# 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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## News & Issues

This is the last issue for the year. We include regulatory and safety information on medicines, information on some new publications as well as the working group recommendations from the Twenty-ninth Annual Meeting of Representatives of the National Centres participating in the WHO Programme for International Drug Monitoring.

In 2006, the Quality Assurance and Safety of Medicines team was kept busy with its prequalification project, standards and normative work for quality pharmaceuticals and pharmacovigilance issues: 44 medicines were 'prequalified'; the fourth edition of the WHO International Pharmacopoeia was published; the INN advisory group for the nomenclature of biologicals was established; the total number of member countries in the WHO Programme for International Drug Monitoring increased to 98; the Expert Committee on Drug Dependence had its thirty-fourth meeting; the International Working Group for Drug Statistics Methodology met twice; numerous training courses were carried out and the International Medical Products Anti-Counterfeiting Taskforce (IMPACT) was established. These were some of the highlights, all of which are important in our progress towards achieving the millennium development goals (http://www.un.org/millenniumgoals/).

In the year 2007 the Safety team will continue to focus on public health programmes, with renewed emphasis on capacity building in pharmacovigilance.

We wish all our readers a very happy and fulfilling year in 2007.

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## Regulatory Matters



## Safety of Medicines



## Feature

# Adalimumab, etanercept, infliximab

## Previous HBV infection to be evaluated

**New Zealand.** Medsafe, the New Zealand Medicines and Medical Devices Safety Authority is notifying health-care professionals that hepatitis B virus (HBV) reactivation has been reported internationally in patients receiving tumour necrosis factor antagonists (anti-TNF) etanercept (Enbrel), adalimumab (Humira) and infliximab (Remicade). In the majority of these reports patients were also receiving concomitant treatment with other immunosuppressants, confounding a clear causal relationship between HBV reactivation and TNF antagonists. However, Medsafe is advising that patients who are at risk for HBV infection should be evaluated for prior HBV infection before TNF antagonist therapy is initiated; those who are carriers of HBV infection should be closely monitored for HBV reactivation during TNF antagonist therapy and for several months after therapy termination. TNF antagonists should be stopped, and effective antivirals and appropriate supportive treatment should be initiated in patients who develop HBV reactivation. According to Medsafe, the New Zealand data sheets for the relevant anti-TNF products (Remicade, Humira and Enbrel) have been updated to include this safety information.

***Reference:***
*'Dear Health-care Professional' letter from New Zealand Medicines and Medical Devices Safety Authority (Medsafe), 8 November 2006 (www.medsafe.govt.nz).*

# Dextro-propoxyphene-paracetamol combination products

## Risk of overdose; updated prescribing information

**New Zealand.** The prescribing information for dextropropoxyphene/ paracetamol (acetaminophen)-containing products (Capadex and Paradex) has been updated in New Zealand to manage the risks associated with these products. In 2005, the Medicines Adverse Reactions Committee (MARC) and Medsafe reviewed the risk of overdose associated with dextropropoxyphene/ paracetamol-containing products (like Capadex and Paradex) after deaths were reported following intentional and accidental overdose. Several changes have been made to the prescribing information for these products (Capadex and Paradex), which include:

- narrowing of the indication to the relief of chronic pain of moderate severity;
- restriction to second-line therapy for patients who have not tolerated, or have inadequately responded to therapeutic doses of alternative analgesics;
- restriction of the recommended dose to two tablets up to every four hours, with a maximum daily dose of eight tablets (equivalent to paracetamol 2.6g);
- reducing dose in the elderly and in patients with renal or hepatic impairment.

Medsafe has urged prescribers to avoid the concurrent use of these products with alcohol or with other paracetamol-containing products, and to warrant caution while prescribing them in patients receiving anxiolytics or antidepressants.
(Reports in WHO database: Death -10).

***Reference:***
*Prescriber Update, Vol 27(2): 21, 2006 (www.medsafe.gov.nz).*

# Dopamine agonists

## Increased libido, gambling: class effects

**Europe.** A European Review has concluded that pathological gambling and increased libido including hypersexuality may be class effects of all dopamine receptor agonists. New wording has now been recommended for all products containing dopamine receptor agonists. According to the Public Assessment Report for dopamine agonists (available on the UK Medicines and Healthcare products Regulatory Agency (MHRA) website):

- cases of pathological gambling have been reported for bromocriptine, cabergoline, pergolide, piribedil, pramipexole, quinagolide and ropinirole; this is also a recognized adverse reaction with the new dopaminergic drug rotigotine;
- although there were no reports of pathological gambling in patients taking levodopa monotherapy, levodopa may have attributed to the development of pathological gambling in patients receiving combination therapy;
- cases of increased libido have also been received for levodopa, apomorphine, bromocriptine, cabergoline, pergolide, piribedil, pramipexole, quinagolide and ropinirole;
- both spontaneous observations and literature cases support a temporal relationship with reports of pathological gambling after starting dopaminergic drug therapy and with recovery after drug withdrawal;

- spontaneous reports and literature cases also support a temporal association between dopamine agonists and increased libido, with evidence of increased libido after starting therapy or following an increase in the dose of the dopamine agonist; positive dechallenge and rechallenge data also exist for these effects;
- no reports have been identified of pathological gambling, increased libido, or hypersexuality in association with α-dihydroergocryptine and lisuride.

