

WHO PHARMACEUTICALS NEWSLETTER



prepared in collaboration with the
WHO Collaborating Centre for
International Drug Monitoring,
Uppsala, Sweden

The aim of this Newsletter is to disseminate information on the safety and efficacy of pharmaceutical products, based on communications received from our network of "drug information officers" and other sources such as specialized bulletins and journals, as well as partners in WHO. The information is produced in the form of résumés in English, full texts of which may be obtained on request from:

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News & Issues

This issue covers regulatory and safety information on twenty drug (monocomponent and group) products. Also included are the recommendations from the WHO Consultation on Global Monitoring of Adverse Events Following Immunization (AEFI) held in Geneva 9-10 January 2006. This Consultation highlighted some important gaps in communication between groups monitoring adverse events following immunization (AEFIs) and groups recording adverse drug reactions (ADRs) at the country level. While both AEFI and ADR monitoring operations are less than optimal in most countries, any national surveillance system currently in place should be put to full use, to cover both AEFI and ADR functions. But whatever the measure, quality and comprehensive reporting will remain key factors in determining the practical use of pharmacovigilance.

WHO warns that while medicines are essential to alleviate suffering and are a core element in all international relief efforts, inappropriate donations may cause more harm than good. The WHO guidelines for appropriate drug donations should be consulted when contributing medicines for relief efforts. These guidelines can be accessed at:
http://www.euro.who.int/document/EHA/PAR_Donate_Guidelines.pdf

Two pharmacovigilance training courses will be offered in the month of September: one on pharmacovigilance for HIV/AIDS medicines in Barbados and the other in Botswana, on the general principles of pharmacovigilance. A report from these as well as relevant course materials will be made available on the WHO Medicines website in the near future.

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ADHD Drugs Labelling revised

Canada. According to Health Canada, the prescribing information for all attention deficit hyperactivity disorder (ADHD) drugs has been revised in Canada to include standardized prescribing information that identifies risk factors for cardiac-related adverse events (AEs), and to provide recommendations to reduce these risks. This applies to the following drugs and all products containing these drugs: methylphenidate (e.g., Ritalin) and methylphenidate extended release (Ritalin SR), dexamethylphenidate (Attenade), dexamphetamine (Dexedrine), atomoxetine (Strattera). The revisions affect the Dosing recommendations, Contraindications, Warnings and Precautions, and Information for the Patient. Health professionals are advised that ADHD drugs should be started at the lowest dose and increased slowly, and should not be given to patients with a symptomatic heart disorder, advanced arteriosclerosis, hyperthyroidism, moderate to severe hypertension, or structural cardiac abnormalities; further cardiovascular (CV) system evaluation may be considered before starting ADHD drugs in patients with relevant risk factors, and patients who require long-term ADHD drugs should undergo periodic CV status evaluation. Patients are advised to not discontinue ADHD drugs without consulting their doctor, and to inform their doctor if they are using other ADHD drugs, are involved in strenuous activity, have certain heart disorders or a family history of sudden cardiac death, before using these drugs. Health Canada states that, theoretically, a pharmacological potential for all ADHD drugs to increase the risk of sudden cardiac death exists, but ADHD drugs are generally safe and beneficial when used as directed. (See WHO Pharmaceuticals Newsletter No. 2, 2006 for similar

directives in the UK following the conclusion of a Europe-wide review on the health risks and benefits of atomoxetine).

Reference:

Advisories, Warnings and Recalls. Health Canada, 26 May 2006
(<http://www.hc-sc.gc.ca>).

Cimicifuga racemosa (Black Cohosh) Concerns of liver injury

Europe. The European Medicines Agency (EMA) and the Committee on Herbal Medicinal Products (HMPC) have become aware of case reports of hepatotoxicity in patients receiving *Cimicifuga racemosa* (Black Cohosh) root and, after reviewing available data, the HMPC considered that there is a potential association between hepatotoxicity and herbal medicines containing *Cimicifuga* (1).

Black Cohosh has been used traditionally for various purposes, including amenorrhoea and menopause symptoms. According to the EMA, 16 of the 42 case reports of hepatotoxicity evaluated by the HMPC were sufficiently documented to enable the HMPC to assess if *Cimicifuga* may be linked to the liver injuries and, as a result of the assessment, five cases were excluded, seven were thought to be unlikely related and there was a temporal association between the initiation of *Cimicifuga* treatment and the occurrence of the hepatic reaction in four cases. All new safety information related to this issue will continue to be reviewed by the HMPC, says the EMA.

