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:

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

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No. 4, 2007

News & Issues

In addition to the drug safety and regulatory sections, two feature items may be of special interest to readers in this issue: a brief overview of the ATC/DDD course offered by the WHO Collaborating Centre in Oslo, Norway and a summary of the meeting of the Global Advisory Committee on Vaccine Safety. Including these feature items is in keeping with our promise to bring you more information on vaccine safety and on the work of our Norwegian Collaborating Centre. We look forward to your comments.

Three meetings are due in October in pharmacovigilance: the Annual Meeting of National Centres participating in the WHO Programme for International Drug Monitoring will be held in Buenos Aires, 11-13 October. We hope that the meeting this year will be just as well attended as in the previous years. Working group exercises at the meeting will cover the areas of information access, medicine safety in special populations, and methodologies to complement spontaneous adverse drug reaction reporting.

The 22nd Meeting of the WHO International Working Group for Drug Statistics Methodology will be held in Oslo, Norway, 23-25 October, 2007. The meeting will be preceded by the 25th anniversary celebration of the Norwegian Centre, the WHO Collaborating Centre for Drug Statistics Methodology. The anniversary celebration will be marked by several presentations including one by Dr Lembit Rago, Coordinator, Quality Assurance and Safety: Medicines, WHO.

The CIOMS/WHO working group for vaccine pharmacovigilance will meet 29-30 October, in Washington, USA. This working group was created in November 2005 to develop general definitions focused on Vaccine Pharmacovigilance. The working group will contribute to the development, review, evaluation and approval of definitions on adverse events following immunization.

We will bring you highlights from these meetings in our later issues of the newsletter.

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Safety of Medicines

Feature

Ceftriaxone

Some deaths due to calcium-ceftriaxone precitpitates

USA. Roche USA has issued a 'Dear Health-care Professional' letter to advise that the prescribing information of ceftriaxone sodium (Rocephin) for injection has been updated with information on the potential risks associated with the concomitant use of ceftriaxone with calcium and calcium-containing products. The company says that over the past few years, there have been isolated reports worldwide of neonatal deaths associated with calcium-ceftriaxone precipitates in the lungs and kidneys. In some cases, the ceftriaxone and calcium-containing products were administered at different times and by different routes.
Ceftriaxone is a third generation broad spectrum cephalosporin, an antibiotic effective against gram positive and gram negative bacteria. Roche advises that the Contraindications, Warnings, Precautions, Adverse Reactions and Dosage and Administration sections of the ceftriaxone prescribing information have been updated.
According to Roche the revised prescribing information aims to more prominently reinforce that hyperbilirubinaemic neonates, especially those who are premature, should not receive ceftriaxone. The updated labelling advises that ceftriaxone must not be mixed or administered simultaneously with calcium-containing solutions or products, even via separate infusion lines. Furthermore, calcium-containing solutions or products must not be administered within 48 hours of the last ceftriaxone administration.

Reference:
'Dear Health-care Professional' letter from Roche Laboratories Inc., June 2007 (*www.fda.gov*).

Cinacalcet

Labelling updated for restrictions in use

Canada. Amgen Canada Inc., in consultation with Health Canada, has issued a 'Dear Health-care Professional' letter and a Public Communication that cinacalcet (Sensipar) is no longer indicated in the treatment of secondary hyperparathyroidism in patients with chronic kidney disease (CKD) who are not receiving dialysis. The use is now restricted for the treatment of secondary hyperparathyroidism in patients with CKD who are receiving dialysis. This restriction follows study results involving cinacalcet recipients with secondary hyperparathyroidism and CKD which showed that patients not receiving dialysis were more likely to develop serum calcium levels below the lower limit of the normal range (8.4 mg/dL) compared with those receiving dialysis. Furthermore, results of a third study initiated by Amgen showed that the incidence of calcium levels below 8.4 mg/dL was consistent with the previous results. Based on these findings, the Product Monograph will be updated. Amgen advises that patients receiving cinacalcet for secondary hyperparathyroidism who are not receiving dialysis should contact their doctor immediately. The company emphasizes that patients should not stop taking cinacalcet without first contacting their doctor.

