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MANATŪ HAUORA

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Eltroxin update

Four brands of levothyroxine now have Ministerial consent for distribution in New Zealand. These brands are Eltroxin (GlaxoSmithKline), Synthroid (Abbott), Goldshield Levothyroxine, and Eutroxsig (Sigma). The Eltroxin and Goldshield Levothyroxine brands are fully subsidised by PHARMAC.

Prescribers are reminded that the different brands of levothyroxine are not interchangeable. This means a change in brand will require thyroid function monitoring, and in some cases dose adjustment. Prescribers are also reminded to specify the brand of levothyroxine on each prescription to ensure the correct brand is dispensed for each patient.

The Centre for Adverse Reactions Monitoring (CARM) continues to receive adverse reaction reports for all brands of levothyroxine available in New Zealand; however the number of reports has tailed off in recent months. As at 31 December 2008, CARM had received 1384 reports for Eltroxin, 9 reports for Synthroid, and 5 reports for Goldshield Levothroyxine. Adverse drug reactions to Eltroxin have not been reported to the same extent in other countries where the new formulation is used.

For further information on Eltroxin, the actions taken by Medsafe in response to the increased number of adverse reaction reports, and Medsafe's evaluation process, please see: www.medsafe.org.nz/hot/alerts/EltroxinInfo.asp

Prescribers are also reminded to continue to report adverse reactions to all levothyroxine brands to CARM.

Black cohosh and hepatotoxicity – ask about use and look for signs

Very rare hepatotoxic reactions have been reported in association with the use of the herb black cohosh (*Cimicifuga racemosa*). Reported reactions include abnormal or elevated liver function test results, hepatitis, and hepatic failure sometimes requiring liver transplantation.[1]

Black cohosh is used predominantly by women seeking a natural alternative to hormone replacement therapy for the relief of symptoms associated with menopause. It is found in a number of dietary supplement-type products marketed directly to consumers, typically as the dried root/rhizome or a dried alcoholic extract.

Prescribers are advised to look for signs of liver toxicity in patients taking black cohosh. This is also a timely reminder to prescribers of the importance of seeking information from patients about their use of complementary medicines (including herbal medicines and dietary supplements) and to report any adverse reactions in patients taking complementary medicines to CARM.

References

1. Chow E C-Y, Teo M, Ring JA & Chen JW (2008) Liver failure associated with the use of black cohosh for menopausal symptoms *Medical Journal of Australia* 188(7): 420-2.

Conventional antipsychotics and mortality risk – carefully assess risks and benefits before use in elderly dementia patients

The risk of death is significantly increased in elderly patients with dementia who are prescribed conventional antipsychotics, compared with non-users. The risk appears to be similar to, or possibly greater than, the risk previously identified for atypical antipsychotics. As with the atypical antipsychotics, the risk of death is highest in the months immediately after commencement of treatment.

Prescribers are advised that the use of antipsychotics in elderly dementia patients should only be considered after a careful assessment of the risks and benefits of treatment. Recently published guidance on the rational and safe use of antipsychotics in dementia patients by BPAC^{NZ} is available at www.bpac.org.nz/a4d/resources/guide/guide.asp.

The data sheets for all conventional antipsychotics available in New Zealand are in the process of being updated to include information about this risk, in line with warnings included in the data sheets for atypical antipsychotics.

Selective serotonin re-uptake inhibitors (SSRI) in children and adolescents

Prescribers are reminded of the risks and benefits associated with SSRI antidepressants when used to treat major depressive disorder (MDD) in children and adolescents.

Medsafe and the Medicines Adverse Reaction Committee have recently conducted a review on the use of SSRI antidepressants in children and adolescents. Following this review, Medsafe advises the following:

1. The most common reason for suicidality and completed suicide is an untreated or worsening mood disorder.
2. The only antidepressant with overall data indicating efficacy better than placebo in children and adolescents is fluoxetine. This may indicate a positive risk benefit balance for fluoxetine.
3. All SSRIs have consistently been associated with an increase in suicidality in meta-analyses of clinical trials of the use of SSRIs to treat MDD in children and adolescents. The term suicidality includes suicidal thinking and suicide attempts, but has not been proven to correlate with or lead to completed suicide.
4. No antidepressant has ministerial consent for the indication of treating MDD in children and adolescents. This means informed consent must be obtained from the patient or parent prior to initiating an SSRI for MDD in children or adolescents.
5. Any patient diagnosed with MDD should be monitored closely for suicidality. If the treatment of a specific patient warrants antidepressant use, this should be considered in consultation with a Child and Adolescent Psychiatrist, an adult Psychiatrist, or a Paediatrician. Particular care should be taken in the period shortly after initiating antidepressant treatment, after a change in dosage, and after discontinuing treatment.