The EMA advises patients to discontinue use of *Cimicifuga* and consult their doctor immediately if symptoms and signs suggestive of liver injury develop, and to inform their doctor if they are using herbal

medicine products. The EMA advises health-care professionals to ask patients about the use of *Cimicifuga*-containing products, and to report suspected hepatic reactions to the national adverse reaction reporting schemes. The United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) says that warnings are to be added to the labels of *Cimicifuga* products, and that the Agency is working with the herbal sector to ensure the public is aware of the possible risk (2). Professor Kent Woods, MHRA Chief Executive, says that the labels of *Cimicifuga* products "will point out the possible symptoms so that appropriate action can be taken without delay".

(Reports in WHO database: *Cimicifuga racemosa*: Hepatic function abnormal - 14, Hepatic failure - 2, Gamma-GT increased - 3).

References:

1. *Public Statement. European Medicines Agency, 18 July 2006*
(<http://www.emea.eu.int>).
2. *Press Release. Medicines and Healthcare products Regulatory Agency (MHRA), 18 July 2006,*
(<http://www.mhra.gov.uk>).

Fluoxetine Use extended to include paediatric patients

Europe. The EMA has approved that the indication for fluoxetine (Prozac and associated products) can be extended to include the treatment of moderate to severe depression in children, eight years of age or older, who do not respond to psychological therapy. The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of fluoxetine in this indication outweigh its potential risks. However, the Marketing Authorization Holder (Eli Lilly for Prozac) has been directed to

carry out additional studies to ensure that the safety profile (of Prozac) remains acceptable.

Reference.

Press Release. EMEA,
6 June 2006
(<http://www.emea.eu.int>).

Natalizumab Reintroduced under Restricted Distribution/ Risk Management Plan

USA. The United States Food and Drug Administration (US FDA) has approved the reintroduction of natalizumab (Tysabri) as a monotherapy for patients with relapsing forms of multiple sclerosis (MS). Earlier this year, the concerned companies had voluntarily suspended natalizumab (Tysabri) from the US market due to reports of progressive multifocal leukoencephalopathy (PML). PML is an opportunistic viral infection of the brain that usually leads to death or severe disability. Natalizumab (Tysabri) will now be available only through a special restricted distribution and risk management program called the Tysabri Outreach: Unified Commitment to Health (TOUCH) Prescribing Program. The TOUCH Program was developed to ensure the proper use of natalizumab (Tysabri) and to evaluate the PML incidence, PML risk factors and other serious opportunistic infections associated with the drug. Elements of the TOUCH Program include the following:

- Revised labelling, including a boxed warning highlighting the PML risk, and warnings against the use of natalizumab (Tysabri) concurrently with chronic immunosuppressants or immunomodulators, and in patients who are immunocompromised.
- Centralized and controlled distribution solely to authorized infusion centres, and compulsory enrolment for all prescribers, central pharmacies, patients and infusions centres who want to prescribe, distribute, receive

and infuse natalizumab (Tysabri), respectively.

- Prior to natalizumab (Tysabri) initiation, health professionals are to obtain the patient's MRI scan to help distinguish potential future MS symptoms from PML.
- Natalizumab recipients are to be evaluated at three and six months after the first infusion and then every six months, and their status is to be regularly reported to Biogen Idec.
- Compulsory FDA-approved educational tools, including a monthly pre-infusion checklist, patient medication guide and a TOUCH enrolment form.
- A five-year observational study, the Tysabri Global Observation Program in Safety (TYGRIS), and ongoing evaluation of overall safety and the PML risk.

Reference:

'Dear Health-care Professional' letter. Biogen Idec Inc., July 2006
(<http://www.fda.gov>).

SSRIs Challenges in pregnancy

USA. The US FDA is advising (1) of two new studies that provide important information to be considered when using antidepressants during pregnancy. The first study illustrates the potential risk of relapsed depression after stopping antidepressant medication (2). The second study (3) suggests a persistent pulmonary hypertension in newborn babies (PPHN) born to mothers treated with selective serotonin reuptake inhibitors (SSRIs) during pregnancy; PPHN, a serious life threatening lung-condition, was six times more common in babies whose mothers took an SSRI antidepressant after the 20th week of pregnancy compared to babies whose mothers did not

take an antidepressant. The study size was too small to allow comparison among antidepressants. This (second) study adds to concerns coming from previous reports that infants of mothers taking SSRIs late in pregnancy may experience irritability, difficulty feeding and rarely, difficulty breathing. The US FDA notes that uncertainties about these rare events as well as their potential impact on the newborn, along with the potential risk to the mother of recurring depression if she stops her antidepressant medicines during pregnancy, may pose special challenges in treating depression in pregnant women. Women who are pregnant or are planning to get pregnant should not stop their antidepressant treatment but should first consult their physician. Any decision to continue or stop medication should be based on a careful analysis of potential benefits and risks for each individual pregnant patient. The US FDA has asked sponsors of all SSRIs to change prescribing information to describe the potential risk for PPHN.

