WHO PHARMACEUTICALS NEWSLETTER

World Health Organization

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.

Quality Assurance and Safety: Medicines, EMP-HSS
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
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.

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No 2, 2009

In this issue, we report the suspension of efalizumab in Europe and elsewhere, and the withdrawal of fenfluramine in China. We bring you information on risks and restrictions with some group products (anticonvulsants, antipsychotics, bisphosphonates, SSRIs etc) and advice on some individual drugs in the section on Safety of Medicines. The Feature section includes a short report from the nineteenth meeting of the Global Advisory Committee on Vaccine Safety.

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Feature

Aliskiren

New contraindication and warning

Europe. The European Medicines Agency (EMEA) has recommended adding a contraindication to the Product Information for aliskiren, which states that it is not to be used in patients who have experienced angioedema when taking aliskiren in the past. The Agency has also recommended including a warning, stating that patients who develop signs of angioedema should stop treatment and seek medical attention. Aliskiren is authorized for the treatment of essential hypertension.

According to the EMEA, there were reports of cases of angioedema or similar reactions in association with aliskiren-containing medicines. The EMEA's Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of aliskiren-containing medicines in the treatment of essential hypertension outweigh their risks, but that angioedema can occur as a rare and serious adverse effect.

Reports in WHO Global Individual Case Safety Reports (ICSR) database, VigiBase: Aliskiren

A total of 54 reports of angioedema

Reference:
Press Release, EMEA, 19 February 2009 (www.emea.europa.eu).

Atomoxetine

Risk of psychotic or manic symptoms

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) has alerted that atomoxetine can be associated with treatment-emergent psychotic or manic symptoms, including hallucinations, delusional thinking, mania and agitation, in children and adolescents without a history of psychotic illness or mania. Health-care professionals have been advised to consider a possible causal role of atomoxetine and discontinuation of treatment, if such symptoms occur. Atomoxetine (Strattera) is a selective noradrenaline reuptake inhibitor, authorized for use in the treatment of attention-deficit/hyperactivity disorder (ADHD) as part of a comprehensive treatment regimen.

Product information for prescribers has been updated to reflect the safety information.

Reference:
Drug Safety Update, MHRA, Volume 2, Issue 8, March 2009 (www.mhra.gov.uk).

Cough and cold medicines

New advice on use of over-the-counter cough and cold medicines for children

Kenya (1). The Kenya Pharmacy and Poisons Board (PPB) stated that the following over-the-counter (OTC) cough and cold medicines are not recommended in children under six years of age:
• Antitussives (dextromethorphan and pholcodine)
• Expectorants (guaifenesin and ipecacuanha)
• Nasal decongestants (ephedrine, oxymetazoline, phenylephrine, pseudoephedrine and xylometazoline)
• Antihistamines (brompheniramine, chlorpheniramine, diphenhydramine, doxylamine, promethazine and tripolidine).

Cough and cold medicines containing these ingredients will be available for children between ages 6 to 12 years, but only in pharmacies.

The PPB notes that these medicines provide only symptomatic treatment and that there is no information that they are really effective. Serious and potentially life-threatening side effects can occur, if these medicines are taken inappropriately: these include death, convulsions, increased heart rates and reduced levels of consciousness.

UK (2). The Medicines and Healthcare products Regulatory Agency (MHRA) has announced a comprehensive package of measures to promote the safer use of OTC cough and cold medicines for children under 12 years, based on the advice from the Commission on Human Medicines.

The MHRA has recommended that parents and carers should no longer use OTC cough and cold medicines in children under the age of six, because there is no evidence that these medicines work and due to the fact that they can cause side effects such as allergic reactions, effects on sleep or hallucinations. For six to 12 year old children, the Agency says that these medicines will continue to be available but only in pharmacies, with clearer advice on the packaging and from the pharmacist. This is because the risks of side effects is reduced in older children since they weigh more, get fewer colds and can say if the medicine is doing any good. More research is being done by industry on how well these medicines work in children aged six to 12 years.

Some combinations which are illogical (such as cough suppressants and expectorants) are being phased out, and all liquid cough and cold medicines

will be packaged in child resistant containers.

The products affected are the medicines containing the following active ingredients:
- Antitussives: dextromethorphan and pholcodine
- Expectorants: guaifenesin and ipecacuanha
- Nasal decongestants: ephedrine, oxymetazoline, phenylephrine, pseudoephedrine and xylometazoline
- Antihistamines: brompheniramine, chlorphenamine, diphenhydramine, doxylamine, promethazine and tripolidine.

The labelling will be updated and the legal status of medicines authorized for children aged six to 12 years will be changed from general sale to pharmacy.

(See WHO Pharmaceuticals Newsletter No. 4, 2007 for a public health advisory regarding OTC cough and cold medicines for use in children in the USA).

