zealand.
2. Consider the following questions before providing a prescription for a medicine obtained from an online business.
  - Is the patient under your care?

- Is the medicine, dose and quantity appropriate for the patient?
- Is the patient aware of the risks of using medicines purchased over the internet?
- Are you willing to take responsibility for prescribing your patient an unapproved medicine that is likely to be of unknown quality and origin?
- Are you satisfied that your actions will meet ethical standards?

3. If a patient presents with unexplained symptoms after taking any medicines or dietary supplements, consider that the patient may have used a medicine or dietary supplement purchased over the internet.
4. Report adverse reactions to the Centre for Adverse Reactions Monitoring (CARM). Reports can be submitted on paper or electronically (<https://nzphvc.otago.ac.nz/>).
5. Report any suspicions you have that a product is substandard, adulterated or fake to Medsafe ([recalls@moh.govt.nz](mailto:recalls@moh.govt.nz)).

For more information on Operation PANGAEA IX visit [www.interpol.int/News-and-media/News/2016/N2016-076](http://www.interpol.int/News-and-media/News/2016/N2016-076)

## About the Medication Error Reporting Programme

### Key Messages

- ⌘ The Medication Error Reporting Programme (MERP) is operated by the New Zealand Pharmacovigilance Centre.
- ⌘ The MERP collects reports of errors to supplement, contribute to and improve the safe use of medicines.
- ⌘ The MERP is an online, national, voluntary, no-blame reporting system.
- ⌘ Reports to the MERP are utilised to inform and drive national medication safety initiatives.

Medication errors are unintentional errors in the use of a medicine. Errors may arise at any stage of medicine use; prescribing, dispensing, administration and monitoring. Errors include those of commission (where an error occurs as a result of an action taken) and those of omission

(where an error occurs as a result of an action not taken). Medication errors occur across all healthcare settings. Fortunately, most errors are detected and corrected before reaching the patient. However, some errors are not and may result in serious patient harm.

The Medication Error Reporting Programme (MERP) is an initiative of the New Zealand Pharmacovigilance Centre (NZPhvC) and operates alongside the Centre for Adverse Reactions Monitoring (CARM). The MERP aims to improve the safe use of medicines for New Zealanders.

The MERP is an online, national, voluntary, no-blame reporting system for primary care, where reports can be made anonymously if preferred. Voluntary reporting of actual and 'near miss' errors can help to identify hazards and risks. This information highlights vulnerabilities in systems that can be targeted for improvement to reduce the risk of harm to patients.



## Importance of the MERP and synergy with CARM

Beyond local systems for managing medication errors, sharing events with the NZPhvC contributes to a national database of events which:

- complements the CARM programme, as harms from medicines may arise not only from adverse reactions but also errors in use
- helps identify rare events that may otherwise go unrecognised
- provides timely insights into New Zealand-specific error trends and patterns over time
- informs national medication safety initiatives.

## How reporting to the MERP helps toward improving medication safety in New Zealand

The NZPhvC works with the Health Quality & Safety Commission (the Commission) to improve medication safety in New Zealand. Reports to the MERP are utilised to inform and drive national initiatives through a continual process involving reporting, analysis, solution development and systems change as shown in Figure 1.

### Who can report to the MERP?

- Any healthcare professional can report a primary care medication error electronically (<https://nzphvc.otago.ac.nz/merp/report/>).
- Organisations who collate data on medication errors can contribute to the MERP. Please email [merpnz@otago.ac.nz](mailto:merpnz@otago.ac.nz) for further information.

## What to report to the MERP

Actual and 'near miss' errors pertaining to prescribing, product labelling/packaging/names, compounding, dispensing, distribution, administration and monitoring. Reports of 'near misses' or unsafe situations that could lead to patient harm are encouraged as this allows a more proactive approach to prevention.

Reporting of errors covers all types of medicines, vaccines, as well as complementary and herbal remedies, but excludes blood products.

Report a suspected medicine-related reaction, error or safety problem to the NZPhvC:

### MERP

Errors in the use of a medicine, vaccine or related product (including 'near misses' and potential safety problems)

<https://nzphvc.otago.ac.nz/merp/report/>

### CARM

Suspected adverse reactions to a medicine, vaccine or related product

<https://nzphvc.otago.ac.nz/report/>

If unsure, please report to CARM or phone for advice **0800 4MONITOR (0800 466648)**.