References:

1. Public Health Advisory. United States Food and Drug Administration, 19 July 2006
(<http://www.fda.gov>).
2. Cohen LS et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. *The Journal of the American Medical Association*, 2006, 295(5): 499.
3. Chambers CD et al. Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. *The New England Journal of Medicine*, 2006, 354: 579.

SSRIs and SNRIs Combined use with anti- migraine medicines could be life-threatening

USA. The US FDA is warning that life-threatening serotonin syndrome could result when triptans (used in treating migraine headaches) are taken together with antidepressants that are selective serotonin reuptake inhibitors (SSRIs) or serotonin and norepinephrine reuptake inhibitors (SNRIs). Serotonin syndrome occurs when the body has too much serotonin, a chemical found in the nervous system and symptoms include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overactive reflexes, nausea, vomiting and diarrhoea. The US FDA advises that physicians prescribing a triptan, SSRI or SNRI should:

- bear in mind that triptans are often used intermittently and each of the medications (SSRI, SNRI, triptan) might be prescribed by a different physician;
- weigh the potential risk of serotonin syndrome with the expected benefit of using a triptan with a SSRI or SNRI
- discuss the possibility of serotonin syndrome with patients if a triptan and a SSRI or SNRI will be used together;
- follow patients closely if a triptan and a SSRI or SNRI are used together, particularly during treatment initiation, with dose increases, or with the addition of another serotonergic medication;
- instruct patients who take a triptan and a SSRI or SNRI together to seek medical attention immediately if they experience the symptoms of serotonin syndrome.

The US FDA has requested all manufacturers of triptans, SSRIs and SNRIs to update their prescribing information to warn of the possibility of serotonin syndrome when triptans and

SSRIs or SNRIs are taken together.

Reference:

Public Health Advisory. United States Food and Drug Administration, 19 July 2006
(<http://www.fda.gov>).

Telithromycin New safety information in label

USA. The US FDA has announced that it has completed its safety assessment of telithromycin (Ketek, used in treating mild to moderate respiratory infections), that additional warnings are needed, and that it is advising patients and health practitioners to be aware of rare but potentially serious health risks associated with the drug. According to the FDA, telithromycin's labelling is to be revised by its manufacturer, Sanofi Aventis, to highlight that the drug has been associated with rare cases of serious liver injury and liver failure, including one liver transplant and four reported deaths. The Agency concluded that the drug's benefits outweigh its risks and support its continued availability. The Agency will continue to evaluate telithromycin (Ketek)-associated safety issues and will take further actions if necessary. Dr Steven Galson, Director for US FDA's Center for Drug Evaluation and Research, says that patients experiencing signs or symptoms of liver problems should discontinue telithromycin (Ketek) and seek medical assessment.

(Reports in WHO database: Hepatic enzymes increased - 20, Hepatocellular damage - 4).

Reference:

FDA News. United States Food and Drug Administration, 29 June 2006
(<http://www.fda.gov>).

Tipranavir Reports of intracranial haemorrhage

Canada, USA, Switzerland. Boehringer Ingelheim Pharmaceuticals has issued a 'Dear Health-care Professional' letter in Canada (1), in the USA (2) and in Switzerland (3) regarding intracranial haemorrhage (ICH) in patients receiving tipranavir (Aptivus) capsules; tipranavir is coadministered with low-dose ritonavir in treatment experienced HIV patients who have HIV-1 strain that are resistant to multiple protease inhibitors. As of 7 June 2006, Boehringer Ingelheim has received 14 reports of ICH, eight of which were fatal, in 6840 patients with HIV-1 infection receiving tipranavir (Aptivus) in clinical trials. Boehringer Ingelheim is revising the product monograph to include information on ICH risk, platelet aggregation inhibition findings from in vitro studies and changes in coagulation parameters observed in preclinical animal studies. A new paragraph will be added to the boxed warning for tipranavir (Aptivus), stating that the drug has been associated with fatal and nonfatal ICH when co-administered with ritonavir 200 mg. The insert will advise health-care professionals to use caution when prescribing tipranavir/ritonavir for patients who may have an increased risk of haemorrhage or are receiving drugs with a known increased risk of haemorrhage, and to inform patients of the ICH reports associated with the combination.

References:

1. Dear Health-care Professional' letter. Boehringer Ingelheim Pharmaceuticals Inc., 29 June 2006
(<http://www.hc-sc.gc.ca>).
2. Dear 'Health-care Professional' letter. Boehringer Ingelheim Pharmaceuticals Inc.,

30 June 2006

(<http://www.fda.gov>).

3. As posted on Swissmedic website, 13 July 2006

(<http://www.swissmedic.ch>).

