

# Prescriber Update

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## NSAIDs and Risk of Cardiovascular Events

### Key Messages

- ⌘ All non-steroidal anti-inflammatory drugs (NSAIDs) are associated with a small increased risk of serious cardiovascular adverse events.
- ⌘ The risk is increased with high doses, increasing duration of use and in patients with other cardiovascular risk factors.
- ⌘ The lowest effective NSAID dose should be used for the shortest possible duration.
- ⌘ The overall benefit to risk of harm balance of NSAIDs remains positive.
- ⌘ Patients requiring long-term NSAID therapy should be regularly reviewed for efficacy, adverse effects and the development of cardiovascular risk factors.
- ⌘ Effectiveness of different NSAIDs may vary between individual patients.

Medsafe and the Medicines Adverse Reactions Committee (MARC) have recently reviewed the risk of cardiovascular events associated with the use of diclofenac.

The MARC concluded that all systemically administered non-steroidal anti-inflammatory drugs (NSAIDs) are associated with an increased risk of serious cardiovascular events, including myocardial infarction and stroke. However, overall the benefit to risk balance for NSAIDs remains positive<sup>1</sup>.

The MARC considered the new data was inadequate to show a clear difference in the risk between individual NSAIDs. Most studies did not provide any data on the efficacy of

individual NSAIDs. Therefore, it is not possible to recommend one NSAID over another for all patients.

The available data suggests that patients with cardiovascular risk factors such as hypertension, hyperlipidaemia, diabetes mellitus, ischaemic heart disease, congestive heart disease and smoking, may be at greater risk of cardiovascular events.

The associated risk also increases with increasing dose and duration of use of NSAIDs. Therefore, the lowest effective dose for the shortest effective duration should be used when possible.

Benefit risk assessments should be undertaken in all patients prior to prescribing a specific NSAID. In addition to cardiovascular risk, the risk of other NSAID adverse reactions, such as gastrointestinal events, renal injury and severe skin reactions, should also be considered.

If the benefit risk balance is unfavourable, other pain relievers may be considered as an alternative to NSAIDs. However, the MARC noted that there are undesirable effects associated with alternatives to NSAIDs as well.

All patients taking long-term NSAIDs should be regularly reviewed as the use of NSAIDs may lead to new hypertension or worsen pre-existing hypertension, both of which may increase the risk of cardiovascular events. Consideration should therefore be given to monitoring blood pressure as well as haemoglobin levels and renal function.

### References

1. Medsafe. 2008. Non-selective NSAIDs — Cardiovascular, skin and gastrointestinal risks. *Prescriber Update* 29(1): 15–6. URL: [www.medsafe.govt.nz/profs/PUArticles/NSAIDSRisks.htm](http://www.medsafe.govt.nz/profs/PUArticles/NSAIDSRisks.htm) (accessed 12 August 2013).

## Early Warning System Communications

The Trans-Tasman early warning system provides information on safety concerns for medicines and medical devices.

A monitoring communication provides information on newly identified potential safety concerns. These concerns have not been fully investigated.

An alert communication is issued once a review of the safety concern is complete. Alerts contain more information on the safety concern and provide specific advice on actions that may need to be taken by healthcare professionals and consumers. Early warning system communications issued in the last quarter can be found on page 29.

## Rituximab and Hepatitis B Reactivation

### Key Messages

- ⌘ Rituximab has been associated with cases of hepatitis B reactivation.
- ⌘ All patients should be screened for hepatitis B virus before initiation of treatment with rituximab.
- ⌘ Rituximab should not be used in patients with active hepatitis B.
- ⌘ Healthcare professionals should consult with a liver specialist prior to initiating rituximab treatment in patients with positive hepatitis B serology.

Hepatitis B virus screening is now recommended for **all patients** before initiating treatment with rituximab (Mabthera) for all oncology and rheumatoid arthritis indications. Previously, only patients that were at high risk for hepatitis B virus infection were recommended for screening prior to starting treatment.

