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 information 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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No. 5, 2005

News & Issues

This is the last issue for the year 2005 and includes the usual sections on Regulatory Matters and Safety of Medicines. The article on nevirapine under Problems of Current Interest highlights the need to support improved access and use of medicines with matching patient-monitoring facilities. This has been an eventful year in pharmacovigilance. Rofecoxib, withdrawn towards the end of 2004, continued to occupy our interest with many debates and discussions on the lessons learnt and the way forward. Drug safety in children received a lot of attention and several initiatives are underway for establishing guidelines for the safe use of medicines in this vulnerable population. The 'donation' of expired medicines and poor quality devices such as contaminated syringes to tsunami hit regions highlighted the quality and safety issues in drug donation practices, calling attention to the expanding role for pharmacovigilance centres in promoting medicine safety. The year ended with a meeting of the WHO Advisory Committee on Safety of Medicinal Products which reviewed various issues on drug safety; the Committee's recommendations will be published early next year.

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Regulatory Matters

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Ibritumomab

Skin reactions warning added to labels

USA. Biogen Idec, in consultation with the United States Food and Drug Administration (US FDA) has written to health-care professionals that post-marketing reports of severe cutaneous or mucocutaneous reactions, some with fatal outcome, have been received for ibritumomab tiuxetan (Zevalin), a radio-immunotherapy approved for the treatment of non-Hodgkin's lymphoma. The product label has been updated with a boxed warning to reflect this information. Health-care professionals are advised that the potential risk of these reactions should be considered when using the ibritumomab tiuxetan (Zevalin) regimen. Patients experiencing a severe cutaneous or mucocutaneous reaction should not receive any further components of the regimen and should receive prompt medical evaluation.

Reference:
'Dear Health-care Professional' letter from Biogen Idec, October 2005 (http://www.fda.gov).

Morphine sulfate extended release capsules

Alcohol promotes rapid release

USA. Ligand Pharmaceuticals Inc. has strengthened the product label for morphine sulfate extended release capsules (Avinza) with the warning that patients should not consume alcohol while taking these capsules since alcohol could result in the rapid release and absorption of a potentially fatal dose of morphine. Additionally, patients are also warned not to use prescription or non-prescription medications containing alcohol while on these capsules.

Reference:
'Dear Health-care Professional' letter from Ligand Pharmaceuticals Inc., October 2005 (www.fda.gov).

Pemoline

Withdrawn due to liver toxicity risk

USA. The US FDA has concluded that the overall risk of liver toxicity from pemoline (Cylert) outweighs the benefits of this drug indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). FDA is aware of 13 reports of liver failure resulting in liver transplant or death associated with pemoline use. A boxed warning was added to the label regarding the liver toxicity. This led to fewer prescriptions being written for pemoline (1/5 the earlier number). But, the FDA is of the opinion that the risk remains, particularly when considering the fact that one new case of pemoline-associated liver failure was reported even after the improved labelling intervention. The manufacturer (Abbott) of the proprietary version (Cylert) of the product discontinued its sales in May 2005. Subsequently, manufacturers of the generic versions have also agreed to stop sales and marketing of pemoline products. Health-care providers who currently prescribe pemoline products are advised to switch their patients to an alternative therapy.

Reference:
Alert. United States Food and Drug Administration, October 2005 (http://www.fda.gov).

Tamsulosin hydrochloride

Risk of Intraoperative Floppy Iris Syndrome (IFIS)

Canada. Ophthalmologists are being informed that a surgical condition known as IFIS could occur during phaco-emulsification cataract surgery in some patients previously (or currently) treated with alpha-1 adrenoceptor blocking agents such as tamsulosin hydrochloride (Flomax). The syndrome is characterized by the combination of a flaccid iris that billows in response to intraoperative irrigating currents, progressive intraoperative miosis despite preoperative dilation with standard mydriatic drugs, and potential prolapse of the iris toward the phacoemulsification incisions. Tamsulosin hydrochloride is used in the treatment of signs and symptoms of benign prostatic hyperplasia. The etiology of IFIS is not very clear at present. In the meantime, Health Canada is advising that in order to minimize the potential consequences of IFIS during phacoemulsification surgery, planned measures such as iris hooks, iris dilator rings etc. should be considered in male patients who have previously received (or, are currently receiving) tamsulosin hydrochloride treatment.

