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Dabigatran – is there a bleeding problem?

Dabigatran etexilate (Pradaxa) is an anticoagulant that has been funded in both New Zealand (by PHARMAC) and Australia since 1 July 2011.

Dabigatran is a direct thrombin inhibitor and is approved in New Zealand to:

- Prevent Venous Thromboembolism (VTE) in patients following major orthopaedic surgery.
- Prevent stroke, systemic embolism and reduce vascular mortality in patients with atrial fibrillation.

This anticoagulant represents an alternative treatment option to warfarin in patients who are unable to take it or may not have their INR well controlled. A recommendation to use dabigatran for stroke prevention in patients with atrial fibrillation has been incorporated into a number of clinical guidelines. Examples are guidelines produced by the European Society of Cardiology, the Canadian Cardiovascular Society,[1] and the American College of Cardiology.

Prescribers are reminded that the recommended dose of dabigatran differs between the two approved indications, as does the need for dose reductions in special patient groups. These are presented in Table 1.

Prescribers are advised to check the data sheet for full details.[2] Capsules must not be opened as this increases absorption and bleeding risk.

Switching patients from warfarin to dabigatran requires monitoring. Most notably, after stopping warfarin treatment the INR **must** fall below 2 **before** dabigatran is initiated. Full details are contained in the dabigatran data sheet.

As expected for any anticoagulant medicine the main side effect is bleeding.

Clinical studies suggest the risk of bleeding with dabigatran is equivalent to enoxaparin when used for VTE prophylaxis.[3]

Table 1: Overview of dabigatran dosing

	VTE prophylaxis	Prevention of stroke in atrial fibrillation
Adults	**220mg once daily**	**150mg twice daily**
Moderate renal impairment (30 – 50 mL/min CrCl)	**150mg once daily**	**150mg twice daily**
Severe renal impairment (<30ml/min CrCl)	Contraindicated	Contraindicated
Elderly over 80 years	**220mg once daily**	**110mg twice daily**
Children up to 18 years	Not recommended	Not recommended
Weight	No adjustment necessary	No adjustment necessary
Use with ketoconazole	Contraindicated	Contraindicated
Use with potent P-glycoprotein inhibitors (amiodarone, quinidine, verampamil)	**150mg once daily; initiation of verapamil should be avoided.**	**No adjustment necessary**
Use with other P-glycoprotein inhibitors: clarithromycin	No adjustment necessary	No adjustment necessary
Use with P-glycoprotein inducers: rifampicin	No recommendations made; if dabigatran plasma concentrations are reduced by more than half there is a risk of lack of efficacy	
Patients at risk of bleeding (including those taking other anticoagulants)	**No adjustment recommended**	**Consider 110mg twice daily**

In patients with atrial fibrillation the RE-LY study found the overall risk of bleeding was lower in patients taking dabigatran versus warfarin (16.4% vs 18.2%); however dabigatran had a higher incidence of gastrointestinal bleeds.[4,5]

As for all anticoagulants, patients taking dabigatran should be monitored for signs of bleeding or anaemia. The Ecarin Clotting Time (ECT) provides the most sensitive prediction of bleeding risk and should be used when available.[6] The aPTT test may also be useful in patients considered to be at high risk of bleeding, such as the elderly.[6] INR measurement is not affected by dabigatran and should not be used to monitor its anticoagulant effect.

There is no specific reversal agent for dabigatran currently available. Supportive measures and maintenance of adequate diuresis is recommended in cases of bleeding or overdose.[7]

Although dabigatran is not metabolised by the cytochrome P450 enzymes, it is a substrate for P-glycoprotein. Strong P-glycoprotein inhibitors have the potential to increase dabigatran plasma levels and increase the risk of bleeding. P-glycoprotein inducers have the potential to decrease dabigatran plasma levels resulting in a lack of efficacy. Further information about P-glycoprotein and its effect on medicine pharmacokinetics is provided on page 21 of this bulletin.

