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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This Newsletter is also available on our Internet website: http://www.who.int/medicines

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No. 6, 2010

In this issue as usual we report regulatory actions taken around the world on grounds of safety issues, among them new restrictions in the use of rosiglitazone, and the market withdrawal of sibutramine. We also give you updates on the safety of several medicines.

The feature article in this issue gives you conclusions from working groups at the thirty-third meeting of representatives of national pharmacovigilance centres participating in the WHO Programme for International Drug Monitoring.

We wish all our readers a very good year in 2011, and thank you for your interest in the newsletter.

Printed by the WHO Document Production Services, Geneva, Switzerland

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Bisphosphonates

Label update for atypical fractures

USA. The United States Food and Drug Administration (US FDA) notified the public that the drug labels of all bisphosphonate products approved for the prevention or treatment of osteoporosis will be revised to include updated information on the risk of atypical fractures of the thigh, known as subtrochanteric and diaphyseal femur fractures. The labels will also include a new Limitations of Use statement that will describe the uncertainty of the optimal duration of use of bisphosphonates for the treatment and/or prevention of osteoporosis. The Agency states that although the optimal duration of bisphosphonate use for osteoporosis is unknown, these atypical fractures may be related to long-term term bisphosphonate use. In addition, a Medication Guide will be required to be given to patients. This Medication Guide will describe the symptoms of atypical femur fracture and recommend that patients notify their health-care professional if they develop symptoms.

The US FDA explains that atypical femur fractures appear to account for less than one percent of all hip and femur fractures overall, and that although it is not clear if bisphosphonates are the cause, atypical femur fractures have been predominantly reported in patients taking bisphosphonates.

Health-care professionals are advised to discontinue potent antiresorptive medicines (including bisphosphonates) in patients who have evidence of a femoral shaft fracture, and to consider periodic re-evaluation of the need for continued bisphosphonate therapy, particularly in patients who have been treated for over five years.

Reference:
FDA Drug Safety Communication, US FDA, 13 October 2010 (www.fda.gov)

Codeine-containing liquid over-the-counter medicines

Advice against use for cough in children under 18 years

UK. Medicines and Healthcare products Regulatory Agency (MHRA) has announced that a UK review on the benefits and risks of over-the-counter (OTC) oral liquid cough medicines containing codeine has concluded that the risks outweigh the benefits in children and young people under 18 years. Therefore, it has been advised that codeine-containing OTC liquid medicines should not be used for cough suppression in children and people younger than age 18 years. In February 2009, the MHRA announced new measures for safer use of OTC cough and cold medicines for children younger than age 12 years.

(See WHO Pharmaceuticals Newsletter No.2, 2009).

***Reference**:*
Drug Safety Update, MHRA, Volume 4, Issue 3, H3 October 2010 (www.mhra.gov.uk).

Gonadotropin-releasing hormone agonists

Label change due to increased risk of diabetes and cardiovascular disease

USA. The US FDA has announced that new safety information on increased risk of diabetes and certain cardiovascular diseases (heart attack, sudden cardiac death, stroke) will be added to the *Warnings and Precautions* section of the drug labels for Gonadotropin-Releasing Hormone (GnRH) agonists. The decision is based on the Agency's review of several published studies. The US FDA states that most of the studies reviewed by the Agency reported small, but statistically significant increased risks of diabetes and/or cardiovascular events in patients receiving GnRH agonists. GnRH agonists are approved to treat the symptoms (palliative treatment) of advanced prostate cancer.

The US FDA advises that although the risk for diabetes and cardiovascular diseases appears to be low in men receiving GnRH agonists for prostate cancer, it is important for health-care professionals to evaluate patients for risk factors for these diseases. Health-care professionals are also advised to monitor blood glucose and/or glycosylated haemoglobin periodically in patients receiving GnRH agonists; to monitor patients for signs and symptoms suggestive of development of cardiovascular disease; to ensure that cardiovascular risk factors such as cigarette smoking, high blood pressure, high cholesterol, high blood sugar, and being overweight

are managed according to current clinical practice.

Reference:
FDA Drug Safety Communication, US FDA, 20 October 2010 (www.fda.gov).

