WHO PHARMACEUTICALS NEWSLETTER

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

The aim of the 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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Feature

No. 6, 2011

The WHO Pharmaceuticals Newsletter provides you with the latest information on the safety of medicines and legal actions taken by regulatory authorities across the world. Recent events and topics of concern are addressed in the Feature section. This issue includes a brief summary of a training course on the active monitoring of the safety of antiretroviral medicines.

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Atomoxetine

Association with increased blood pressure and heart rate

Canada. Eli Lilly Canada Inc. in collaboration with Health Canada informed of important information from clinical studies regarding the risk of increased blood pressure and heart rate with the use of atomoxetine (Strattera®). The monograph has recently been revised to include these new safety findings. Atomoxetine is a selective norepinephrine reuptake inhibitor indicated for treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in children and adults.

Recommendations are:
- Atomoxetine is contraindicated in patients with symptomatic cardiovascular diseases, moderate to severe hypertension or severe cardiovascular disorders whose condition would be expected to deteriorate if they experienced increases in blood pressure or in heart rate that could be clinically important;
- Atomoxetine should be used with caution in patients whose underlying medical conditions could be worsened by increases in blood pressure or heart rate, such as patients with hypertension, tachycardia, or cardiovascular or cerebrovascular disease;
- Atomoxetine should be used with caution in patients with congenital or acquired long QT syndrome or a family history of QT prolongation;
- patients should be screened for pre-existing or underlying cardiovascular or cerebrovascular conditions before initiation of treatment with atomoxetine and monitored during the course of treatment;
- it is recommended that heart rate and blood pressure be measured in all patients before treatment with atomoxetine is started, after the dose is increased, and periodically during treatment to detect possible clinically important increases, particularly during the first few months of therapy.

(See WHO Pharmaceuticals Newsletter No. 2, 2006 for new recommended warnings in UK).

Reference:
Advisories, Warnings and Recalls, Health Canada, 21 October 2011 (*www.hc-sc.gc.ca*).

Buflomedil-containing medicines

Suspension of all buflomedil-containing medicines recommended

Europe. The European Medicines Agency (EMA)'s Committee for Medicinal Products for Human Use (CHMP) concluded a review of the safety and efficacy of buflomedil, stating that the risks of these medicines, particularly the risks of severe cardiological and neurological adverse reactions, are greater than their limited benefits in the treatment of patients with chronic peripheral arterial occlusive disease (PAOD). The Committee therefore recommended that the marketing authorisations of all buflomedil-containing medicines be suspended in all European Union (EU) Member States where they are currently authorized.

The EMA advised that doctors should stop using buflomedil and consider alternative treatment options, including managing underlying health problems which can increase the risk of PAOD, such as diabetes, high blood pressure as well as smoking. And the EMA advised patients using buflomedil-containing medicines to make an appointment with their doctor at a convenient time to discuss their ongoing treatment.

The CHMP considered all available data on the benefits and risks of buflomedil, including the benefit-risk assessment carried out by France, data from clinical studies, post-marketing surveillance and published literature, as well as from poison control centres in the EU.

Following review of these data the Committee concluded that:
- there was a risk of serious neurological and cardiac side effects in patients taking buflomedil under normal conditions of use and that risk minimization measures such as changes to the packaging of the medicine, recommendations on adjusting the dose for patients with kidney problems and restrictions on the medicines' use in certain patients had not been able to reduce these risks to an acceptable level;
- due to the narrow therapeutic index (i.e. the small difference between buflomedil's therapeutic dose and its toxic dose) there was a significant risk of adverse events, particularly in elderly patients and in patients with certain conditions such as kidney problems, which are common in PAOD;
- data in support of the benefit of the medicine for patients were limited and of poor quality.

The Committee was therefore of the opinion that the benefits of buflomedil-containing medicines do no longer outweigh their risks, and recommended that marketing of these medicines should be suspended throughout the EU.

(See WHO Pharmaceuticals Newsletter No. 2, 2011 for the

decision by Afssaps to suspend marketing authorizations, No. 3, 2011 for recommendation for suspension of oral buflomedil-containing medicines in Europe and reports in WHO global ICSR database).

