# WHO PHARMACEUTICALS NEWSLETTER

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 information 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. 1, 2005

## News & Issues

This is the first issue for the year 2005. The cover page is green, representing, we like to think, the need for fresh ideas and out-of-the-box thinking in pharmacovigilance. Inside you will find the usual format, with items on safety of medicines and their regulation. We welcome additional comments on how we could make this publication more valuable.

Two training programmes/workshops in pharmacovigilance have already been held this year, one in India, as part of the launch of the new system for promoting Indian Pharmacovigilance (details on page 8) and one in Spain, the workshop on 'New Challenges in Clinical Safety, Pharmacovigilance and Vaccine Vigilance' by the International Society of Pharmacovigilance, ISOP. The WHO Collaborating Centre, in Uppsala, will conduct its training course on Pharmacovigilance in May.

Selective Serotonin Reuptake Inhibitors (SSRIs) are again in the news, this time for potential neonatal withdrawal effects in children following SSRI exposure, *in utero*. Using this as a case-in-evidence (see section on Drugs of Current Interest) we appeal, yet again, to all Member States to step-up reporting to the WHO global database for adverse drug reactions.

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## DRUGS OF CURRENT INTEREST


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# AMIODARONE

## Medication Guide to be dispensed along with medicine

**USA.** Wyeth Pharmaceuticals Inc., under advice from the United States Food and Drug Administration (US FDA), is directing health professionals to distribute a medication guide to all patients while dispensing amiodarone (Cordarone) tablets to those patients. Amiodarone, an antiarrhythmic drug, is associated with substantial toxicity and is, therefore, indicated only in patients with life-threatening arrhythmias. The medication guide highlights some of the serious and potentially fatal side-effects that may result from the use of amiodarone and provides general information to the patient about amiodarone, conditions when amiodarone may not be taken, relevant medical history that a patient needs to share with the physician before starting the medication, etc. However, this guide is not to be used as a substitute for talking to patients about the risks relative to benefits associated with taking amiodarone tablets.

***Reference:***
*'Dear Health-care Professional' letter from Wyeth Pharmaceuticals Inc., 30 December 2004. Available on the Internet at www.fda.gov*

# ATOMOXETINE

## Labelling to include liver injury warning

**USA.** The US FDA has issued a Talk Paper advising of changes to the US atomoxetine (Strattera) labelling, following two reports of severe liver injury in patients who had received the agent for several months. Atomoxetine is a selective norepinephrine reuptake inhibitor indicated in the treatment of attention deficit hyperactive disorder (ADHD) in children, adolescents and adults. The atomoxetine labelling is to be updated to include a bolded warning regarding the risk of severe liver injury that could progress to liver failure, requiring liver transplantation or resulting in death, although it is noted that the actual number of cases is unknown. The new warning advises discontinuation of atomoxetine if patients develop jaundice or laboratory evidence of liver injury. Eli Lilly has agreed to issue a 'Dear Health-care Professional' letter regarding these changes, and will update the atomoxetine patient package insert to include information about the signs and symptoms of liver disorders.

***Reference:***
*FDA Talk Paper, 17 December 2004. Available on the Internet at www.fda.gov*

# BENZATHINE BENZYL-PENICILLIN/ PROCAINE BENZYL-PENICILLIN

## Label changes highlight appropriate use

**USA.** King Pharmaceuticals Inc., has issued a 'Dear Health-care Professional' letter advising of changes to the US labelling of benzathine benzylpenicillin/procaine benzylpenicillin (Bicillin C-R) and benzathine benzylpenicillin (Bicillin L-A) that highlight appropriate use and administration of these products. The letter advises that benzathine benzylpenicillin (Bicillin L-A) is the only approved benzylpenicillin indicated for the treatment of venereal disorders, including syphilis, in the USA. However, King Pharmaceuticals has been made aware of post-marketing reports of benzathine benzylpenicillin/procaine benzylpenicillin (Bicillin C-R) being used to treat patients with syphilis; they warn that use of Bicillin C-R instead of Bicillin L-A may result in inadequate treatment. To reflect this important difference, the cartons and syringe labels of the two agents have been modified. In addition, a boxed warning has been added to the labelling of both Bicillin C-R and Bicillin L-A to emphasize that these products are not intended for IV use, which has been associated with heart arrest and death.

