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:

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
Box 1051
751 40 Uppsala
Tel: +46-18-65.60.60
Fax: +46-18-65.60.80
E-mail: info@who-umc.org
Internet: http://www.who-umc.org

Contents

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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.

In September, the International Pharmaceutical Federation (FIP) Pharmacy Information Section organized a one-day seminar on pharmacovigilance prior to the FIP's 71st International Congress in Hyderabad. In this issue we include a summary of the seminar.

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TABLE OF CONTENTS

Regulatory Matters

Safety of medicines

Feature

Aprotinin

The benefits outweigh the risks when it is used as authorized

Canada. Health Canada concluded that the benefits of aprotinin (Trasylol®) outweigh the risks when aprotinin is used as authorized by Health Canada. Aprotinin is authorized for patients undergoing Coronary Artery Bypass Graft (CABG) surgery, also known as heart bypass surgery. The evidence does not suggest an increased risk of death in this use. Health Canada requested that strong warnings, in the form of a Boxed Warning, be added to the prescribing information emphasizing that there have been reports of an increased risk of death in some studies associated with aprotinin use outside of its authorized indication, and that aprotinin should only be used as authorized after careful consideration of the potential benefits and risks. Warnings have also been added emphasizing that physician should adhere to the recommended procedures for the management of blood clotting. Information on the risk of abnormal kidney function has also been added to the Boxed Warning.

Aprotinin marketing was temporarily suspended in November 2007 at Health Canada's request after a clinical trial, the Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART) study. It was stopped due to a higher number of deaths in patients receiving aprotinin relative to two drugs also used to reduce blood loss. The BART study included higher-risk patients undergoing complex cardiac surgeries, a use for which aprotinin and the other two drugs are not authorized in Canada.

Health Canada's decision is based on a comprehensive review of the totality of evidence, which included an evaluation of BART study data, other clinical trial data, post-market studies, and information from Bayer as well as an Expert Advisory Panel on aprotinin that was convened by Health Canada. As a result of this assessment, the manufacturer, Bayer Inc., can resume the marketing of aprotinin in Canada.

(See WHO Pharmaceuticals Newsletter No. 6, 2007 and No. 1, 2008 for temporary market suspension of aprotinin worldwide).

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

Asenapine maleate

Serious allergic reactions

USA. The U.S. Food and Drug Administration (US FDA) notified healthcare professionals and patients that serious allergic reactions have been reported with the use of asenapine maleate (Saphris®). The Contraindications, Warnings and Precautions, Adverse Reactions, and Patient Counselling Information sections have been revised to include information about type I hypersensitivity reactions which may include anaphylaxis, angioedema, low blood pressure, rapid heart rate, swollen tongue, difficulty breathing, wheezing, or rash. In several cases, these reactions occurred after the first dose. Asenapine maleate is used to treat symptoms of schizophrenia and bipolar disorder.

The US FDA recommended healthcare professionals to be aware of the risk of hypersensitivity reactions with asenapine maleate and to counsel patients who are receiving the drug about how to recognize the signs and symptoms of a serious allergic reaction. They also recommended that asenapine maleate should not be used in patients with a known hypersensitivity to the drug.

Reference:
FDA Drug Safety Communication, US FDA, 1 September 2011 (*www.fda.gov*).

Ceftriaxone

The use with calcium containing iv solutions in neonates is contraindicated due to the risk of calcium precipitation

New Zealand. Medsafe (New Zealand Medicines and Medical Devices Safety Authority) announced the updated safety information with the following recommendations:
•ceftriaxone must not be administered simultaneously with calcium-containing intravenous solutions, including continuous calcium-containing infusions via a Y site, because calcium precipitation can occur;
•ceftriaxone is contraindicated in neonates if they require (or are expected to require) treatment with calcium-containing intravenous solutions due to the risk of calcium precipitation;
•in patients over 28 days of age, ceftriaxone and calcium-containing solutions may be administered sequentially to one another if the infusion lines are flushed between infusions with a compatible fluid.

In February 2008, Medsafe advised healthcare professionals that ceftriaxone should not be mixed or administered with calcium-containing solutions due to the risk of precipitation. These recommendations follow Medsafe's review of two *in vitro* studies to assess the potential for precipitation of ceftriaxone and calcium when mixed in infusion lines. The *in vitro* studies were conducted in neonatal and adult plasma; but only showed an increased risk in neonatal plasma.

