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MANATŪ HAUORA

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Prescription medicines obtained via the internet – advice for prescribers

The internet has now become a significant resource for patients to obtain supplies of prescription medicines from overseas. When these medicines are held at the New Zealand border prescribers are usually asked to provide a prescription to enable their release.

Prescribers are reminded to consider the following prior to providing a prescription for medicines obtained from an overseas source:

- Is this 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 on the responsibility for prescribing your patient an unapproved medicine that is likely to be of unknown quality and origin?

Patients who order medicines online commonly believe they are importing genuine branded medicines from countries with highly regulated systems such as Canada or the USA. These websites, which may be linked to spam emails, are sophisticated and misleading as the website may be based in a country different to where it appears to be hosted. A recent study conducted by the FDA of medicines ordered from websites claiming to be Canadian found only 15% of the medicines inspected actually originated in Canada.[1]

Several websites offer medicines for sale without a prescription or in some cases require an online questionnaire to be completed. It is usually not clear whether a healthcare professional is involved in the process.

Medicines coming into New Zealand are intercepted by New Zealand Customs and passed to Medsafe for inspection. Last year approximately 11,000 parcels containing 17,000 medicines were inspected by Medsafe; it is estimated that up to 30% of these medicines may have been ordered over the internet. Medsafe's experience is that many of the prescription medicines crossing the border are of poor quality and may be adulterated or counterfeit. For example, recent testing revealed four undeclared active ingredients in one product ordered over the internet.

The New Zealand medicines legislation requires anyone who imports, distributes, sells or possesses a prescription medicine to have a 'reasonable excuse'. A patient will have a reasonable excuse if a New Zealand registered prescriber has prescribed the medicine. If a prescriber provides a prescription for a medicine that has been intercepted at the border they take on all the responsibilities of prescribing, including responsibility for the quality and appropriateness of the medicine for that patient. Without a prescription a patient is unlikely to have a reasonable excuse and would be in breach of this provision.

In addition to quality concerns, Medsafe is also concerned about the dangers of self-medication. Individuals may not have seen a medical professional, had an adequate diagnosis made, or received information on the risks and benefits of using a particular medicine.

Medsafe advises prescribers to carefully consider these issues before agreeing to authorise supply of a medicine purchased over the internet.

Reference

1. FDA (2005). FDA operation reveals many drugs promoted as "Canadian" products really originate from other countries. Accessed 3/7/09 from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2005/ucm108534.htm

Topical oral choline salicylate gels – safety in children

In New Zealand three topical products for oral use contain choline salicylate: Bonjela Teething Gel, Bonjela Mouth Ulcer Gel and Ora-sed gel.

Medsafe advises prescribers it is satisfied that the safety of these products in children is acceptable when used at recommended doses.

Medsafe's advice follows a review of the recent decision by the United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA) to contraindicate the use of all topical oral choline salicylate gels in children under 16 years of age.

The MHRA decision was based on a case report published in the British Medical Journal in June 2008. The report described a suspected case of Reye's syndrome in a 20 month old child following the use of Bonjela oral gel. Following its review the MHRA concluded that the symptoms described in this case could not be considered to be Reye's syndrome and were more likely due to salicylate toxicity from overuse of the product. The MHRA subsequently contraindicated the use of these

products in children under 16 years of age due to a theoretical risk of Reye's syndrome.

Medsafe reviewed data from the MHRA, the manufacturer of Bonjela, the Centre for Adverse Reactions Monitoring (CARM) and the New Zealand Poisons Centre. Medsafe's review found no evidence linking Reye's syndrome to the use of topical oral choline salicylate containing products.

Medsafe's review has however highlighted that the recommended dose of these products is sometimes exceeded. The New Zealand Poisons Centre has advised Medsafe that 279 calls relating to the use of these products in children have been received since 2002.