Figure 1: The MERP national reporting and learning system for primary care

## Soya-based Excipients – a Problem for People with Peanut Allergy?

### Key Messages

- ⌘ A few people with peanut allergy are also allergic to soya.
- ⌘ Soya and peanut (arachis) oils are sometimes used as excipients in medicines.
- ⌘ No safe level for residual protein in soya or peanut oils has been established for allergic people.
- ⌘ Pharmaceutical companies are encouraged to follow European guidelines for these excipients and to alert healthcare professionals and patients when medicines contain soya and/or peanut oil.

Peanuts are the seed of the legume *Arachis hypogaea*<sup>1</sup>. The prevalence of peanut allergy is estimated at about 1% of the population<sup>2</sup>. Peanut allergy causes more concern than most other food allergies as it is more severe and more persistent<sup>3</sup>.

Soyabean is the seed of the legume *Glycine max*. Soya allergy usually manifests in childhood. The prevalence in adults is poorly described, but has been estimated at around 0.4%<sup>3</sup>. Isolated soya allergy seems to be rare; 88% of children with soya allergies also have peanut allergies<sup>3</sup>. Allergic symptoms to soya include atopic dermatitis and enterocolitis<sup>3</sup>. Anaphylaxis caused by soya is very rare. It has been postulated that the presence of anti-inflammatory chemicals in soya may reduce the allergic response<sup>3</sup>. In the few cases where death was reported after ingestion of soya the patients also had severe peanut allergies<sup>3</sup>.

Food induced allergenic reactions can be classified into two groups according to the type of immune reaction<sup>4</sup>.

- Immunoglobulin E (IgE) mediated symptoms (includes anaphylaxis).
- Non-IgE mediated gastrointestinal symptoms; these reach a peak approximately 48 hours after ingestion.

Several methods have been used for diagnosing suspected food allergy<sup>4</sup>.

- Skin prick testing; gives a large number of false positive results and shows sensitisation rather than allergy.
- Food-specific IgE measured by ELISA or immunoblotting.

- Double blind placebo controlled food challenge.
- Skin patch testing.
- Basophil activation test.

The results of some of these tests show only that a person is sensitised to an allergen, but is not necessarily allergic.

Cross-reactivity is less common than cross-sensitisation. Cross-sensitisation generally implies a positive skin test or IgE test but the patient is clinically tolerant, whereas a cross-reactivity implies that clinical symptoms are experienced<sup>5</sup>.

Cross-reactivity relies on the presence of conserved anti-body accessible surface structures of proteins and is often observed between members of the same protein family<sup>1</sup>. Plants in the same genus such as legumes are likely to have similar proteins.

Peanuts contain 12 known allergens which are categorised into six families:<sup>1,2</sup>

- the cupin superfamily (Ara h 1, 3)
- the prolamin superfamily (Ara h 2, 6, 7, 9)
- the profilin family (Ara h 5)
- bet v-1-related proteins (Ara h 8)
- oleosin/glycosyl transferase GT-C (Ara h 10, 11)
- defensin/scorpion toxin-like knottin (Ara h 12, 13).

The peanut allergens Ara h 8, 5 and 9 are responsible for allergic cross-reactivity across a wide variety of unrelated plants and are considered to be panallergens<sup>1</sup>.

Several soya allergens share high sequence homology to their counterparts in peanut. Soya Gly m 5 ( $\beta$ -conglycinin, 7 S) is close to Ara h 1. Ara h 3 and soyabean Gly m 6 (glycinin, 11 S) share a similar 3D structure<sup>1</sup>.

Approximately 50% of peanut-allergic patients have positive skin prick tests to other legumes, but less than 5% are clinically symptomatic upon ingestion of legumes<sup>2,5</sup>.

Peanut allergic people have a high theoretical risk of cross-reactivity to soyabean but double-blinded food challenges have shown a low rate of cross-reaction<sup>4</sup>. In a group of 39 peanut sensitised patients, 33 (87%) were also sensitised to soyabean and 11 (33%) reported symptoms to a wide variety of soya products<sup>1</sup>. In a study of 32 children with

peanut allergy, 10 (31%) had a positive skin test to soya whilst one (3%) had a clinical reaction<sup>5</sup>.

