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Safety signal – serious hyponatraemia

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This article is a summary of a more detailed article to be published by NZPhvC

The New Zealand Centre for Adverse Reactions Monitoring (CARM) has examined recent reports of hyponatraemia in its database.

Hyponatraemia, defined as plasma sodium < 135mmol/L, is caused by a range of medicines and clinical conditions. Medicine-related hyponatraemia occurs most often in the elderly early in the course of treatment. The mechanism is most often syndrome of inappropriate antidiuretic hormone secretion (SIADH) or renal loss.

Medicines most often implicated in recent reports to CARM are selective serotonin or noradrenaline reuptake inhibitors (SSRIs/SNRIs) and thiazide diuretics. Other medicines reported more than once in 2007 and 2008 were anticancer agents, proton pump inhibitors, sodium valproate and ACE inhibitor/diuretic combinations. Carbamazepine has also been frequently implicated in the database.

Serious hyponatraemia (plasma sodium < 120mmol/L) can lead to confusion, convulsions and serious neurological damage. Examination of serious symptomatic reports to CARM revealed that in most cases more than one hyponatraemic medicine was implicated. Reports for three patients indicated that they each had persistent mild to moderately low plasma sodium levels (128 to 133mmol/L) while taking two hyponatraemic medicines. Following addition of a third hyponatraemic agent a much more profound fall ranging from 104 to 121mmol/L occurred.

The reports that CARM has received supports current advice that plasma sodium should be measured shortly after starting potentially hyponatraemic medicines, especially SSRIs or diuretics. Measurements should be repeated both before and after adding another hyponatraemic medicine. If there is mild persistent hyponatraemia the addition of further medicines or the development of clinical conditions that can decrease plasma sodium may lead to a more profound and symptomatic reaction.

Lantus (insulin glargine) and cancer – no conclusive evidence of higher risk

Four epidemiological studies were recently published in Diabetologia suggesting a possible association between insulin glargine (Lantus) use and an increased risk of cancer.

Medsafe and the Medicines Adverse Reactions Committee (MARC) have closely reviewed these studies in conjunction with data provided by the sponsor of Lantus.

The results of the studies are summarised in the table below:

Study	Any malignancy, hazard ratio (95% CI)
Hemkens et al[1]	1.18 (1.08-1.28)¶
Currie et al[2]	0.81 (0.59-1.11)¤
Jonasson et al[3]	1.06 (0.90-1.25)§
Colhoun et al (incident cohort)[4]	0.87 (0.63-1.21)§

Comparators: ¶ Human insulin alone. ¤ Long acting insulin – derived data § Non glargine insulin.

The MARC considered that these studies have methodological problems including: potential exposure misclassification, selection bias, differing comparator groups, lack of adjustment for confounding factors, short duration, and incomplete information on risk factors.

As a result of the issues and the inconsistency of the study results, the MARC could not determine if there was an increased risk of cancer in patients taking insulin glargine.

The MARC has advised that until further information is available, newer insulins such as Lantus should only be used when there is additional benefit to the patient, compared with other treatments.

Medsafe's media release and "Dear Healthcare Professional letter" can be found at:
http://www.medsafe.govt.nz/hot/MediaContents.asp

References

1. Hemkins LG, Grouven U, Bender R, et al. Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study. *Diabetologia* 2009;52(9):1732-44.
2. Currie CJ, Poole CD, Gale AM. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. *Diabetologia* 2009;52(9):1766-77.

3. Jonasson JM, Ljung R, Talback M, et al. Insulin glargine use and short-term incidence of malignancies – a population based follow-up study in Sweden. *Diabetologia* 2009;52(9):1745-54.

4. Colhoun HM, SDRN Epidemiology Group. Use of insulin glargine and cancer incidence in Scotland: a study from the Scottish Diabetes Research Network Epidemiology Group. *Diabetologia* 2009;52(9):1755-65.

Lamotrigine – reduced dose required in patients already taking sodium valproate

Prescribers are reminded to adhere to the recommended dose guidelines when prescribing lamotrigine to patients already taking sodium valproate. Adhering to these dosing guidelines reduces the risk of serious skin reactions.