Triaminic Vapour Patch

Risk of ingestion

Canada, USA. Health Canada (1) is warning against the use of the Triaminic Vapour Patch, which contains camphor, eucalyptus oil and menthol, due to serious adverse effects that could occur if the product is ingested by accident by children. Reported adverse effects from ingesting products containing camphor or eucalyptus oils range from minor symptoms, such as mouth burning sensations, headaches, nausea and vomiting, to more severe and life-threatening reactions, such as seizures, says Health Canada. The Agency is aware of one adverse reaction associated with the patch; this involved a child who had a seizure after chewing the patch. Health Canada says that a recall of the product will be initiated, and that consumers should stop using the product; those who have used the patch and have health concerns should contact their physician or health-care practitioner. In the meantime a nationwide voluntary recall of all Triaminic Vapor Patch products is being conducted in the US (2) by Novartis Consumer Health.

References:

1. *Advisories, Warnings and Recalls.* Health Canada, 30 May 2006

(<http://www.hc-sc.gc.ca>).

2. *Public Health Advisory.* United States Food and Drug Administration, 20 June 2006

(<http://www.fda.gov>).

Venlafaxine

Information update to minimize overdose-side effects

UK. The MHRA has concluded its review into all the latest safety evidence, toxicity in overdose in particular, relating to venlafaxine (Efexor).

Venlafaxine is an antidepressant belonging to the class of medicines known as serotonin and noradrenaline reuptake inhibitors (SNRIs). In December 2004, concerns about potential cardiotoxicity and toxicity in overdose with venlafaxine led to the drug being restricted to specialist initiation and contraindicated in patients with heart disease. The updated prescribing advice following the conclusion of the review, includes the following:

- The need for specialist supervision in those severely depressed or hospitalized patients who need doses of 300 mg daily or more.
- Cardiac contraindications are more targeted towards high risk groups.
- As previously, patients with uncontrolled hypertension should not take venlafaxine, and blood pressure monitoring is recommended for all patients.
- Updated advice on possible drug interactions.

In addition, a smaller pack size will soon be available to minimize the risk of overdose.

(Reports in WHO database: Cardiomyopathy - 27).

Reference:

Press Release. Medicines and Healthcare products Regulatory Agency, 31 May 2006
(<http://www.mhra.gov.uk>).

Angiotensin-converting enzyme (ACE) inhibitors

Risk of birth defects

USA, Canada. According to a US FDA Public Health Advisory (1), results of a recent study (2) suggest that the use of ACE inhibitors during the first three months of pregnancy may be associated with an increased risk of birth defects. The FDA says that although these results do not establish a causal relationship between birth defects and the use of the drugs during early pregnancy, the results are worrying.

The prescribing information for all ACE inhibitors already highlights that ACE inhibitors should be discontinued in women who become pregnant, to avoid fetal exposure in the second and third trimesters due to risk of fetal abnormalities, and the importance of this recommendation is confirmed by the findings from the recent study, says the Agency. The US FDA states that the labels for all ACE inhibitors start with a boxed warning that highlights that these drugs may harm unborn babies in the second and third pregnancy trimesters.

The Agency recommends the following: women of reproductive age who are treated with an ACE inhibitor should be counselled by their health-care provider about the possible risk of these drugs throughout pregnancy, particularly during the second and third trimesters; ACE inhibitors should only be prescribed to pregnant women if the benefit clearly exceeds the possible risk; women who become pregnant should have their ACE inhibitor promptly switched to a different drug; and women receiving ACE inhibitors should inform their health-care professional if they believe they are pregnant or

are planning to become pregnant.

The FDA says that, based on this one study, the Agency does not plan to alter the pregnancy categories for ACE inhibitors, and that it will work with the Agency for Healthcare Quality and Research to identify other possible data sources that will help establish the degree of risk associated with first trimester exposure to these drugs.

Similar advice has been issued by Health Canada (3).

References:

1. *Public Health Advisory. United States Food and Drug Administration, 6 June 2006* (<http://www.fda.gov>).
2. Cooper WO et al. *Major congenital malformation after first-trimester exposure to ACE inhibitors. New England Journal of Medicine, 2006, 354(23): 2443-2451.*
3. *Advisory. Health Canada, 29 June 2006* (<http://www.hc-sc.gc.ca>).

Chemotherapy/Immuno-suppressive therapy Reactivation of hepatitis B virus infection

Australia. Five reports of reactivation of hepatitis B virus infection in patients who had received cancer chemotherapy or immunosuppressive therapy for autoimmune disease have been received by the Australian Adverse Drug Reactions Advisory Committee in the last two years. These patients were chronic carriers (HBsAg positive). Two of the cases were fatal and one required liver transplantation. The first fatal case, a 61-year-old man, received seven cycles of cyclophosphamide, doxorubicin, vincristine and prednisolone for large B cell lymphoma; he died from decompensated liver

disease despite lamivudine therapy. The other fatal case, a 29-year-old woman with mixed connective tissue disease, received prednisolone and hydroxychloroquine; hydroxychloroquine was later replaced by chloroquine. She developed progressive liver failure and died from multi-organ failure despite lamivudine therapy.