The European Pharmacovigilance Working Party has concluded that both pathological gambling and increased libido, including hypersexuality, may be class effects of dopamine agonists and should be included in the Summary of Product Characteristics (SPC) for all dopamine agonists.

***Reference:***

*Public Assessment Report - dopamine agonists, 7 November 2006 (www.mhra.gov.uk).*

# Imatinib

## Prescribing information revised for cardiac effects

**USA.** Novartis US has issued a `Dear Health-care Professional' letter (1) regarding the severe congestive heart failure and left ventricular dysfunction in patients treated with imatinib (Gleevec) used in the treatment of chronic myeloid leukaemia. The letter provides information about imatinib (Gleevec) and refers to an article published in Nature Medicine (2) that reported severe congestive heart failure and ventricular dysfunction in 10 patients receiving imatinib (Gleevec). Novartis points out that most of these 10 patients had pre-existing conditions such as hypertension, coronary artery disease and diabetes. Since publication of this article, Novartis has further evaluated all available data from spontaneous reporting and clinical trials. The company concludes that "while cardiac events remain uncommon, severe congestive heart failure and left ventricular dysfunction have occasionally been reported". The company advises that patients with known cardiac disease or risk factors for heart failure should be carefully monitored while on imatinib, and those with symptoms of heart failure should be evaluated and treated. Novartis advises that the Precautions Section of the imatinib (Gleevec) prescribing information has been revised accordingly.

(Reports in WHO database: Cardiac failure - 20).

***References:***

*1. 'Dear Health-care Professional' letter from Novartis Pharmaceuticals Corporation, 19 October 2006 (www.fda.gov).*
*2. Kerkela R, Grazette L, Yacobi R et al. Cardiotoxicity of the cancer therapeutic agent imatinib mesylate. Nature Medicine, 2006, 12(8): 881-882.*

# Oseltamivir

## Prescribing information updated with neuropsychiatric events

**USA, Canada.** The prescribing information for oseltamivir (Tamiflu) has been updated in the US (1) for neuropsychiatric adverse events reported during the post-marketing clinical use of the drug. Roche Laboratories Inc., the Marketing Authorization Holder for oseltamivir (Tamiflu) in the USA has revised the product information with the following: 'Precautions/Neuropsychiatric Events: There have been post-marketing reports (mostly from Japan) of self-injury and delirium with the use of oseltamivir (Tamiflu) in patients with influenza. The reports were primarily among paediatric patients. The relative contribution of the drug to these events is not known.' The revised information also states that people with flu, particularly children, may be at an increased risk of self-injury and confusion shortly after taking oseltamivir (Tamiflu) and should be closely monitored for signs of unusual behaviour.

Health Canada has issued a Public Information Update (2) for the above post-marketing events and has requested the manufacturer, Hoffman-La Roche to update the Canadian prescribing information for oseltamivir (Tamiflu).

(Reports in WHO database: Delirium - 5).

***References:***

*1. 'Dear Health-care Professional' letter from Roche Laboratories Inc., 13 November 2006 (www.fda.gov).*
*2. Information Update. Health Canada, 29 November 2006 (www.hc-sc.gc.ca).*

# Rituximab

## Bowel obstruction and gastrointestinal perforation

**Canada.** Hoffman-La Roche Limited, in consultation with Health Canada, has issued a `Dear Health-care Professional' letter (1) and a Public Communication (2) with new safety information on rituximab (Rituxan). Post-marketing reports of abdominal pain, intestinal obstruction, gastro intestinal (GI) perforations and death have been observed in patients receiving rituximab (Rituxan), a recombinant monoclonal antibody indicated for the treatment of B-cell Non-Hodgkin's Lymphoma (NHL) and Rheumatoid Arthritis (RA). According to Roche,

- the pharmacovigilance database for rituximab (Rituxan) contains 47 cases of bowel obstruction (nine deaths) and 37 cases of GI perforations

(four deaths), based on about 730 000 patient exposures; these cases include reports from spontaneous sources as well as clinical studies;

- the majority of these events have occurred in patients receiving rituximab (Rituxan) in combination with chemotherapy for NHL;
- interpretation of data for most of the cases of bowel obstruction was confounded by the presence of multiple risk factors, including GI lymphoma, various other GI disorders and concomitant treatments, such as chemotherapy, steroids, and radiation therapy; despite these, a contributory role of rituximab (Rituxan) in causing GI perforations has not been excluded;
- the mean time to onset of symptoms was six days from rituximab (Rituxan) initiation in patients with NHL who developed GI perforations.

