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 from:

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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. It also provides signals from the Uppsala Monitoring Centre's SIGNAL document.

The feature articles in this issue give you a brief summary of a course offered by the WHO Collaborating Centre for Drug Satistics Methodology; and a pilot project being launched by the Uganda National Drug Authority, to collect pharmacovigilance data in their HIV treatment programmes.

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New warning and contraindication

USA. The U.S. Food and Drug Administration (US FDA) notified health-care professionals of possible risks when using blood pressure medicines containing aliskiren with other drugs called angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in patients with diabetes or renal impairment. These drug combinations are contraindicated in patients with diabetes. In addition, avoid use of aliskiren with ARBs or ACEIs in patients with moderate to severe renal impairment (i.e., where glomerular filtration rate [GFR] < 60 mL/min). The labels for the aliskiren drugs are being updated based on preliminary data from a clinical trial, "Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE)."

The US FDA recommended that concomitant use of aliskiren with ARBs or ACEIs in patients with diabetes is contraindicated because of the risk of renal impairment, hypotension, and hyperkalemia. Avoid use of aliskiren with ARBs or ACEIs in patients with renal impairment where GFR < 60 mL/min. Patients should not stop taking aliskiren without talking to a healthcare professional. Stopping aliskiren suddenly can cause problems if high blood pressure (hypertension) is not treated.

(See WHO Pharmaceuticals Newsletter No. 1, 2012 for contraindication in patients with diabetes taking an ACE inhibitor or an ARB in Canada and No.2, 2012 in Europe).

Reference:
FDA Drug Safety Communication, US FDA, 20 April 2012 (*www.fda.gov*).

Belimumab

Association with Hypersensitivity and Infusion Reactions

Canada. GlaxoSmithKline Inc., in consultation with Health Canada, informed health-care professionals of important new safety information related to hypersensitivity and infusion reactions associated with belimumab (BENLYSTA™) treatment.

At the time of authorization, the Product Monograph included information and warnings related to a reported higher incidence of hypersensitivity reactions in treated patients compared to placebo. After the review of post-marketing reports, the Product Monograph for belimumab has been updated with the following new safety information:

- administration of belimumab may result in infusion and hypersensitivity reactions, which can be severe, and can be fatal;
- patients with a history of multiple drug allergies or significant hypersensitivity may be at increased risk;
- health-care professionals should monitor patients during and for an appropriate amount of time after administration of belimumab, because a delay in the onset of acute hypersensitivity reactions has been observed. Patients should be informed of the potential risks.

Important information for health-care professionals is:

- in the event of a severe reaction, belimumab administration must be interrupted and appropriate medical therapy administered;
- patients treated with belimumab should be informed of the symptoms of hypersensitivity reactions, and the importance of immediately seeking medical attention.

Health-care professionals are reminded that:

- infusion reactions occurred more frequently with the first two infusions and tended to decrease with subsequent infusions;
- belimumab treatment should be initiated and supervised by a qualified physician experienced in the diagnosis and treatment of SLE;
- belimumab should be administered by qualified health-care providers trained to give infusion therapy and prepared to manage anaphylaxis;
- in clinical trials, severe and/or serious infusion or hypersensitivity reactions were reported in 1.2% and 0.6% of subjects receiving belimumab 10 mg/kg and placebo, respectively.

Reference:
Advisories, Warnings and Recalls, Health Canada, 3 May 2012 (*www.hc-sc.gc.ca*).

Boceprevir

Drug Interactions with ritonavir-boosted Human Immunodeficiency Virus (HIV) protease inhibitor drugs

USA. The US FDA notified health-care professionals that the drug label has been revised to state that co-administration of boceprevir (Victrelis®) along with certain ritonavir-boosted HIV protease inhibitors is not recommended. The findings of a drug-drug interaction study and clinical trial showed that co-administration increased of the possibility of reducing the effectiveness of the medicines, permitting the amount of HCV or HIV virus in the blood to increase. Ritonavir-boosted

HIV protease inhibitors include ritonavir-boosted atazanavir (Reyataz®), ritonavir-boosted darunavir (Prezista®), and lopinavir/ritonavir (Kaletra®).

(See WHO Pharmaceuticals Newsletters No. 2, 2012 for drug interactions with ritonavir-boosted HIV protease inhibitor drugs in the USA and in Europe).

Reference:
FDA Drug Safety Communication, US FDA, 26 April 2012 (*www.fda.gov*).