As for all new medicines patients should be closely monitored for any suspected adverse reactions. All suspected adverse reactions associated with dabigatran should be reported to the Centre for Adverse Reactions Monitoring (CARM).

Summary & Key messages

- Dabigatran (Pradaxa) is approved for VTE prophylaxis following orthopaedic surgery and prevention of stroke in patients with atrial fibrillation.
- Care needs to be taken when prescribing the dose, as this differs depending on the indication.
- Bleeding is the main risk associated with dabigatran treatment; patients should be monitored for signs of bleeding.
- P-glycoprotein inhibitors/inducers may interact with dabigatran and a dose adjustment may be necessary.
- Dabigatran must not be used in patients with severe renal impairment (CrCl < 30mL/min).
- Renal function may need to be monitored in patients taking dabigatran, particularly those at risk of worsening renal impairment.

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Medicines interactions: the role of P-glycoprotein

P-glycoprotein is the most well known of the transmembrane efflux transporters and first surfaced in the 1970's as the reason for multidrug resistance in cancer cells.

The general function of P-glycoprotein is now known to protect the body from harmful substances by:

- Removing drugs absorbed in the intestines back into the gut lumen.
- Maintaining the integrity of the blood brain barrier.
- Removing drugs from the kidneys and liver into the urine and bile respectively.

P-glycoprotein and medicine interactions

P-glycoprotein is partly responsible for the clearance of medicines via the renal and hepatic systems. This active transport system is saturable and can be inhibited or induced, leading to the potential for medicine-medicine interactions and medicine-food interactions.

The location in the body of P-glycoprotein mediated interactions varies and is important in determining whether an interaction is plausible or clinically relevant.

For example the interaction between loperamide and quinidine is due to the inhibition of P-glycoprotein at the blood brain barrier, resulting in adverse effects in the central nervous system. The interaction between digoxin and verapamil takes place at P-glycoprotein located in the liver and kidneys, reducing the excretion of digoxin.

A medicine's pharmacokinetic properties also influence P-glycoprotein interactions. Medicines that exhibit almost complete absorption from the gastrointestinal tract are less susceptible to interactions with P-glycoprotein inhibitors. Clearly gastrointestinal tract based P-glycoprotein interactions are irrelevant for intravenously administered medicines. The interaction between ketoconazole and dabigatran takes place in the intestine and results in increased absorption of dabigatran etixilate.

Clinically relevant P-glycoprotein mediated interactions

Up until recently, only digoxin and the beta blocker talinolol (not available in New Zealand) have been identified as medicines that are substrates for P-glycoprotein but are not metabolised by cytochrome P450.

Dabigatran is an anticoagulant medicine that is also now known to be influenced by P-glycoprotein. Dabigatran etexilate is a prodrug converted to its active form (dabigatran) following absorption from the gastrointestinal tract. Dabigatran etexilate is a substrate for P-glycoprotein; but the active dabigatran is not.

Since dabigatran etexilate is rapidly converted by plasma and liver esterases to its active form, P-glycoprotein interactions only take place in the gastrointestinal tract. This means the clinical significance of interactions with potent inhibitors is variable. For example, while clarithromycin increases the serum concentration of digoxin (renal site of interaction) it has no clinically relevant interaction with dabigatran (gastrointestinal site of interaction).

Table 2: Medicines affected by p-glycoprotein

Inhibitors	Inducers	Substrates
Amiodarone	Rifampicin	Digoxin
Ketoconazole / Itraconazole	St John's Wort	Loperamide
Clarithromycin / Erythromycin	Carbamazepine	Colchicine
Ciclosporin	Phenytoin	Dabigatran etexilate
Verapamil		
Diltiazem		
Quinidine		
Protease inhibitors		
Sirolimus / Tacrolimus		
Grapefruit juice		

P-glycoprotein interactions do not routinely change plasma concentrations nearly as much as CYP450 interactions. Up until the approval of dabigatran these interactions were only clinically relevant for digoxin, due to its a low therapeutic index. Consequently extensive interaction studies have been performed for digoxin. To date only four substances have been reported to result in a greater than two fold change in digoxin C_{max} or AUC due to a P-glycoprotein interaction: valspodar, quinidine, amiodarone and ciclosporin.