(See WHO Pharmaceuticals Newsletter No.3, 2009 and No. 4, 2007 for the interaction with calcium containing products in the USA and No.4, 2008 in Canada).

Reference:
Prescriber Update Vol. 32 No. 3, September 2011 (*www.medsafe.govt.nz*).

Citalopram hydrobromide

Abnormal heart rhythms associated with high doses

USA. The US FDA notified healthcare professionals and patients that the antidepressant citalopram hydrobromide (Celexa®) should no longer be used at doses greater than 40 mg per day, because it can cause abnormal changes in the electrical activity of the heart. Changes in the electrical activity of the heart (prolongation of the QT interval of the electrocardiogram [ECG]) can lead to an abnormal heart rhythm (including Torsade de Pointes), which can be fatal. Patients at particular risk for developing prolongation of the QT interval include those with underlying heart conditions and those who are predisposed to low levels of potassium and magnesium in the blood.

According to the US FDA, studies did not show a benefit in the treatment of depression at doses higher than 40 mg per day. Previously, the citalopram drug label stated that certain patients may require a dose of 60 mg per day. The citalopram drug label has been revised to include the new drug dosage and usage recommendations, as well as information about the potential for QT interval prolongation and Torsade de Pointes.

Reference:
FDA Drug Safety Communication, US FDA, 24 August 2011 (*www.fda.gov*).

Clopidogrel and proton-pump inhibitors

Not all proton pump inhibitors reduce the effectiveness of clopidogrel to the same degree

Canada. Health Canada informed healthcare professionals and patients of updated recommendations involving the use of clopidogrel (Plavix®) in combination with proton pump inhibitors (PPIs). New evidence has shown that while PPIs do interact with clopidogrel, not all reduce the effectiveness of clopidogrel to the same degree.

In 2009, the labelling for clopidogrel was updated to indicate that the use of any PPI in patients taking clopidogrel should be discouraged, as emerging data suggested that PPIs potentially reduced the ability of clopidogrel to protect against blood clots.
Since that time, new studies have shown that, while PPIs do interact with clopidogrel, not all PPIs interact to the same degree: some have a strong effect on clopidogrel, while others do not.

The labelling for clopidogrel has been updated with new recommendations regarding the use of PPIs:
•PPIs known to strongly or moderately reduce clopidogrel effectiveness should be avoided. Omeprazole is one of these;
•if a PPI must be used in a patient taking clopidogrel, consider a PPI that does not interact as strongly. Pantoprazole is one of these.

Patients taking Plavix should continue taking it as directed and should talk to their health professional regarding any questions or concerns about their treatment. There are alternatives to PPIs for the treatment of stomach ulcers and heartburn.

(See WHO Pharmaceuticals Newsletter No. 2 and No. 3, 2010 for interactions in Europe, New Zealand, the USA and the UK).

Reference:
Advisories, Warnings and Recalls, Health Canada, 22 September 2011 (*www.hc-sc.gc.ca*).

Dasatinib

Safety information regarding pulmonary arterial hypertension

Canada. Health Canada announced Bristol-Myers Squibb Canada's (BMS) new safety information regarding reports of serious pulmonary arterial hypertension (PAH) in patients treated with dasatinib (Sprycel®).

PAH, a subtype of pulmonary hypertension (PH), is a rare,

severe and progressive disease with no apparent cause, characterized by vascular proliferation and remodelling of the small pulmonary arteries, leading to increased pulmonary artery pressure and vascular resistance. PAH is diagnosed by right heart catheterization and defined by haemodynamic criteria including a mean pulmonary arterial pressure of 25 mmHg or higher and pulmonary capillary wedge pressure of 15 mmHg or lower (pre-capillary PH in the absence of post-capillary PH).

A total of 60 serious PH cases have been reported worldwide, between June 2006 and June 2011, including 12 cases of pulmonary arterial hypertension (PAH) confirmed by right heart catheterization, in association with dasatinib treatment.

Some patients diagnosed with PAH during dasatinib therapy were taking concomitant medications or had co-morbidities in addition to the underlying malignancy.

It is recommended that:
- patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease before initiating dasatinib therapy;
- patients who develop symptoms suggestive of PAH such as dyspnea and fatigue after initiation of treatment with dasatinib should be evaluated for more common etiologies and treatment should be withheld during evaluation, if symptoms are severe;
- the diagnosis of PAH should be considered if no alternative diagnosis can be found;
- Dasatinib should be permanently discontinued if the diagnosis of PAH is confirmed.