Cases of hepatitis B reactivation, including fulminant hepatitis, have been reported worldwide in subjects receiving rituximab. Patients with positive hepatitis B surface antigen (HBsAg+ve) and patients with negative hepatitis B surface antigen and positive anti-hepatitis B core antibody (HBsAg-ve/HBcAb+ve) have reported hepatitis B reactivation, particularly when administered in combination with steroids or chemotherapy. Some of these cases were fatal.

Healthcare professionals should consult with a liver specialist prior to initiating rituximab

treatment in patients with positive hepatitis B serology as patients will need to be monitored and managed to prevent hepatitis B reactivation. Patients with active hepatitis B disease should not be treated with rituximab.

Rituximab is an anti-CD20 monoclonal antibody. Rituximab binding to CD20 results in complete but transient depletion of B cells from peripheral circulation<sup>1</sup>.

Rituximab is approved for use in New Zealand for the treatment of non-Hodgkin's lymphoma, chronic lymphocytic leukaemia and rheumatoid arthritis. Worldwide, cases of hepatitis B reactivation have been reported in patients treated for both the oncology and the rheumatoid arthritis indications.

The Centre for Adverse Reactions Monitoring (CARM) has received one report of hepatitis B reactivation following treatment with rituximab. In this report, rituximab was used to treat lymphoproliferative disease that developed following a liver transplant.

The sponsor of rituximab, Roche Products (New Zealand) Limited, has sent out a dear healthcare professional letter informing healthcare professionals of this issue. The warnings and precautions section of the New Zealand data sheet has been updated to include the new recommendations<sup>1</sup>.

### References

1. Roche Products (New Zealand) Ltd. 2013. *Mabthera Data Sheet*. 26 June 2013. URL: [www.medsafe.govt.nz/profs/datasheet/m/Mabtherainf.pdf](http://www.medsafe.govt.nz/profs/datasheet/m/Mabtherainf.pdf) (accessed 5 August 2013).

## Removal Difficulties with Jadelle and Implanon

### Key Messages<sup>1-3</sup>

- ⌘ Jadelle and Implanon must only be administered by healthcare professionals who have been fully trained in insertion and removal procedures.
- ⌘ Women should be informed of the risks of removal or location difficulties prior to receiving Jadelle or Implanon.
- ⌘ Women should be advised to return to their healthcare professional if they notice any changes with their implant or if they cannot feel their implant.
- ⌘ Removal instructions in the data sheet must be carefully followed.
- ⌘ If difficulty arises with implant removal, it should be localised by ultrasound before being removed.



Jadelle (levonorgestrel) and Implanon (etonogestrel) are long acting reversible contraceptive implants that are inserted sub-dermally in the upper arm. Removal and/or location difficulties have been reported in clinical studies and with post-marketing use of both these devices. Patients should be advised of these risks prior to insertion.

Since PHARMAC funding began in August 2010, more than 38,000 women have received Jadelle in New Zealand. It is unknown how many women have received Implanon.

Up until June 2013, the Centre for Adverse Reactions Monitoring (CARM) had received 21 reports of location or removal difficulties with Jadelle and three reports with Implanon. In many of these reports, the implant required removal under ultrasound guidance.

Jadelle and Implanon provide effective contraception for at least three years to five years depending on the implant used. Following insertion, women should be advised to return to their healthcare professional if:

- they cannot feel their implant
- they notice any change to the shape of the implant
- the implant appears to have broken
- there are skin changes or pain around the site of the implant.

As with other progestogen-only contraceptives, menstrual bleeding changes (irregular, prolonged and/or inter-menstrual bleeding, spotting and amenorrhoea) are very common with both products. In clinical studies, 14% of Jadelle users and 33% of Implanon users had their implant removed early because of menstrual difficulties<sup>1,2</sup>.

The CARM reports are consistent with the implants being removed early. However, insufficient information was provided in the reports to confirm that this was due to menstrual bleeding changes.

Please report any adverse reactions to Jadelle or Implanon, including any removal difficulties, to CARM.

