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 Collaborationg Centre for International Drug Monitoring
Box 1051
751 40 Uppsala
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, 2010

A three-year project with the aim to promote safety monitoring of medicines, and in particular to involve consumers in the process, has just been launched. The project which goes under the name Monitoring Medicines has been made possible by a grant from the European Commission. The project involves WHO, the Uppsala Monitoring Centre and many other partners throughout the world.

Read more about this project in a 'Feature article' in this issue of the WHO Newsletter. The Newsletter also includes an article about the WHO Prequalification of Medicines Programme: Inspection of Finished Pharmaceutical Product Manufacturers to increase quality of medicines, as well as the usual sections on Regulatory Matters and Safety of Medicines.

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Becaplermin

Contraindication recommended

Europe. The European Medicines Agency (EMA) has recommended contraindication for becaplermin (Regranex) in patients with any pre-existing cancer, following a review of the available data at the Agency's Committee for Medicinal Products for Human Use (CHMP) on a possible risk of cancer in patients using the medicine. A similar restriction previously applied, but only for patients who had a skin cancer close to the area where the gel was to be applied. Becaplermin (Regranex) is a gel that is used together with other wound care measures to treat long-term neuropathic skin ulcers in people with diabetes.

The EMEA explains that in an observational study, which compared Regranex-users with a control group of patients who did not use Regranex, the overall risk of developing cancer was not found to be significantly different between Regranex-users and non-users. However, patients who used three or more tubes of becaplermin (Regranex) and who developed cancer had a greater risk to die of their cancer than patients who did not use becaplermin (Regranex). The study had several limitations in its design, including a small number of cases of cancer and is therefore not considered to be robust.

The CHMP noted that becaplermin (Regranex) was modestly effective in treating neuropathic ulcers in patients with diabetes, but that its long-term effectiveness (over 20 weeks) had not been proven. The Committee also noted that while there was no firm evidence of a link between becaplermin (Regranex) and cancer, there was also not enough evidence to rule out such a link. Therefore, the CHMP concluded that the benefits of becaplermin (Regranex) continue to outweigh its risks, but that, as a precautionary measure, the gel must not be used in patients with any pre-existing cancer. In addition, the manufacturer has been asked to conduct more research to investigate the way the medicine is absorbed by the body and its potential risks.

Reports in WHO Global ICSR database, Vigibase:

Becaplermin

Number of reports: 343

Most reported reactions (number of events):

Condition aggravated:	*31*
Pain:	*45*
Death:	*23*
Therapeutic response decreased:	*33*
Paraesthesia:	*29*
Skin hypertrophy:	*55*
Infection:	*25*
Skin disorder:	*36*
Rash etythematous:	*21*

(See WHO Pharmaceuticals Newsletter No.3, 2008 for a boxed warning about increased cancer risk in the USA.)

Reference:
Press Release, Questions and answers, EMEA, 18 February 2010 (www.emea.europa.eu).

Clopidogrel

Boxed Warning about reduced effectiveness in certain patients

USA. The US Food and Drug Administration (US FDA) notified health-care professionals and patients that a Boxed Warning has been added to the prescribing information for clopidogrel (Plavix). The Boxed Warning is about patients who do not effectively convert clopidogrel (Plavix) to its active form in the body (poor metabolizers) because of low CYP 2C19 activity. Clopidogrel (Plavix) is an anti-blood clotting medicine that is used to reduce the risk of heart attack, unstable angina, stroke, and cardiovascular death in patients with cardiovascular disease.

The Boxed Warning in the drug label will include the following information:

- to warn about reduced effectiveness in patients who are poor metabolizers of clopidogrel (Plavix).
- to inform health-care professionals that tests are available to identify genetic differences in CYP2C19 function.
- to advise health-care professionals to consider use of other anti-platelet medications or alternative dosing strategies for clopidogrel (Plavix) in patients identified as poor metabolizers.

The US FDA also advises that although a higher dose regimen (600 mg loading dose followed by 150 mg once daily) in poor metabolizers increases antiplatelet response, an appropriate dose regimen for poor metabolizers has not been established in a clinical outcome trial.

***Reference**:*
Safety Information, US FDA 12 March 2010 (www.fda.gov).

Clopidogrel and proton-pump inhibitors

Updates on warning about interaction

Europe (1). The EMA recommended to update the

existing warning over the concomitant use of clopidogrel-containing medicines and proton-pump inhibitors (PPIs). In May 2009, the Agency's Committee for Medicinal Products for Human Use (CHMP) recommended that the product information for all clopidogrel-containing medicines be amended to discourage the concomitant use of PPIs and clopidogrel unless absolutely necessary. The EMA states that two recent studies, completed at the end of August 2009, confirmed that omeprazole can reduce the levels of the active form of clopidogrel in the blood and reduce its anti-platelet effects, therefore supporting the conclusion that there is an interaction between clopidogrel and omeprazole and esomeprazole. Based on the currently available data, the CHMP have concluded that there are no solid grounds to extend the warning to other PPIs. Therefore, the class warning for all PPIs has been replaced with a warning stating that only the concomitant use of clopidogrel and omeprazole or esomeprazole should be discouraged.