Citalopram hydrobromide

Revised recommendations, potential risk of abnormal heart rhythms

USA. The US FDA is clarifying dosing and warning recommendations for citalopram hydrobromide (Celexa®; also available in generic form). In August 2011, the US FDA issued a Drug Safety Communication (DSC) stating that citalopram should no longer be used at doses greater than 40 mg per day because it could cause potentially dangerous abnormalities in the electrical activity of the heart. Citalopram use at any dose is discouraged in patients with certain conditions because of the risk of QT prolongation. However, it may be important for some of those patients to use citalopram therefore the drug label has been changed to describe the particular caution that needs to be taken when citalopram is used in such patients. The revised drug label also describes lower doses that should be used in patients over 60 years of age.

Revised recommendations are:

- Citalopram is not recommended for use at doses greater than 40 mg per day because such doses cause too large an effect on the QT interval and confer no additional benefit;
- Citalopram is not recommended for use in patients with congenital long QT syndrome, bradycardia, hypokalemia, or hypomagnesemia, recent acute myocardial infarction, or uncompensated heart failure;
- Citalopram use is also not recommended in patients who are taking other drugs that prolong the QT interval;
- The maximum recommended dose of citalopram is 20 mg per day for patients with hepatic impairment, patients who are older than 60 years of age, patients who are CYP2C19 poor metabolizers, or patients who are taking concomitant cimetidine (Tagamet®) or another CYP2C19 inhibitor, because these factors lead to increased blood levels of citalopram, increasing the risk of QT interval prolongation and Torsade de Pointes.

(See WHO Pharmaceuticals Newsletters No. 5, 2011 for abnormal heart rhythms associated with high doses in the USA, No. 1, 2012 for QT interval prolongation in the UK and No.2, 2012 for association with dose-dependent QT Prolongation in Canada and Australia).

Reference:
FDA Drug Safety Communication, US FDA, 28 March 2012 (*www.fda.gov*).

Dabigatran etexilate

Updated labelling regarding renal function assessment and use in patients with severe valvular disease or prosthetic heart valves

Canada (1). Boehringer Ingelheim (Canada) Ltd., in consultation with Health Canada, informed health-care professionals of important new recommendations for dabigatran etexilate (Pradax®) regarding renal function assessment and use in patients with severe valvular disease or prosthetic heart valves.

Based on post-marketing reports of serious bleeding and the use of dabigatran etexilate in the elderly and patients at high risk of bleeding or patients with renal impairment, the Product Monograph has been updated to include new recommendations to assess renal function in patients being considered for, or already being treated with dabigatran etexilate and is as follows:

- prior to initiation of treatment with dabigatran etexilate, renal function should be assessed in all patients by calculating the creatinine clearance (CrCl) to exclude patients with severe renal impairment (i.e. CrCl < 30 mL/min);
- while on treatment with dabigatran etexilate, renal function should be assessed in clinical situations when it is suspected that renal function could decline or deteriorate rapidly, such as hypovolemia, dehydration, and with certain co-medications. These clinical situations may result in an increase of dabigatran exposure;
- in the elderly (> 75 years), or in patients with moderate renal impairment (CrCl 30-50 mL/min), renal function should be assessed routinely by calculating the creatinine clearance at least once a year.

Health-care professionals are also reminded that dabigatran etexilate is contraindicated in patients with severe renal impairment (i.e. CrCl < 30 mL/min), patients at high risk of bleeding should not be prescribed the drug, patients should be monitored clinically for signs of bleeding or anaemia and treatment with the drug should be discontinued if severe bleeding occurs, and the source of

bleeding should be investigated.

Safety and efficacy of dabigatran etexilate have not been studied in patients with hemodynamically significant rheumatic valvular heart disease, especially mitral stenosis, or patients with prosthetic heart valves. There are no data to support that dabigatran etexilate provides adequate anticoagulation in patients with prosthetic heart valves, with or without atrial fibrillation. Therefore, the use of dabigatran etexilate is not recommended in patients with hemodynamically significant rheumatic valvular heart disease or in patients with prosthetic heart valves.

Saudi Arabia (2). The Saudi Food and Drug Authority (SFDA) shared important safety information with health-care professionals about an increased number of spontaneous reports of fatal cases resulting from bleeding episodes in patients treated with dabigatran etexilate. In Saudi Arabia, the drug is only approved for prevention of venous thromboembolism (VTE) in patients following hip or knee replacement surgery.

In October 2011, the Committee for Medicinal Products for Human Use (CHMP) at the European Medicine Agency (EMA) published a press-release notifying that clinicians should be aware of increasing number of spontaneous safety reports concerning death cases resulting from major bleeding events. CHMP urged the manufacturer to update the product labelling to ensure that patients receiving dabigatran are eligible for treatment.