Reference.

Australian Adverse Drug Reactions Bulletin, June 2006, 25(3): 10-11.

Colchicine Toxic in overdose: reminder

New Zealand. Prescribers are reminded of the revised dosage advice for colchicine because of the risk of serious dose-related adverse effects, in a recent Prescriber Update article. New Zealand's Medsafe Pharmacovigilance Team reminds prescribers that colchicine is now indicated as second-line therapy for acute gout. The team warns that colchicine is extremely toxic in overdose, and that fatalities have occurred. They say that the use of high doses in acute gout is not appropriate, especially in patients who are elderly, have impaired renal or hepatic function, or weigh less than 50 kg. According to Medsafe, in otherwise healthy adults, the maximum colchicine dose is 2.5 mg in the first 24 hours and the total dose should not exceed 6 mg over four days in an acute attack; the dosing interval has been increased to every six hours instead of every two to three hours. In addition, the team advises that continued dosing until adverse gastrointestinal events occur "is no longer considered safe or appropriate". Medsafe urges prescribers to write clear dosage advice on the prescription, inform patients of the revised dosage advice, stress how important it is not to

exceed the maximum doses, warn patients of colchicine toxicity symptoms and advise them to immediately stop the drug and see a doctor if symptoms occur.

Reference:

Prescriber Update, June 2006, 27(1): 2

Colloids

Safety considerations important in choosing resuscitation fluids

Australia. The Australian Adverse Drug Reactions Advisory Committee (ADRAC) has received 83 reports for succinylated gelatin (Gelofusine) since the product was first registered in 1998, 70 of which were of hypotension and/or hypersensitivity reactions. For 27 of these reports, hypotension or anaphylactoid reactions were the only feature listed, while the remaining 43 mentioned signs and symptoms consistent with anaphylactoid reactions, including cardiac (10), respiratory (18) or cutaneous (35) manifestations. In 60 reports, recovery was documented; one patient died following a cardiac arrest. ADRAC has received similar reports associated with other plasma expanders, albumin (Albumex), polygeline (Haemaccel) and dextran. For all cases, the number of reports of anaphylactoid reactions, as a proportion of the total reports, was similar to the proportion of reports of such reactions received for gelatin (Gelofusine). In view of a study showing saline and albumin to have equivalent efficacy, ADRAC comments that "the safety of colloids such as gelatin should be considered carefully in the initial choice of resuscitation fluid"

Reference:

Australian Adverse Drug Reactions Bulletin, June 2006, 25(3): 11.

Dolasetron mesylate

Contraindicated in patients below 18 years of age; not for use in post-operative nausea and vomiting

Canada. Health Canada has reminded hospitals that dolasetron (Anzemet) is contraindicated in patients below 18 years of age, and in the prevention and treatment of postoperative nausea and vomiting in adults; the contraindications apply to both oral and intravenous formulations. Health Canada advises that there have been reports of myocardial infarction, sustained arrhythmias, and one fatal heart arrest associated with the use of dolasetron (Anzemet) in children and adolescents, and says that there is a negative risk/benefit ratio for postoperative use of the drug in patients aged ≥ 18 years. The Agency warns that dolasetron (Anzemet) is only indicated for use in the prevention of nausea and vomiting associated with emetogenic cancer chemotherapy in adults. Dolasetron is a serotonin-3 receptor antagonist. Health Canada has requested that all manufacturers of serotonin-3 receptor antagonists analyse their safety databases; the Agency will take appropriate action after reviewing the data.

Reference:

Advisories, Warnings and Recalls. Health Canada, 23 June 2006 (<http://www.hc-sc.gc.ca>).

Gadodiamide

Reports of nephrogenic systemic fibrosis

Canada. GE Healthcare Canada has issued a 'Dear Health-care Professional' letter highlighting that, to date, it has received 25 cases of nephrogenic systemic fibrosis/nephrogenic

fibrosing dermopathy (NSF/NFD) following the administration of gadodiamide (Omniscan) injection. Gadodiamide is indicated for intravenous use in MRI to visualize tissues with abnormal vascularity. According to GE Healthcare, of the 25 cases, 15 were serious and involved disability with or without hospitalization, and 10 cases were non-serious with mild symptoms; furthermore, all patients had severely impaired renal function and most were receiving regular dialysis before gadodiamide administration. GE Healthcare states that, based on current evidence, no causal relationship between gadodiamide exposure and NSF/NFD has been established, that NSF/NFD is rapidly developing, rare, mild-to-disabling, potentially fatal, and has only been reported in patients with severe renal function impairment, and that the company has received no reports of NSF/NFD in patients without renal impairment or in patients with renal impairment who received only the recommended doses. GE Healthcare says that alternatives to gadodiamide-enhanced magnetic resonance angiography (MRA) should be considered in patients with severe renal impairment, that gadodiamide is not approved for MRA in Canada, and that current prescribing information recommends using gadodiamide with caution in patients with renal impairment. The company is working with worldwide regulatory authorities, medical experts and reporting hospitals, to further investigate this issue.