### References

1. Faculty of Sexual and Reproductive Healthcare. 2009. *Faculty of Sexual and Reproductive Healthcare Clinical Guidance: Progestogen-only Implants*. London: Faculty of Sexual and Reproductive Healthcare. URL: [www.fsrh.org/pdfs/CEUGuidanceProgestogenOnlyImplantsApril08.pdf](http://www.fsrh.org/pdfs/CEUGuidanceProgestogenOnlyImplantsApril08.pdf) (accessed 1 August 2013).
2. Bayer New Zealand Limited. 2010. *Jadelle Data Sheet* 30 August 2010. URL: [www.medsafe.govt.nz/profs/datasheet/j/Jadelleimplant.pdf](http://www.medsafe.govt.nz/profs/datasheet/j/Jadelleimplant.pdf) (accessed 1 August 2013).
3. Merck Sharp & Dohme. 2012. *Implanon Data Sheet* 4 July 2012. URL: [www.medsafe.govt.nz/profs/datasheet/i/Implanonimplant.pdf](http://www.medsafe.govt.nz/profs/datasheet/i/Implanonimplant.pdf) (accessed 1 August 2013).

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## Anticoagulant Effect of Warfarin Increased by Benzbromarone

An interaction reported to the Centre for Adverse Reactions Monitoring (CARM) serves as a reminder to all healthcare professionals to take care when prescribing unapproved medicines.

A 78-year-old patient with ischaemic heart disease and chronic renal failure was taking warfarin for atrial fibrillation and an artificial mitral valve. The patient was started on benzbromarone for polyarticular gout. About one month after starting benzbromarone, the patient had an INR of 9.7 with widespread bruising.

Benzbromarone is a uricosuric drug that is not approved for use in New Zealand. Benzbromarone is known to selectively inhibit the metabolism of warfarin reducing its elimination and increasing its effects<sup>1</sup>. Because

this medicine is unapproved, no data sheet is published on the Medsafe website.

The New Zealand Formulary (NZF) website ([www.nzf.org.nz/](http://www.nzf.org.nz/)) covers unapproved as well as approved medicines. Other references also contain information on the use of unapproved medicines (eg, Martindale, Stockley's).

Prescribers need to discuss the benefits and risks of treatment with unapproved medicines with patients (the Code of Health and Disability Services Consumers' Rights 1996). Information on the use of unapproved medicines is available on the Medsafe website ([www.medsafe.govt.nz/profs/RIss/unapp.asp](http://www.medsafe.govt.nz/profs/RIss/unapp.asp)).

### References

1. Stockley IH. 2002. *Stockley's Drug Interactions*. London: Pharmaceutical Press.

## Joint Swelling Associated with Zoledronate and Pamidronate

The Centre for Adverse Reactions Monitoring (CARM) has received a total of 16 reports of joint swelling reactions associated with zoledronate and pamidronate. Eleven of these reports have been received since the beginning of 2012. This represents a substantial increase in reporting of these reactions.

Cases of joint swelling, particularly synovitis, associated with alendronate have been reported to CARM and highlighted previously<sup>1</sup>. Joint swelling may occur as part of a severe acute phase-like response (reaction). Symptoms of an acute phase response generally include fever and influenza-like symptoms, joint, bone and muscle pains, and fatigue.

Changes in inflammatory markers have been noted in patients experiencing acute phase-like reactions to bisphosphonates. These changes include an increase in C-reactive protein, transient decrease in white cell count, increase in interleukin-6 and increase in TNF-alpha. Acute phase reactions have only been associated with aminobisphosphonates (ie, not with etidronate).

Of the 16 reports received by CARM, four reports were associated with pamidronate (5% of the total pamidronate reports) and 12 reports with zoledronate (7% of the total zoledronate reports).

In 10 of the cases, the patient was reported to have experienced influenza-like symptoms (seven cases) or to have had a positive C-reactive protein test (three cases). This suggests that these cases are consistent with an acute phase-like reaction.

In the cases reported to CARM, onset of symptoms was within 24 hours in eight of the cases and within seven days for the remaining cases.

Most patients are expected to recover, usually within two to four weeks. Some patients will have a recurrence of symptoms with the next infusion or with treatment with an alternative aminobisphosphonate.