***Reference:***
*'Dear Health-care Professional' letter from King Pharmaceuticals Inc., November 2004. Available on the Internet at www.fda.gov*

# MEFLOQUINE

## Patient Information Leaflet to help recognize adverse symptoms

**Canada.** Hoffman-La Roche is introducing an updated Patient Information Leaflet in every box of mefloquine (Lariam), used in the prophylactic treatment of malaria. The updated leaflet

- is intended to help patients recognize symptoms, including the sudden onset of unexplained anxiety, depression, restlessness, irritability, confusion, a persistently abnormal heart-beat, or palpitations, that may precede rare but potentially serious psychiatric, neurologic, or cardiac adverse events;
- advises patients who develop these symptoms to contact a health-care professional to assess the need for discontinuation of Lariam® (mefloquine) treatment and,
- includes a wallet card containing a summary of the most essential information, that may be cut out and carried by the patient during travel to areas with malaria.

***Reference:***
*'Dear Health-care Professional' letter from Hoffman-La Roche, 24 January 2005. Available on the Internet at www.hc-sc.gc.ca*

# PARACETAMOL-DEXTROPROP-OXYPHENE

## To be withdrawn due to risk of toxicity in overdose

**UK.** The UK Medicines and Healthcare products Regulatory Agency (MHRA), under advice from its Committee on Safety of Medicines (CSM), has announced the withdrawal of the paracetamol-dextropropoxyphene combination product (co-proxamol) in the UK. The CSM undertook a recent review of the risks and benefits of co-proxamol and has concluded that the efficacy of co-proxamol is poorly established and that the risk of toxicity in overdose, both accidental and deliberate, is unacceptable.

Co-proxamol contains paracetamol (325 mg) and the weak opioid analgesic dextropropoxyphene (32.5 mg). Each year 300-400 fatalities involving co-proxamol are known to occur in England and Wales following deliberate or accidental overdose. Approximately one-fifth of these deaths are considered to be accidental.

The CSM has announced that, in order to minimize disruption of healthcare provision, co-proxamol will be phased out so that patients currently receiving co-proxamol may be switched to alternative pain management regimes at their next routine medication review. The CSM has issued the following interim prescribing advice, pending withdrawal of co-proxamol:

- Co-proxamol is only indicated in the treatment of mild to moderate pain in adults where first-line analgesics have proved ineffective or are inappropriate. It should not be used for any acute pain management.
- Co-proxamol therapy should not be initiated in new patients.
- Co-proxamol should not be used in patients aged <18 years.
- Co-proxamol is contraindicated in patients who are alcohol-dependent, who are likely to consume alcohol whilst taking co-proxamol, and in those patients who are suicidal or addiction prone.

***Reference:***
*Letter from the Chairman, UK Committee on Safety of Medicines, 31 January 2005. Available on the Internet at www.mhra.gov.uk*

# SMALLPOX VACCINE

## Label to highlight reports of myopericarditis

**USA.** A black box warning has been added to the labelling of Wyeth's smallpox vaccine, Dryvax, to highlight reports of acute myopericarditis in healthy adults. Although Wyeth no longer manufactures Dryvax, as the World Health Assembly certified the world free of naturally occurring smallpox in the 1980s, the US Government asked Wyeth to test stored batches of the vaccine, and the black box warning applies to those vaccines which have been repackaged for immediate use by firefighters, medical personnel and other first responders. The black box warning states that "acute myopericarditis has been observed after administration of Dryvax to healthy adults", and also warns of encephalitis, progressive vaccinia and severe vaccinial skin infections following vaccination with the agent. The warning states that immunocompromised persons should not receive the vaccine in non-emergency situations.

***Reference:***
*Smallpox vaccine dried, calf lymph type. Prescribing Information, 15 November 2004. Available on the Internet at www.fda.gov*

# THIORIDAZINE

## Withdrawn due to poor benefit/risk profile

**Worldwide.** Novartis has announced that it will discontinue all forms of thioridazine (Melleril™) worldwide by 30 June 2005, because the benefit/risk profile of the drug no longer meets current clinical and regulatory expectations. Specifically:

- There is evidence of a connection between QTc prolongation, a known side-effect of thioridazine, and cardiac arrhythmias and sudden death in patients with schizophrenia.
- New, improved antipsychotic treatments are now available.