Reference:

Advisories, Warnings and Recalls. Health Canada, 12 July 2006 (<http://www.hc-sc.gc.ca>).

Nitrofurantoin Reports of interstitial lung disease

New Zealand. The Centre for Adverse Reactions Monitoring (CARM) continues to receive reports of acute and chronic pulmonary adverse reactions in association with nitrofurantoin indicated in the treatment of uncomplicated urinary tract infections. According to Medsafe, the pulmonary function of patients receiving prolonged nitrofurantoin therapy should be monitored. Medsafe recommends careful vigilance for early features of emerging pulmonary toxicity, which may be evidenced by dyspnoea or cough, indicating the need for prompt discontinuation of nitrofurantoin and further investigations such as spirometry and chest x-ray. Patients who have developed pulmonary toxicity associated with nitrofurantoin should not be re-exposed, says Medsafe.

(Reports in WHO database: Pulmonary infiltration - 37).

Reference:
Prescriber Update, June 2006, 27(1): 3.

Proton pump inhibitors Update on reports of interstitial nephritis

New Zealand. Since publication of information on interstitial nephritis associated with omeprazole in 2000, there have been a further 21 cases reported to the Centre for Adverse Reactions Monitoring (CARM) in New Zealand. Nine of these cases were reported in 2005. Medsafe says that interstitial nephritis has also been reported with pantoprazole and lansoprazole, and three such reports for pantoprazole have been received by CARM. According to Medsafe, acute renal impairment due to interstitial

nephritis is a recognized complication of omeprazole therapy and patients may present with non-specific symptoms such as fever, malaise, weight loss, nausea, skin eruptions and eosinophilia. Medsafe advises that patients with these symptoms known to be receiving omeprazole should undergo urine microscopy and renal function assessment and if either are abnormal, omeprazole should be stopped pending nephrology assessment.

Reference:
Prescriber Update, June 2006, 27(1): 3.

Sibutramine ADR update from ADRAC

Australia. According to the Australian Adverse Drug Reactions Advisory Committee (ADRAC), sibutramine has been available in Australia since January 2002 and, to date, ADRAC has received 138 reports (404 adverse reactions) associated with sibutramine use. ADRAC says that the common adverse reactions reported are consistent with sibutramine product information and include the following adverse drug reaction (ADR) reports in major system organ classes: 62 neurological ADR reports, including headache (n = 20), dizziness (14) and serotonin syndrome (5); 50 psychiatric ADR reports, including depression (12), anxiety (11), aggression (6), insomnia (10) and agitation (6); 33 GI ADR reports, including nausea (9), xerostomia (6) and constipation (6); 31 cardiac ADR reports, including palpitations (9), chest pain (4) and rhythm disorders (11); 26 vascular ADR reports, including hypertension (8); and 15 respiratory ADR reports, including dyspnoea (11). Furthermore, sibutramine was the sole suspected drug in 11 of the depression cases, two of

the three mania reports, and 27 of the cardiovascular adverse reaction cases. Sibutramine, used in the management of obesity, is not recommended in patients with a history of heart disease because it tends to increase blood pressure and heart rate, and sibutramine should not be used concomitantly with other CNS-active medicines, such as SSRIs or monoamine oxidase inhibitors, due to the risk of serotonin syndrome and a potential interaction, states ADRAC.

(Reports in WHO database: Sibutramine - All adverse reactions - 6275 (since 1999).

Reference:
Australian Adverse Drug Reactions Bulletin, June 2006, 25(3): 11.

SSRIs and tricyclic antidepressants (TCAs) Potential for interaction

New Zealand. The Medsafe Pharmacovigilance Team has reminded prescribers that interactions can potentially occur when an SSRI and a tricyclic antidepressant (TCA) are co-prescribed. The team advises that TCA plasma concentrations can be elevated 2- to 4-fold with concurrent SSRI administration, resulting in toxicity. They explain that the mechanism involves SSRI inhibition of the cytochrome P450 enzyme CYP2D6, resulting in decreased metabolism, and therefore accumulation, of TCA. The team says that reported symptoms include seizures, constipation, urinary hesitancy and delirium, and that serotonin syndrome is also a potential consequence. They comment that, although both SSRIs and TCAs can cause serotonin syndrome on their own, the risk is increased with their

concurrent use. The Medsafe team recommends that, if SSRIs and TCAs are co-prescribed, the TCA dose should be decreased, the patient should be monitored for signs of TCA toxicity and serotonin syndrome, and the patient should be advised about the possible interactions and warning symptoms. They advise that key treatment of serotonin syndrome involves prompt withdrawal of the suspect drugs, and supportive care.