### References

1. Savage R. 2006. Alendronate and inflammatory adverse reactions. *Prescriber Update* 27(1): 4-6. URL: [www.medsafe.govt.nz/profs/PUarticles/alendinflam.htm](http://www.medsafe.govt.nz/profs/PUarticles/alendinflam.htm) (accessed 2 August 2013).

### Quarterly Summary of Medsafe Early Warning System 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)).

Date	Communication	Topic
4 June 2013	Alert	Topical tissue glues/adhesives and risk of deep tissue injuries
17 June 2013	Monitoring	Champix (varenicline) and a possible interaction with alcohol based on post-marketing reports
8 July 2013	Alert	Diclofenac (Voltaren) and risk of cardiovascular events (heart attack and stroke)
8 July 2013	Monitoring	Hydroxyethyl starch solutions (Voluven, Volulyte 6%) associated with increased risk of mortality and renal impairment

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)

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## Donepezil: Syncope, Heart Block and Beta-adrenergic Blockade

The Centre for Adverse Reactions Monitoring (CARM) has received two reports of bradycardia and syncope occurring in patients taking donepezil and metoprolol.

One of these patients developed recurrent syncope with initially normal telemetry. Syncopal episodes persisted for two months. On further telemetry, heart block was observed requiring a temporary pacemaker. The second patient did not have telemetry. Both patients recovered when donepezil and metoprolol were discontinued.

CARM has also received one report of symptomatic bradycardia and first degree heart block. This occurred when donepezil was added to long-term treatment with metoprolol and diltiazem. The patient showed subsequent improvement when all three medicines were discontinued. There was no relapse when metoprolol was reintroduced.

Donepezil is a cholinesterase inhibitor indicated for Alzheimer's disease and vascular dementia<sup>1</sup>. Donepezil affects parasympathetic innervation of the myocardium. The main effect is suppression of atrioventricular node conduction.

Beta-adrenergic blocking agents, such as metoprolol, block catecholamine-induced increases in heart rate, myocardial contractility and blood pressure<sup>2</sup>.

Donepezil alone can therefore cause bradycardia, heart block and syncope and this is a possibility in all three case reports<sup>1,3</sup>. However, where there

is an enhanced parasympathetic effect on the myocardium due to donepezil, and metoprolol has blocked the usual sympathetic response of increasing blood pressure then the possibility of postural syncope of central cardiac origin is increased.

The combination of donepezil and a beta-blocker is not contraindicated but, if there is new-onset syncope, whichever of the two medicines was added most recently should be discontinued. A synergistic effect on cardiac conduction is also possible<sup>1</sup>.

All patients taking donepezil, with or without a beta-blocker, should be monitored for syncope, clinically important bradycardia or heart block. The possibility of these being accentuated by concomitant beta blockade should be considered. Particular watchfulness is needed for patients with pre-existing conduction abnormalities<sup>1</sup>.

*Dr Ruth Savage*

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### References

1. Pfizer New Zealand Ltd. 2012. *Aricept Data Sheet*. 25 October 2012. URL: [www.medsafe.govt.nz/profs/datasheet/a/AricepttabAriceptDtab.pdf](http://www.medsafe.govt.nz/profs/datasheet/a/AricepttabAriceptDtab.pdf) (accessed 2 August 2013).
2. AFT Pharmaceuticals Ltd. 2009. *AFT-Metoprolol CR Data Sheet*. 1 December 2009. URL: [www.medsafe.govt.nz/profs/datasheet/a/AFTMetoprololCRtab.pdf](http://www.medsafe.govt.nz/profs/datasheet/a/AFTMetoprololCRtab.pdf) (accessed 2 August 2013).
3. Bordier P, Garrigue S, Barold SS, et al. 2003. Significance of syncope in patients with Alzheimer's disease treated with cholinesterase inhibitors. *Europace* 5(4): 429–31.

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## Hair-loss, a Sun-sensitive Issue

Medsafe has been made aware of a case of a patient who suffered a chemical burn to the forehead following the application of an oil-based scalp product.