This advice should be read in conjunction with current clinical treatment guidelines for depression published by: The Royal Australian and New Zealand College of Psychiatrists; The New Zealand Guidelines Group; The Werry Centre for Child and Adolescent Mental Health Workforce Development; and Best Practice Advocacy Centre (BPAC)[NZ].

An association between paracetamol and asthma

A recent paper published in *The Lancet* has highlighted the growing body of evidence of an association between paracetamol use and the development of asthma. The paper finds an increased risk of asthma symptoms in children aged 6 - 7 years who used paracetamol in their first year of life or in the year preceding the study.[1]

A number of studies have found that the strength of the association increases with increased frequency of paracetamol use and is found following exposure in-utero, in children, and in adults.[2,3] The association remains significant after controlling for many of the known risk factors for asthma; however no studies have been able to demonstrate a causal association.

Although there is growing evidence of an association between paracetamol use and developing asthma, there is no analgesic or antipyretic which could currently be considered a safer alternative.

Considering the finding that the association is strongest with highest frequency of use of paracetamol, any clinical intervention should be aimed at reducing excessive use of paracetamol.

References

1. Beasley R, Clayton T, Crane J, Von Mutius E, Lai CKW, Montefort S, StewartA, 2008, Association between paracetamol use in infancy and childhood, and risk of asthma, rhinoconjunctivitis, and eczema in children aged 6 – 7 years: analysis from Phase Three of the ISAAC programme *The Lancet* 372:1039-48.
2. McKeever TM, Lewis SA, Smit HA, Burney P, Britton JR, Cassano PA, 2005, The Association of Acetaminophen, aspirin and ibuprofen with respiratory disease and lung function *American Journal of Respiratory and Critical Care Medicine* 171:966-71.
3. Shaheen SO, Newson RB, Henderson AJ, Headley JE, Stratton FD, Jones RW, Strachan DP and ALSPAC Study Team, 2005, Prenatal paracetamol exposure and risk of asthma and elevated immunoglobulin E in childhood *Clinical and Experimental Allergy* 35:18-25.

Phosphodiesterase type 5 (PDE-5) inhibitors associated with sudden hearing loss

Prescribers are advised of the risk of sudden hearing loss associated with PDE-5 inhibitors (sildenafil, tadalafil, vardenafil).

A case has been published describing a 44-year old male who developed bilateral deafness during treatment with sildenafil for erectile dysfunction.[1]

As of 30 April 2008 the Centre for Adverse Reactions Monitoring had received three reports of sudden decrease or loss of hearing with sildenafil (2) and tadalafil (1).

Hearing loss is commonly reported in ageing populations, especially in patients with risk factors for erectile dysfunction. However, sudden hearing loss is an uncommon event in any age group. Although this adverse reaction is rare, prescribers are reminded to advise patients to consult a physician immediately should a sudden decrease or loss of hearing occur.

The data sheets for these medicines have been updated to provide prescribers with information on the risk and steps to take should sudden hearing loss occur.

References

1. Mukherjee B, et al. (2007). A case of sensorineural deafness following ingestion of sildenafil. *The Journal of Laryngology & Otology* 121:395-7.

Ezetimibe and pancreatitis – emerging evidence

Prescribers are reminded that medicines are a common, but under recognised, cause of acute pancreatitis. Medicines frequently implicated include anti-HIV agents, statins, tetracyclines, and valproate.

There is emerging evidence that ezetimibe, with or without a statin, can also cause pancreatitis. Reports in the CARM database indicate that there are proportionately more reports of pancreatitis with ezetimibe than with statins.

Prescribers are reminded to consider medication history in patients presenting with acute pancreatitis.

Acute pancreatitis is typically confirmed by the presence of elevated levels of serum amylase and/or lipase and characteristic finding by radiological imaging. If acute pancreatitis is confirmed, the suspect medicine should be discontinued and supportive treatment initiated.

Bisphosphonates and atrial fibrillation – risk update

No clear association between oral bisphosphonate use and atrial fibrillation has been confirmed. Most clinical and observational studies published to date on this issue have not been sufficiently powered to detect rare or uncommon adverse events. One adequately powered observational study, which studied hospital admissions of women diagnosed with atrial fibrillation and atrial flutter, found there was no increased risk for users of oral etidronate and alendronate.[1]

Medsafe will continue to closely monitor the safety of oral bisphosphonates as new information becomes available. In the meantime, prescribers are advised not alter their prescribing patterns for oral bisphosphonates.