Examples of medicines that may affect, or be transported by, P-glycoprotein are outlined in Table 2.

Healthcare professionals are advised to refer to the medicine data sheets available on the Medsafe website to check whether the potential interaction is clinically relevant.

Healthcare professionals are also reminded to report all suspected medicine-medicine and medicine-food interactions to CARM.

References for further reading:

Fenner KS, Troutman MD, Kempshall S et al. 2008. 'Drug-drug interactions mediated through p-glycoprotein: clinical relevance and in vitro-in vivo correlation using digoxin as a probe drug' .Clin Pharmacol and Therapeut. 85 :173-181

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Gadolinium based contrast agents and Nephrogenic Systemic Fibrosis

Prescribers are reminded of a rare but severe side effect associated with gadolinium based contrast agents, often used during MRI. This reminder follows a recent publication that describes five cases of Nephrogenic Systemic Fibrosis (NSF) associated with the use of Omniscan (gadodiamide) in New Zealand.[1]

A review by the European Medicines Agency in 2010 concluded that GBCAs are associated with varying degrees of risk of developing NSF.[3] This difference appears to be related to their ability to release free gadolinium ions into the circulation.

Using the European classification, the GBCAs approved for use in New Zealand can be placed in the following risk categories:

- **High risk**: Omniscan (gadodiamide), Magnevist (gadopentetic acid)
- **Medium risk**: Multihance (gadobenic acid)
- **Low risk**: Gadovist (gadobutrol), Dotarem (gadoteric acid)

NSF is a very rare systemic disease characterised by thickening and hardening of the skin with fibrosis of the dermis.[2] It can also affect other organs such as the lungs and the heart.

NSF presents with pain, pruritis, joint stiffness, tightness, swelling of the hands and feet, paraesthesias and burning.[2] Dry skin, weakness and warmth can also occur. Skin findings can be localised or generalised and the distribution is often symmetric and bilateral.

Although the progression of NSF can be unpredictable, all patients eventually develop limitation of movement.[2] In some cases the disease is fatal. Although a number of treatments have been proposed, there is currently no single effective treatment for NSF.

Key advice for healthcare professionals:

- All patients should be screened for renal dysfunction prior to receiving a GBCA.
- Omniscan and Magnevist are contraindicated for use in patients with severe renal insufficiency (GFR < 30mL/min/1.73m^2).
- Omnisan and Magnevist are contraindicated for use in patients with acute renal insufficiency of any severity due to the hepato-renal syndrome, or in the peri-operative liver transplantation period.
- GBCAs, other than Omniscan and Magnevist, should be used with caution in patients with severe renal insufficiency. However, the minimum recommended dose should be used and sufficient time should be allowed between doses to ensure complete elimination.

Product data sheets for GBCAs are available at: **http://medsafe.govt.nz/profs/Datasheet/dsform.asp**

References

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High dose simvastatin increases myopathy risk

Simvastatin data sheets are in the process of being updated to warn prescribers about the increased risk of myopathy in patients who receive high doses.

Prescribers are advised that high dose (80mg) simvastatin should only be considered in patients who have not achieved their treatment target with lower doses. This advice follows an analysis of the **S**tudy of the **E**ffectiveness of **A**dditional **R**eductions in **C**holesterol and **H**omocysteine (SEARCH) trial, which showed an increased risk of myopathy in patients taking 80 mg/day simvastatin compared with lower doses.[1]

The incidence of myopathy seen in the SEARCH trial increased with increasing dose. For patients taking 80 mg simvastatin daily, the incidence of myopathy was 0.9%, compared with 0.02% for patients taking 20 mg daily. In terms of efficacy, the trial found that treatment with 80 mg simvastatin did not provide clinically significant benefits over 20 mg or 40 mg daily.