The patient had purchased shampoo and hair tonic to combat hair loss. The products contained oils and herbal extracts, and were described as being made primarily of Himalayan herbs, 100% natural, and with no side effects.

After using these products, the patient's scalp became irritated and dry. The hair loss clinic

suggested that the oil-based product would help to calm the scalp.

Following a brief period of outdoor exposure after applying the oil, the patient experienced a weepy scaly rash along with a severe burning sensation. The reaction was of such a severity that the patient visited an after-hours medical clinic. The patient was diagnosed with a burn on the forehead together with an acute outbreak of seborrhoeic dermatitis.

Information in the Natural Medicines Comprehensive Database indicates that many of



the ingredients in the three products could cause reactions such as dermatitis, hypersensitivity, and photosensitivity<sup>1</sup>. These included *Salvia officinalis* (sage), *Zingiber officinale* (ginger), lavender oil, rosemary oil and citronella oil.

Drug-induced photosensitivity occurs when a drug or chemical is activated by ultra-violet radiation to cause a phototoxic or photoallergic reaction<sup>2</sup>. These reactions can occur both with oral and topical agents, including those commonly used such as sunscreens and fragrances<sup>2</sup>. Reactions can occur relatively quickly after exposure to light, or up to three days later<sup>2</sup>.

A photoallergic reaction may present as a scaly, itchy rash, possibly spreading to areas of skin which have not been exposed<sup>2</sup>. The more severe

phototoxic type reactions may present as an exaggerated sunburn reaction, possibly with blisters, which is limited to the areas of exposed skin<sup>2</sup>.

Healthcare professionals are reminded to ask about the use of all medicines and topically applied products, including cosmetic-type products, if a patient presents with similar symptoms to those described above.

## References

1. *Natural Medicines Comprehensive Database*. (nd). Stockton: Therapeutic Research Faculty. URL: [naturaldatabase.therapeuticresearch.com](http://naturaldatabase.therapeuticresearch.com) (accessed 6 August 2013).
2. New Zealand Dermatological Society Incorporated. *DermNet NZ: The Dermatology Resource*. URL: [www.dermnet.org.nz/reactions/drug-photosensitivity.html](http://www.dermnet.org.nz/reactions/drug-photosensitivity.html) (accessed 6 August 2013).

## Purchasing Medicines over the Internet

### Key Messages

- ⌘ New Zealand Customs intercepts parcels suspected to contain medicines.
- ⌘ Many of the intercepted parcels contain prescription medicines, undeclared or hidden ingredients, or medicines that were imported by companies not licensed in New Zealand.
- ⌘ Intercepted prescription medicines need authorisation from a New Zealand prescriber.
- ⌘ Prescribers should discuss the potential adverse reactions interactions with other medicines and appropriate use before authorising medicines.

Healthcare professionals are advised to inform patients about the serious health risks associated with purchasing medicines over the internet. This follows a joint Medsafe and New Zealand Customs crackdown on substandard, illegal or counterfeit medicines.

Medsafe and Customs participated in the week-long Operation PANGEA VI led by INTERPOL (June 18–25). This is the sixth time New Zealand authorities have participated in the largest global internet-based operation focusing on illicit websites selling fake or counterfeit medicines.

Internationally, the operation engages police, customs and national regulatory authorities from around the world to target websites supplying fake and illicit medicines. The operation targets the main areas involved in the illegal online medicine trade such as Internet Service Providers (ISPs), electronic payment systems and delivery services.

More than 9,000 websites linked to illicit online pharmacies were identified and shut down, in addition to the suspension of payment facilities of illegitimate pharmacies and the disruption of a substantial number of spam messages.

Customs targets all incoming international mail suspected to contain medicines, and thousands of these are referred to Medsafe each year. As a result of Operation PANGEA VI, 298 packages were held by Medsafe requiring further investigation. This is more than double the number investigated last year (124). These parcels originated from 32 different countries around the world (21 in 2012).

Parcels were stopped because they contained prescription medicines, were not labelled or were known to contain undeclared or hidden ingredients or medicines that were imported for sale or distribution in New Zealand by commercial entities that are not properly licenced to do so. The most common sources of these products were India (79), USA (59) and China (30).