Propoxyphene

Withdrawal due to risk of cardiac toxicity

USA. The US FDA has recommended against continued use of propoxyphene after receiving new data that indicate the risk of cardiac toxicity. Propoxyphene is an opioid pain reliever used to treat mild to moderate pain. The US FDA has announced that the manufacturer Xanodyne Pharmaceuticals Inc. has agreed to withdraw propoxyphene from the United States market at the Agency's request. The Agency also requested that the generic manufacturers of propoxyphene-containing products remove their products. The Agency's recommendation was made based on all available data including new clinical data showing that when propoxyphene was taken at therapeutic doses, there were significant changes to the electrical activity of the heart: prolonged PR interval, widened QRS complex and prolonged QT interval. These changes can increase the risk for serious abnormal heart rhythms. The US FDA concluded that the safety risks of propoxyphene outweigh its benefits for pain relief at recommended doses. Health-care professionals are advised to stop prescribing and dispensing propoxyphene-containing products to patients, to ask patients to discontinue the medicine, and to discuss alternative pain management strategies with their patients.

(Propoxyphene is USAN, dextropropoxyphene is the equivalent INN).

Reports in WHO Global ICSR database, Vigibase:

Dextropropoxyphene

Number of reports (SOC Cardiovascular disorders, general and SOC heart rate and rhythm disorders): 278

Most reported reactions (number of events):

Cardiomegaly:	*26*
Hypertension:	*22*
Hypotension:	*39*
Bradycardia:	*14*
Cardiac arrest:	*146*
Palpitation:	*18*
Tachycardia:	*27*

(See WHO Pharmaceuticals Newsletter No. 4, 2009 for recommendation to withdraw the marketing authorizations for dextropropoxyphene-containing medicines in Europe).

***Reference**:*
MedWatch, Safety Information, US FDA, 19 November 2010 (www.fda.gov).

Rosiglitazone

New restrictions due to risk of cardiovascular events

Canada. GlaxoSmithKline Inc. and Health Canada have informed the public that the Canadian Product Monographs for rosiglitazone-containing products (Avandia® (rosiglitazone), Avandamet® (rosiglitazone and metformin) and Avandaryl® (rosiglitazone and glimepiride)) have been updated to include new restrictions on the use of these medicines, informed consent process and a new boxed warning because of cardiovascular risks.
The rosiglitazone-containing products are now indicated only in patients with type 2 diabetes mellitus for whom all other oral antidiabetic agents, in monotherapy or in combination, do not result in adequate glycaemic control or are inappropriate due to contraindications or intolerance.
The new boxed warning includes the following information.

- Rosiglitazone-containing products, like other thiazolidinediones, can cause fluid retention and congestive heart failure.
- Rosiglitazone-containing products may be associated with an increased risk of cardiac ischemia. These medicines are not recommended in patients with a history of ischaemic heart disease, particularly those with myocardial ischaemic symptoms.

Health-care professionals are advised to counsel new and currently treated patients about the risks of initiating and/or continuing rosiglitazone therapy and obtain their written informed consent.

(See WHO Pharmaceuticals Newsletter No.5, 2010 for information on suspension of marketing authorizations in Europe, new restrictions in the USA and reports in WHO global ICSR database).

***Reference**:*
Advisories, Warnings and Recalls, Health Canada, 18 November 2010 (www.hc-sc.gc.ca).

Saquinavir

Change to prescribing information regarding QT/PR interval prolongation

Europe (1). European Medicines Agency (EMA) has announced that it has completed a review of saquinavir (Invirase®) and its cardiovascular safety. The Committee for Medicinal Products for Human Use (CHMP) has reviewed all available data on saquinavir and the potential risk of arrhythmia, and concluded that the benefit of the medicine continues to outweigh its risks. However, the CHMP has recommended that treatment-naïve patients should take a reduced dose of saquinavir during the first week of treatment, as a precautionary measure. Ritonavir-boosted saquinavir in combination with other antiretroviral medicines is indicated for the treatment of HIV-infected adult patients.

EMA explains that the CHMP started the review following the results of a study conducted by the marketing authorisation holder, showing that saquinavir prolonged the QT and PR intervals in healthy volunteers. In June 2010, the Committee recommended restrictions on the use of saquinavir, including a contra-indication in patients at high risk of arrhythmia and in patients using other medicines that may cause QT or PR prolongation, warnings for patients at moderate risk of arrhythmia, and recommendations to perform electrocardiogram monitoring.

In October 2010, the CHMP conducted a full review of the benefit-risk balance of saquinavir. It was noted that the effectiveness of saquinavir has been demonstrated in several clinical studies. Although the dedicated study in healthy volunteers did show QT and PR interval prolongation, this signal has not been confirmed in post-marketing safety reports on the medicine since the medicine was first authorised in 1996. The risk of QT and PR prolongation has been shown to be dose dependent, and is expected to be higher in patients who have not been treated with any anti-HIV medicines before. Therefore, to minimise the potential cardiovascular risk, the CHMP recommended a reduced dose for these patients in the first week of treatment.