It is also informed that improvements in hemodynamic and clinical parameters have been observed in patients with PAH following cessation of dasatinib therapy.

Reference:
Advisories, Warnings and Recalls, Health Canada, 30 August 2011 (www.hc-sc.gc.ca).

Dronedarone

Information on increase in cardiovascular events in patients with permanent atrial fibrillation

Canada(1). Health Canada announced that Sanofi-aventis Canada Inc. informed new safety information regarding dronedarone (Multaq®):

- Dronedarone should be prescribed only in patients with a history of, or current non-permanent atrial fibrillation (AF) to reduce the risk of cardiovascular hospitalization due to AF;
- Dronedarone must not be prescribed in patients with permanent AF (duration for at least six months or duration unknown), and in whom an attempt to restore sinus rhythm is no longer considered;
- it is recommended to closely monitor patients taking dronedarone. If patients treated with dronedarone develop permanent AF, treatment with dronedarone should be discontinued.

Contraindications, warnings and precautions in the current Product Monograph should be followed. In relation to cardiovascular risk the following are particularly relevant:

- Dronedarone is contraindicated in patients with:
  - severe congestive heart failure (Stage NYHA IV) and other unstable haemodynamic conditions
  - Bradycardia < 50 bpm;
- Dronedarone should be used with caution in patients with moderate congestive heart failure (Stage NYHA III) and only if the benefits are deemed to outweigh the risks involved;
- if heart failure develops or worsens, consider the suspension or discontinuation of dronedarone.

Dronedarone is authorized for the treatment of patients with a history of, or current AF to reduce the risk of cardiovascular hospitalization due to AF.

Europe(2). The European Medicines Agency (EMA)'s Committee for Medicinal Products for Human Use (CHMP) has recommended restricting the use of dronedarone (Multaq®). The Committee also recommended a number of other risk minimization measures to reduce the risk of injuries to liver, lung and cardiovascular system. Patients who are currently taking dronedarone are also recommended to have their treatment evaluated by their doctor at their next scheduled appointment.

The review of the overall balance of benefits and risks of dronedarone was initiated in January 2011 because of reports of severe liver injury in patients treated with the medicine. On the basis of the evaluation of currently available data, the Committee concluded that:
- treatment with dronedarone should be restricted to patients with paroxysmal or persistent atrial fibrillation when sinus rhythm has been obtained. It is no longer indicated for use in patients when atrial fibrillation is still present;
- treatment with dronedarone should only be started and monitored by a specialist

after other anti-arrhythmic medicines have been considered;
- Dronedarone must not be used in patients with permanent atrial fibrillation, heart failure or left ventricular systolic dysfunction (impairment of the left side of the heart);
- doctors should consider discontinuation of treatment if atrial fibrillation re-occurs;
- Dronedarone must not be used in patients who have had previous liver or lung injury following treatment with amiodarone, another anti-arrhythmic medicine;
- patients on dronedarone should have their lung and liver function as well as their heart rhythm regularly monitored. Especially the liver function should be closely monitored during the first few weeks of treatment.

The Committee's opinion has been forwarded to the European Commission for the adoption of a decision.

(See WHO Pharmaceuticals Newsletter No. 4, 2011 for increased risk of death or serious cardiovascular events in Canada and the USA).

Reference:
(1) Advisories, Warnings and Recalls, Health Canada, 4 August 2011 (www.hc-sc.gc.ca).
(2) Press release, EMA, 22 September 2011 (www.ema.europa.eu).

Finasteride

Potential rare risk of breast cancer in men

Canada. Health Canada is informing healthcare practitioners and patients of a labelling update for finasteride that includes information on rare reports of breast cancer in men. The labelling for finasteride products has already been updated to include information on the potential risk of male breast cancer. Health Canada recommended patients taking finasteride to report any changes in their breasts to their doctor. Changes might include breast enlargement, lumps, tenderness, pain or nipple discharge.

Male breast cancer has been reported in a small number of patients worldwide with both the 1 mg and 5 mg formulations of finasteride. Most of the reports have been in association with the 5 mg formulation. Based on the currently available evidence, it is not known with certainty whether finasteride can cause breast cancer, nor can this possibility be ruled out at this point in time.

(See WHO Pharmaceuticals Newsletter No. 1, 2010 for potential risk of male breast cancer in the UK).