Reference:
Press release, EMA, 17 November 2011 (*www.ema.europa.eu*).

Dasatinib

Risk of pulmonary arterial hypertension

USA. The U.S. Food and Drug Administration (US FDA) notified healthcare professionals that dasatinib (Sprycel®) may increase the risk of a rare but serious condition in which there is an abnormally high blood pressure in the arteries of the lungs (pulmonary arterial hypertension [PAH]). Symptoms of PAH may include shortness of breath, fatigue and swelling of the body (such as the ankles and legs). In reported cases, patients developed PAH after starting dasatinib, including after more than one year of treatment. Information about this risk has been added to the Warnings and Precautions section of the Sprycel drug label. Dasatinib is used to treat certain adult patients with Philadelphia chromosome-positive chronic myeloid leukemia (CML) or acute lymphoblastic leukemia (ALL).

FDA recommended that healthcare professionals should evaluate patients for signs and symptoms of underlying cardiopulmonary disease prior to starting dasatinib and also during treatment. If PAH is confirmed, dasatinib should be permanently discontinued.

(See WHO Pharmaceuticals Newsletter No. 5, 2011 for Safety information regarding pulmonary arterial hypertension in Canada).

Reference:
FDA Drug Safety Communication, US FDA, 11 October 2011 (*www.fda.gov*).

Drotrecogin alfa (activated)

Market Withdrawal - Failure to Show Survival Benefit

USA (1). The U.S. Food and Drug Administration (US FDA) notified healthcare professionals and the public that on 25 October 2011, Eli Lilly and Company announced a worldwide voluntary market withdrawal of drotrecogin alfa (activated) (Xigris®). In a recently completed clinical trial (PROWESS-SHOCK trial), drotrecogin alfa (activated) failed to show a survival benefit for patients with severe sepsis and septic shock.

Drotrecogin alfa (activated) is indicated for the reduction of mortality in adult patients with severe sepsis who have a high risk of death.

The FDA recommended that drotrecogin alfa (activated) treatment should not be started in new patients and should be stopped in patients currently being treated. All remaining products should be returned to the supplier from whom they were purchased.

Canada (2). Health Canada informed Candians of the withdrawal of drotrecogin alfa (Xigris®) from the Canadian market, in light of the company's decision to withdraw the products from the market worldwide. Drotrecogin alfa is used solely in hospital intensive care units to treat patients at a high risk of death due to serious complications of a blood infection (called sepsis or septic shock).

The withdrawal is in light of a large international clinical trial, known as the PROWESS-SHOCK study that showed no benefit for patients receiving drotrecogin alfa compared to patients who did not receive it.

(See WHO Pharmaceuticals Newsletter No. 2, 2009 for increased risk of serious bleeding events and death in the US).

Reference:
(1) FDA Drug Safety Communication, US FDA, 25 October 2011 (*www.fda.gov*).
(2) Advisories, Warnings and Recalls, Health Canada, 25 October 2011 (*www.hc-sc.gc.ca*).

Drospirenone-containing combined oral contraceptives

Possible increased risk of blood clots

Australia (1). The Therapeutic Goods Administration (TGA) announced that new information about the risk of venous thromboembolism (VTE) is being included in the Product Information documents for drospirenone-containing combined oral contraceptives (Yaz®, Yasmin®) as a result of a recent safety review by the TGA.

TGA reminded health professionals that oral contraceptives are contraindicated in women with severe or multiple risk factor(s) for venous or arterial

thrombosis. Risk factors include, for example, ages > 35 years, smoking and prolonged immobilisation. The clinical needs of patients should be weighed against the possible slight increase in the risk of VTE, and patients should be educated to recognize the signs and symptoms of VTE.

USA (2). The US FDA notified healthcare professionals of the release of the final report of the FDA-funded study that evaluated the risk of blood clots in users of several different hormonal contraceptives. The FDA's review of the results of this study, specifically those results related to drospirenone-containing birth control pills, will be presented and discussed at the joint meeting of the Reproductive Health Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee on 8 December 2011.

(See WHO Pharmaceuticals Newsletter No. 3, 2010 and No. 4, 2011 for update on the risk of venous thromboembolism in the UK and No. 4 and No. 5, 2011 in the USA).