Reference:
'Dear Health-care Professional' letter from Amgen Canada Inc., 19 June 2007 (*www.hc-gc.sc.ca*).

Edaravone

Report of fulminant hepatitis

Japan. A new warning about possible fulminant hepatitis has been added to the precautions for edaravone (Radicut) by the Japanese Ministry of Health, Labour and Welfare. Edaravone was approved for use in Japan in 2001 as a product to protect the brain cells of patients who have suffered a stroke, or a restriction of blood to the brain. The possibility of liver disorders, including jaundice and standard hepatitis, is already included in the precautions section of the product label. But the current update was prompted by six case reports of fulminant hepatitis (one fatal) associated with edaravone between April 2003 and February 2007.

Reference:
Reactions Weekly, 1159:3, 7 July 2007 (www.adisonline.com).

Piroxicam

Restrictions in use

Europe. The European Medicines Agency (EMEA) has recommended restrictions on the use of piroxicam-containing medicinal products because of the risk of gastrointestinal side effects and serious skin reactions. The Agency's Committee for Medicinal Products for Human Use (CHMP) has determined that piroxicam should no longer be used for short-term painful and inflammatory conditions. Piroxicam can still be prescribed to relieve the symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis, but should not be used as a first-line treatment for these disorders.
Piroxicam should be initiated by a physician with experience in the treatment of such conditions and the drug should be used at the lowest dosage

(no more than 20 mg/day) for as short a time as possible. Treatment should be reviewed after 14 days. Topical medications containing piroxicam are not included in the new restrictions.

Reports in the WHO database:

Gastrointestinal system disorders (General) 6692*
(for whole GI system)

gastritis	224
GI haemorrhage	1167
haematemesis	568
melaena	1003
abdominal pain	764
dyspepsia	503
nausea	472
gastric ulcer	522
gastric ulcer haemorrhagic	413
skin disorder	26

Reference:
Press Release. EMEA, 25 June 2007 (*www.emea.europa.eu*).

Rimonabant

Contraindicated in patients with major depression

Europe. The European Medicines Agency (EMEA) has announced that rimonabant (Acomplia) is contraindicated in patients with ongoing major depression or who are being treated with antidepressants because of the risk of psychiatric adverse effects. Rimonabant is a cannabinoid receptor antagonist and has been authorized as an adjunct to diet and exercise for the treatment of obese or overweight adult patients. The EMEA had previously warned doctors in the European Union about the risk of psychiatric adverse effects with rimonabant. The Agency's Committee for Medicinal Products for Human Use (CHMP) has reviewed all available data on psychiatric adverse effects with rimonabant that it received from Sanofi-aventis and has concluded that

- the benefits of rimonabant outweigh the risks, except in patients who have ongoing major depression or who are receiving anti-depressants. The CHMP recommends adding a warning to the product label that the drug should be discontinued if a patient develops depression;
- the risk of depression is approximately doubled in patients receiving rimonabant compared with obese or overweight patients not receiving the drug, and this could lead to suicidal ideation or even suicide attempts in a small minority of cases.

The CHMP recommends strengthening the product label with information about the psychiatric effects and adding a warning that the drug should be discontinued if a patient develops depression.

Reference:
Press Release. EMEA, 18 July 2007 (www.emea.europa.eu).

Tegaserod

Suspended in China; withdrawn in Switzerland; permitted for restricted use in the USA

China (1). The production, sale and use of tegaserod (Zelnorm) have been suspended by the Chinese State Food and Drug Administration (SFDA). Tegaserod was originally authorized for the treatment of symptoms associated with irritable bowel syndrome in women. The drug has been associated with an increased risk of strokes and heart attacks, this being the reason for the SFDA decision. According to the SFDA, local and international reports of adverse reactions suggest a negative benefit-risk balance for tegaserod: the risks of treatment with tegaserod outweigh the possible benefits for some patients. 98 adverse reaction reports involving tegaserod have been received by the National Centre for Adverse Drug Reaction Monitoring since the product was first marketed in China in 2003. Major reactions were reported to be diarrhoea and nausea, but there was one case of tachycardia, two involving heart palpitations and one case of low blood pressure.