Healthcare professionals are advised to remind parents and carers about the importance of reading the information provided with the medicine and adhering to the recommended dose. The approved dosing in New Zealand is to apply a small quantity of gel (ie tip of index finger) to the affected area no more than every three hours when required for the relief of pain and discomfort associated with infant teething. Parents and carers should also be reminded to keep all medicines out of sight and reach of children.

Etanercept and uveitis

Etanercept (Enbrel) is a TNFα inhibitor indicated for the treatment of rheumatoid arthritis, ankylosing spondolitits, juvenile idiopathic arthritis, psoriasis and psoriatic arthritis.

A review of spontaneous post-marketing reports submitted to CARM indicated that there may be a risk of uveitis associated with the use of etanercept.

This association has been considered by the Medicines Adverse Reaction Committee (MARC) and has resulted in the Enbrel datasheet being updated to include uveitis as an uncommon adverse reaction. The Enbrel data sheet is available at **http://www.medsafe.govt.nz/profs/Datasheet/e/Enbrelinj.htm**

Clopidogrel and proton pump inhibitors – possible interaction

Prescribers are advised that Medsafe is reviewing a possible medicine interaction between clopidogrel and proton pump inhibitors.

Clopidogrel inhibits platelet function and is indicated for the prevention of vascular ischaemia associated with atherothrombotic events. Proton pump inhibitors are frequently co-prescribed with clopidogrel to reduce gastrointestinal irritation which can be associated with clopidogrel use.

Some published reports[1,2] have suggested that concomitant use of proton pump inhibitors can reduce the efficacy of clopidogrel.

Medsafe has reviewed the available evidence relating to this risk and has required the data sheets for clopidogrel to be updated. This update includes additional information in the warnings and precautions section about genetic factors influencing clopidogrel metabolism, specifically in patients with genetically reduced CYP2C19 function. As a precaution the clopidogrel data sheets are also being updated to include information discouraging the use of concomitant medicines that inhibit CYP2C19 metabolism, e.g. omeprazole.

Medsafe is continuing to monitor the evidence in support of an interaction between clopidogrel and proton pump inhibitors. Further information will be communicated when the results of definitive interaction studies currently underway become available and are fully analysed to determine their clinical significance.

Until these data are available Medsafe recommends that healthcare professionals continue their current prescribing practices for clopidogrel. However patients requiring concomitant treatment with a proton pump inhibitor should have their treatment reviewed. If possible an H2-receptor blocker and/or antacid should be considered instead of a proton pump inhibitor in these patients.

References

1. Ho PM, Maddox TM, Wang L et al. (2009) Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome JAMA 301(9): 937-44.
2. Juurlink DN, Gomes T, Ko DT et al. (2009) A population-based study of the drug interaction between proton pump inhibitors and clopidogrel CMAJ 180:713-8

Medical oxygen in the home – safety considerations

Prescribers of medical oxygen are reminded of the potential hazards when used in the home and that these hazards need to be managed to ensure the safety of all concerned.

The patient's capabilities, access to support and home environment should be assessed prior to initiating medical oxygen in the community. This assessment should ensure safe storage of equipment and ensure the patient or carer is able to manage their oxygen therapy at home. This includes an understanding of the operation of the equipment and the ability to manage shut off valves, flow meters and other controls.

Patients or carers should be given basic training in the use of home oxygen equipment and how to manage simple problems, preferably with available reference material. Appropriate signage should also be provided to alert healthcare professionals and emergency services that oxygen therapy equipment is on the premises.

Patients or carers need to be made aware of the dangers when oxygen is used or stored in proximity to readily combustible materials, particularly:

- Open fires.
- LPG or other fuel gases (includes gas stoves and gas fires).
- Oils, including cooking oils and lubricating oils.
- Petrol, kerosene and paint solvents.

Also, consideration should be given to the type of equipment provided. When oxygen concentrators are provided it is important to ensure:

- An electrical circuit with sufficient capacity is used to prevent overloading and power outages.
- The concentrator is not used in proximity to electric fires or heaters as these pose a fire hazard.
- The concentrator is never operated in confined spaces such as cupboards or behind curtains or drapes. This may also pose a fire hazard due to a build up of heat in the presence of high oxygen concentrations.

