# 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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**No. 3, 2008**

**NEWS & ISSUES**

This issue has been delayed considerably on account of some of our support staff leaving the unit, and due to teething difficulties with an all new global resource management system in WHO. But things are slowly getting back on track and we apologize for the inconvenience to our readers. Some of the information in this issue may be a bit old but we thought it would be useful to record them nevertheless, as a way of archiving the information for your future reference. Thank you for your continuing interest.

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## Regulatory Matters



## Safety of Medicines



## Feature

## Conventional antipsychotics

### Boxed warnings on fatalities in elderly patients

**USA.** The United States Food and Drug Administration (US FDA) is requiring manufacturers of conventional antipsychotics to add Boxed Warnings about the increased risk of death in elderly patients treated for dementia-related psychosis. The FDA based this requirement on recent studies together with earlier evidence for atypical antipsychotics, that both atypical and conventional antipsychotics have an increased risk of death in elderly patients with dementia-related psychosis.

Manufacturers of antipsychotics are being asked to update labelling so that all drugs have the same warnings.

The FDA advises health-care professionals that:

- antipsychotics are not approved for treatment of dementia-related psychosis
- physicians who prescribe antipsychotics to elderly patients with dementia-related psychosis should discuss the increased mortality risk with their patients, patients' families and caregivers.

***Reference:***
*Media Release, FDA, 16 June 2008 (www.fda.gov).*

## Becaplermin

### Boxed warning added about increased cancer risk

**USA.** The US FDA has added a boxed warning to the label of 0.01% becaplermin gel (Regranex) regarding the increased risk of cancer mortality in patients who have used three or more tubes of the product. Becaplermin is mainly used to heal wounds in patients with diabetes. This action follows the Agency's review of safety data from a retrospective study showing a five-fold increased risk of cancer mortality in patients exposed to three or more tubes of becaplermin (see WHO Pharmaceuticals Newsletter No. 2, 2008). The US FDA cautions health-care professionals to carefully weigh the risks and benefits of treating patients with becaplermin.

Reports in WHO ICSR database:

Total 58 reports, 2004 – 2008 all from USA:

| | |
|---|---|
| Melanoma malignant | 1 |
| Adenocarcinoma NOS | 1 |
| Pulmonary carcinoma | 1 |
| Skin hypertrophy | 55 |

***Reference:***
*Becaplermin Information, US FDA, 6 June 2008 (www.fda.gov).*

## Epoetins

### Warning for use in cancer patients

**Europe.** European Medicines Agency (EMEA) has recommended updating the product information for epoetin-containing medicines with a new warning for their use in cancer patients stating that blood transfusion should be the preferred method of correcting anaemia in patients suffering cancer.

Epoetin-containing medicines are indicated in patients with chronic renal failure and for the treatment of anaemia in symptomatic patients with non-myeloid tumours receiving chemotherapy. New data from studies that show an increased risk of tumour progression, venous thromboembolism and shorter overall survival in cancer patients who received epoetins compared to patients who did not receive them.

***Reference:***
*EMEA Press Release, 26 June 2008 (www.emea.europa.eu).*

## Etanercept

### Label to indicate risk of infections in children

**USA.** The US FDA's Dermatologic and Ophthalmic Drugs Advisory Committee is recommending that labelling for Amgen's etanercept (Enbrel) include warnings that use of the agent in paediatric patients may lead to moderate to severe infections and can result in death.

The committee recommended the following labelling changes:

- Under the 'Adverse Reactions in Patients with Juvenile Idiopathic Arthritis' section, the wording should be changed to reflect that use of etanercept therapy in the paediatric population may lead to moderate to severe infections and can result in serious outcomes, including death and hospitalisation.
- In the same section, the list of serious adverse events reported in the postmarketing period should be updated to include macrophage activation syndrome, malignancies, diabetes mellitus and systemic lupus erythematosus.

***Reference:***
*Media Release, US FDA, 18 June 2008, (www.fda.gov).*

## Etoricoxib

### Risk of cardiovascular side effects

**Europe.** The European Medicines Agency (EMEA) recommended that the product information for etoricoxib-containing products should be updated concerning the risk of cardiovascular side effects.

Etoricoxib is a non-steroidal anti-inflammatory drug (NSAID). It is currently indicated to relieve the symptoms of osteoarthritis, rheumatoid arthritis and pain and signs of inflammation associated with acute gouty arthritis. In addition, an application is currently under evaluation to extend the indication of the etoricoxib-containing medicine Arcoxia to treat ankylosing spondylitis.