References:

(1) Statement on cough and cold medicines, Frequently Asked Questions, PPB, 13 March 2009 (www.pharmacyboardkenya.org)
(2) Safety information, MHRA, 28 February 2009 (www.mhra.gov.uk).

Efalizumab

Suspension of marketing authorization recommended in Europe and other countries

Canada (1). Health Canada has issued recommendation to suspend efalizumab (Raptiva) in Canada, after the EMEA has determined that the benefit/risk for the product has become unfavourable due to safety concerns.

Prescribers in Canada are advised not to issue any new prescriptions for efalizumab (Raptiva) and to review the treatment of patients taking this medicine to assess the most appropriate alternative. The public are warned not to change or stop their treatment without first consulting doctors because abrupt discontinuation of the medicine without alternative treatment may be followed by a return of psoriasis or onset of new psoriasis.

(See WHO Pharmaceuticals Newsletter No. 1, 2009 for warnings of progressive multifocal leukoencephalopathy (PML) in Canada and UK).

Europe (2). The EMEA has recommended the suspension of the marketing authorization for efalizumab (Raptiva), which is authorized to treat adult patients with moderate to severe chronic plaque psoriasis, following the opinion of the CHMP that the risks of this medicine outweigh its benefits. The CHMP reviewed the reports of serious side effects, including three confirmed cases of PML in patients who had taken efalizumab (Raptiva) for more than three years. Two out of the three cases resulted in death. There was also a suspected case of PML reported.

The CHMP concluded the following:
- Efalizumab (Raptiva)'s benefits are modest.
- In addition to PML, efalizumab (Raptiva) is associated with other serious side effects, including Guillain-Barré and Miller-Fisher syndromes, encephalitis, encephalopathy, meningitis, sepsis and opportunistic infections.
- There is not enough evidence to identify a group of patients in which the benefits of efalizumab (Raptiva) outweigh its risks, in particular there is a lack of data on effectiveness and safety in patients who have no other treatment options and who may already have a weakened immune system as a result of previous treatments.

The EMEA has advised prescribers not to issue any new prescriptions for efalizumab (Raptiva) and to review the treatment of patients currently receiving the medicine to assess the most appropriate alternative.

(Also see WHO Information Exchange System Alert No. 121, Drug Alert URL: www.who.int/medicines)

Switzerland (3). The Swiss Agency for Therapeutic Products (Swissmedic) has announced its intention to suspend authorization of efalizumab (Raptiva), following EMEA's recommendation of the suspension of the marketing authorization for the product.

Swissmedic has recommended that physicians should no longer issue any new prescriptions for efalizumab (Raptiva). The Agency has also warned that control by a physician is necessary to change the treatment for patients currently using the product, adding that stopping the product abruptly on a patient's own initiative can lead to an acute worsening of psoriasis and symptoms of inflammation.

USA (4). The United States Food and Drug Administration (US FDA) has issued a Public Health Advisory to notify health-care professionals of three confirmed cases and one possible case of PML in patients treated with efalizumab (Raptiva), and to provide recommendations for health-care providers and patients when treatment with this product is considered.

The US FDA says that it will take appropriate steps to minimize the risks from efalizumab, and ensure that patients prescribed the product are clearly informed of the signs and symptoms of PML, and that health-care professionals carefully monitor patients for the possible development of PML.

In October 2008, the product labelling was revised to highlight the risks of life-threatening infections including PML in a Boxed Warning. The US FDA also directed the manufacturer to develop a Risk Evaluation and Mitigation Strategy (REMS) to include a Medication Guide to ensure that patients receive risk information about the medicine.

(Argentina and Turkey have informed WHO that the authorization/commercialization of efalizumab (Raptiva) has been suspended in their countries).

Reports in WHO Global ICSR database, VigiBase: Efalizumab

Central and peripheral nervous system disorders: 461
Encephalopathy (including encephalitis) 4
Meningitis 40
Polyneuropathy 5
Neuritis (Miller-Fisher syndrome) 11

Resistance mechanism disorders: 166
Sepsis 18
Infection (including bacterial, fungal, secondary, staphylococcal, susceptibility increased, and viral) 69

References:

(1). Advisories, Warnings and Recalls, Health Canada, 20 January 2009 (www.hc-sc.gc.ca).
(2). Press Release, EMEA, 19 February 2009 (www.emea.europa.eu).
(3). Announcements, Swissmedic, 20 February 2009 (www.swissmedic.ch).
(4). Media Release, US FDA, 19 February 2009 (www.fda.gov).

Exenatide

Risk of severe pancreatitis and renal failure

UK. The MHRA has announced that suspected adverse reaction reports of necrotising and haemorrhagic pancreatitis, some of which were fatal, have been received in association with exenatide (Byetta). Health-care professionals have been advised that if pancreatitis is diagnosed, exenatide should be permanently discontinued. Exenatide is indicated for treatment of type 2 diabetes mellitus in combination with metformin.