When oxygen cylinders are provided it is important to ensure:

- They are securely supported to prevent accidental toppling when in use and during storage.
- They are stored in a well-ventilated area away from combustible materials or ignition sources.
- They are positioned during use so the user can operate the flow meter controls and shut off valves without having to move or tilt the cylinder.

Guidelines on the use of oxygen in homecare environments have been published by the European Industrial Gases Association (EIGA). While based on European regulation, the document 89/09E "Medical Oxygen Systems for Homecare Supply" also includes patient training material and an environment risk assessment template. This document is available at **www.eiga.org**, from within the IGC/MGC Documents listed under "Publications".

Electronic adverse reaction reports – please include medication dates

As reported in the May edition of *Prescriber Update*, an electronic adverse reaction reporting tool has been launched in New Zealand.

The reporting tool, developed in conjunction with the Best Practice Advisory Centre (BPAC), is being rolled out to GP practices across the country. To date over half of all GP practices in New Zealand now have access to the reporting tool.

Early feedback has so far been positive, with comments centred on the short time taken to submit adverse reaction reports and the ability to include data such as laboratory results. Although it is too early to see the impact of the tool on the number of adverse reactions reported, the number of electronic reports submitted to CARM continues to increase.

The new reporting tool has been specifically designed to reduce the time taken to submit adverse reaction reports; however reporters are reminded to include as much information as possible.

CARM would like to remind prescribers that start and stop dates for all medicines are extremely important to enable proper assessment of a report. For non-suspect medicines where the dates are uncertain more general entries are acceptable eg "years". Reporters are also asked, where possible, to provide the brand name of the medicine(s) especially if the suspected reaction is associated with a change in medicines. The brand name of the medicine can be entered manually either after the generic name in the patient medication list or to the description of the adverse reaction.

Including as much information as possible also helps provide more information back to the reporter.

Healthcare professionals with any questions on access or availability of the electronic reporting tool should contact BPAC on (03) 477 5418.

Methaemoglobinaemia – signs and risk factors

Prescribers are reminded that a number of medicines have been associated with the development of methaemoglobinaemia.

Methaemoglobin is formed when the iron in haemoglobin is oxidised to its ferric state. This reduces the oxygen carrying capacity of haemoglobin. Methaemoglobin is normally present in the blood at concentrations below 2%; symptoms are only likely to develop when methaemoglobin levels exceed 20% to 30%.

Signs and symptoms of methaemoglobinaemia include headache, fatigue, cyanosis, tachypnoea, dyspnoea, tachycardia, altered levels of consciousness, myocardial infarction and diffuse hypoxic brain injury. Severe cases have resulted in death.

In confirming the diagnosis of methaemoglobinaemia, pulse oximetry is not considered a reliable measurement.[1] Diagnosis of methaemoglobinaemia requires co-oximetry testing on arterial blood samples.

Risk factors for developing methaemoglobinaemia include:[2]

- Topical or injectable administration of local anaesthetics such as prilocaine, benzocaine, lidocaine (lignocaine) and tetracaine (amethocaine).
- Use of amyl nitrite (and other nitrites and nitrates), chloroquine, primaquine, dapsone or sulphonamides.
- Age – children under three months of age have a higher risk due to being more susceptible to oxidant stress.
- Systemic infection.
- Anaemia.
- Presence of congenital methaemoglobinaemia or G6PD deficiency.

References

1. Sharma V, Haber A, (2002) Acquired methaemoglobinaemia: a case report of benzocaine-induced methaemoglobinaemia and a review of the literature, *Clinical Pulmonary Medicine*, 9(1): 53 – 8.
2. Kane G, Hoehn S, Behrenbeck T et al (2007) Benzocaine-induced methaemoglobinaemia based on the Mayo Clinic experience from 28,478 transoesophageal echocardiograms, *Archives of Internal Medicine*, 167(18): 1977 – 82.