In the evaluation of etoricoxib concerns were raised over the cardiovascular safety of etoricoxib-containing medicines when used to treat ankylosing spondylitis at a dose of 90 mg once a day. These concerns also extended to the treatment of rheumatoid arthritis which is used at the same dose.

The Committee for Medicinal Products for Human Use (CHMP) recommended updating the existing contraindication in patients with hypertension that is not adequately controlled to state that patients whose blood pressure is persistently above 140/90 mmHg and has not been adequately controlled should not take etoricoxib.

***Reference:***
*EMEA Press Release, 26 June 2008 (www.emea.europa.eu).*

## Fluoroquinolones

### Boxed warning against increased risk of tendinitis and tendon rupture

**USA.** US FDA notified health-care professionals that a BOXED WARNING and Medication Guide are to be added to the prescribing information to strengthen existing warnings about the increased risk of developing tendinitis and tendon rupture in patients taking fluoroquinolones for systemic use.

Fluoroquinolones are associated with an increased risk of tendinitis and tendon rupture. This risk is further increased in those over age 60, in kidney, heart, and lung transplant recipients, and with use of concomitant steroid therapy. Physicians should advise patients, at the first sign of tendon pain, swelling, or inflammation, to stop taking the fluoroquinolone, to avoid exercise and use of the affected area, and to promptly contact their doctor about changing to a non-fluoroquinolone antimicrobial drug. Selection of a fluoroquinolone for the treatment or prevention of an infection should be limited to those conditions that are proven or strongly suspected to be caused by bacteria.

***Reference:***
*Information for Healthcare Professionals, US FDA, 8 July 2008 (www.fda.gov).*

## Label changes for use in pregnancy

### Risks and benefits highlighted

**USA.** The US FDA has proposed extensive changes to labelling for prescription medications, including biological products, to better inform patients of the risks and benefits of drugs that are used during pregnancy and breastfeeding. Drug labelling would be required to outline the potential risks and benefits of the medication for both the mother and the foetus, and how these risks may vary throughout the course of the pregnancy.

***Reference:***
*Media Release, US FDA, 28 May 2008 (www.fda.gov).*

## Moxifloxacin

### Hepatic reactions - restriction in use in upper respiratory infections

**Europe.** EMEA has concluded that moxifloxacin-containing medicines for oral use should only be prescribed in the treatment of acute bacterial sinusitis, acute exacerbation of chronic bronchitis and community acquired pneumonia when other antibiotics cannot be used or have failed. The Agency also recommended strengthening the warnings for oral moxifloxacin medicines. The reason is increased risk of hepatic reactions.

The EMEA's Committee for Medicinal Products for Human Use (CHMP) has reviewed all available information on the safety of moxifloxacin-containing medicines for oral use, following concerns over their liver safety when used for acute bacterial sinusitis, acute exacerbation of chronic bronchitis and community-acquired pneumonia. The CHMP concluded that the benefits of oral moxifloxacin medicines continue to outweigh its risks. However, due to safety concerns, mainly related to an increased risk of adverse hepatic reactions, the CHMP recommended restricting their use in these indications.

The CHMP also recommended that the warnings of oral moxifloxacin-containing

medicines should be strengthened concerning the risk of diarrhoea, heart failure in women and older patients, severe skin reactions and fatal liver injury.

Reports in WHO ICSR database:
*Moxifloxacin (terms with more than 15 reports)*

| | |
|---|---|
| Hepatic enzymes increased | 57 |
| SGOT increased | 26 |
| SGPT increased | 25 |
| Hepatic failure | 18 |
| Hepatic function abnormal | 35 |
| Hepatitis | 32 |
| Hepatitis cholestatic | 17 |
| Hepatocellular damage | 18 |
| Bilirubinaemia | 23 |
| Jaundice | 54 |

(See also WHO Pharmaceuticals Newsletter No. 2, 2008, for reports of multifocal leukoencephalopathy).

***Reference:***
*EMEA Press Release, 24 July 2008 (www.emea.europa.eu).*

## Norfloxacin

### Restricted use in urinary infections

**EMEA.** The CHMP has concluded that the marketing authorisations for oral norfloxacin-containing medicines, when used in the treatment of acute or chronic complicated pyelonephritis (kidney infection), should be withdrawn because the benefits of these medicines do not outweigh their risks in this indication. This is based on the fact that the efficacy has not been adequately demonstrated for this type of infection.