The Advisory Committee for Pharmacovigilance at SFDA reviewed all available data on the concerned risk. In addition, it reviewed 260 fatal cases of bleeding attributed to dabigatran etexilate. It was concluded that there is a need to emphasize the risk of bleeding based on post-marketing reports of bleeding occurring with the use of dabigatran etexilate in the elderly and patients with high risk of bleeding or patients with severe renal impairment. The advisory committee recommended that the Patient Information Leaflet as well as the Summary of Product Characteristics should be updated to include new safety information. In addition, the committee required the marketing authorization holder to distribute a Dear Health Care Professional Letter to emphasize the risk of bleeding.

Based on that, the SFDA advised concerned physicians to consider the following recommendations when initiating dabigatran etexilate therapy:

1. Dabigatran etexilate is contraindicated in patients with severe renal impairment (CrCl<30 ml/min);
2. renal function should be assessed by calculating the creatinine clearance (CrCl) in all patients prior to initiating the therapy;
3. while on treatment, renal function should be assessed in clinical situations where a decline in renal function is suspected, such as hypovolemia, dehydration, and with certain co-medications, etc.;
4. in elderly patients (>75 years) or in patients with renal impairment the renal function should be assessed at least once a year.

(See WHO Pharmaceuticals Newsletters No. 1, 2012 for abnormal heart rhythms associated with high doses in the USA, No. 1, 2012 for QT interval prolongation in the UK and No. 2, 2012 for association with dose-dependent QT Prolongation in Canada and Australia).

References:

(1) Advisories, Warnings and Recalls, Health Canada, 16 March 2012 (www.hc-sc.gc.ca).
(2) Communication from National Pharmacovigilance and Drug Safety Centre, SFDA, 23 May 2012.

Escitalopram

Updated information regarding the dose-related risk of QT interval prolongation

Canada. Health Canada informed that a warning on the dose-related risk of QT interval prolongation has been added to the drug label for escitalopram (Cipralex®), as well as revised prescribing and dosing recommendations.

It is recommended that escitalopram should not be used in patients with a heart condition known as congenital long QT syndrome, or in patients with QT interval prolongation. Use of escitalopram is discouraged in patients who are also taking drugs that prolong QT interval or that decrease electrolyte levels in the body. Examples of drugs that affect QT interval include: drugs used to treat heart rhythm problems, certain antipsychotics, certain antidepressants, opioid painkillers and certain drugs used to treat infections. Examples of drugs that may affect electrolyte levels include: diuretics and laxatives (including enemas). 10 mg per day is the maximum recommended dose for patients who are 65 years of age or older, or have liver problems, or are taking the heartburn drugs omeprazole or cimetidine which can increase the blood level of escitalopram. 20 mg per day is still the maximum recommended dose for most other patients.

Health Canada advised that before starting escitalopram, patients should tell a health-care professional if the patient has had any heart problems, what other medications the patient is taking (including natural health products), if the patient has a history of fainting, if the patient has a history of electrolyte disturbances (low levels of potassium, magnesium or calcium in the blood) or conditions that might lead to electrolyte disturbances such as vomiting, diarrhoea, dehydration, and if the patient is following a strict diet.

Patients are also advised to consult with a health-care professional when considering stopping or reducing the dose, as abruptly stopping or reducing the dose may cause side effects such as dizziness, unusual dreams, electric shock sensations, agitation, anxiety, difficulty concentrating, migraine, headache, shakiness, sweating, nausea, or vomiting. If patients experience any symptoms of abnormal heart rhythms such as heart palpitations, dizziness, fainting, or seizures while taking escitalopram, contact a health-care professional immediately. Patients with questions or concerns about their escitalopram treatment should speak to a health-care professional.

Reference:
Advisories, Warnings and Recalls, Health Canada, 7 May 2012 (*www.hc-sc.gc.ca*).

Finasteride and dutasteride

May increase the risk of high-grade prostate cancer

Canada. Health Canada informed health-care professionals and the public that finasteride (Proscar®, Propecia® and their generic equivalents) and dutasteride (Avodart® and Jalyn® (a combination drug product containing dutasteride and tamsulosin)) may be associated with an increased risk of developing a serious form of prostate cancer known as high-grade prostate cancer. High-grade prostate cancer is an aggressive type of prostate cancer that grows and spreads more quickly than low-grade prostate cancer. This type of cancer is rare, and the increased risk seen with finasteride and dutasteride drugs is still considered very small.

Finasteride and dutasteride are for use in men only. Proscar®, Avodart®, and Jalyn® are used for the treatment of benign prostatic hyperplasia (BPH), which is an enlargement of the prostate that is not cancerous. BPH is a common condition in men over 40. Propecia® is used to treat male pattern hair loss.