It is recommended that when discontinuing treatment with thioridazine, a gradual reduction in dosage over several weeks is recommended to prevent recurrence of symptoms. There are no evidence-based specific recommendations on initiating treatment with an alternative antipsychotic or other psychotropic medication, and formal practical guidelines for switching antipsychotic medication are also lacking. However, a substantial body of information has been published in peer-reviewed journals reviewing the techniques commonly employed in clinical practice and the important factors that should be considered. All generic versions of thioridazine are also to be discontinued.

***Reference:***
*News & Updates, 25 January 2005. Available on the Internet at www.druginfozone.nhs.uk*

# ATAZANAVIR-RITONAVIR

## Not to be co-administered with omeprazole

**Europe.** The European Medicines Agency (EMEA) has issued a public statement that warns physicians against the co-administration of atazanavir (Reyataz) combined with ritonavir (RTV) and 40 mg omeprazole, a proton pump inhibitor. This warning is based on the observations from a randomized, open-label, multiple-dose drug interaction study performed in healthy volunteers. The study demonstrated a 76% reduction in atazanavir area under the concentration curve (AUC) and a 78 % reduction in atazanavir trough plasma concentration (Cmin) when atazanavir / ritonavir (300/100 mg) was co-administered with omeprazole 40 mg. The exact mechanism for this interaction is yet to be determined. In the meantime, physicians are advised not to co-administer atazanavir / ritonavir (300/100 mg) with any dose of omeprazole or with any other proton pump inhibitor to avoid risk of reduction in the atazanavir exposure levels in these patients.

***Reference:***

*EMEA Public Statement, EMEA/CHMP/202649/2004, 21 December 2004. Available on the Internet at www.emea.eu.int*

# CELECOXIB

## Increased risk of cardiovascular events

**Europe, New Zealand, USA.** Pfizer has announced that the US National Cancer Institute Data Safety and Monitoring Board has stopped drug administration in the Adenoma Prevention with Celecoxib (Celebrex; APC) trial, as the risk of major cardiovascular events was significantly higher in patients receiving celecoxib than in patients receiving placebo. The US FDA and the EMEA have issued statements detailing the preliminary results, and have requested the full results for review[1-4].

In the APC study, 2400 patients received celecoxib 400 mg/day, celecoxib 800 mg/day or placebo, for a mean duration of 33 months. The relative risk (RR) of major fatal or nonfatal cardiovascular events (composite endpoint of cardiovascular death, acute myocardial infarction or stroke) was statistically significantly higher in the celecoxib 400 mg/day group (RR 2.5) and in the celecoxib 800 mg/day group (RR 3.4), compared with the placebo group.

Two other celecoxib trials, the Prevention of Spontaneous Adenoma Polyps (PreSAP) trial and the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT), have also been evaluated[4]. The PreSAP trial has been stopped, based on the results of the APC trial, although an increased risk of cardiovascular events with celecoxib 400 mg/day compared with placebo was not observed[3]. However, the ADAPT study is still ongoing[4].

The FDA has issued an Alert for Practitioners regarding the possible increased risk of cardiovascular events in patients receiving celecoxib[4]. Physicians are encouraged to inform patients of the evolving information about this risk, and are advised to consider alternatives to celecoxib; when this is not appropriate, the lowest effective celecoxib dose should be used. The New Zealand Medicines Adverse Reactions Committee has issued similar advice with regard to all COX-2 inhibitors, broadly supporting the UK National Institute of Clinical Excellence guidance that was distributed to all New Zealand general practitioners[5].