According to the Agency, up to February 2009, six case reports of pancreatitis and a further three cases of acute pancreatitis were reported in the UK. There have been approximately 800 000 patient-years of exposure worldwide since licensing. Up to September 2008, 396 case reports of pancreatitis have been received worldwide and 80% of these reports were considered to be possibly related to exenatide, and in several cases there was evidence of positive rechallenge. Nine reports of necrotising or haemorrhagic pancreatitis have been received worldwide, two of which had a fatal outcome. After a Europe-wide review, product information for exenatide is being updated to include further information about this risk.

Up to 30 January 2009, there were seven case reports of acute renal failure in the UK in association with exenatide. The Agency has emphasized that exenatide is not recommended for use in patients with end-stage renal disease or severe renal impairment.

Reference:

Drug Safety Update, MHRA, Volume 2, Issue 8, March 2009 (www.mhra.gov.uk).

Fenfluramine

Withdrawal of the drug approval

China. According to the State Food and Drug Administration (SFDA), fenfluramine hydrochloride (including raw materials) will be withdrawn from China's market because of the risk of causing heart valve damage and pulmonary arterial hypertension. The production, sale and use of fenfluramine hydrochloride (including raw materials) will be suspended, and the drug approval number has been revoked.

Reference:

Media Release, SFDA, 12 January 2009 (eng.sfda.gov.cn/eng/)

Fluoroquinolones

Boxed warning about tendon disorders

Kenya. The PPB has alerted that fluoroquinolones are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. The Agency has informed prescribers and other stakeholders that the Committee on Drug Registration (Human) has recommended that all fluoroquinolones should include a boxed warning on the package, patient information leaflet and prescriber information leaflet with this information.

(See WHO Pharmaceuticals Newsletters No. 3, 2008 and No. 1, 2003 for a boxed warning against increased risk of tendinitis and tendon rupture in the USA and reports of tendon disorders in Australia, respectively)

Reference:
Fluoroquinolones and tendon disorders: letter from PPB, 3 March 2009.

Metoclopramide

Warning against chronic use

USA. The US FDA has required manufacturers of metoclopramide to add a boxed warning to the labels about the risk of its long-term or high-dose use. Chronic use of metoclopramide has been linked to tardive dyskinesia. Those at greatest risk include the elderly, especially older women, and people who have been taking the drug for a long time. Metoclopramide is used as a short-term treatment of gastroesophageal reflux disease and diabetic gastroparesis. It is recommended that treatment not exceed three months. The Agency has become aware of continued spontaneous reports of tardive dyskinesia in patients who used metoclopramide and the majority of them had taken the drug for more than three months.

Manufactures will be required to implement REMS for metoclopramide-containing drugs to ensure that patients are provided with a medication guide that discusses this risk.

Reports in WHO Global ICSR database, VigiBase: Metoclopramide

Mycophenolate mofetil

Introduction of Medication Guide

USA. The US FDA and Roche Laboratories Inc. notified health-care professionals of the introduction of a Medication Guide for mycophenolate mofetil (CellCept) to provide important safety information in a language that patients can easily comprehend. Pharmacists are required to distribute a copy of the Medication Guide to every patient who fills a prescription of this product. The US FDA has also required the introduction of a Medication Guide for mycophenolic acid (Myfortic) marketed by Novartis.

The Medication Guide states that the product can cause serious side effects including possible loss of pregnancy and higher risk of birth defects, and increased risk of getting serious infections and certain cancers.

(See WHO Pharmaceuticals Newsletters No. 2, 2008 and No.6, 2007 for reports of PML in Europe and USA, and risk of pregnancy loss and congenital malformations in USA, respectively.)

Reference:
Media Release, US FDA, 12 February 2009 (*www.fda.gov*).

Natalizumab

treatment of patients with relapsing-remitting multiple sclerosis. PML is a known risk of this product. Combination therapy is contraindicated.

Since the product became available on the market worldwide, five confirmed cases of PML have been reported in patients receiving natalizumab (Tysabri) monotherapy. One case had a fatal outcome. As of the end of December 2008, approximately 37 600 patients were receiving the medicine worldwide.

(See WHO Pharmaceuticals Newsletter No. 4, 2006 for elements of the risk management programme for natalizumab in USA.)

Reference:
Advisories, Warnings and Recalls, Health Canada, 13 January 2009 (*www.hc-sc.gc.ca*).

Phosphodiesterase type 5 inhibitors

Risk of sudden hearing loss

New Zealand. The New Zealand Medicines and Medical Devices Safety Authority (Medsafe) advised prescribers of the risk of sudden hearing loss associated with phosphodiesterase type 5 (PDE-5) inhibitors (sildenafil, tadalafil, vardenafil). As of 30 April 2008, the Centre for Adverse Reactions Monitoring received three reports of sudden decrease or loss of hearing with