The risk of myopathy also increases with age (≥ 65 years), female gender, uncontrolled hypothyroidism, and renal impairment.

Although myopathy is a well known adverse effect of simvastatin the risk increases with increasing dose. Prescribers are advised to consider this risk in light of the limited increase in benefit seen with high dose simvastatin therapy.

Updated contraindications

The findings of the SEARCH study have also led to changes to contraindications for simvastatin.

The use of simvastatin is now additionally contraindicated in patients who have experienced myopathy when treated with other lipid lowering agents. In addition the use of simvastatin is contraindicated when a patient is treated with either potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, posaconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone), or gemfibrozil, cyclosporin or danazol.

A comprehensive list of medicines that interact with simvastatin, and recommendations about how to manage potential interactions is available in the medicine data sheet at: **http://www.medsafe.govt.nz/profs/Datasheet/dsform.asp**

Prescribers are reminded to advise patients about the risk of myopathy and to report unexplained muscle pain, tenderness or weakness to a healthcare professional promptly. This advice applies to patients either starting treatment, or following a dose increase.

Simvastatin therapy should be discontinued immediately if myopathy is suspected.

Key messages:

- High dose (80mg) simvastatin should only be considered in patients who have not achieved their treatment target with lower doses or with alternative agents.
- Do not use simvastatin in patients with a history of statin-induced myopathy.
- Do not use simvastatin with potent CYP3A4 inhibitors, gemfibrozil, cyclosporin or danazol.
- Inform patients about the risk of myopathy associated with simvastatin and to get in contact with a healthcare professional if they experience symptoms.
- Discontinue simvastatin immediately if myopathy is suspected.

References

1. US Food and Drug Administration. 8 June 2011. Safety Communication: New restrictions, contraindications, and dose limitations for Zocor (simvastatin) to reduce the risk of muscle injury. Accessed online: **http://www.fda.gov/Drugs/DrugSafety/ucm256581.htm#Simvastatin_Dose_Limitations**

Reminder: Keeping an eye on bisphosphonates

Prescribers are reminded that bisphosphonates have been associated with a number of rare but serious ocular inflammatory effects, including uveitis and scleritis.

As of 30 June 2011, CARM had received a total of 28 reports of uveitis (including iritis) associated with a variety of medicines. Of these reports over one third (8) were assessed by CARM as being causally associated with the use of bisphosphonates.

Alendronate was associated with the majority of the reports received (4); reports of uveitis have also been received in association with the use of pamidronate (3) and zoledronate (1). Due to the indications for which bisphosphonates are approved, the cases generally involved older females.

Time to onset of the reaction after bisphosphonate administration was generally short, with all cases occurring within one month of treatment initiation. The majority of cases noted that the patient had recovered or improved at the time of the report.

Uveitis is characterised by inflammation of the uvea – the pigmented, vascular inner coat of the eye consisting of the choroid, ciliary body and iris.[1] Uveitis can be classified anatomically based on which part of the eye is inflammed: [2]

- Anterior – inflammation of the iris and anterior chamber (most common form).
- Intermediate or 'pars planitis' – inflammation of the ciliary body.
- Posterior – inflammation of the retina and choroid.
- Panuveitis – inflammation of the entire uveal tract.

The most common symptoms of uveitis include redness of the eye (particularly around the margin of the cornea), photophobia, eye pain (typically an ache), decreased or blurred vision, and floating spots in the visual field.

In anterior uveitis, the pupil may be smaller in size and sometimes irregular. In severe cases of anterior uveitis, a collection of creamy coloured inflammatory debris (hypopion) may be visible overlying the lower part of the iris.[4] Uveitis can affect one or both eyes.[2]

Serious complications of uveitis include cataracts, glaucoma, retinal oedema and permanent blindness.[2]

In patients with suspected drug-induced uveitis the suspected medicine should be discontinued and the patient referred to an ophthalmologist for examination and treatment to control the inflammation. With prompt diagnosis and treatment, drug-induced uveitis is almost always reversible.[5]

Uveitis had also been linked with autoimmune diseases, systemic conditions, and infections.[3]

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Premature ovarian failure with Avastin

Prescribers are advised to discuss the possibility of ovarian failure with all female patients prior to treatment with Avastin. Patients should also be monitored for the development of signs and symptoms of ovarian failure during treatment.

