WHO PHARMACEUTICALS NEWSLETTER

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

The aim of the 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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As usual, the WHO Pharmaceuticals Newsletter provides you with the latest safety reports, advice, warnings and other updates from regulatory authorities across the world.

In this edition of the WHO Pharmaceuticals Newsletter readers will also find reports of two important meetings that have recently taken place.

The twenty-second meeting of the Global Advisory Committee on Vaccine Safety (GACVS) was held in Geneva in June 2010. Discussions of the main topics at the meeting are summarised in a feature article on page 18.

WHO Consultants Network for Pharmacovigilance in Africa held its 4th meeting in Lomé, Togo, from 6 to 10 September 2010. The report shows the great and important developments in pharmacovigilance taking place in the African region right now.

A short account of complaints reported to WHO prequalified medicines during 2007-2009 is also included.

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Bevacizumab

Association with hypersensitivity and infusion reactions

Canada. Health Canada and Hoffmann-La Roche Limited have warned that hypersensitivity reactions and infusion reactions have been identified as risks in patients treated with bevacizumab (Avastin®). Bevacizumab is a recombinant humanized monoclonal antibody against the vascular endothelial growth factor, and used to treat certain types of cancer. Health-care professionals are notified that a risk of developing serious hypersensitivity reactions, including anaphylactic and anaphylactoid reactions, has been reported in up to 5% of patients receiving bevacizumab in clinical trials. Post-marketing reports have also captured cases of serious hypersensitivity and infusion reactions. Health-care professionals are also advised that patients should be closely monitored for signs and symptoms of hypersensitivity or infusion reactions during and following the administration of bevacizumab infusion. If a reaction occurs, the infusion should be interrupted and appropriate medical therapies should be administered. The Canadian Product Monograph has been updated to include this information.

Reference:
Advisories, Warnings and Recalls, Health Canada, 19 August 2010, Prescriber Update Vol. 31 (www.hc-sc.gc.ca).

Calcium gluconate injection

New contraindications due to risk of aluminium exposure

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) notified health-care professionals that calcium gluconate injection packed in small-volume glass containers is now contraindicated for use as repeated or prolonged treatment, including an intravenous infusion, in children younger than 18 years and in patients with renal impairment. The Agency states that aluminium can be leached from glass after contact with calcium gluconate solution, leading to a risk of exposure to aluminium which might have adverse effects on bone mineralisation and neurological development in children and those with renal impairment. To limit aluminium exposure, calcium gluconate injection in small-volume glass containers is also contraindicated in the preparation of total parenteral nutrition solutions. Use of calcium gluconate injection packed in plastic containers is recommended to reduce aluminium burden in vulnerable patients. In the UK, parenteral administration of calcium gluconate is authorized where the pharmacological action of a high calcium ion concentration (e.g. in acute hypocalcaemia) is required.

Reference:
Drug Safety Update, MHRA, Volume 4, Issue 1, August 2010 (www.mhra.gov.uk).

Daptomycin

Risk of eosinophilic pneumonia

USA. The U.S. Food and Drug Administration (US FDA) notified health-care professionals and patients about the potential for developing eosinophilic pneumonia during treatment with daptomycin (Cubicin®). The medicine is an antibacterial indicated to treat serious skin infections and bloodstream infections. The Agency identified six cases of eosinophilic pneumonia reported to the Agency's Adverse Event Reporting System (AERS) between 2004 and 2010 that were most likely associated with daptomycin. One additional case of eosinophilic pneumonia most likely associated with daptomycin was identified in the medical literature. In addition, the Agency identified 36 possible cases of eosinophilic pneumonia associated with the use of daptomycin.

Based on the review, the US FDA states that there appears to be a temporal association between daptomycin administration and the development of eosinophilic pneumonia. Eosinophilic pneumonia may lead to progressive respiratory failure and is potentially fatal if not quickly recognized and appropriately managed. The Agency requested that the manufacturer of the product revise the drug label to include this association.