In a study investigating factors associated with the development of peanut allergy in childhood, consumption of soya was independently associated with peanut allergy<sup>6</sup>.

Refined soya and peanut oil contain low quantities of allergenic protein, depending on the refining process. No safe level for these residual proteins has been established. Neither is it clear that long-term consumption of medicines containing these oils will not induce allergy<sup>7,8</sup>.

Whilst the risk appears to be low, the European Medicines Agency (EMA) has taken a precautionary approach in their guidelines on excipients<sup>7,8</sup>. The EMA guideline recommends that medicinal products containing soya oil should include a contraindication for patients allergic to peanut or soya. In New Zealand, pharmaceutical companies are encouraged to follow this guidance, particularly if the allergenic potential of the peanut or soya based excipient has not been characterised.

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## 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
Ticagrelor	Depression, Suicidality	30 September 2016
Rivaroxaban, Dabigatran, Apixaban	Hair loss (Alopecia)	31 December 2016

- **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)



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



## Beta-lactam Antibiotics and Cross-reactivity

### Key Messages

- ⌘ Cross-reactivity occurs between beta-lactams with a closely related structure and affects antibiotic choice in allergic patients.
- ⌘ The beta-lactam ring, the thiazolidine/dihydrothiazine ring and the side-chains are all potentially immunogenic.
- ⌘ Cross-reactivity between penicillin and third-generation cephalosporins occurs in 2% to 3% of penicillin-allergic patients.
- ⌘ Cross-reactivity may be much higher for beta-lactams with a side chain that is similar or identical.
- ⌘ Allergy test results are useful when positive, but a negative result does not adequately exclude allergy to the specific antibiotic.

### Allergy to Beta-lactam Antibiotics

Patients commonly report an allergy to penicillin, however reaction details are often vague and many patients may be incorrectly labelled 'penicillin allergic'<sup>1,2</sup>.

Careful individual risk-benefit assessment is essential when considering the use of a beta-lactam antibiotic, taking into consideration details of the history of the prior reaction and allergy test results<sup>3,4</sup>.

In addition, consideration should be given to the structure of the beta-lactam antibiotic that was responsible for the reaction. Cross-reactivity occurs between beta-lactams with a closely related structure and affects antibiotic choice.

### Beta-lactam Antibiotic Structure and Degradation Pattern

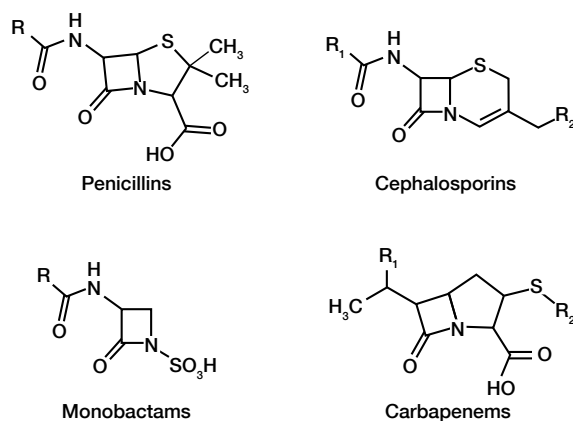
The basic structure of all beta-lactam antibiotics consists of a four-membered beta-lactam ring (Figure 1). In addition to the four-membered beta-lactam ring:

- penicillins have a thiazolidine ring and a single side-chain that differs for each type of penicillin
- cephalosporins have a dihydrothiazine ring and two side-chains instead of one
- carbapenems have a slightly different thiazolidine ring structure to penicillin

- aztreonam, a monobactam, has a beta-lactam ring with no adjacent ring.

The beta-lactam ring, the thiazolidine/dihydrothiazine ring and the side-chains are all potentially immunogenic<sup>4,5</sup>.

Despite their similar structure, penicillins and cephalosporins differ in their degradation pattern. Penicillins break down to form the stable penicilloyl moiety and a range of reactive intermediates. These derivatives have the potential to elicit an immune response<sup>4,6</sup>. In contrast, the degradation of cephalosporins involves the rapid fragmentation of the structural rings and the degradation products are less immunogenic.