New Zealand (2). New Zealand Medicines and Medical Devices Safety Authority (Medsafe) has advised that an interaction between clopidogrel and omeprazole has been confirmed following two pharmacokinetic/pharmacodynamic interaction studies. The results from these studies indicate that co-administration of clopidogrel with omeprazole results in significantly reduced exposure to the active metabolite of clopidogrel. Clopidogrel is a pro-drug that is converted to its active form by CYP3A4 and 3A5, with contributions from CYP2C19, CYP2C9, and CYP1A2. Omeprazole is an inhibitor of CYP2C19.

According to Prescriber Update, in the first randomized crossover study where clopidogrel and omeprazole were administered at the same time, reductions of 42% and 40% were observed in maximum plasma concentration (Cmax) and exposure (Area Under the Curve, AUC0-24) to the active metabolite of clopidogrel, respectively. In the second crossover study where clopidogrel and omeprazole were given 12 hours apart, findings were similar to those in the first study, indicating that administering clopidogrel and omeprazole at different times does not prevent this interaction.

Health-care professionals are advised to avoid the concomitant use of clopidogrel with omeprazole and other CYP2C19 inhibitors e.g. esomeprazole, cimetidine, fluconazole, ketoconazole, viriconazole, etravirine, fluoxetine, and fluvoxamine. The New Zealand data sheets for clopidogrel will be updated to include information to avoid concomitant use with omeprazole and other CYP2C19 inhibitors

(See WHO Pharmaceuticals Newsletters No. 2, No. 3, No. 4 and No.5, 2009 for information on the possible interaction between clopidogrel and proton pump inhibitors in the USA, Ireland, Europe, Canada and New Zealand).

***References**:*
(1). Public statement, EMEA 17 March 2010 (www.emea.europa.eu).
(2). Prescriber Update Vol. 31, No.1 February 2010 (www.medsafe.govt.nz).

Deferasirox

New Boxed Warning

USA. Novartis Oncology and the US FDA notified health-care professionals about recent changes in the prescribing information (PI) for deferasirox (Exjade). The medicine is indicated for the treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older. A Boxed Warning was added to the PI, stating that deferasirox (Exjade) may cause:

- renal impairment, including failure.
- hepatic impairment, including failure.
- gastrointestinal hemorrhage.

In some reported cases, these reactions were fatal. These reactions were more frequently observed in patients with advanced age, high risk myelodysplastic syndromes, underlying renal or hepatic impairment or low platelet counts. Exjade therapy requires close patient monitoring, including measurement of serum creatinine and/or creatinine clearance as specified in the PI and serum transaminases and bilirubin as specified in the PI.

New language was also added to the Contraindications, Warnings and Precautions, and Drug Interactions sections of the product information.

Reports in WHO Global ICSR database, Vigibase:

Deferasirox

Number of reports with liver and biliary system disorders and neoplasm: 133
Number of reports with urinary system disorders: 147
Number of reports with haemorrhage: 38

Most reported reactions (number of events):
Hepatic enzymes increased: 56
Hepatic failure: 27
Hepatic function abnormal: 54

Renal failure acute: 51
Renal failure chronic: 39

Renal function abnormal: 41
Renal tubular disorder: 10
Gastrointestinal haemorrhage: 21
Haemorrhage rectum: 14
Melaena: 12

(See WHO Pharmaceuticals Newsletter No.1, 2010 for potential revisions to prescribing information in Canada and the USA, No. 2, 2008 for reports of hepatic failure in Canada and the USA, and No. 2, 2007 for reports of renal failure in Canada and Switzerland).

***Reference**:*
Safety Information, US FDA 18 February 2010 (www.fda.gov).

Dextropropoxyphene

Risk-benefit balance unfavourable

New Zealand. The New Zealand Medicines and Medical Devices Safety Authority (Medsafe) has announced that it is currently implementing the recommendations by the Medicines Adverse Reactions Committee (MARC) that consent to distribute dextropropoxyphene-containing medicines be revoked. In the meantime, Medsafe advises prescribers not to start any new patients on dextropropoxyphene-containing medicines and to start reviewing the analgesic requirements of patients currently taking these medicines.

The MARC concluded the following.

- Efficacy studies had demonstrated that dextropropoxyphene-containing medicines were no better than paracetamol used at the maximum recommended dose.
- The available data on adverse reactions showed that these medicines have the potential to cause more adverse reactions than paracetamol used at recommended doses.
- These medicines are more dangerous than other analgesics in overdose.
- Overall the benefits of these medicines do not outweigh the risks associated with their use.