The CARM database contains reports of toxic epidermal necrolysis (TEN) and Stevens Johnson's syndrome (SJS) in patients taking concomitant lamotrigine and sodium valproate. It has been identified that risk factors included exceeding the recommended starting dose of lamotrigine or the rate of dose escalation.

The incidence of serious skin reactions (including TEN and SJS) in clinical trials using recommended lamotrigine dosing is approximately 1 in 500 epilepsy patients and 1 in 1000 patients with bipolar disorder. The incidence of serious skin reactions is greater in children with estimates ranging from 1 in 300 to 1 in 100 children. Serious skin reactions generally occur within 8 weeks of commencing lamotrigine therapy; the risk is increased by high initial doses of lamotrigine, exceeding recommended doses, rapid dose escalation and concomitant use of sodium valproate.

Lamotrigine is approved in New Zealand as adjunctive therapy in adults and children with epilepsy, and for the prevention of mood disorders in adults with bipolar disorder. In adult patients already taking sodium valproate the starting dose of lamotrigine is 12.5mg/day (or 25mg on alternate days) for 14 days, increased to 25mg/day for a further 14 days. The dose of lamotrigine can thereafter be increased by 25–50mg/day every 7 –14 days.

Further information on the use of lamotrigine and dose regimens for children can be found in data sheet on the Medsafe website: **www.medsafe.govt.nz/profs/Datasheet/dsform.asp**

Intravenous promethazine – reports of serious tissue injuries

Promethazine injection is highly caustic to the intima of blood vessels and surrounding tissues.[1] Reports from the United States describe serious tissue reactions including thrombosis, nerve damage, tissue necrosis and gangrene in patients who have received intravenous promethazine. In rare cases surgical intervention such as skin graft, fasciotomy or amputation has been required.[1,2]

In New Zealand promethazine injection is approved for the treatment of vomiting, allergic reactions (including anaphylaxis) and to induce sedation.

After reviewing the published literature, assessing the New Zealand case reports and consulting with healthcare professionals, Medsafe has concluded that there remains a clinical need for intravenous promethazine in New Zealand.

Medsafe however recommends that intravenous promethazine should only be used if the benefits clearly outweigh the risks in each patient. This may include emergency situations (such as treatment of anaphylaxis) or situations where intramuscular or oral administration is contraindicated.

To maximise the safe use of this medicine, Medsafe offers the following advice:

1. Deep intramuscular injection is the preferred route of administration of promethazine injection.
2. Promethazine must not be administered subcutaneously or intra-arterially.
3. An alternative medicine should be considered if intravenous administration is required.
4. Promethazine should be administered through large patent veins. Veins in the hand and wrist should be avoided if possible.[1]
5. If intravenous administration is required, the maximum recommended concentration is 25mg/mL and the maximum recommended rate of administration is 25mg/minute. Further dilution and administration over 10-15 minutes may reduce the risks even further.[1]
6. The injection should be stopped immediately if pain or a burning sensation occurs.
7. Patients should be advised to seek medical assistance if pain, a burning sensation, swelling or blistering occurs at any time after the administration of intravenous promethazine.

The New Zealand data sheet for DBL-Promethazine is currently being updated in line with this advice. The New Zealand data sheet is available at: **www.medsafe.govt.nz/profs/Datasheet/dsform.asp**

As with all medicines, adverse reactions associated with the use of intravenous promethazine should be reported to the CARM.

References

1. Grissiner M. Preventing Serious Tissue Injury with Intravenous Promethazine (Phenergan). *P&T* 2009;34(4):175-176.
2. FDA. Information for Health Professionals – Intravenous Promethazine and Severe Tissue Injury, Including Gangrene. 16 September 2009. www.fda.gov/Drugs. Accessed 28 October 2009.

Alendronate – risk of low-energy femoral shaft fracture

A number of published case reports have described atypical low energy stress fractures of the subtrochanteric and proximal femoral shaft in patients taking alendronate long-term.[1-3] In some cases the patient experienced prodromal pain in the affected area weeks to months before a complete fracture occurred.