This advice follows the publication of a recent study, NSABP-C08, which found ovarian failure occurs commonly in association with Avastin use.[1]

Although ovarian failure is a well recognised complication of chemotherapy, it has not previously been reported in clinical trials of Avastin. Prescribers are advised to refer to the Avastin data sheet for the full prescribing information, available at: **http://medsafe.govt.nz/profs/Datasheet/dsform.asp**

Study NSABP-C08 was designed to evaluate the use of Avastin with a novel chemotherapy

agent (mFOLFOX6) for the treatment of colon cancer. This study found a substantially higher incidence of ovarian failure in premenopausal women treated with Avastin + mFOLFOX6 (39%) compared to mFOLFOX6 alone (2.6%). Ovarian function returned in 86% of women after Avastin was discontinued.

Avastin (bevacizumab) is a recombinant monoclonal antibody that inhibits tumour angiogenesis and tumour growth. Avastin is approved for use in New Zealand for the treatment of various cancers including colorectal cancer, renal cell cancer, non-squamous non-small cell lung cancer, breast cancer, and high grade malignant glioma.

Patients with ovarian failure usually present with amenorrhoea (or irregular menses) with or without symptoms of oestrogen deficiency (such as hot flushes, night sweats, and emotional lability).[2] Medical intervention may be required for symptom control and to prevent the long term consequences of oestrogen deficiency, such as osteoporosis.

References

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2. Rebar R W .2009. Premature Ovarian Failure. Obstetrics and Gynecology 113: 1355-1363.

Proton pump inhibitors and interstitial nephritis

CARM continues to receive reports of acute renal reactions, primarily interstitial nephritis, in association with the use of proton pump inhibitors (PPIs).

As of 30 June 2011, CARM had received a total of 65 reports of interstitial nephritis associated with omeprazole (62) and pantoprazole (3). The limited use of lansoprazole and esomeprazole in New Zealand may explain the lack of reports to CARM for these PPIs.

Patients with acute interstitial nephritis can present with the non-specific symptoms consistent with acute renal failure.[1] Presenting symptoms include fever, rash, eosinophilia, malaise, myalgia, arthlargia, weight loss, altered urine output, blood or pus cells in the urine and/or high blood pressure.[2,3] In some cases symptoms may also mimic those of vasculitis.[4]

In patients presenting with symptoms suggestive of interstitial nephritis the involvement of PPIs should be considered among a number of other risk factors. Other risk factors include: the use of β-lactams, NSAIDs, sulfonamides and diuretics; the presence of infection; and immune and neoplastic disorders.[2,3]

A definitive diagnosis of interstitial nephritis can only be confirmed with renal biopsy. If interstitial nephritis is suspected, urine microscopy and renal function should be assessed.

In cases of medicine-induced interstitial nephritis, the offending agent should be discontinued immediately and the patient referred to a renal physician for further assessment.

References

1. Kodner C., Kudrimoti A. 2003. Diagnosis and management of acute interstitial nephritis. *American Family Physician*. 67(12): 2527-2534.
2. Perazella M., Markowitz G. 2010. Drug-induced acute interstitial nephritis. Nature Reviews – *Nephrology*. 6:461-470.
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Acne, isotretinoin and depression – inform and monitor

Prescribers are reminded that all patients treated with isotretinoin need to be informed of the risk of depression and be monitored for the development of depression during treatment.

Isotretinoin is approved for use in the treatment of severe forms of nodulo-cystic acne that are resistant to other treatment. Isotretinoin should only be prescribed by prescribers who are experienced in the use of isotretinoin and understand the risk of teratogenicity.