Combination anticoagulants – increased bleeding risk

Medsafe is aware that ACC has recently received a number of claims for treatment injury from patients prescribed a combination of warfarin and aspirin.

The adverse events included major bleeding events such as subdural haematoma and intra-cerebral haemorrhage. Importantly some of these events have occurred in patients with an INR within the therapeutic range who were also taking low dose aspirin (100 mg to 150 mg each day).

Warfarin has been prescribed in these patients for anticoagulation in the presence of atrial fibrillation and in patients with prosthetic heart valves. As prescribers may be aware, anticoagulant combinations are also sometimes used for secondary prevention of ischaemic stroke and myocardial infarction.

For many of the therapeutic indications for warfarin the evidence does not suggest that a combination of aspirin and warfarin is more effective than warfarin alone.[1]

The literature indicates there is an increased risk of major bleeding events when warfarin and aspirin are used in combination;[2] therefore prescribers are reminded to consider these risks before prescribing this combination.

Prescribers are also reminded to ask patients if they are taking aspirin prior to commencing warfarin.

References

1. Hurlen M, Abdelnoor M, Smith P et al (2002) Warfarin, Aspirin, or both after myocardial infarction, *New England Journal of Medicine*, 347 (13):969 – 74.
2. Shireman T, Howard P, Kresowik T et al (2004) Combined anticoagulant – antiplatelet use and major bleeding events in elderly atrial fibrillation patients *Stroke*, 35:2362 – 67.

Nitrous oxide – side effects reminder

Prescribers are reminded that prolonged use of nitrous oxide has been associated with neurological and haematological side effects such as megaloblastic anaemia and myelopathy due to inactivation of vitamin B_{12}. Neurological symptoms can occur without any overt haematological changes.

Where possible, prescribers are advised:

- To check vitamin B_{12} levels in those with risk factors for vitamin B_{12} deficiency prior to using nitrous oxide and to seek specialist advice if necessary.

- Not to use nitrous oxide continuously for more than 24 hours or more frequently than every 4 days without clinical supervision and haematological monitoring.

Glyceryl trinitrate for rectal use now pharmacist-only

Healthcare professionals are reminded that glyceryl trinitrate for rectal use has been reclassified from a pharmacy to a pharmacist-only medicine.

Glyceryl trinitrate for rectal use is indicated in New Zealand for treatment of anal fissure and to relieve the pain and discomfort associated with haemorrhoids. Rectogesic is currently the only glyceryl trinitrate product for rectal use approved in New Zealand.

The reclassification is due to concerns about the potentially serious adverse effects associated with the concomitant use of erectile dysfunction (ED) medications such as sildenafil, tadalifil and vardenafil. Specifically, the interaction may potentiate the hypotensive effects of organic nitrates. The reclassification enables pharmacists to provide advice about this interaction at the point of sale.

Healthcare professionals are reminded to ask about other medicines being used by the patient prior to prescribing, dispensing or selling Rectogesic. An alternative treatment should be offered to patients who are also being prescribed an ED medicine.

Further information on the use of glyceryl trinitrate for rectal use can be found in the Rectogesic data sheet at **www.medsafe.govt.nz/profs/Datasheet/r/rectogesicoint.htm**

Use of unapproved medicines in New Zealand

Prescribers may be aware that Section 25 of the Medicines Act 1981 permits practitioners to procure for sale or supply any medicine for a particular patient in their care. In addition, Section 29 of the Medicines Act 1981 enables a New Zealand company to obtain and supply an unapproved medicine when authorised by a prescriber.

Prescribers are reminded, however, that unapproved medicines supplied under Section 29 of the Act are not regulated by Medsafe. This means a data sheet is normally not available on the Medsafe website for these medicines. Prescribers should be aware that Medsafe dose not normally monitor the safety of these medicines or issue warnings about new safety issues.