The 298 consignments detained or seized by Medsafe often contained several different types of prescription medicines. The consignments were found to contain assorted antibiotics, painkillers, oral contraceptives and prescription medicines for the treatment of heart disease, weight loss, mental health conditions, erectile dysfunction, hair loss, insomnia, gastrointestinal illness and respiratory illness.

Prescription medicines are referred to Medsafe by Customs to ensure they have been imported in accordance with the Medicines Act 1981 and Medicines Regulations 1984.

The main reason prescription medicines were detained by Medsafe during the operation was to give the importer an opportunity to obtain a prescription or letter from a New Zealand doctor. This serves to satisfy Medsafe that the importer has a reasonable excuse for having imported a personal supply of a prescription medicine.

Healthcare professionals should discuss the potential adverse reactions, interactions with other medicines and the appropriate use of the medicines before agreeing to authorise medicines purchased over the internet.

## Reminder: Warfarin and Miconazole Oral Gel

### Key Messages

- ⌘ Miconazole oral gel inhibits the metabolism of warfarin via inhibition of CYP2C9.
- ⌘ Healthcare professionals are advised to avoid miconazole oral gel in patients taking warfarin.
- ⌘ If concomitant use of miconazole oral gel and warfarin is necessary, the patient's INR should be carefully monitored.
- ⌘ Miconazole oral gel is available as a pharmacist-only medicine.

Loss of anticoagulant control is one of the most frequent causes of medicine-related hospital admissions in New Zealand. In many cases, an agent which alters the anticoagulant effect of warfarin is implicated<sup>1</sup>.

The risk of interactions was highlighted recently in two serious case reports submitted to the Centre for Adverse Reactions Monitoring (CARM). Both patients were taking warfarin and had miconazole oral gel added to their treatment regimes. The addition of miconazole oral gel resulted in an increased INR and haemorrhage. Both patients required hospitalisation.

The interaction between warfarin and miconazole tablets is a well-established and potentially serious interaction. Importantly, this interaction can also occur with miconazole oral

gel applied solely to the mouth due to absorption via mucosal surfaces.

CARM has received 16 reports of adverse effects in association with miconazole oral gel and warfarin. Of these reports, three were life-threatening and 10 patients required hospitalisation. The majority of cases resulted in an increase in INR and bleeding.

Miconazole inhibits the metabolism of warfarin through the liver by inhibiting the cytochrome P450 isoenzyme, CYP2C9<sup>2</sup>. This can result in an increase and/or prolongation of the effects of warfarin, including adverse effects such as bleeding<sup>2</sup>.

Miconazole oral gel is a commonly supplied pharmacist-only medicine, as well as being available on prescription.

Healthcare professionals are reminded of this potentially serious interaction. Healthcare professionals are advised to avoid miconazole oral gel in patients taking warfarin. If the concomitant use of miconazole oral gel and warfarin is necessary, the patient's INR should be carefully monitored and the dose of warfarin adjusted as required.

### References

1. Best Practice Advocacy Centre. 2007. Interactions with warfarin. *Best Practice Journal* 4: 28–31. URL: [www.bpac.org.nz/magazine/2007/april/pdfs/bpj4\\_warfarin\\_pages\\_28-31\\_pf.pdf](http://www.bpac.org.nz/magazine/2007/april/pdfs/bpj4_warfarin_pages_28-31_pf.pdf) (accessed 6 August 2013).
2. Stockley IH. 2002. *Stockley's Drug Interactions*. London: Pharmaceutical Press.



## Interaction: Methotrexate and Proton Pump Inhibitors

### Key Messages

- ⌘ Concomitant use of high-dose methotrexate and Proton Pump Inhibitors (PPIs) may delay methotrexate elimination and increase the risk of adverse reactions.
- ⌘ Prescribers should take care when high-dose methotrexate and PPIs are used together and consider temporary withdrawal of the PPI.
- ⌘ Some PPIs are available over-the-counter.
- ⌘ Prescribers should continue to follow recommendations in the current data sheets.

