WHO PHARMACEUTICALS NEWSLETTER

World Health Organization

prepared in collaboration with the
WHO Collaborating Centre for
International Drug Monitoring,
Uppsala, Sweden

The aim of this 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, PSM–HTP
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,
Stora Torget 3,
753 20 Uppsala, Sweden
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

Contents

No. 6, 2007

This is the last newsletter for this year. There are two feature items in this issue that readers may find interesting: one is a summary of recommendations from the working groups at the thirtieth meeting of the national pharmacovigilance centres that was held in October this year, in Argentina. The other is a summary of events leading to, and scientific basis for the decision to suspend nimesulide in Ireland.

We wish all our readers a very healthy and happy year ahead.

Printed by the WHO Document Production Services, Geneva, Switzerland

TABLE OF CONTENTS

Aprotinin

Temporary suspension while awaiting review of BART-study mortality data

Worldwide. Following consultation with Health Canada, the United States. Food and Drug Administration (US FDA), the German Federal Institute for Drugs and Medical Devices (BfArM), and other health authorities, Bayer has temporarily suspended marketing of Trasylol® (aprotinin), a drug used to control bleeding during heart surgery. This action follows the recent termination of a clinical study in Canada (Blood conservation using antifibrinolytics: a randomized trial in a cardiac surgery population (BART) clinical study), the preliminary interim data analysis from which indicated an increase in all-cause mortality in patients receiving aprotinin (Trasylol) compared to the other study drugs. The study was designed to compare aprotinin to epsilon-aminocaproic acid and tranexamic acid in decreasing the occurrence of massive bleeding associated with high-risk cardiac surgery. Data are now being collected from centres throughout Canada and a final data analysis will be undertaken by BART trial investigators. Further actions that may be undertaken in response to the analysis of that information will be made public.
During this temporary marketing suspension, Bayer Inc. in consultation with regulatory authorities have developed a process to make aprotinin available for high-risk patients where the practitioner is of the opinion that aprotinin is required and falls within the current approved indication.

References:

1. Communication from Bayer Healthcare Canada, 5 November 2007 (www.bayerhealth.ca)
2. Drug Safety Update, Volume 1(5): December 2007 (www.mhra.gov.uk)

Carisoprodol

Suspended due to greater risks than benefits

Europe. The European Medicines Agency (EMEA) has issued a press release recommending the suspension of the marketing authorization for all medicinal products containing carisoprodol. The Agency made this recommendation following a review by the Committee for Medicinal Products for Human Use (CHMP) which concluded that the risks of these medicines are greater than their benefits. The CHMP has assessed all available information on the safety of carisoprodol-containing products and has concluded that there is evidence for carisoprodol associated risk of abuse or addiction as well as intoxication and events related to psychomotor impairment. The CHMP undertook this assessment following plans made for the products' withdrawal from the Norwegian market due to new information available on the above adverse events. Carisoprodol is a centrally acting muscle relaxant, which is used mainly for the treatment of acute lower back pain. The EMEA advises that due to the risk of withdrawal symptoms, patients should not stop carisoprodol treatment prior to seeking advice from their doctor. Any switch to a new medication should be made gradually and under medical supervision.

Reference:

Press Release. EMEA, 16 November 2007 (www.emea.europa.eu)

Desmopressin

Risk of hyponatraemia and seizures; intranasal formulations no longer indicated in PNE

USA. The US FDA is warning that certain patients, including children treated with the intranasal formulation of desmopressin for primary nocturnal enuresis (PNE), are at risk for developing severe hyponatraemia that can result in seizures and death. Desmopressin intranasal formulations (marketed as DDAVP Nasal Spray, DDAVP Rhinal Tube, DDAVP, DDVP, Minirin, and Stimate Nasal Spray) are no longer indicated for the treatment of PNE and should not be used in hyponatraemic patients or patients with a history of hyponatraemia. The Agency advises that PNE treatment with desmopressin tablets should be interrupted during acute illnesses that may lead to fluid and/or electrolyte imbalance. All desmopressin formulations should be used cautiously in patients at risk for water intoxication with hyponatraemia. The US FDA has requested manufacturers to update the prescribing information for desmopressin.