Switzerland (2). The Swiss Institute of Therapeutic Products, Swissmedic has declined to extend the marketing authorization for tegaserod (Zelmac) in Switzerland after a new analysis of clinical data showed that tegaserod had an increased risk of cardiovascular disorders compared with placebo. Tegaserod was authorized towards the end of October 2001 in Switzerland in the treatment of irritable bowel syndrome in women. Swissmedic advises that tegaserod has an unfavourable risk-benefit ratio. Novartis Pharma Schweiz AG will inform health-care professionals of the withdrawal in Switzerland.

USA (3). The United States Food and Drug Administration (US FDA) is permitting the restricted use of tegaserod (Zelnorm) as an investigational new drug for the treatment of irritable bowel syndrome with constipation, and chronic idiopathic constipation. The use of tegaserod (Zelnorm) for such treatment is restricted to women aged < 55 years whose physicians decide that treatment with tegaserod is medically necessary. The FDA previously suspended the sales and marketing of tegaserod following a safety analysis that demonstrated an increased risk of myocardial infarction, stroke and unstable angina associated with tegaserod, compared with placebo (see WHO Pharmaceuticals Newsletter No. 3, 2007).

Reports in the WHO database:
Tegaserod (Zelmac): Cardiac failure - 3; myocardial infarction - 3
Tegaserod (Zelnorm): Hypotension - 27; diarrhoea - 406; palpitation - 36; tachycardia - 39

References:

1. Reactions Weekly, 1157:3, 23 June 2007 (www.adisonline.com)
2. Journal Swissmedic, p342, June 2007 (*www.swissmedic.ch*)
3. FDA News. U.S. Food and Drug Administration, 27 July 2007 (*www.fda.gov*)

Thiazolidinedione antidiabetics

Boxed warning on label about heart failure risk

USA. The US FDA, based on a review of post-marketing adverse event reports, has decided that an updated label with a boxed warning on the risks of heart failure is needed for all thiazolidinedione class of antidiabetic drugs. This class includes rosiglitazone (Avandia), pioglitazone (Actos), rosiglitazone and glimepiride (Avandaryl), among others. FDA's review of the post-marketing adverse event reports found cases of significant weight gain, and edema, both of which are warning signs of heart failure; some reports were associated with poor treatment outcomes, including death, when treatment was continued. The strengthened warning advises health-care professionals to observe patients carefully for the signs and symptoms of heart failure, including excessive and rapid weight gain, shortness of breath, and edema after starting drug therapy. Patients with these symptoms who develop heart failure should receive appropriate management of heart failure and, use of the thiazolidinedione antidiabetic drug should be reconsidered. The warning also states that these drugs should not be used by people with serious or severe heart failure.

The issue of whether rosiglitazone increases the risk of heart attacks or not is still unresolved (see WHO Pharmaceuticals Newsletter No. 3, 2007). The FDA's review of this issue is ongoing. In the meantime the Agency advises that rosiglitazone (Avandia) will continue to be marketed with a label that includes information on the risk of heart attacks (ischemia) with the product.