The new safety information is based on Health Canada's review of two large international clinical trials: the Prostate Cancer Prevention Trial (PCPT) and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial. The trials showed that the long-term daily use (over four years) of finasteride (5 mg) and dutasteride in men aged 50 years and older was associated with a small but statistically significant increased risk of high-grade prostate cancer. The 1 mg finasteride strength (Propecia®) was not included in these trials but a potential risk has not been ruled out.

The purpose of the clinical trials was to provide evidence in support of a new use for finasteride and dutasteride: to prevent prostate cancer. Both trials showed that the possible benefits of these drugs in preventing low-grade prostate cancer are small relative to the risk of developing high-grade prostate cancer. Finasteride and dustasteride are not approved for the prevention of prostate cancer in Canada.

The Canadian labels for the brand name drugs have been updated to inform about the increased risk of high-grade prostate cancer associated with these drugs and to emphasize that these drugs are not approved for the prevention of prostate cancer. Updates to the generics will follow.

As noted in the drug labels, before prescribing Proscar®, Avodart®, and Jalyn®, health-care practitioners should evaluate patients thoroughly to rule out other urological diseases, including prostate cancer as the symptoms of BPH and prostate cancer are similar.

Health Canada advised that patients with questions or concerns about their treatment with finasteride or dutasteride should talk to their health-care professional. Patients should not stop taking their medication unless they have been advised to do so by their health-care professional. Patients taking these drugs should see their doctor for periodic follow-up evaluations.

(See WHO Pharmaceuticals Newsletter No. 4, 2011 for Increased risk of prostate cancer in the USA).

Reference:
Advisories, Warnings and Recalls, Health Canada, 19 March 2012 (*www.hc-sc.gc.ca*).

Fingolimod

New advice to better manage risk of adverse effects on the heart

Europe (1). The European Medicines Agency recommended new advice to health-care professionals to reduce the risk of adverse effects on the heart associated

with the use of fingolimod (Gilenya®). Following a review of the latest evidence of the safety of the medicine, the Agency's Committee for Medicinal Products for Human Use (CHMP) recommended that doctors should not prescribe Gilenya to patients with a history of cardiovascular and cerebrovascular disease or who take heart-rate lowering medication. However, when treatment with fingolimod is considered necessary in these patients, their heart activity should be monitored at least overnight following the first dose of fingolimod and doctors should seek advice from a cardiologist on appropriate monitoring.

The CHMP also recommended that all patients starting treatment with fingolimod should have their heart activity monitored before receiving the first dose of the medicine and continuously for at least six hours after. Monitoring should be extended for at least two hours in patients whose heart rate is lowest six hours after receiving the first dose of fingolimod. In patients who develop clinically significant heart problems such as bradycardia or atrioventricular (AV) block monitoring should continue at least overnight and until the problems have been resolved.

USA (2). The US FDA announced that the agency completed its evaluation of a report of a patient who died

Data show that, although the maximum heart rate lowering effect of Gilenya usually occurs within six hours of the first dose, the maximum effect may occur as late as 20 hours after the first dose in some patients. For this reason, fingolimod is now contraindicated in patients with certain pre-existing or recent (within last six months) heart conditions or stroke, or who are taking certain antiarrhythmic medications. In addition, the US FDA is now also recommending that the time of cardiovascular monitoring be extended past six hours in patients who are at higher risk for or who may not tolerate bradycardia. Extended monitoring should include continuous ECG monitoring that continues overnight.

(See WHO Pharmaceuticals Newsletter No. 1, 2012 for safety review of a reported death after the first dose in the USA and for review of fingolimod and advise to intensify cardiovascular monitoring after first dose in EU, and No. 2, 2012 in Canada).

References:

(1) Press release, EMA, 20 April 2012 (*www.ema.europa.eu*).
(2) FDA Drug Safety Communication, US FDA, 14 May 2012 (*www.fda.gov*).

Lenalidomide

receiving lenalidomide and dexamethasone (3.98 per 100 patient-years) compared to controls (1.38 per 100 patient-years).

- In clinical trials of newly diagnosed multiple myeloma (not an authorized indication in Canada), a 4-fold increased incidence of SPM has been observed in patients receiving the drug.
- The risk of occurrence of SPM must be taken into account before initiating treatment with the drug. Physicians should carefully evaluate patients before and during treatment to screen for the occurrence of new malignancies.

On-going safety review - Increased risk of developing new malignancies

USA (2). The US FDA notified the public of an increased risk of second primary malignancies in patients with newly-diagnosed multiple myeloma who received lenalidomide (Revlimid®). Clinical trials conducted after the drug was approved showed that newly-diagnosed patients treated with the drug had an increased risk of developing second primary malignancies compared to similar patients who received a placebo. Specifically, these trials showed there was an increased risk of developing acute myelogenous leukemia, myelodysplastic syndromes, and Hodgkin lymphoma