Reference:

FDA Alert. US FDA, 4 December 2007 (www.fda.gov)

Eltroxin tablets

New formulations that should not be halved or crushed

New Zealand. GlaxoSmithKline New Zealand is advising that since July 2007, a new formulation of levothyroxine (Eltroxin®) (also known as thyroxine) 50 mcg and 100 mcg tablets has been available in the country. These reformulated tablets are no longer scored and should not be halved, so patients who require a dose of 25mcg daily must instead be prescribed one 50mcg tablet to be taken every second day. It is also recommended by the manufacturer that, due to lack of data on crushing the tablets, these tablets should only be prescribed to patients who are

able to swallow the tablets whole. These tablets should be taken on an empty stomach, preferably before breakfast.

Reference
Prescriber Update, 28(1):6, November 2007 (www.medsafe.govt.nz).

Erythropoiesis stimulating agents

Labels to address risks to cancer and chronic kidney failure patients

USA, Australia. Labels for erythropoiesis-stimulating agents (ESAs) will now include information on the evidence of risks that these agents pose to patients with cancer and patients with chronic kidney failure. The ESAs available in the USA include darbepoetin alfa (Aranesp), and epoetin alfa (Epogen, Procrit). These are indicated in the treatment of certain types of anaemia. For patients with cancer, the new boxed warnings emphasize that ESAs caused tumour growth and shortened survival in patients with advanced breast, head and neck, lymphoid and non small-cell lung cancer when they received a dose that attempted to achieve a haemoglobin level of 12 grams per deciliter (g/dL) or greater. For patients with chronic kidney failure, the new boxed warning states that ESAs should be used to maintain a haemoglobin level between 10 g/dL to 12 g/dL. There are study results that show that maintaining higher haemoglobin levels in patients with chronic kidney failure increases the risk of death and other serious conditions. The new labelling provides specific instructions for dosage adjustments and haemoglobin monitoring for chronic kidney failure patients who do not respond to ESA treatment with an adequate increase in their haemoglobin levels. Additionally, the new boxed warnings clarify that ESAs should only be used in patients with cancer when treating anaemia specifically caused by chemotherapy and not for other causes of anaemia; and that ESAs should be discontinued once the patient's chemotherapy course has been completed.
Health-care professionals have been notified of similar label updates in Australia. The three ESAs currently available in Australia are erythropoietin alfa (Eprex), erythropoietin beta (NeoRecormon), and darbepoetin alfa (Aranesp). They are approved for the treatment of anaemia associated with chronic renal failure and with the treatment of certain malignancies in Australia.

Reference:
1. MedWatch Alert. US FDA, 8 November 2007 (www.fda.gov).
2. Australian Adverse Drug Reactions Bulletin, 26(6): 22-23, 2007.

Lumiracoxib

Suspended in the United Kingdom due to risk of liver damage

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) has suspended the license for lumiracoxib (Prexige) due to the safety concerns about possible liver damage for patients. UK joins Australia, Canada and others in this decision (see WHO Pharmaceuticals Newsletter No. 5, 2007). Lumiracoxib, used to treat painful symptoms of osteoarthritis of the knee and hip, was first made available in the UK in December 2005. In August 2007, following analysis of data available at that time, the MHRA introduced new prescribing restrictions (contraindications) for patients with current or previous liver problems, and additional requirements for blood tests before and during lumiracoxib treatment for all other patients. The Commission on Human Medicines (CHM) has now reviewed the latest worldwide data on the safety of lumiracoxib which show an increase in the number of cases of serious liver reactions that have occurred with the licensed 100 mg dose; in some cases the reactions were associated with short-term use (less than one month). In the light of these latest data, the CHM has advised that previous measures could not be relied upon to guarantee patient safety and has therefore recommended a suspension of the products. Patients taking lumiracoxib are advised to make an appointment to see their doctor at the next convenient opportunity.