Reports in the WHO database for rosiglitazone:

Cardiac Failure	803
Myocardial Infarction	163
Cardiovascular Disorders (as a term)	2

Reference:

FDA News. U.S. Food and Drug Administration, 14 August 2007 (*www.fda.gov*)

Warfarin

Label to explain influence of genetic makeup on drug response

USA. The US FDA has approved an updated labelling for warfarin (generic versions and the proprietary brand, Coumadin) to explain that people's genetic makeup may influence how they respond to the drug. The current labelling changes are based on an analysis of recent studies that found people respond to the drug differently based, in part, on whether they have variations of certain genes. Warfarin is a blood thinning drug and is used to prevent blood clots, heart attacks and strokes. It is a difficult drug to use because the optimal dose varies and depends on many risk factors including a patient's diet, age and the use of other medications. Patients who take a dose larger than they can tolerate are at risk of life-threatening bleeding. On the other hand, too low a dose can leave patients at risk of blood clots. Research has shown that some of the unexpected response to warfarin depends on a patient's variants of the genes CYP2C9 and VKORC1. Genetic testing can identify who has these genetic variants. The new updated label for warfarin will highlight the opportunity for health-care providers to use genetic tests to improve their initial estimate of what is a reasonable warfarin dose for individual patients. According to the US FDA, this update is a step towards personalized medicine, to get the right drug in the right dose for the right patient.

Reference:

FDA News. U.S. Food and Drug Administration, 16 August 2007 (*www.fda.gov*).

Colistemethate

Premixed formulations must be administered promptly

USA. The US FDA is investigating a possible association between the use of a liquid colistimethate sodium solution that had been premixed for nebuliser inhalation, and the death of a patient with cystic fibrosis (CF). Colistemethate is used to treat infections caused by certain types of bacteria, including the bacteria *Pseudomonas aeruginosa* which is known to cause serious lung infections in patients with CF. In the reported death, the pharmacy-prepared colistimethate solution had been dispensed, as prescribed, in premixed vials, ready for use. However, within hours, the patient developed respiratory distress that progressed to acute respiratory failure. The patient had copious thin, pink pulmonary secretions and was admitted to an ICU. A CT scan showed ground glass infiltrates indicative of acute respiratory distress syndrome. Approximately 19 days later, the patient died from multiorgan system failure. Colistimethate is FDA-approved for IM or IV injection but is not approved as a liquid to be inhaled via a nebuliser. In the treatment of CF patients with pseudomonas infections, however, colistimethate is frequently mixed with sterile promptly after it has been mixed. Patients are advised to discard any unused vials of ready-to-use, premixed liquid forms of colistimethate.

Reference:
Public Health Advisory. U.S. Food and Drug Administration, 28 June 2007 (*www.fda.gov*)

Fluidione, pentoxyfylline

Same trade name caused serious medication error; need to promote use of INNs

France. The French health-care products regulatory agency AFSSAPS is warning that having the same trade name for two different medicines can lead to serious medication errors. The Agency gives the example of a recent case that occurred in France: a 42 year-old male patient had been using fluidione (Previscan) since 2003 as an anticoagulant medication for atrial fibrillation. The patient forgot to carry his medication when he travelled to Spain in June 2005. There was no product by the name Previscan in Spain. The Spanish pharmacy then gave the patient pentoxyfylline based on a reference that pentoxyfylline is sold as Previscan in Argentina. On returning back to France on 27 June 2006 the patient switched back to his original French Previscan (fluidione) AFSSAPS has informed the Spanish and Argentinean regulatory Agencies, the Argentinean Previscan (pentoxifylline) MAH and, the European Pharmacovigilance Working Party about the event. AFSSAPS has also warned health-care professionals and the public about the risks of potential medical errors that could occur when different drugs have the same trade name. AFSSAPS also advises that this is an important case for promoting the use of International Nonproprietary Names (INN) for medicines since an INN is a unique identifier for every medicinal product.

Reference:
Communication from Dr Carmen Kreft-Jais, Head, Pharmacovigilance Unit, AFSSAPS, 20 June 2007.

US FDA, EMEA and the European Commission: expanding the areas of cooperation

The US FDA, EMEA and the European Commission have agreed to expand the areas of cooperation under their confidential information sharing agreement. The parties agreed to include the areas of paediatrics and medicinal products for rare diseases (orphan drugs) in the agreement. In addition, scientific discussions have