The Canadian Product Monograph for rituximab (Rituxan) has been updated to include the above information. In its Public Advisory, Roche says that intestinal obstruction and GI perforations "are serious conditions that require immediate medical attention". The company has advised patients to immediately contact their physicians if they experience abdominal pain, nausea, vomiting, constipation or diarrhoea, abdominal swelling, abdominal tenderness, high fever, chills or any other unusual symptoms during rituximab (Rituxan) treatment.

(Reports in WHO database: Intestinal obstruction - 8; Abdominal pain - 84; Death - 100).

***References:***

*1. 'Dear Health-care Professional' letter from Hoffman-La Roche Limited, 10 November 2006 (www.hc-sc.gc.ca).*
*2. Public Communication. Health Canada, 10 November 2006 (www.hc-sc.gc.ca).*

# Rotavirus vaccine

## For oral administration only

**Europe.** GlaxoSmithKline (GSK) has written to health professionals that the rotavirus vaccine (Rotarix) should be administered orally. The company points out that unlike most other vaccines, rotavirus vaccine (Rotarix) is given orally, with an applicator that resembles a syringe. GSK has received 20 reports worldwide describing the wrong route of administration of this vaccine when it was injected intramuscularly or subcutaneously. The company says there have been six non-serious adverse events reported from outside the European Union in association with the improper route of administration of the rotavirus vaccine (Rotarix). These reports described reactions that were mild, such as local erythema. All reactions were reported on the day of vaccination and did not persist beyond 24 hours. GSK is reinforcing the product information and labelling accordingly.

***Reference:***

*'Dear Doctor' letter from GlaxoSmithKline (Vaccines), October 2006 (www.mhra.gov.uk).*

## Benzocaine (local anaesthetic)

### Risk of methaemoglobinaemia

**Canada.** A Health Canada Advisory is warning Canadians about a link between the local anaesthetic benzocaine and a potentially serious blood condition known as methaemoglobinaemia (MHb). Benzocaine is a topical anaesthetic used to numb the skin or mucous membranes in surgical, dental and other medical procedures. MHb, an adverse reaction known to be associated with benzocaine, reduces the ability of red blood cells to deliver oxygen throughout the body. MHb can lead to stupor, coma and death. To date, Health Canada has received reports of nine cases of suspected MHb associated with the use of benzocaine. None of the cases were fatal. All cases of benzocaine-induced MHb have been associated with high-concentration (14 - 20 per cent) spray forms of the product used on mucous membranes during various medical procedures. Health Canada warns that infants as well as individuals with pre-existing mucous membrane inflammation or damage, with heart disease, suffering from malnutrition or with specific conditions (e.g. G6PD

## Cholesterol lowering drugs

### Linked with psychiatric reactions

**New Zealand.** The Centre for Adverse Reactions Monitoring (CARM) in New Zealand has been receiving an increasing number of reports of psychiatric reactions occurring with fibrates, statins and ezetimibe. These reports account for up to one-fifth of the total adverse reaction reports for some of these agents. Of particular concern are reactions of aggressive behaviour. Other notable reactions include memory impairment, mood, cognitive and sleep and perception disorders. Medsafe advises prescribers to consider cholesterol-lowering drugs as a potential causal explanation in patients who present with psychiatric symptoms.

***Reference:***
*Prescriber Update, Vol 27(2):18, 2006 (www.medsafe.gov.nz).*

## Ezetimebe

### Reports of depression

**Australia.** There are 265 reports of suspected adverse reactions associated with the use of ezetimebe in Australia. The Australian Adverse Drug Reactions Advisory Committee (ADRAC) notes that twelve of these reports describe

ADRAC advises that reports of depression/depressed mood, as a proportion of total reports received, are higher for ezetimebe. At present there is no mention of depression in the product information for ezetimebe (Ezetrol). ADRAC will continue to monitor reports of depression associated with ezetimebe treatment.

***Reference:***
*Australian Adverse Drug Reactions Bulletin, 25 (5):19, 2006 (www.tga.gov.au).*

## Ezetimebe

### Reports of muscular disorders

**New Zealand.** Medsafe warns that ezetimebe (Ezetrol, also Vytorin, which contains ezetimebe with simvastatin) has the potential to cause myopathy or rhabdomyolysis. Ezetimebe, used in the management of hypercholesterolemia, can be given alone or with a statin. Among the 44 reports of suspected adverse reactions to ezetimebe received up to 30 June 2006 at CARM, there were nine reports of myalgia, one report of suspected myopathy, and one report of myalgia and muscle weakness. Six patients were not taking a fibrate or a statin, both of which are known to cause muscle disorders. Four of these patients recovered when