Concomitant use of methotrexate and proton pump inhibitors (PPIs) may increase the levels of methotrexate in the blood and lead to adverse reactions.

The risk is greatest for patients taking high-dose methotrexate. Potential adverse reactions include renal toxicity, haematologic events, mucositis and myalgia.

Methotrexate is used to treat some forms of cancer and some autoimmune diseases. PPIs (which include omeprazole, esomeprazole, pantoprazole, lansoprazole and rabeprazole) are used for the symptomatic relief of gastric reflux-like symptoms.

The potential interaction with methotrexate relates to all PPIs.

There have been several studies and case reports that have identified the potential interaction between methotrexate and PPIs<sup>1-5</sup>.

In one study (79 patients and 197 cycles of methotrexate), the co-administration of PPIs with high-dose methotrexate was a risk factor for delayed elimination of methotrexate (odds ratio 6.66, 95% confidence interval 3.13–14.17)<sup>4</sup>.

Another study (74 patients and 171 cycles of methotrexate) also found that PPI use was a risk

factor for delayed elimination of methotrexate (adjusted odds ratio 2.65, 95% confidence interval 1.03–6.82) and was also a risk factor for renal and liver dysfunction<sup>5</sup>.

Most of the studies and case reports were in patients who were receiving high-dose methotrexate.

Prescribers are asked to take care when high-dose methotrexate and PPIs are used together. PPIs should be used at the lowest dose and for shortest duration possible. Prescribers could consider temporarily withdrawing the PPI.

Prescribers are also reminded that PPIs are available over-the-counter.

Medsafe are currently working with the relevant pharmaceutical companies to ensure all methotrexate and PPI data sheets contain information on this interaction.

Healthcare professionals are reminded to report any adverse events to the Centre for Adverse Reactions Monitoring (CARM).

Reporting can be done via either the Medsafe website ([www.medsafe.govt.nz/profs/adverse/reactions.asp](http://www.medsafe.govt.nz/profs/adverse/reactions.asp)) or by reporting directly to CARM (<http://carm.otago.ac.nz/>).

### References

1. Bezabeh S, Mackey AC, Kluetz P, et al. 2012. Accumulating evidence for a drug-drug interaction between methotrexate and proton pump inhibitors. *Oncologist* 17(4): 550–554.
2. Ranchon F, Vantard N, Gouraud A, et al. 2011. Suspicion of drug-drug interaction between high-dose methotrexate and proton pump inhibitors: a case report — should the practice be changed? *Chemotherapy* 57(3): 225–229.
3. Santucci R, Leveque D, Kemmel V, et al. 2010. Severe intoxication with methotrexate possibly associated with concomitant use of proton pump inhibitors. *Anticancer Research* 30(3): 963–965.
4. Santucci R, Leveque D, Lescoute A, et al. 2010. Delayed elimination of methotrexate associated with co-administration of proton pump inhibitors. *Anticancer Research* 30(9): 3807–3810.
5. Suzuki K, Doki K, Homma M, et al. 2009. Co-administration of proton pump inhibitors delays elimination of plasma methotrexate in high-dose methotrexate therapy. *British Journal of Clinical Pharmacology* 67(1): 44–49.

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## Pharmacist Jailed for Breaches of the Medicine Act

A recent court case highlights that consumers need to be cautious before buying products that are advertised for a therapeutic purpose on the internet, particularly those advertised to treat erectile dysfunction.

A 32-year-old Auckland pharmacist has been sentenced to four months and two weeks in prison for a series of breaches of the Medicines Act 1981. Mr Iskander was convicted of 47 charges laid by the Ministry of Health.

The charges related to a wide variety of breaches of the Medicines Act 1981. Mr Iskander operated a website from which he was selling unapproved prescription medicines for the treatment of erectile dysfunction. Mr Iskander was also found to have possessed medicines at two addresses without having a reasonable excuse to do so.

The products sold by Mr Iskander contained vardenafil and phentolamine. The products were sold under various versions of the trade name 'Exotic'.