Canada (2). Hoffmann-La Roche Limited and Health Canada notified health-care professionals that the warnings regarding QT/PR interval prolongation have been strengthened in the Canadian Product Monograph for saquinavir mesilate (Invirase®). The main updates include the following:

- An electrocardiogram should be completed prior to initiation of ritonavir-boosted saquinavir;
- Patients with a QT interval greater than 450 msec should not use ritonavir-boosted saquinavir;
- An on-treatment electrocardiogram is recommended after three to four days of treatment. If a patient's QT interval is greater than 20 msec above pre-treatment values, or greater than 480 msec, then ritonavir-boosted saquinavir should be discontinued;
- Caution is advised when co-administering ritonavir-boosted saquinavir and other therapies that may increase the QT interval. Electrocardiogram monitoring should be performed in this patient population.

USA (3). The US FDA has notified the public that new safety information has been added to the label of saquinavir (Invirase®), describing the risk of prolongation of the PR or QT intervals when saquinavir is used with ritonavir (Norvir®). Saquinavir and ritonavir are given together to treat HIV infection. In addition, the US FDA will require that a Medication Guide, which will include information on the risk of abnormal heart rhythms, be given to patients.

The US FDA explains that this new information was derived from a clinical study designed to study a drug's impact on the electrical activity of the heart. A prolonged QT interval can lead to torsades de pointes. A prolonged PR interval can lead to complete heart block. Torsades de pointes and complete heart block have been reported in patients taking saquinavir with ritonavir.

The Agency advises that patients at particular risk are those with underlying heart conditions or those who have existing heart rate or rhythm problems. Health-care professionals are advised to perform an electrocardiogram prior to initiation of treatment, and to consider whether ongoing electrocardiogram monitoring is appropriate for your patient and when it should be done.

Reports in WHO Global ICSR database, Vigibase:

Saquinavir

Number of reports (SOC heart rate and rhythm disorders): 71

Most reported reactions (number of events):

Bradycardia:	*10*
Cardiac arrest:	*12*
Arrhythmia ventricular:	*9*
Extrasystoles:	*12*
QT prolonged:	*7*
Palpitation:	*12*
Tachycardia:	*10*
Torsade de pointes:	*12*

(See WHO Pharmaceuticals Newsletters No.5, 3 and 2, 2010 for warnings about risk of QT and PR interval prolongation in Canada, the UK and the USA).

References:
(1) Press release, Questions and answers, EMA, 21 October 2010 (www.ema.europa.eu).
(2)Advisories, Warnings and Recalls, Health Canada, 2 November 2010 (www.hc-sc.gc.ca).
(3) FDA Drug Safety Communication, US FDA, 21 October 2010 (www.fda.gov).

Sibutramine

Market withdrawal due to risk of serious cardiovascular events

Australia (1). Therapeutic Goods Administration (TGA) has announced that Abbott Australasia will cease supply of sibutramine (Reductil®) in Australia from 9 October 2010. Sibutramine is indicated for weight loss. This follows an analysis of the results of the Sibutramine Cardiovascular OUTcomes (SCOUT) study, which showed a higher rate of cardiovascular events in obese and overweight patients using sibutramine than in patients managing their weight through exercise and diet alone.

SCOUT was conducted as a post-market requirement to evaluate the cardiovascular safety of long-term sibutramine use, after the European approval of the medicine. The TGA also states that the increased risk of the cardiac events is not significantly different across various patient subgroups in the study, including the subgroup that most closely approximates the approved use of sibutramine in Australia.

Canada (2). Health Canada has informed the public of voluntary withdrawal of sibutramine (Meridia® and Apo-sibutramine, it has been concluded that the benefits no longer outweigh the risks for sibutramine.

Prescribers are advised not to issue any further prescriptions for sibutramine. Patients currently taking sibutramine are advised to contact their healthcare practitioner regarding potential alternatives.

USA (3). The US FDA and Abbott Laboratories notified health-care professionals and patients about the voluntary withdrawal of sibutramine (Meridia®) from the United States market because of clinical trial data indicating an increased risk of heart attack and stroke. The Agency states that its recommendation for market withdrawal is based on new data from the SCOUT trial. SCOUT demonstrated a 16% increase in risk of major adverse cardiovascular events (a composite of non-fatal heart attack, non-fatal stroke, resuscitation after cardiac arrest and cardiovascular death) in patients treated with sibutramine compared to patients taking a placebo. At the end of the trial (60 months), patients in the sibutramine group lost a small amount of body weight compared to patients in the placebo group. The US FDA has concluded that the risk for an adverse cardiovascular