Reference:
Press Release. MHRA, 19 November 2007 (www.mhra.gov.uk).

Mycophenolate mofetil

Revised as Category D drug, to reflect risk of fetal harm

USA. US FDA has notified transplant specialists and other health-care professionals that the prescribing information for mycophenolic acid has been revised. Mycophenolate mofetil (CellCept) is an immunosuppressant indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal transplants. It is administered in combination with cyclosporine and corticosteroids. The US FDA is advising that there is now definite post marketing evidence of increased risk of first trimester pregnancy loss and congenital malformations, especially external ear malformations, facial abnormalities including cleft lip and palate, anomalies of the distal limbs, heart, oesophagus, and kidney associated with the use of this drug during pregnancy. In post marketing data (collected from 1995 to 2007) on 77 women exposed to systemic mycophenolate mofetil during pregnancy, 25 had spontaneous abortions and 14

had a malformed infant or fetus. The pregnancy category for this product has now been changed from Category C (risk of fetal harm cannot be ruled out) to Category D (positive evidence of fetal risk). Within one week of beginning mycophenolate mofetil therapy, women of childbearing potential should have a negative serum or urine pregnancy test. In addition, women of childbearing potential (including pubertal girls and peri-menopausal woman) taking this product must receive contraceptive counselling and use effective contraception. Health-care professionals and patients should be aware that mycophenolate mofetil reduces blood levels of the hormones in the oral contraceptive pill and could theoretically reduce its effectiveness. Additionally, the Agency advises that a patient who is planning a pregnancy should not use this product unless she cannot be successfully treated with other immunosuppressant drugs. Health-care professionals should discuss the risks and benefits of mycophenolate mofetil as well as alternative immunosuppressant therapy with the patient. The risks and precautions described above also apply to the mycophenolic acid delayed-release tablets (Myfortic).

Reference:
Medwatch Alert. US FDA, 27 November 2007 (www.fda.gov).

Rosiglitazone

Revised prescribing information due to adverse cardiac events

Canada (1). GlaxoSmithKline Inc. has written to health-care professionals that there are new restrictions on the use of rosiglitazone-containing products (AVANDIA®, AVANDAMET® and AVANDARYL™) indicated in the treatment of type 2 diabetes. These restrictions follow the Health Canada assessment of adverse event reports, published articles and other available information on congestive heart failure, myocardial infarction and related events associated with the use of these products. According to the new restrictions:

- rosiglitazone is no longer approved as monotherapy for type 2 diabetes except when metformin use is contraindicated or not tolerated.
- rosiglitazone is no longer approved for use in combination with a sulfonylurea, except when metformin is contraindicated or not tolerated.
- treatment with all rosiglitazone products is now contraindicated in patients with any stage of heart failure

Health professionals are also reminded that;

- rosiglitazone is not indicated for use with insulin. This combination is associated with an increased risk of heart failure.
- rosiglitazone is not indicated for triple therapy (that is, therapy with rosiglitazone in combination with both metformin and a sulfonylurea). Increases in congestive heart failure and other fluid retention-related events have been reported in patients receiving rosiglitazone as part of triple therapy.

When adequate glycaemic control is not obtained through diet and exercise plus monotherapy, then rosiglitazone can be used in dual therapy, as follows: use in combination with metformin; or when metformin is contraindicated or not tolerated, use in combination with a sulfonylurea. Rosiglitazone can be added to (not substituted for) the monotherapy agent.

Health Canada is advising patients to talk to their doctors about the risks of continuing rosiglitazone therapy if they have underlying heart disease, or are at high risk of heart attack or heart failure.