Reference:

(1) Medicines Safety Update Vol. 2, No. 5, October 2011 (www.tga.gov.au).
(2) FDA Drug Safety Communication, US FDA 27 October 2011 (*www.fda.gov*).

Fenofibric acid

Label Change: found no significant difference in the risk of a major adverse cardiac event between the group treated with or without fenofibrate

USA. The US FDA notified healthcare professionals that the cholesterol-lowering medicine fenofibric acid (Trilipix®) may not lower a patient's risk of having a heart attack or stroke. The FDA reviewed the data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid trial. The ACCORD Lipid trial found no significant difference in the risk of experiencing a major adverse cardiac event between the group treated with fenofibrate plus simvastatin compared with simvastatin alone. Information from the trial has been added to the Important Limitations of Use and Warnings and Precautions sections of the fenofibric acid physician label and to the patient Medication Guide.

Fenofibric acid was approved by the FDA in 2008 to treat cholesterol in the blood by lowering the total amount of triglycerides and low-density lipoprotein (LDL) cholesterol, and increasing the high-density lipoprotein (HDL) cholesterol.

According to the FDA, fenofibrate at a dose equivalent to 135 mg of Trilipix® was not shown to reduce coronary heart disease morbidity and mortality in patients in two large randomized controlled trials of patients with type 2 diabetes mellitus. The FDA recommended that healthcare professionals should consider the benefits and risks of fenofibric acid when deciding to prescribe the drug to patients, and counsel patients about those benefits and risks.

Reference:

FDA Drug Safety Communication, US FDA, 9 November 2011 (*www.fda.gov*).

Fluoroquinolone

Patients with myasthenia gravis may risk increased muscle weakness

Canada. Health Canada informed that patients with a rare condition known as myasthenia gravis who take a fluoroquinolone antibiotic may risk a worsening of their symptoms, including muscle weakness or breathing problems and recommended that use of fluoroquinolone antibiotics should be avoided in patients with a known history of myasthenia gravis. According to Health Canada, the risk is considered rare, but serious. The risk to myasthenia gravis patients appears to apply to formulations taken by mouth (liquids and tablets/extended release tablets) or that are injected intravenously (into a vein). Based on available data, the risk does not appear to apply to ear or eye drops.

Fluoroquinolone drugs currently marketed in Canada are moxifloxacin, ciprofloxacin, levofloxacin, norfloxacin and ofloxacin.

Myasthenia gravis is a rare, chronic (long-lasting and recurring) disease that causes progressive muscle weakness. Muscles affected by this condition include eye and face muscles, neck and throat muscles, and limb muscles. Activity makes the muscle weakness worse, and symptoms generally improve with rest.

Health Canada has notified the Canadian manufacturers of fluoroquinolone antibiotics to update the labelling to include a warning on this risk.

Reference:

Advisories, Warnings and Recalls, Health Canada, 7 November 2011

(www.hc-sc.gc.ca).

Lenalidomide

Risk of second primary malignancy—update

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) advised that healthcare professionals should consider the possibility of second primary malignancy in patients treated with lenalidomide. The MHRA also advised that use of lenalidomide in unlicensed indications is not recommended unless it takes place as part of a clinical trial and that patients should be carefully evaluated before and during treatment with lenalidomide using routine cancer screening for occurrence of second primary malignancy; treatment should be instituted as indicated.

The available evidence suggests that there may be a small increased risk of development of second primary malignancy. Overall in the trials this was compensated by greater overall survival and progression-free survival in patients treated with lenalidomide for relapsed or refractory myeloma. The balance of benefits and risks for lenalidomide remains favourable in its licensed indication.

In clinical trials of newly diagnosed multiple myeloma (unauthorised indication), a four-fold increased incidence of second primary malignancy has been observed in patients receiving lenalidomide (7%) compared with controls (1.8%). The median follow-up for participants with newly diagnosed myeloma in clinical trials ranges from 27.2 months to 36.5 months.

The MHRA concluded that the possibility of second malignancy should be considered in all patients treated with lenalidomide because the available data do not allow identification of potential risk factors for the development of second primary malignancy.