Medsafe reminds healthcare professionals and consumers to treat any products advertised and sold for a therapeutic purpose outside of the usual medicines supply system with caution. These products may be being sold illegally, may have false claims, or may be adulterated with undisclosed active ingredients.

Consumers also cannot be sure of the safety, quality, and legality of medicines purchased over the internet (see article on page 31).

The Pharmacy Council of New Zealand has suspended Mr Iskander's pharmacy practicing certificate.

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## MARC's Remarks: June 2013 Meeting

The Medicines Adverse Reactions Committee (MARC) met on 13 June 2013 to review a number of medicine related safety issues.

The MARC discussed a recent review by Medsafe following reported cases of synovitis in association with **zoledronate** and **pamidronate**. The MARC considered that the association of bisphosphonates and the risk of synovitis may be under-recognised. The MARC recommended that awareness be raised. Further information can be found in this edition of Prescriber Update<sup>1</sup>.

The MARC reviewed studies published on **diclofenac** since the previous MARC review in 2007. The MARC concluded that there was a small increase in the risk of cardiovascular events with the use of diclofenac, particularly with increasing dose and duration of use.

The MARC agreed that the latest studies had a number of limitations and the risk was very low. However, with the widespread use of diclofenac, the MARC agreed that even a small increased risk of cardiovascular adverse effects may translate to a large number of patients potentially affected. Overall, the MARC agreed that the benefit-risk balance of diclofenac remains positive.

The MARC recommended changes to the diclofenac data sheets, package inserts and

consumer medicine information. The MARC also recommended that this information be communicated via a Prescriber Update article and by publishing an early warning system alert communication on the Medsafe website<sup>2,3</sup>.

The MARC reviewed a report on the use of **diphtheria, pertussis and tetanus combination vaccine** (Tdap, Boostrix®) in pregnant women during the current pertussis epidemic in New Zealand. The MARC agreed that pertussis is an important cause of infant death both in New Zealand and worldwide. The MARC considered that the potential benefits of vaccinating pregnant women with Boostrix outweighed any potential harm.

Further information on these issues can be found on the Medsafe website ([www.medsafe.govt.nz/profs/adverse/Minutes154.htm](http://www.medsafe.govt.nz/profs/adverse/Minutes154.htm)).

### References

1. Medsafe. 2013. Joint swelling associated with zoledronate and pamidronate. *Prescriber Update* 34(3): 29.
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3. Medsafe. 2013. Diclofenac (Voltaren) and risk of cardiovascular events (heart attack and stroke). *Alert Communication* 8 July 2013. URL: [www.medsafe.govt.nz/Projects/B2/2013/diclofenac-cardio.asp](http://www.medsafe.govt.nz/Projects/B2/2013/diclofenac-cardio.asp) (accessed 6 August 2013).

## Reminder: Electronic Adverse Reaction Reporting Tool

In 2009, Medsafe launched the electronic adverse reaction reporting tool to help reduce barriers to reporting in New Zealand.

The system is now installed in over 95% of GP practices throughout New Zealand and is integrated into GP Practice Management Systems. A recent review of the system identified that close to half of all reports received from GPs are now submitted using this electronic tool.

When the reporting form is opened in the GP's Practice Management Systems, the tool automatically pre-populates the patient's medical history, medicine history and provides an option to include laboratory results. If the report involves a vaccine, details such as batch number and date of administration are included. Once a description of the reaction is entered, the report is sent directly to the Centre for Adverse Reactions Monitoring (CARM) via a secure electronic pathway.

This system is one of the first in the world to significantly reduce the data entry required for reports and deliver direct electronic reporting of adverse reactions to GPs.

Medsafe hopes the use of this tool will continue to increase the number of adverse reactions reported. In addition, providing more detailed information such as laboratory results helps the clinicians reviewing the reports to determine whether the medicine may have caused the reaction.

Further information about the electronic adverse reaction reporting tool can be obtained from the Best Practice Advocacy Centre, who is contracted to maintain the system.

Although this system is currently only available to General Practice, Medsafe hopes to expand access to other groups, such as community pharmacy, in the future.

### 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
Varenicline	Interaction with alcohol	31 December 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)



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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.



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