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

***Reference**:*
Prescriber Update Vol. 31, No.1 February 2010 (www.medsafe.govt.nz).

Didanosine

Risk of non-cirrhotic portal hypertension

USA. The U.S. FDA has alerted health-care professionals and patients about non-cirrhotic portal hypertension in patients using didanosine (Videx or Videx EC). Didanosine is used to treat human immunodeficiency virus (HIV) infection. The US FDA has received 42 post-marketing cases of non-cirrhotic portal hypertension in patients using didanosine with 4 deaths in those reported cases. The Agency explains that the cause of death in the four patients was due to: hemorrhage from esophageal varices in two patients; progressive liver failure in one patient; and a combination of multi-organ failure, cerebral hemorrhage, sepsis, and lactic acidosis in one patient.

Based on the number of well-documented cases and exclusion of other causes of portal hypertension such as alcohol-related cirrhosis or hepatitis C, the US FDA has concluded that there is an association between use of didanosine and development of non-cirrhotic portal hypertension. Because of the potential severity of portal hypertension, the Agency has revised the Warning and Precautions section of the didanosine label to include information about non-cirrhotic portal hypertension. Didanosine already has a Boxed Warning for lactic acidosis and hepatomegaly with steatosis.

The US FDA states that the clinical benefits of didanosine for certain patients with HIV continue to outweigh its potential risks. The decision to use this medicine, however, must be made on an individual basis between the treating physician and the patient.

Reports in WHO Global ICSR database, Vigibase:

Didanosine

Number of reports with cardiovascular disorders, general: 134

Most reported reactions (number of events):
Hypertension portal: 25
Cardiac failure: 26
Hypertension: 23
Hypotension: 34

Reference:
Safety Information, US FDA 29 January 2010 (www.fda.gov).

Erythropoiesis-stimulating agents

Risk management programme required

USA. The US FDA has notified health-care professionals and patients that all Erythropoiesis-stimulating agents (ESAs) must be used under a risk management programme, called a risk evaluation and mitigation strategy (REMS). The Agency has required a REMS because studies show that ESAs can increase the risk of tumor growth and shorten survival in patients with cancer (breast, non-small cell lung, head and neck, lymphoid, and cervical cancer) who use these products. Studies also show that ESAs can increase the risk of heart attack, heart failure, stroke or blood clots in patients who use these drugs for other conditions. ESAs are approved for the treatment of anemia resulting from chronic kidney failure, chemotherapy, certain treatments for Human Immunodeficiency Virus (HIV), and also to reduce the number of blood transfusions during and after certain major surgeries.

As part of the REMS, a Medication Guide explaining the risks and benefits of ESAs must be provided to all patients receiving an ESA. In addition to the Medication Guide, the manufacturer of the products (Amgen) was required to develop the ESA APPRISE

dispense ESAs to patients with cancer

Reference:
Safety Information, US FDA 16 February 2010 (www.fda.gov).

Human immune globulin

Risk of intravascular haemolysis

Canada and USA. Cangene Corporation, Baxter Healthcare Corporation, Health Canada and the US FDA notified health-care professionals that cases of intravascular hemolysis (IVH) and its complications, including fatalities, have been reported in patients treated for immune thrombocytopenic purpura (ITP) with Rho(D) immune globulin intravenous (human) (WinRho® SDF), which is a gamma globulin (IgG) fraction containing antibodies to the Rho(D) antigen. Fatal outcomes associated with IVH and its complications have occurred most frequently in patients aged over 65 with co-morbid conditions.

The Boxed Warning informs health-care professionals of the following.
- IVH can lead to clinically compromising anemia and multi-system organ failure including acute respiratory distress syndrome.
- Serious complications

prior to the end of the monitoring period.
- Patients should be alerted to and monitor for signs and symptoms of IVH, including back pain, shaking chills, fever, and discoloured urine or hematuria. Absence of these signs and/or symptoms of IVH within eight hours do not indicate that IVH cannot occur subsequently.
- If signs and/or symptoms of IVH are present or if IVH is suspected after the administration of the medicine, post-treatment laboratory tests should be performed including plasma haemoglobin, urinalysis, haptoglobin, LDH and plasma bilirubin (direct and indirect).

The new contraindications have been added, stating that WinRho® SDF should not be administered to ITP patients:
- with ITP secondary to other conditions including leukemia, lymphoma, or active viral infections with EBV (Epstein-Barr virus) or HCV (hepatitis C)
- who are elderly with co-morbidities predisposing to acute hemolytic reaction (AHR) or its complications
- with evidence of autoimmune hemolytic anemia (Evan's Syndrome), or Systemic Lupus Erythematosus (SLE) or anti phospholipid antibody syndrome (APS)
- who are IgA deficient.

Physicians are advised that if a patient has evidence of hemolysis (reticulocytosis greater than 3%) prior to ITP