WHO PHARMACEUTICALS NEWSLETTER

World Health Organization

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:

Quality Assurance and Safety: Medicines, PSM–HTP
World Health Organization,
1211 Geneva 27, Switzerland
E-mail address: pals@who.int

This Newsletter is also available on our Internet website:
http://www.who.int/medicines

Further information on adverse reactions may be obtained from the WHO Collaborating Centre for International Drug Monitoring,
Stora Torget 3,
753 20 Uppsala, Sweden
Tel: +46-18-65.60.60
Fax: +46-18-65.60.80
E-mail: sten.olsson@who-umc.org
Internet: http://www.who-umc.org

Contents

No. 4, 2006

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.

Printed by the WHO Document Production Services, Geneva, Switzerland

TABLE OF CONTENTS

Regulatory Matters

Safety of Medicines

Feature

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), dexmethylphenidate (Attenade), dexamfetamine (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 (EMEA) 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 EMEA, 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 EMEA.

The EMEA 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 EMEA 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 EMEA 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 wil 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:

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