(See WHO Pharmaceuticals Newsletter No. 3, 2011 for investigation of risk of second primary malignancies in myeloma in the UK and No. 5, 2011 for the risk of new cancers but benefit-risk balance remains positive in EU and reports in WHO global ICSR database).

Reference:
Drug Safety Update, November 2011, Vo.5, issue 4, A1, MHRA, (www.mhra.gov.uk).

Modafinil

Product information updated

Australia. The Therapeutic Goods Administration (TGA) announced that several safety-related changes and recommendations have been included in the recently updated Product Information for modafinil (Modavigil®) as a result of a recent benefit-risk review by the TGA.

The TGA has reviewed the available clinical trial data, national and international post-marketing spontaneous adverse event data and published literature relating to modafinil adverse drug reactions from 1 October 2010. This review was initiated because of post-market reports of serious skin, psychiatric, nervous system and cardiovascular adverse events.

The TGA concluded that:

- following additional safety information should be included in the Product Information: multi-organ hypersensitivity reactions; psychiatric disorders including exacerbation of pre-existing psychiatric disorders and psychiatric symptoms occurring de novo; cardiovascular disease; dependence potential; use in children and adolescents; and dose-related adverse reactions;
- the benefits of modafinil continued to outweigh the risks for the indications to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy and in patients with obstructive sleep apnoea/hypopnoea syndrome as an adjunct to continuous positive airway pressure (CPAP);
- the indication to treat excessive sleepiness associated with moderate-to-severe chronic shift work sleep disorder should be revised to include only patients where non-pharmacological interventions (e.g. planned napping) are unsuccessful or inappropriate.

The TGA recommended that modafinil should only be used as an adjunct to CPAP when used to improve wakefulness in patients with obstructive sleep apnoea/hypopnoea syndrome, because modafinil can improve the symptom of excessive sleepiness but does not treat the underlying cause. Treatment with modafinil should be initiated and supervised by physicians with appropriate experience in the treatment of sleep disorders who have access to sleep laboratory diagnostic facilities. Modafinil is contraindicated in pregnancy.

The TGA also recommended that the effectiveness of oral contraceptives may be impaired due to the induction of the metabolising enzyme cytochrome P450 3A4. Evaluate cardiovascular,

psychiatric and substance abuse status before starting modafinil and monitor patients regularly for skin reactions, cardiovascular disease, psychiatric illness and signs of modafinil abuse. Start with the lowest recommended dose and monitor the patient at every dose adjustment.

(See WHO Pharmaceuticals Newsletter No. 5, 2010 for a review of the benefits and risks of modafinil in Europe and No. 1, 2011 for restriction of the use to narcolepsy in the UK).

Reference:
Medicines Safety Update Vol. 2, No. 5, October 2011 (www.tga.gov.au).

Pioglitazone

An increased risk of bladder cancer

Australia. The Therapeutic Goods Administration (TGA) advised health professionals to consider the risk of bladder cancer when prescribing pioglitazone and to avoid pioglitazone in patients with bladder cancer or a history of bladder cancer.

According to the TGA, this advice is based on the assumption that pioglitazone or a metabolite may affect bladder cancer initiation, possible signs or symptoms of bladder cancer such as blood in the urine, urinary urgency, pain on urination, or back or abdominal pain.

(See WHO Pharmaceuticals Newsletter No. 5, 2010 for ongoing safety review on potential increased risk of bladder cancer in the USA and No. 4, 2011 for the suspension in France and risk-characterization study in EU and reports in WHO global ICSR database)

Reference:
Medicines Safety Update Vol. 2, No. 5, October 2011 (www.tga.gov.au).

Rosiglitazone

Risk Evaluation and Mitigation Strategy (REMS) - Risk of cardiovascular events includes Avandia, Avandamet and Avandaryl

USA. The US FDA announced that healthcare providers must enrol in the Avandia-Rosiglitazone Medicines Access Program if they wish to prescribe rosiglitazone medicines to outpatients or patients in long-term care facilities after 18 November 2011.

Reference:
FDA Drug Safety Communication, US FDA, 4 November 2011 (www.fda.gov).