Reference:

Prescriber Update, June 2006, 27(1): 2.

According to an overview of adverse drug reaction (ADR) reporting in Malaysia, there has been a marked increase in the number of reports received in 2005 compared with previous years; 2363 reports were received in 2005, compared with 1665 in 2004 and 1067 in 2003, corresponding to an increase of 41.9% and 121.5%, respectively. Doctors based in government hospitals submitted the most reports (49.9% of the total number received). Reporting by product registration holders has increased; 368 industry-driven reports were received in 2005, almost twice the number received in 2004. Furthermore, the number of reports submitted by pharmacists increased by 72% in 2005 compared with the year before.

Reference:

Malaysian Adverse Drug Reactions Newsletter, March 2006.

WHO Consultation on Global Monitoring of Adverse Events Following Immunization (AEFI) 9-10 January 2006: A Report

At its June 2005 meeting¹, WHO's Global Advisory Committee on Vaccine Safety (GACVS) acknowledged the work of the WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (UMC)², in analysing drug-related adverse events. However, GACVS noted limitations with respect to vaccine safety monitoring, including the comparatively small number of reports to the UMC and limited information in those reports, inherent difficulties with using signalling tools developed for non-vaccine adverse drug reactions (ADRs), and problems with communicating vaccine safety signals. The GACVS recommended that WHO convene an in-depth consultation with international experts to discuss means for improving reporting and analysis of vaccine safety information globally. Participants at the September 2005 annual meeting of National Pharmacovigilance Centres (or National Centres)³ supported this initiative and called for a number of issues to be deliberated during the consultation⁴.

A need for this consultation has been highlighted by, among other things, the current environment of greater political interest in patient safety, increasing recognition among immunization programmes of the relevance of safety to vaccine uptake, the importance of pharmacovigilance to public health programmes and recognition that the collaboration between groups monitoring adverse events following immunization (AEFIs) and ADRs at country level is not optimal in many situations.

The Consultation, jointly organized by the Departments of Medicines Policy and Standards and of Immunization, Vaccines and Biologicals, was held in Geneva, Switzerland on 9-10 January 2006. It brought together experts from WHO, representatives of selected National Centres, drug regulatory authorities, immunization and vaccine safety experts, the Brighton Collaboration⁵, pharmaceutical industry, and the GACVS.

The overall objective of the meeting was to review and make recommendations for building a high-quality global system for AEFI monitoring. Specific objectives included identifying concrete steps to:

- improve the quality and comprehensiveness of AEFI reporting by countries to the UMC database;
- strengthen communication and exchange mechanisms relating to AEFI monitoring and signalling between National Centres, national regulatory authorities (NRAs), immunization programme managers and other surveillance departments at country level; and
- improve the handling and analysis of AEFI at UMC for rapid signal identification and action.

Participants were informed of ongoing activities for AEFI and ADR reporting. Currently, 35% of 192 Member States, and only 25% of 165 non-industrialized countries, have an adequately functioning AEFI monitoring system. WHO supports countries to strengthen AEFI monitoring and management through direct technical support, capacity building for NRAs, training, and development and provision of technical documents. Specific initiatives to support global monitoring and investigative capacity as well as communication of vaccine safety issues

¹ WER, No. 2, 2006, pp 15-19

² www.who-umc.org

³ http://www.who.int/medicines/areas/quality_safety/safety_efficacy/safety/en/index.html

⁴ WHO Pharmaceuticals Newsletter No. 4, 2005

⁵ www.brightoncollaboration.org

include the GACVS and its related activities, the Vaccine Safety Net project, a proposal to establish a Network of Sentinel Countries for monitoring effectiveness and safety of newly introduced vaccines, and through collaboration with other partners/initiatives, such as the WHO Programme for International Drug Monitoring, the Brighton Collaboration, and the Council for International Organizations of Medical Sciences (CIOMS)/WHO Working Group on Vaccine Pharmacovigilance.

The WHO Programme for International Drug Monitoring originated in 1968 and provides a forum for Member States to collaborate in pharmacovigilance. Policy decisions are handled by the WHO secretariat while the UMC receives case reports of suspected AEFIs and ADRs from National Centres and maintains a global database, now containing over 3.5 million reports and analysed quarterly. Anatomical Therapeutic Chemical (ATC) codes are included in the ADR reports in the UMC database. The ATC classification system and Defined Daily Dose (DDD) for drugs, developed and maintained by the WHO Collaborating Centre for Drug Statistics Methodology, serve as tools for drug utilization research.

The Brighton Collaboration, the CIOMS/WHO Working Group on Vaccine Pharmacovigilance, and other groups such as the CIOMS Working Group on Standardized MedDRA Queries play a critical role in the development and dissemination of standardized case definitions and terminologies for data collection, analysis and presentation.