UK (2). According to the MHRA a Europe-wide review of available data for the safety and efficacy of thiazolidinediones (the class to which rosiglitazone belongs) has resulted in revised prescribing information for this class of antidiabetic drugs. The revised prescribing information emphasizes that the benefits of rosiglitazone (and piaglitazone) for treatment of type 2 diabetes continue to outweigh the risks but that rosiglitazone should be used in patients with ischaemic heart disease only after careful evaluation of every patient's individual risk; and that rosiglitazone, combined with insulin should be used only in exceptional cases and under close medical supervision.

(See WHO Pharmaceuticals Newsletter No. 4, 2007 for related message from US FDA).

References:
1. Dear Health-care Professional letter from GlaxoSmithKlne Inc, 1 November 2007 (www.hc-gc.sc.ca).
2. Drug Safety Update, Volume 1(5), December 2007 (www.mhra.gov.uk).

Cefepime

Reports of death being investigated

USA. The US FDA has issued an early communication(1) about the ongoing review of new safety data and the request for additional data to further evaluate the risk of death in patients treated with cefepime. An article in the May 2007 issue of The Lancet Infectious Diseases (2) raised the question about increased mortality with the use of cefepime, a broad spectrum B-lactam antibiotic currently approved for the treatment of a variety of infections due to susceptible strains of microorganisms. The article describes higher all-cause mortality in patients treated with cefepime compared to other B-lactam antibiotics. The US FDA advises that until the evaluation is completed, health-care professionals who are considering the use of cefepime should be aware of the risks and benefits described in the product's prescribing information and the new information from this meta-analysis.

References:

1. Early Communication. US FDA, 14 November 2007 (www.fda.gov).
2. Lancet Infectious diseases, 7:338-348, 2007.

Clozapine

Constipation could be

patients and regular monitoring of neutrophil counts is mandatory throughout treatment. In New Zealand one death from agranulocytosis has been reported to the IMMP. In contrast, four deaths from complications of severe constipation have been reported with the drug. Clozapine-induced constipation may be associated with serious effects such as intestinal obstruction, bowel perforation and toxic megacolon. The four deaths reported to IMMP demonstrate that these effects can be fatal. The authors note that although many anticholinergic drugs are known to cause dysmotility, clozapine has a much more potent effect through its interaction with multiple receptors, (including anticholinergic and serotonergic receptors) affecting gastrointestinal activity. This action is exacerbated by co-prescription of anticholinergic agents such as benztropine and tricyclic antidepressants. The IMMP reminds health professionals that the gastrointestinal effects of clozapine are potentially serious. Awareness of this issue may prevent life-threatening complications. Patients should be asked about bowel function and dietary advice should be provided if needed.

Reference:

Prescriber Update, 28(1):7, November 2007 (www.medsafe.govt.nz).

Glitazones

warns that glitazone antidiabetic drugs (example, pioglitazone, rosiglitazone used in type 2 diabetes) can cause dose-related but severe fluid retention, which is more likely to occur when these drugs are used in combination with insulin or sulphonylureas. Consequences include new or worsening cardiac failure and macular oedema. Pioglitazone and rosiglitazone are contraindicated in patients with NYHA Class III and IV heart failure, and not recommended in patients with symptomatic heart failure. Dr Savage advises that patients taking glitazones need to be informed of possible symptoms, and monitored for fluid retention and associated complications. If signs or symptoms develop, prescribers should stop or reduce the dose of glitazone. According to Dr Savage, reports of fluid retention leading to oedema and related conditions made up the greatest proportion of adverse reactions to glitazones reported to the WHO Global Individual Case Safety Reports (ICSR) database, Vigibase, until December 2006. In the cases reported to CARM, one patient was admitted to hospital with oedema extending from the legs to the chest while taking pioglitazone 15 mg daily. Another developed oedema of the legs and abdomen, and shortness of breath on exertion three weeks after starting rosiglitazone 4 mg daily. There was no evidence of cardiac failure. He recovered with furosemide treatment and