***References:***

1. *FDA Statement, 17 December 2004.Available on the Internet at www.fda.gov*
2. *EMEA Statement, EMEA/205831/2004, 17 December 2004. Available on the Internet at www.emea.eu.int*
3. *EMEA Statement, EMEA/212271/2004, 22 December 2004. Available on the Internet at www.emea.eu.int*
4. *FDA Alert for Practitioners (celecoxib), 17 December 2004. Available on the Internet at www.fda.gov*
5. *Medsafe Media Release, 21 December 2004. Available on the Internet at www.medsafe.govt.nz*

# DARBEPOETIN ALFA

## Adverse outcomes associated with off-label dosing strategies

**USA.** The US FDA and Amgen notified health-care professionals of revisions to the WARNINGS and PRECAUTIONS sections of the prescribing information for darbepoetin alfa (Aranesp), indicated for the treatment of chemotherapy-induced anaemia in patients with non-myeloid malignancies. This safety information alerts physicians to the adverse effects observed with other products in this class in association with off-label dosing strategies. Two recent investigational studies with other erythropoietic products permitted or required dosing to achieve haemoglobin levels of greater than 12 grams per decilitre. An increased frequency of adverse patient outcomes, including increased mortality and thrombotic vascular events were reported in these studies. As indicated in the darbepoetin alfa (Aranesp) prescribing information, the target haemoglobin level should not exceed 12 grams per decilitre in men or women.

***Reference:***

*'Dear Health-care Professional' letter, 11 January 2005. Available on the Internet at www.fda.gov*

## GALANTAMINE

### Ineffective and possibly unsafe in mild cognitive impairment

**Canada.** Janssen-Ortho Inc., under advice from Health Canada, is warning health professionals that according to preliminary data from two investigational studies, galantamine (Reminyl), a cholinesterase inhibitor, does not appear to be effective in treating patients with mild cognitive impairment (MCI). In addition, the initial analysis of both studies showed that 15 patients died in the galantamine (Reminyl) treatment group and five in the placebo treated group. The causes of death were mainly cardiovascular or cerebrovascular in nature. Janssen-Ortho is reminding that galantamine (Reminyl) is approved only for the symptomatic treatment of patients with mild to moderate dementia of the Alzheimer's type and that it is not to be used outside of its approved indication.

***Reference:***
*'Dear Health-care Professional' letter from Janssen-Ortho Inc., 21 January 2005. Available on the Internet at www.hc-sc.gc.ca*

## GLUCOSAMINE

### Concerns about hypercholesterolaemic effects

cholesterol levels in three patients, possibly as a result of glucosamine use. There are 67 side-effect reports associated with glucosamine use in the Danish Medicines Agency database, most of which are described in the product summary. However, there are also reports of suspected adverse effects that are not identified in the product summary, including increased INR (n = 3), vision disorders (3), peripheral oedemas (3), dyspnoea (2), pulmonary embolism (1), seizures (1), myocardial infarction (1), increased liver enzymes (1), an increased serum creatinine level (1), and an increased cholesterol level (1). The agency advises that the Swedish authorities have also received two reports of hypercholesterolaemia. The companies marketing glucosamine are invited to join the Danish Medicines Agency in addressing the problem, by submitting the statutory safety updates.

***References:***

1. *Scrip World Pharmaceutical News No 3000, 29 October 2004.*
2. *Stenver DI. Possible interaction between glucosamine and cholesterol. Reply. Ugeskrift for Laeger 25, No. 44, October 2004. (Danish; summarized from a translation.)*

## NAPROXEN

### Investigated

these studies to determine whether additional regulatory action is needed. In the meantime, prescribers are cautioned:

- to carefully weigh the benefits and risks in patients currently on naproxen therapy,
- to always prescribe within the recommended dose of 250-500 mg twice a day and,
- to advise patients to adhere to the recommended daily dose indicated in over-the-counter naproxen preparations.

Several of the cyclooxygenase-2 (enzyme) specific inhibitor drugs (rofecoxib, celecoxib etc.) are currently under investigation for a full understanding of their adverse cardiovascular effects (see WHO Pharmaceuticals Newsletter No. 5, 2004 and section under 'Celecoxib' in this issue). Naproxen, a non-selective over-the-counter NSAID, is also being investigated to determine appropriate regulatory action. The US FDA is planning an advisory committee meeting in February 2005 to discuss the issues surrounding these drugs.

***Reference:***
*FDA Alert for Health-care Providers (Naproxen), 23 December 2004. Available on the Internet at www.fda.gov*

## NEVIRAPINE