Reports in WHO Global ICSR database, Vigibase:

Finasteride

Number of reports: 429 (SOC Neoplasm, Male)

Most reported reactions (number of events):

Carcinoma:	*83*
Neoplasm NOS:	*74*
Pulmonary carcinoma:	*40*
Genital neoplasm malignant male:	*39*
Gastric carcinoma:	*27*
Breast neoplasm male:	*21*
Bladder carcinoma	*16*
Leukaemia	*12*

Reference:
Advisories, Warnings and Recalls, Health Canada, 4 August 2011 (www.hc-sc.gc.ca).

Fluconazole

Long-term, high-dose use during pregnancy may be associated with birth defects

USA. The US FDA announced to the public that treatment with chronic, high doses (400-800 mg/day) of fluconazole (Diflucan®) during the first trimester of pregnancy may be associated with a rare and distinct set of birth defects in infants. This risk does not appear to be associated with a single, low dose of fluconazole 150 mg to treat vaginal yeast infection (candidiasis). Based on this information, the US FDA changed the pregnancy category for fluconazole indications (other than vaginal candidiasis) from category C to category D. Pregnancy category D means there is positive evidence of human fetal risk based on human data but the potential benefits from use of the drug in pregnant women with serious or life-threatening conditions may be acceptable despite its risks. The pregnancy category for a single, low dose of fluconazole has not changed and remains category C.

The US FDA recommends that healthcare professionals should counsel patients if the drug is used during pregnancy or if a patient becomes pregnant while taking the drug; patients should notify their healthcare professionals if they are or become pregnant while taking fluconazole. If a patient uses fluconazole during pregnancy, the patient should be informed of the potential risk to the fetus.

Reports in WHO Global ICSR database, Vigibase:

Fluconazole

Number of reports: 149 (SOC Foetal Disorders)

Most reported reactions (number of events):

Abortion:	*39*
Drug exposure in pregnancy:	*36*
Congenital anomaly NOS:	*14*
Death foetal:	*11*
Cleft palate:	*8*
Malformations multiple:	*7*
Malformation skull:	*7*
Face malformation:	*7*

Reference:
FDA Drug Safety Communication, US FDA 3 August 2011 (*www.fda.gov*).

Fusidic acid and Statins

A strict warning against concomitant use with statins: risk of rhabdomyolysis

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) announced that product information for systemic fusidic acid (Fucidin®) is being updated to include a strict warning against concomitant use with statins because of a risk of serious and potentially fatal rhabdomyolysis. The MHRA advised that healthcare professionals should be aware of strengthened warnings regarding this potential drug interaction.

Fusidic acid and its salts

The product information for systemic fusidic acid and for simvastatin and atorvastatin lists this interaction and warns of the associated risk.

According to the MHRA, in recent years, the number and severity of case reports of rhabdomyolysis (including those with a fatal outcome) suspected to be due to an interaction between fusidic acid and a statin have increased.

The MHRA also advised healthcare professionals that:
- in patients for whom the use of systemic fusidic acid is essential, statin treatment should be temporarily discontinued throughout the duration of fusidic acid treatment;
- to ensure clearance of systemic fusidic acid, statin therapy may be reintroduced seven days after the last dose of systemic fusidic acid;
- in exceptional cases where prolonged systemic fusidic acid treatment is necessary, the need for co-administration of a statin should be considered on an individual basis and only under close medical supervision;
- patients should be clearly advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain, or tenderness;
- any muscle symptoms reported in patients who are

Heart-related risk in men treated for prostate cancer

Canada. Health Canada informed healthcare professionals and patients about a possible increased risk of certain heart-related events in men being treated for prostate cancer with a type of prescription drug known as a Gonadotropin-Releasing Hormone (GnRH) agonist. The labelling for GnRH agonist drugs has been updated to add a warning on the potential increased risk of heart-related side effects. There have been reports of heart attacks, stroke and heart-related deaths in patients treated with GnRH agonists for prostate cancer. Based on information collected from scientific literature, the risk appears to be low.

GnRH agonists work by reducing or suppressing male hormones (androgens, such as testosterone), which in turn leads to shrinkage of prostate tumours or slowing of the growth of prostate cancer. This therapy belongs to a category of therapies known as Androgen Deprivation Therapy. GnRH agonist drugs used in the treatment of prostate cancer currently marketed in Canada are leuprolide acetate (Eligard®), leuprolide acetate (Lupron®), buserelin acetate (Suprefact®), triptorelin pamoate (Trelstar®), histrelin acetate (Vantas®) and goserelin acetate (Zoladex®).