Recently published evidence does however support an association between infusions of zoledronic acid and serious atrial fibrillation.[2] The risk was only 0.6-0.7% higher than placebo, with around 1.3% of patients treated with zoledronic acid diagnosed with serious atrial fibrillation. Medsafe advises prescribers the risk to benefit ratio for zoledronic acid remains highly favourable. The data sheets for zoledronic acid infusions available in New Zealand already contain information regarding this risk. Medsafe is currently reviewing clinical data for pamidronic acid in respect of atrial fibrillation and will update prescribers if any increased risk is identified.

References

1. Sorenson HT, Christensen S, Mehnert F, Pederson L, Chapurlat RD, Cummings SR & Baron JA (2008) Use of bisphosphonates among women and risk of atrial fibrillation and flutter: population based case-control study *British Medical Journal* 336:813-6.
2. Black DM, Delmas PD, Easell R, Reid IR, Boonen S, Cauley JA, Cosman F, Lakatos P, Leung PC, Man Z, Mautalen C, Mesenbrink P, Hu H, Sellmeyer D, Eriksen EF & Cummings SR (2007) Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis *New England Journal of Medicine* 356(18):1809-22.

Anticonvulsants and congenital malformations

Prescribers are reminded of the risk of congenital malformations associated with the use of anticonvulsants (anti-epileptics) during pregnancy, and the importance of counselling for all women of child-bearing age prescribed anticonvulsants.

Observational data from 3500 females included in the United Kingdom Epilepsy and Pregnancy Registry demonstrated the following:

- 4.2% congenital malformations for all antiepileptics versus 3.5% with untreated epilepsy.
- 6.0% congenital malformations with polytherapy versus 3.7% with monotherapy.
- 6.2% congenital malformations with valproate monotherapy.
- 2.2% congenital malformations with carbamazepine monotherapy.[1]

A prospective observational study across 25 epilepsy centres (NEAD study) demonstrated that serious adverse outcomes for monotherapy ranged from 1% for lamotrigine to 20.3% for valproate.[2]

Common craniofacial anomalies include epicanthal folds, broad nose with a flat bridge, anteverted nostrils, shallow philtrum and a thin upper and thick lower lip. Associated disorders may include developmental delay, neurologic abnormalities, congenital heart defects and finger abnormalities.

As uncontrolled epilepsy in pregnant woman is a serious and potentially life-threatening condition for both mother and child, treatment options must be carefully considered. Medsafe recommends that the most effective medicine should be used at its lowest effective dose.

It is important that all women of child-bearing age taking anticonvulsants receive counselling on the risk of congenital malformations associated with the use of anticonvulsants. However, the occurrence of an unexpected pregnancy should not trigger sudden discontinuation of therapy.

References

1. Breen D. and Davenport R. (2006). Teratogenicity of antiepileptic drugs: Women should consider stopping, minimizing, or switching drugs before pregnancy *British Medical Journal* 333:615-6.
2. Meador J. et al. (2006). In-utero antiepileptic drug exposure: Fetal death and malformations *Neurology* 67:407-12.

ADVERSE REACTIONS OF CURRENT CONCERN

MARC R 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.28(1), November 2007 & Vol.23(2), July 2002 & No.13, Oct 1996
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

About the IMMP

The purpose of the Intensive Medicines Monitoring Programme (IMMP) is to identify previously unrecognised adverse reactions to new medicines. It also develops adverse reaction profiles for these medicines, as well as measuring incidence and characterising reactions of clinical concern. In addition, the IMMP is able to identify any high-risk groups amongst the patients being treated. The results of IMMP findings are used to enhance the safe use of medicines.

Which medicines are monitored?

Medicines of a new class may be added to the IMMP so that unknown adverse effects can be identified as soon as possible. Medicines may also be included in the programme if they are similar to other medicines for which safety concerns exist.

The medicine currently being monitored is: **Varenicline (Champix)**

What to report

Please report **all clinical events** in patients taking IMMP medicines, 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

What to tell patients prescribed IMMP medicines

Please remember to tell patients that they have been prescribed a monitored medicine. This means the IMMP receives details of their prescriptions and that their doctor may be asked for clinical information on the patient's experience whilst taking this medicine. If possible, an explanatory IMMP leaflet should be given to the patient (available from the IMMP, NZ Pharmacovigilance Centre, PO Box 913, Dunedin 9054).

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