In current practice, this disease is usually treated using either injectable antibiotics, or other fluoroquinolones taken by mouth or given byinjection. The recommendation of the CHMP does not have an impact on the use of oral norfloxacin-containing medicines in other types of infection.

***Reference:***
*EMEA Press Release, 24 July 2008 (www.emea.europa.eu).*

## Pegvisomant-somatostatin analogues

### Increased risk of hepatic enzyme elevations

**Canada.** Pfizer, in consultation with Health Canada, has issued a 'Dear Healthcare Professional' letter advising of an increased risk of hepatic enzyme elevations in patients receiving the anti-growth hormone pegvisomant (Somavert) in combination with a somatostatin analogue, such as octreotide. Pfizer advises health-care professionals that baseline serum ALT, AST, total bilirubin and ALP levels should be obtained prior to pegvisomant initiation and routinely monitored during the course of treatment. If a patient develops liver test elevations of 3–5 times the upper limit of normal (ULN), pegvisomant may be continued, but liver tests should be monitored weekly. If a patient develops liver test elevations of > 5 times the ULN, transaminase elevations of > 3 times the ULN with any increase in total bilirubin, or signs or symptoms of liver injury, pegvisomant should be immediately discontinued. If liver injury is confirmed, pegvisomant should be permanently discontinued. The Canadian product monograph will be updated to include this new information.

## Perflutren injectable suspension

### Warning section to be revised

**Canada.** Bristol-Myers Squibb Medical Imaging has issued a 'Dear Healthcare Professional' letter, in consultation with Health Canada (HC), advising of changes to the safety information for the contrast medium perflutren injectable suspension, (Definity).

There have been worldwide reports of serious cardiopulmonary reactions, including fatalities, occurring during, within 30 minutes of, and up to several days after administration. As of March 31 2008, there had been one case in Canada of a fatal cardiopulmonary adverse reaction.

The product monograph for Definity is being updated. The warning section will be revised to include guidelines for close monitoring of patients with pulmonary hypertension or unstable cardiopulmonary conditions, during and for at least 30 minutes after administration.

The revised product monograph will include a statement about adverse drug reactions occurring during post marketing use.

Reports in WHO ICSR database:

*Perflutren*

Circulatory failure 1 (USA)
Fibrillation cardiac 1 (USA)

***Reference:***
*Bristol-Myers Squibb Medical Imaging. Updated safety information on DEFINITY (Rm) (Perflutren Injectable Suspension) and serious adverse cardiopulmonary reactions. Internet Document, 23 May 2008 (www.hc-sc.gc.ca).*

## Rotavirus gastroenteritis vaccine

### Additional safety studies required

**USA.** Approving GlaxoSmithKline's (GSK's) oral, live attenuated, human rotavirus vaccine (Rotarix) the US FDA exercised its new authority (Food & Drug Administration Amendments Act (FDAAA), 27 September 2007) to require a postmarketing safety study (1). On 3 April 2008, the Agency approved Rotarix for the prevention of rotavirus gastroenteritis in infants (2). The approval was based on clinical data from nearly 75 000 infants participating in trials conducted in North and South America, Europe, Asia and Africa.

The US FDA considers analyses of spontaneous postmarketing adverse events insufficient to assess potential serious risks. Consequently, GSK is required to conduct a US-based postmarketing observational study of Rotarix to assess the potential serious risk of intussusception and other serious adverse effects (start June 2009; final report by March 2012).

Reports in WHO ICSR database:

*Intestinal obstruction* (2001-2007)

## ADR reporting in Finland

### 2007 Overview

**Finland.** The Finnish National Agency for Medicines received 1174 reports of suspected adverse drug reactions (ADRs) in 2007. They included a total of 2568 ADR symptoms.

- Reports were received for 348 medical substances (excluding vaccines)
- 753 reports (64%) were classified as serious.
- Iomeprol, with 47 reports, was at the top of the list of most frequently reported drugs (≥ 10 reports).
- Most of the drugs on the most frequently reported list had also appeared on the 2006 list, but varenicline (23 reports), aripiprazole (18), buprenorphine/naloxone (11), rimonabant (10) and escitalopram (10) were newcomers to the list.

Iodine-containing contrast media generated 59 reports in total, with urticaria (24) and vomiting and/or nausea (25) the most frequent ADRs. Varenicline, which was granted marketing authorisation for smoking cessation in September 2006, generated reports of nausea and other gastrointestinal symptoms (10), dermatological symptoms (8), muscle cramps or myalgia (5) and oedema or tiredness (4 each).