An association between the use of isotretinoin and the development of depression and/or suicidal ideation was first identified from case reports and published case series. Subsequent epidemiological studies have reported conflicting results.[1] In many cases, confounding factors such as the high prevalence of psychiatric morbidity in adolescents and patients with acne are present and make causality assessment difficult.[2]

A recent study conducted in New Zealand found that mood change occurred in 5-10% of patients taking isotretinoin with the incidence increasing with larger doses.[3]

A recent Swedish cohort study reported a positive association between the use of isotretinoin and suicide attempts.[4] This study found that the risk began to increase two years before starting isotretinoin and peaked six months after stopping treatment. In addition the risk was greatest in patients receiving repeated courses of isotretinoin, suggesting it might be related to the patients' perception of their underlying acne.

Further information is available in the isotretinoin datasheet at: **http://www.medsafe.govt.nz/profs/Datasheet/dsform.asp**

Key messages:

- Patients with acne are at risk of developing depression and/or suicidal ideation.
- All patients treated with isotretinoin should be monitored for symptoms of depression.
- Patients (and parents or caregivers) should be informed of the risk of depression and/or suicidal ideation.
- Patients should be advised to seek medical advice immediately if these symptoms occur even after isotretinoin has been discontinued.
- Simply stopping isotretinoin treatment may not relieve the symptoms of depression; additional treatment may be required for some patients.

References:

1. Magin P and Sullivan J .2010. Editorial. Suicide attempts in people taking isotretinoin for acne. BMJ; 341: c5866 doi:10.1136/bmj.c5866
2. Halvorsen JA and Sterm RS et al .2011. Suicidal Ideation, Mental Health Problems, and Social Impairment Are Increased in Adolescents with Acne: A Population –Based Study. Journal of Investigative Dermatology 131: 363-370.
3. Rademaker M .2010. Adverse effects of isotretinoin: A retrospective review of 1743 patients started on isotretinoin. Australasian Journal of Dermatology 51: 248-253
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Updated advice: ceftriaxone and calcium precipitation

In February 2008, healthcare professionals were advised that ceftriaxone should not be mixed or administered with calcium containing solutions due to the risk of precipitation.

Following further investigation, the safety information for the use of ceftriaxone is now being updated with the following recommendations:

- Ceftriaxone must not be administered **simultaneously** with calcium containing intravenous solutions, including continuous calcium containing infusions via a Y site, because calcium precipitation can occur.
- Ceftriaxone is **contraindicated in neonates** if they require (or are expected to require) treatment with calcium containing intravenous solutions due to the risk of calcium precipitation.
- In patients over 28 days of age, ceftriaxone and calcium-containing solutions may be administered sequentially to one another if the infusion lines are flushed between infusions with a compatible fluid.

These recommendations follow Medsafe's review of two *in vitro* studies to assess the potential for precipitation of ceftriaxone and calcium when mixed in infusion lines. The *in vitro* studies were conducted in neonatal and adult plasma; but only showed an increased risk in neonatal plasma.

Complementary Corner: Echinacea – not to be sneezed at

Many herbal medicines contain pharmacologically active ingredients that have the potential to cause adverse reactions or interact with conventional medicines. One such herbal substance is echinacea.

Preparations containing the roots and aerial parts of *Echinacea* species are traditionally used for the prevention and treatment of the common cold.[1-3] Three *Echinacea* species are used: *E. purpurea, E. angustifolia* and *E. pallida*.[2] As for other herbal medicines, commercial preparations have been found to differ appreciably in their composition, mainly due to the use of variable plant material, extraction methods and the addition of other components.[3]

Constituents identified in echinacea species thought to have pharmacological activity include

saturated pyrrolizidine alkaloids, alkylamides, caffeic acid glycosides and polyacetylenes.[2,5]