**Figure 1: Basic chemical structures of beta-lactam antibiotics showing differences in ring structure and number of side chains (R)<sup>6</sup>**

### Cross-reactivity between Beta-lactams

Individuals with an allergy to one beta-lactam antibiotic may react to other structurally similar beta-lactams. Cross-reactivity between penicillin and first- and early (pre-1980) second-generation cephalosporins has been reported to occur in up to 10% of penicillin allergic patients. However, older studies may have overestimated the degree of cross-reactivity as the early cephalosporins contained traces of penicillin<sup>4,7</sup>. Cross-reactivity between penicillin and third-generation cephalosporins occurs in 2% to 3% of penicillin-allergic patients<sup>4,5,8,9</sup>. The degree of cross-reactivity may be much higher for beta-lactams with similar or identical side-chains<sup>4,5</sup>.

Clinical cross-reactivity among cephalosporins mainly relates to the side-chains<sup>4</sup>. However, it should be noted that cephalosporins cause immune-mediated reactions in 1% to 3% of patients even in the absence of a history of

penicillin allergy. Therefore, administration of a cephalosporin with different side-chains may still result in an allergic response due to co-existing sensitivities<sup>4,5,10</sup>.

### Allergy Testing to Beta-lactam Antibiotics

If a patient has a convincing history of an immediate hypersensitivity reaction or a severe cutaneous adverse reaction to a specific antibiotic, allergy testing is not required for confirmation and the antibiotic concerned should be avoided<sup>2</sup>. Allergy testing is mainly limited to immediate, IgE-mediated hypersensitivity<sup>3</sup>.

A blood test for specific IgE to penicillins is available, but does not include all antigenic determinants. A positive test result is highly predictive of penicillin allergy, but a negative result does not adequately exclude penicillin allergy<sup>4,11</sup>.

Skin testing for allergy to beta-lactams is a specialist procedure and is only offered at certain hospitals<sup>2</sup>. Approximately one-third of patients with a true penicillin allergy have a negative skin test. Therefore, a negative skin test does not adequately exclude allergy<sup>4</sup>.

If a patient reacts to a specific cephalosporin, skin testing to another cephalosporin with a different side chain may be considered. If skin testing is negative, graded oral challenge with the alternative cephalosporin, under specialist supervision, may be considered<sup>4</sup>.

Further information on beta-lactam allergy testing in New Zealand can be found on the Best Practice Advocacy Centre (BPAC) website ([www.bpac.org.nz/bpj/2015/june/allergy.aspx](http://www.bpac.org.nz/bpj/2015/june/allergy.aspx)).

Further information on the management of patients with beta-lactam antibiotic allergies,

including tables of beta-lactam antibiotics that share similar or identical side chains, can be found in the guidance prepared by *The Standards of Care Committee of the British Society for Allergy and Clinical Immunology (BSACI)*<sup>8</sup>.

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## Medicines can Impair Driving

### Key Messages

- ⌘ It is against the law to drive while impaired.
- ⌘ Warn patients taking medicines that may impair their driving ability of potential effects and encourage them to discuss any concerns.
- ⌘ Symptoms of impairment include sedation, blurred vision or inability to focus, as well as feeling manic or overconfident.

It is against the law to drive while impaired. The Land Transport Amendment Act 2009 states that it is an offence to drive while impaired *and* with evidence in the bloodstream of a qualifying drug<sup>1</sup>. Qualifying drugs include controlled drugs and prescription medicines. Further information on the legislation is available at [www.transport.govt.nz/legislation/acts/QAsdrugimpaireddrivinglaw](http://www.transport.govt.nz/legislation/acts/QAsdrugimpaireddrivinglaw)

Healthcare professionals can assist their patients by informing them of the potential impairing effects of medicines (this includes over-the-counter and pharmacist-only medicines as well

as prescription medicines). Medicines with the potential to impair driving ability include some pain relievers, anxiolytics, antidepressants, sleeping aids, antiepileptics, sedating antihistamines, antipsychotics, medicines used in the eyes, cough and cold medicines and some heart medicines<sup>2</sup>.

Not every medicine within each medicine class will impair driving nor cause impairment in every person. However, patients should be informed of the potential risk. Additionally, it is important for patients to continue treatment as some conditions requiring medical treatment may themselves affect driving ability if left untreated<sup>3</sup>.