Reference:
'Dear Ophthalmologist' letter from Boehringer Ingelheim (Canada) Ltd., 14 October 2005 (http://www.hc-sc.gc.ca).

Estrogen / progestin weekly patch

Higher levels of estrogen than birth-control pills

USA. According to the US FDA, a weekly contraceptive skin patch (Ortho Evra) that releases ethinyl estradiol (an estrogen hormone) and norelgestromin (a progestin hormone), exposes women to higher levels of estrogen than most birth control pills. Since the patch is changed once a week, it decreases the risk of pregnancy associated with the typical birth control pills when a woman might miss one or more daily doses. However, this advantage should be considered in the light of the risks due to exposure to a higher level of estrogen with the patch. Women are advised to talk to their physician to see if the patch is the right birth control option for them.

Reference:
FDA News. United States Food and Drug Administration, 10 November 2005 (http://www.fda.gov).

Factor VIII (FVIII) recombinant products

Risk of inhibitor development in previously treated patients

Europe. Recombinant factor VIII (FVIII) products are used for the prevention and treatment of bleeding in patients with haemophilia A. One of the major challenges in the treatment of haemophilia is the development of an antibody against factor VIII (also called an 'inhibitor'), leading to poor bleeding control in these patients. The risk of inhibitor development is higher in haemophilia A patients than in patients with mild or moderate disease. Although the occurrence of inhibitors in previously treated patients should be seen as a natural response of the immune system to a foreign protein, the development of inhibitors in multi-transfused and stable previously treated patients (PTPs) may be due to the characteristics of an individual FVIII product. According to the European Medicines Agency (EMEA), post-marketing monitoring has revealed a higher number of cases of inhibitors in PTPs treated with recombinant FVIII products than would be expected from experience with plasma derived FVIII products. On the basis of available data for all currently authorized recombinant FVIII products, the Committee for Medicinal Products for Human Use (CHMP) could neither assess the true incidence of inhibitor development, nor differentiate the risk of inhibitor development in PTPs among recombinant FVIII products. The EMEA has therefore issued a statement with the following points:

- Inhibitors in PTPs have been reported for all recombinant FVIII products.
- On the basis of current data, it is not possible to quantify and compare the risk between recombinant FVIII products. Additional studies are needed.
- Patients should continue therapy and follow the recommendations of their physicians.
- If bleeding is not controlled with usual doses, patients should consult their physician immediately.

The EMEA advises that a workshop is planned in the first quarter of 2006 to review current knowledge on FVIII products and inhibitor development, to discuss standardization of requirements, definitions and methods used in pre- and post-marketing studies with PTPs and previously untreated patients for FVIII products.

Reference:
Public Statement. European Medicines Agency (EMEA), 18 October 2005 (http://www.emea.eu.int).

Liqiang 4 dietary supplement

Presence of glyburide

Canada. Health Canada is warning consumers that 'Liqiang 4 dietary supplement capsules' contain glyburide, a prescription drug used to treat type 2 diabetes. The supplement could thus have life-threatening consequences in diabetics and in individuals with low blood sugar if used without medical supervision. Liqiang 4 capsules, promoted for use in the control of diabetes, are not approved for sale in Canada. However, consumers could probably buy them through mail-order or over the Internet. Consumers are advised to immediately stop using these products and to seek medical attention, especially if they are currently being treated with anti-diabetic drugs.

Reference:
Advisory. Health Canada, 25 October 2005 (http://www.hc-sc.gc.ca).

Meningococcal vaccine

Reports of Guillain-Barré Syndrome

USA. Five cases of Guillain-Barré syndrome (GBS) have been reported in the United States following the administration of the meningococcal conjugate vaccine A, C, Y and W-135 (trade name Menactra), manufactured by Sanofi Pasteur. It is not known yet