Echinacea is a member of the Asteraceae (Compositae, daisy) family, which are known to cause allergic reactions. Individuals with allergic tendencies, particularly those with known allergy to other members of the Asteraceae family (e.g. chamomile) should be advised to avoid echinacea preparations.[2]

CARM has received four reports of allergic-type reactions in which echinacea has been reported as an ingredient in a suspect medicine. Case reports of allergic reactions to echinacea in the literature describe events such as angioedema, pruritis, rash, urticaria, and erythema. Positive skin-prick test results for echinacea have been reported in patients who have experienced allergic reactions temporally associated with echinacea.[4]

Echinacea is postulated to act by stimulating the immune system. A 2006 Cochrane review found some evidence that preparations based on the aerial parts of *E. purpurea* might be effective for the early treatment of colds in adults; however the results were not consistent between studies.[1]

The review also reported that beneficial effects of other echinacea preparations, and echinacea used for preventive purposes might exist but have not been shown in independently replicated, rigorous randomised controlled trials. Clinical efficacy in children remains unclear.

Healthcare professionals are encouraged to ask patients about their use of complementary and alternative medicines and to report all suspected adverse reactions to CARM.

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MARC roundup and recommendations

The Medicines Adverse reaction committee met on 9 June 2011 and made the following recommendations:

The risk benefit balance for **bisphosphonates** remains positive following a review of a possible association with **oesophageal cancer**. The review demonstrated there is insufficient evidence to support an association at this time; however an association cannot be discounted entirely. Further research is warranted.

The available data does not support an association between the use of **angiotensin receptor blockers** and **cancer**. This review followed the publication of a meta-analysis suggesting there was a modestly increased risk of new cancer diagnoses. The MARC agreed with the authors of the meta-analysis that additional data is required to further investigate this safety signal.

The MARC reviewed two recently published studies concerning the use of **drospirenone.** The Committee noted that the studies did not change previous advice issued that second generation combined oral contraceptives are associated with the lowest risk of **venous thromboembolism** (VTE).

The MARC noted that a case of **bulging fontanelles** in an infant following vaccination had been reported. Although further information is awaited on this case; the MARC noted that a potential safety signal describing benign transient bulging fontanelles has been published previously.[1]

Further information on all of these issues can be found in meeting minutes, available at: **http://medsafe.govt.nz/profs/adverse/Minutes146.htm#2.1.3**

References

1. Freedman SB, Reed J, Burwen DR et al.2005. Transient bulging fontanelle after vaccination: case report and review of the adverse event reporting system. J Pediatr. 147(5):640-4.

WE NEED YOUR HELP!

M² MEDICINES MONITORING

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

Medicine	Potential safety issue	Active monitoring ends
Sildenafil	Thromboembolism	31 March 2012
Lansoprazole, pantoprazole	Hypomagnesaemia	31 March 2012

- The M² scheme does not replace routine adverse reaction reporting. Find out how to report at: http://www.otago.ac.nz/carm or http://www.medsafe.govt.nz

MEDSAFE
NEW ZEALAND MEDICINES AND MEDICAL DEVICES SAFETY AUTHORITY
A BUSINESS UNIT OF THE MINISTRY OF HEALTH

CARM
CENTRE FOR ADVERSE REACTIONS MONITORING

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.

IMMP
INTENSIVE MEDICINES MONITORING PROGRAMME

INTENSIVE MEDICINES MONITORING PROGRAMME

Which medicines are currently being monitored?

Varenicline (Champix)

Dapoxetine (Priligy)

Where to report

Please report all adverse events occurring with IMMP medicines to: IMMP, NZ Pharmacovigilance Centre, PO Box 913, Dunedin 9054. Use the reporting form provided with each edition of *MIMS New Ethicals* or download it from either the NZ Pharmacovigilance Centre or Medsafe websites: **http://carm.otago.ac.nz/reporting.asp** or **www.medsafe.govt.nz/Profs/adverse.asp**

Further information on IMMP is available at: **http://carm.otago.ac.nz/index.asp?link=immp**

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