Experience with AEFI surveillance in two countries was shared to highlight specific issues. For example, in Sri Lanka two parallel systems exist; a university-associated ADR group/National Centre and an AEFI surveillance system linked to the immunization programme and under the responsibility of the Central Epidemiology Unit of the Ministry of Health. The former receives a minority of all AEFI reports directly and shares them with the Central Epidemiology Unit and UMC. The Central Epidemiology Unit receives the majority of AEFI reports but they are not sent systematically to either the National Centre or UMC. A similar situation exists in many non-industrialized countries. The consultation acknowledged that immunization programmes must know about AEFI in order to respond appropriately with public health action at both sub-national and national levels and that there is often a lack of recognition or appropriate emphasis on the need for data sharing.

Examples of challenges in data management were presented in the context of Canada's AEFI reporting system. Through the International Conference on Harmonization, a standard for ADR reporting has been agreed and is known as the E2B format⁶. However, some items essential to vaccine pharmacovigilance are not well handled in the E2B format, including site and method of administration, and other items particularly relevant to vaccines (eg, birth weight, gestational age). While data can be "translated" and exported in an E2B format, there is a potential for country data that are not accommodated by E2B to be lost unless captured in a text field.

An analysis of the UMC database comparing reporting patterns of ADR and AEFI, and results of a survey of National Centres were presented. As of June 2005, most AEFI reported to the UMC (224,000 of 273,000) came from the USA, Canada, and Great Britain. Among 36 countries that responded to the survey and report to the UMC, there is substantial discrepancy between the number of AEFI reports forwarded to the UMC and that recorded on the WHO-UNICEF Joint Reporting Form⁷ (a data collection tool used to collect immunization-related information from countries) from 2001-2003. Overall, fewer reports are submitted to the UMC, however, some countries indicate a smaller number of reports to WHO-UNICEF. This reflects in part the lack of collaboration at country level between National Centres and immunization programmes.

⁶ ICH Guideline on Clinical Safety Data Management. Data elements for transmission of individual case safety reports E2B, www.ich.org

⁷ WER, No. 42, 2005, pp 361-367

The Consultation noted the following:

- the majority of reports in the UMC database involve adults and non-vaccine drugs;
- UMC interacts with all National Centres, but not necessarily with other national or international centres that do only vaccine monitoring;
- the present ATC/DDD system needs to be better adapted for vaccines;
- the UMC database analyses and signal generation should be separated for AEFIs versus ADRs.

Key recommendations

Improving AEFI reporting to the UMC

- (i) Countries are encouraged to report AEFI through the government's designated National Centre.
- (ii) If the national government finds it necessary to have separate systems for reporting AEFI and ADR, a designated AEFI monitoring centre may still be recognized as an independent reporting centre to UMC.
- (iii) Where there is no National Centre, an AEFI monitoring centre should be identified to send reports to the UMC. In such situations, countries are encouraged to expand monitoring to cover all aspects of drug safety reporting.
- (iv) Further work needs to be done to explore the determinants for AEFI reporting.

Improving resources and methods for AEFI reporting and analysis

- (i) *Vigibase on-line*, a web-based tool for ADR reporting, should be made available to countries to improve AEFI reporting in a timely and efficient manner.
- (ii) A focal point for vaccine-related reports should be identified both at National Centres and at the UMC for global data.
- (iii) Harmonized terminology should be developed for vaccine safety monitoring. To that end, the use of Brighton Collaboration case definitions and further guidance from the CIOMS/WHO Working Group on Vaccine Pharmacovigilance should be encouraged.
- (iv) Poor quality reports should not be omitted from the database as developments in signal analysis and other analytical methods may permit better evaluation in the future. Steps are needed to improve the quality of reports at country level.
- (v) Signal search strategies specific for vaccines (by the product or by antigen, additive, adjuvant or other vaccine constituent) will need to be developed.
- (vi) The signal review panel at the UMC should be strengthened to include more vaccine safety experts.
- (vii) Joint training activities for AEFI and ADR groups and regulators, particularly through UMC courses on pharmacovigilance and the Global Training Network course on AEFI are encouraged.
- (viii) The ATC system should be able to differentiate between types of vaccines, for example conjugate, polysaccharide, acellular, whole cell, monovalent, multivalent. A working group should be formed to examine these issues.

Improving advocacy and collaboration

- (i) Advocacy documents on vaccine safety monitoring should be developed and provided to countries.
- (ii) Cross appointment of drug and vaccine safety experts on the GACVS and the Advisory Committee on the Safety of Medicinal Products should be maintained and if possible expanded.
- (iii) Steps should be taken to establish collaboration between UMC and other international vaccine safety groups.

Note: This Consultation has also been reported in the Weekly Epidemiological Record, WER, No. 27, 2006, pp 261-265.