Prescribers are advised to consider the risk of atypical stress fractures in alendronate-treated patients reporting pain of the subtrochanteric or proximal femoral shaft. It is important to note that the reported alendronate-associated fractures were frequently bilateral; therefore the contralateral femur should be examined if a fracture is suspected.

Factors which may increase the risk of fractures include: vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, and chronic alcohol abuse.

It is important to note that atypical stress fractures have also been reported in patients not taking bisphosphonates. In addition, it is possible that other bisphosphonates may be associated with an increased risk of atypical stress fractures.

Medsafe advises that the interruption of bisphosphonate therapy in patients with atypical stress fractures should only be considered following an individual risk-benefit assessment.

References

1. Kwek EB, Goh K, Koh JSB, Png MA, et al. An emerging pattern of subtrochanteric stress fratures: A long-term complication of alendronate therapy. *Injury* 2008;39:224-231.
2. Lenart BA, Lorich DG, Lane JM. Atypical fractures of the femoral diaphysis in postmenopausal women taking alendronate. *New England Journal of Medicine* 2008;358(12):1304-6.
3. Neviaser AS, Lane JM, Lenart BA, et al. Low energy femoral shaft fractures associated with alendronate use. Journal of Orthopaedic Trauma 2008;22:346-50.

Drowsiness – remember to warn patients

A recent CARM case report has highlighted the importance of patient counselling when prescribing or dispensing medicines that can cause drowsiness.

The case report describes adverse events including vertigo, dizziness and sleepiness following the use of 1.5 grams of ornidazole. The patient was not aware that this medicine could cause drowsiness and fell asleep, leading to a small child being inadequately cared for.

Healthcare professionals are reminded to consider if a medicine being prescribed or dispensed may cause drowsiness and to discuss this possibility with the patient.

Further information on known adverse reactions for medicines can be found in product data sheets at: **www.medsafe.govt.nz/profs/Datasheet/dsform.asp**

Omeprazole and pantoprazole now pharmacist-only

Healthcare professionals are reminded that omeprazole and pantoprazole have been reclassified from prescription to pharmacist-only medicines.

These medicines can only be supplied as pharmacist-only medicines for short-term, symptomatic relief of reflux-like symptoms in sufferers aged 18 years and over.

The conditions for reclassification of these medicines are as follows:

- Omeprazole – in tablets or capsules containing 10 milligrams or less and when sold in packs approved by the Minister or the Director-General of Health for distribution as restricted medicines.

- Pantoprazole – in tablets or capsules containing 20 milligrams or less of pantoprazole when sold in a pack approved by the Minister or the Director-General of Health for distribution as a restricted medicine.

In response to this reclassification the New Zealand College of Pharmacists has developed training material for pharmacists, in conjunction with the pharmaceutical industry and specialist gastroenterologists. Although training is not mandatory, the New Zealand College of Pharmacists reports that over 1000 pharmacists have completed training so far.

Further information concerning the use of these medicines is available from the Medsafe website on: **www.medsafe.govt.nz**

Further information on the training material available for health care professionals is available from the New Zealand College of Pharmacists.

Cough and cold medicines – further contraindication recommended

Medsafe recently convened the Cough and Cold Review Group (CCRG) to review the benefits and risks of using cough and cold medicines in children. The CCRG consisted of representatives from CARM, the MARC, the New Zealand College of Pharmacists, the Royal New Zealand College of General Practitioners, the Paediatric Society of New Zealand, the Pharmaceutical Society of New Zealand, the pharmaceutical industry, Plunket and the public.

After considering all available safety and efficacy data, the CCRG considers the risk-benefit balance of these medicines to be unfavourable in children under six years of age. The CCRG has therefore recommended that cough and cold medicines be contraindicated for use in children **under six years of age**.

This recommendation applies to all medicines indicated for the treatment of the symptoms of the common cold that contain one or more of the following substances: brompheniramine, chlorphenamine, dextromethorphan, diphenhydramine, doxylamine, guaifenesin, ipecacuanha, phenylephrine, pholcodine, promethazine, pseudoephedrine, and triprolidine.