Health-care professionals are advised to closely monitor patients being treated with daptomycin for signs and symptoms of eosinophilic pneumonia, including new onset or worsening fever,

dyspnoea, difficulty with breathing, and new infiltrates on chest imaging studies. Health-care professionals are also advised to discontinue daptomycin in patients exhibiting signs and symptoms of eosinophilic pneumonia and to consider treating symptoms as clinically indicated.

Reference:
FDA Drug Safety Communication, US FDA, 29 July 2010 (www.fda.gov).

Droperidol Injection USP

Risk of severe arrhythmia

Canada. Health-care professionals have been notified of changes to the Canadian Product Monograph for Droperidol Injection USP, including the following.

- Droperidol Injection USP should only be used for the prevention and treatment of post-operative nausea and vomiting in patients for whom other treatments are ineffective or inappropriate.
- Droperidol Injection USP is no longer indicated for use in anaesthesia for sedation or tranquilization, neuroleptanalgesia, or in the management of acute stages of Meniere's disease.
- Droperidol Injection USP is contraindicated in patients with known or suspected QT prolongation
- A new Boxed Warning highlights the risk of QT prolongation and measures to minimize this risk, including a recommendation for screening ECG and cardiac monitoring.

According to the letter to health-care professionals, cases of QT prolongation and/or torsades de pointes have been reported in patients receiving intravenous droperidol. Some cases have occurred in patients with no known risk factors for QT prolongation even at low doses. Some cases have been fatal.

Reference:
Advisories, Warnings and Recalls, Health Canada, 25 August 2010 (www.hc-sc.gc.ca).

Inflenza virus vaccine

Label change due to risk of fever and febrile seizure

USA. The US FDA updated the prescribing information for the influenza virus vaccine Afluria®, which is one of the approved vaccines for the 2010-2011 influenza season in the United States, to inform health-care professionals that the Afluria vaccine has been associated with an increased incidence of fever and febrile seizure among young children reported in Australia, mainly among those less than five years of age. The Agency says that the available data suggest that the increased rates of fever and febrile seizure are only associated with the southern hemisphere formulation of the manufacturer (CSL Limited)'s vaccine. The investigations into the cause(s) of the febrile seizures seen with Afluria vaccine are ongoing.

(See WHO Pharmaceuticals Newsletters No.4, 2010 for Australia's report on febrile reactions in young children following 2010 seasonal trivalent influenza vaccination.)

Reference:
Safety Information, US FDA, 30 July 2010 (www.fda.gov).

Lamotrigine

Label change due to risk of aseptic meningitis

USA. The US FDA notified the public that lamotrigine (Lamictal®) can cause aseptic meningitis. The medicine is used for seizures in children two years and older, and for bipolar disorder in adults. The *Warnings and Precautions* section of the prescribing information and the Medication Guide will be revised to include information about this risk. The decision is based on the US FDA's review of adverse event reports submitted between December 1994 (when the medicine was approved) and November 2009. A total of 40 cases of aseptic meningitis occurring in paediatric and adult patients taking lamotrigine were identified. In most cases, the patients' symptoms were reported to have resolved after lamotrigine was discontinued. In 15 cases, symptoms returned when patients restarted lamotrigine.

The US FDA advises that symptoms of meningitis may include headache, fever, stiff neck, nausea, vomiting, rash, and sensitivity to light.

Health-care professionals are advised that if meningitis is suspected, patients should also be evaluated for other causes of meningitis and treated as indicated, and that discontinuation of lamotrigine should be considered if no other clear cause of meningitis is identified.