It is the prescriber's responsibility to ensure that they remain cognisant of any safety issues relating to any unapproved medicines they may be prescribing and communicate the risks and benefits to their patients. Medsafe has a number of links on its website that healthcare professionals may find helpful. These links can be found at: **http://www.medsafe.govt.nz/profs/other.asp**

Complementary Medicine Corner – Safety of Green Tea extracts

Green Tea (*Camellia sinensis*) is a widely used dietary supplement and is often promoted for weight loss.

Recently the United States Pharmacopoeia (USP) published a review of the safety of Green Tea extracts.[1] A total of 216 case reports of suspected adverse reactions were reviewed; 34 reports concerned liver damage.

In 2003 French and Spanish authorities suspended market authorisation of Exolise, a weight loss product containing green tea extract. There had been 13 reports of elevated liver enzymes with an onset time of 9 days to 5 months. Twelve patients recovered after stopping Exolise and one patient, with regular alcohol intake, progressed to liver failure.

More recently the food supplement Hydroxycut, of which some formulations contain Green Tea extract, was removed from sale in New Zealand, Canada and the United States. This action was due to concerns over liver toxicity, seizures, cardiovascular disorders and muscle damage.

In the review conducted by the USP, clinical pharmacokinetic and animal toxicological information indicated that consumption of Green Tea extracts on an empty stomach increased the risk of liver related adverse effects. The USP recommends that complementary medicines containing green tea should only be taken with food.

Prescribers are reminded to ask about the use of complementary medicines and food supplements in patients with elevated liver enzymes and report any suspected adverse reactions to complementary medicines to CARM.

Reference

1. Dandapantula N et al (2008) 'Safety of Green Tea Extracts' Drug Safety 31: 469-484.

ADVERSE REACTIONS OF CURRENT CONCERN

The Medicines Adverse Reactions Committee (MARC) initiated the list of *adverse reactions of current concern* to bring particular medicine adverse reactions to the attention of prescribers. The intention is to encourage prescribers to report these reactions to the Centre for Adverse Reactions Monitoring (CARM) so that more information can be gathered, and further action taken if necessary. The reports provide a New Zealand perspective on emerging medicine safety issues.

As with any adverse reactions monitoring scheme, analysis can only be based on reports that are received. Prescribers are therefore encouraged to continue reporting adverse reactions to CARM so that the MARC can make the best possible recommendations based on information reflecting the New Zealand situation.

Regular amendments to the list of reactions are made either in response to adverse events reported in New Zealand or international pharmacovigilance issues.

Please report **all cases** of the following adverse reactions to: CARM, NZ Pharmacovigilance Centre, PO Box 913, Dunedin 9054. Use the reporting form provided with each edition of *MIMS New Ethicals*, or download the form from the CARM or Medsafe web sites: **www.otago.ac.nz/carm** or **www.medsafe.govt.nz/Profs/adverse.htm**

Medicine/s	Adverse reactions of current concern	*Prescriber Update* references
Complementary and alternative medicines*	all adverse reactions	Vol.30(2), May 2009 & Vol.30(1), February 2009 & Vol.28(1), November 2007 & Vol.23(2), July 2002
Leflunomide	all adverse reactions	Vol.29(1), June 2008 & Vol.27(1), June 2006 & Vol.26(2), December 2005 & Vol.25(1), May 2004
Pioglitazone and Rosiglitazone	all adverse reactions	Vol.29(1), June 2008 & Vol.28(1), November 2007 & Vol.27(1), June 2006

* includes herbal medicines, bee products, homoeopathic products, dietary supplements, minerals, and any other medicines containing animal or plant extracts.

INTENSIVE MEDICINES MONITORING PROGRAMME

Which medicines are currently being monitored?

Varenicline (Champix)

What to report

Please report **all clinical events** in patients taking **varenicline**, including:

- any suspected adverse reaction
- deaths (including cause if known)
- any new clinical events, even if minor or common
- accidents
- change in a pre-existing condition
- abnormal changes in laboratory test results
- possible interactions.

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: **www.otago.ac.nz/carm** or **www.medsafe.govt.nz/Profs/adverse.htm**

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

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