Symptoms of impairment include dizziness, drowsiness, headache, nausea, blurred vision, slowed reactions, inability to focus, being easily confused, slurred speech and feeling manic or overconfident<sup>2</sup>. Importantly, the patient may not always be aware that they are impaired and impairment may continue the following day (eg, zopiclone and next-day impairment, see the *Prescriber Update* article for more information [www.medsafe.govt.nz/profs/PUArticles\\_June2014ZopicloneAndNextDayImpairment.htm](http://www.medsafe.govt.nz/profs/PUArticles_June2014ZopicloneAndNextDayImpairment.htm)).

Further guidance to patients could include:<sup>2,3</sup>

- not driving until the patient knows how the medicine affects them
- avoiding driving completely, particularly during treatment of a short-term condition
- not driving if the patient experiences any symptoms as described above
- considering alternative options, such as a different medicine or if it can be taken at a different time of day.

Please note that this information is advisory only. Data sheets for individual medicines should be checked for information on possible driving effects. Medicine data sheets are available at [www.medsafe.govt.nz/profs/Datasheet/DSForm.asp](http://www.medsafe.govt.nz/profs/Datasheet/DSForm.asp)

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## MARC's Remarks: June 2016 Meeting

The Medicines Adverse Reactions Committee (MARC) met on 29 June 2016 to discuss a number of medicine-related safety issues.

The MARC discussed the use of **dexchlorpheniramine** and other **sedating antihistamines** in children. The MARC recommended that the use of sedating antihistamines should be restricted according to age and indication as follows.

- Contraindicated in children under two years of age for all indications.
- Remain contraindicated in children under six years of age for the treatment of cough and colds.
- Contraindicated in children under 12 years of age for the treatment of insomnia.
- Available as prescription medicines when used in children under six years of age for nausea and vomiting and for travel sickness.

The MARC reviewed the current sedation warning and available evidence on the sedating

effects of **loratadine**- and **desloratadine**-containing products. The MARC considered that a warning should remain for these non-sedating antihistamines but be amended to reflect the low risk of sedation.

The MARC reviewed the available evidence around the use of **tramadol** in children. The MARC recommended that Medsafe request the sponsors of tramadol-containing products to add a contraindication in children under two years of age and update the warnings and precautions section of the medicine data sheets.

The MARC reviewed the available information on the risks of chronic kidney disease and dementia with **proton pump inhibitors**. The MARC concluded that the evidence was insufficient to support an association for either of these risks.

Read further information on the 166th meeting held on 29 June 2016 at [www.medsafe.govt.nz/profs/adverse/Minutes166.htm](http://www.medsafe.govt.nz/profs/adverse/Minutes166.htm)



## New Medicine Approvals

For the period 16 April to 15 July 2016.

Trade Name (Active Ingredient)	Dose Form and Strength	Therapeutic Area
Alacare (aminolevulinic acid)	Dermal patch 8 mg	Actinic keratosis lesions on the face and scalp
Daklinza (daclatasvir)	Tablet 30 mg	Chronic hepatitis C virus (HCV) infection
Duavive (bazedoxifene/ conjugated estrogens)	MR tablet 0.45 mg/20 mg	Oestrogen deficiency symptoms in postmenopausal women with a uterus
Esbriet (pirfenidone)	Capsule 267 mg	Idiopathic pulmonary fibrosis
Mirvaso (brimonidine)	Topical gel 3.3 mg/g	Rosacea
Opdivo (nivolumab)	Concentration for infusion 100 mg/10 mL and 40 mg/4 mL	Unresectable (Stage III) or metastatic (Stage IV) melanoma Advanced or metastatic squamous or non- squamous non-small cell lung cancer (NSCLC)
Simbrinza (brimonidine/ brinzolamide)	Eye drops suspension 1%/0.2%	Open-angle glaucoma or ocular hypertension
Sunvepra (asunaprevir)	Capsule 100 mg	Chronic HCV infection
Visanne (dienogest)	Tablet 2 mg	Endometriosis
VPRIV (velaglucerase alpha)	Powder for infusion 400 units	Type I Gaucher disease

Abbreviations: FC film coated, MR modified release

A full description of each product can be found in individual medicine data sheets at [www.medsafe.govt.nz/profs/Datasheet/dsform.asp](http://www.medsafe.govt.nz/profs/Datasheet/dsform.asp)

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