The CCRG considered that cough and cold medicines containing bromhexine alone, or intra-nasal decongestants (such as oxymetazoline and xylometazoline) should remain available to adults and children over two years of age. This recommendation is due to there being less evidence of harm with these medicines.

Medsafe has accepted the advice of the CCRG and will work closely with the pharmaceutical industry to implement the recommendations as soon as possible. Medsafe has decided not to recall these medicines to ensure stock remains available for adults.

Medsafe will advise healthcare professionals when the contraindication comes into effect, at which point the affected cough and cold medicines must not be used in children under six years of age. In the meantime healthcare professionals are encouraged to familiarise themselves with the risk-benefit information available on the Medsafe website to understand the reasons for the CCRG recommendation.

Further information on the recommendations made by the CCRG, including the minutes of the Group's meetings and a list of the affected medicines, can be found at:
http://www.medsafe.govt.nz/hot/alerts/CoughandCold/CoughandCold.asp

Complementary Medicine Corner: Reporting adverse reactions

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

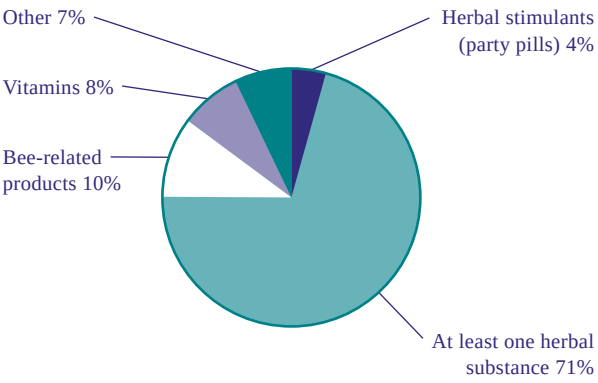
Adverse reactions to complementary and alternative medicines are currently listed as an Adverse Reaction of Current Concern. This includes suspected reactions to herbal medicines, bee products, homoeopathic products, dietary supplements, minerals, and any other medicines containing animal or plant extracts.

Overview of reports to CARM

The number of reports of suspected adverse reactions to complementary medicines in New Zealand is low. From 1992 to March 2009 only 344 reports identified a complementary

medicine as a suspect medicine. Of the 344 reports received 25% described serious adverse events.[1]

Some reports included more than one complementary medicine; a total of 403 complementary medicines were listed as suspect medicines in the reports. Grouping these products into five broad categories indicates that most suspected products contained at least one herbal substance.



The reasons why reporting is low for complementary medicines is unclear but some possible reasons include:

- Uncertainty about what can be reported.
- Lack of association between the use of complementary medicines and the adverse reaction (assumption that natural = safe).
- Lack of discussion between patients and healthcare professionals about the use of complementary medicines.

Information to include when reporting

Increasing the number of good quality reports increases CARM and Medsafe's ability to detect potential side effects and assists in the assessment of risk. Reporting also helps in the identification of interactions with conventional medicines.

When reporting a suspected adverse reaction to a complementary or alternative medicine use the same reporting form as for medicines. It is also important to include as much information about the suspect product as possible, such as:

- The brand name (if it has one).
- The list of ingredients stated on the product label.
- Details of the manufacturer.
- Ideally, a copy of the package label.

For serious adverse reactions, healthcare professionals should consider asking the patient to retain the product in case testing is needed. Medsafe may decide to have the product tested if it is suspected to contain an undeclared ingredient such as a prescription medicine. Prescription medicines have been found in complementary medicines in New Zealand, for example in those used for slimming or erectile dysfunction.

Footnote

1. Serious adverse event – events where the patient either died, required hospitalisation or prolonged existing hospitalisation, required intervention to prevent permanent disability/incapacity, resulted in a congenital abnormality, or where the event was life-threatening.

ADVERSE REACTIONS OF CURRENT CONCERN

MARC Rx ADVICE

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(3), August 2009, Vol.30(2), May 2009 & Vol.30(1), February 2009 & Vol.28(1), November 2007
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

IMMP 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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