whether the adverse events were caused by the vaccine. GBS is a serious neurological disorder that can occur, often in healthy individuals, either spontaneously or after certain infections. GBS typically causes increasing weakness in the legs and arms that can be severe and require hospitalization. Meningococcal infection, which the vaccine (Menactra) prevents, is a major cause of bacterial meningitis, affecting approximately 1 in 100,000 people annually. The infection can be life threatening: 10-14 percent of cases and 11-19 percent of survivors may have permanent disability.
Dr Jesse Goodman, the Director of the FDA's Center for Biologics Evaluation and Research, advises that at the present time there are no changes in recommendations for vaccination; individuals should continue to follow their doctor's recommendations. The FDA is not able to determine if any or all of the cases were due to vaccination. The current information is very preliminary and the two agencies are continuing to evaluate the situation. The Global Advisory Committee on Vaccine Safety (GACVS), an expert clinical and scientific advisory body reporting to WHO, reviewed this issue at its thirteenth meeting in Geneva, 1-2 December 2005. The committee's findings will be published in the next issue of the Weekly Epidemiological Record.

Reference:
FDA News. United States Food and Drug Administration, 30 September 2005 (http://www.fda.gov).

Menze Qianweishu slimming herbs capsule

Found to contain sibutramine

Hong Kong. The Department of Health (DH) has warned the public not to buy or consume a slimming product 'Menze Qianweishu slimming herbs capsule' since laboratory tests have revealed that the product contains sibutramine. Sibutramine can increase blood pressure and heart rate. Sibutramine containing products can therefore only be sold on a doctor's prescription, under the supervision of a pharmacist. Consumers are advised to immediately discontinue using the product, discard any unused portions of the product or return them to the importing company in Hong Kong.

Reference:
Communication from the Department of Health (Leader Sheet), Chinese Medicine Division, Government of Hong Kong, 12 August 2005.

Methadone

Cardiac vigilance recommended

New Zealand. Prescribers are advised that methadone, used in the treatment of opioid dependence and for analgesia in moderate to severe pain, may cause QT prolongation and *torsades de pointes*. Higher doses, concomitant QT interval-prolonging agents and the presence of other risk factors for QT prolongation may predispose patients to the development of potentially fatal arrhythmias with methadone. ECG monitoring is recommended with methadone doses >150 mg/day and in patients with either risk factors for QT prolongation or symptoms that may be attributable to arrhythmia. If QT prolongation occurs, specialist advice should be sought regarding discontinuing or reducing the dose of methadone. There have been two reports of arrhythmia in patients taking methadone in New Zealand. At present there are 282 reports of heart rate and rhythm disorders associated with methadone in the WHO adverse drug reactions database.

Reference:
Prescriber Update Articles. Medsafe, November 2005 (http://www.medsafe.govt.nz).

Nimodipine

Serious events due to IV use of oral formulations

Canada. Bayer Healthcare, in collaboration with Health Canada, is advising health-care professionals that inappropriate IV administration of the contents of oral nimodipine (Nimotop) 30 mg capsules has been temporally associated with serious, life-threatening or fatal adverse events. In a letter to hospital chiefs of medical staff, directors of extended care facilities and directors of nursing homes, Bayer Healthcare states that the contents of nimodipine (Nimotop) capsules must not be administered by way of injection into an IV line or other parenteral routes, and that if the capsule cannot be swallowed by the patient, the contents should be extracted into a syringe and emptied into the patient's naso-gastric tube then washed down with 30 mL of normal saline. Bayer says that it is working with Health Canada to update the monograph of nimodipine (Nimotop) with regard to drug administration.

Reference:
'Dear Health-care Professional' letter from Bayer Healthcare, 21 September 2005 (http://www.hc-sc.gc.ca).

Oseltamivir
Safety update

Europe. The European Medicines Agency (EMEA) has issued a Press Release following reports of alleged suicide in two young boys treated for influenza. In the release the agency notes that:

- oseltamivir (Tamiflu) has been approved in the European Union for the treatment of influenza in children between 1 and 13 years of age and for the prevention and treatment of influenza over 13 years and adults;
- so far no causal relationship has been identified between the use of oseltamivir (Tamiflu) and psychiatric symptoms such as hallucination and abnormal behaviour;
- psychiatric events during oseltamivir (Tamiflu) treatment are difficult to assess because of the presence of concurrent medications and because influenza itself can precipitate psychiatric symptoms, particularly in children and in the elderly.

The Committee for Medicinal Products for Human Use (CHMP) has asked the marketing authorization holder (Roche) to provide a cumulative safety review of all available data on serious psychiatric disorders, including all case reports with a fatal outcome