***Reference**:*
FDA Drug Safety Communication, US FDA, 12 August 2010 (www.fda.gov).

Methylnaltrexone bromide

Association with gastrointestinal perforation

Canada. Health-care professionals have been notified that the Canadian Product Monograph for methylnaltrexone bromide (Relistor®) has been revised to include the following information:

Based on post-marketing experience, patients with advanced illness and being treated with methylnaltrexone bromide may be at an increased risk of gastrointestinal (GI) perforation if they have such conditions that may be associated with localized or diffused reduction of structural integrity in the GI wall. These include conditions such as cancer, GI malignancy, GI ulcer, Ogilvie's syndrome, and concomitant medications [e.g. bevacizumab, nonsteroidal anti-inflammatory drugs and steroids]. Perforations have involved varying regions of the GI tract (e.g. stomach, duodenum and colon).

Methylnaltrexone bromide is indicated for the treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care. Health Canada and the company advise that methylnaltrexone bromide should be discontinued if patients develop severe, persistent, and/or worsening abdominal symptoms, as these could be symptoms of GI perforation.

Reference:
Advisories, Warnings and Recalls, Health Canada, 28 July 2010 (www.hc-sc.gc.ca).

Midodrine hydrochloride

US FDA proposes withdrawal

USA. The US FDA proposed to withdraw approval of midodrine hydrochloride, which is used to treat the low blood pressure condition orthostatic hypotension, because companies failed to provide evidence of clinical benefit of midodrine hydrochloride. The medicine was approved in 1996 under the US FDA's accelerated approval regulations for drugs that treat serious or life-threatening diseases. This approval required that the manufacturer verify clinical benefit to patients through post-approval studies. The US FDA advises that patients who currently take this medicine should not stop taking it and should consult their health care professional about other treatment options.

Reference:
FDA News Release, US FDA, 16 August 2010 (www.fda.gov).

Modafinil

Indications restricted

Europe. The European Medicines Agency (EMA) has recommended that modafinil-containing medicines should only be used to treat narcolepsy, and that doctors and patients should no longer use the medicine for the treatment of idiopathic hypersomnia, obstructive sleep apnoea and chronic shift work sleep disorder. Modafinil is used to promote wakefulness. A review by the Agency's Committee for Medicinal Products for Human Use (CHMP) was initiated because of a number of safety concerns, relating to psychiatric disorders, skin and subcutaneous tissue reactions as well as significant off-label use and potential for abuse.

The EMA states that based on the available data, the CHMP concluded that the benefits of modafinil-containing medicines continue to outweigh their risks only in the treatment of narcolepsy. For obstructive sleep apnoea, shift-work sleep disorder and idiopathic hypersomnia, the CHMP found that the risk for development of skin or hypersensitivity reactions and neuropsychiatric disorders outweighed the evidence for clinically important efficacy. Therefore, the Committee recommended that these indications should be withdrawn from the marketing authorizations of these medicines.

In addition, the CHMP noted that the risk of development of serious skin and hypersensitivity adverse reactions appears to be higher in children than in adults, and advised that the product information should carry a recommendation saying that modafinil should not be prescribed to children. The CHMP also identified particular cardiovascular risks with modafinil and recommended that the use of the medicine be contraindicated in patients with uncontrolled moderate to severe hypertension and in patients with cardiac arrhythmias.

(See WHO Pharmaceuticals Newsletters No.1, 2009 and No.2, 2008 for reports on adverse skin and psychiatric reactions in Australia and the UK.)

Reference:
Press release, Questions and answers, EMA, 22 July 2010 (www.ema.europa.eu).

Modified-release oral opioids

Suspension of marketing authorizations recommended for opioids using polymethacrylate-triethylcitrate controlled-release systems

Europe. The EMA announced the results of a review of modified-release oral opioids of the WHO level III scale for the management of pain. These medicines, such as morphine and related medicines oxycodone and hydromorphone, are used to treat intense pain that has not been controlled sufficiently with other medicines. The review was conducted following concerns that their controlled-release systems may be unstable in alcohol and that the active substance may be released too quickly when patients take them together with alcohol. This effect called and would only have a minor effect on the release of the active substance. However, for once-daily capsules using a polymethacrylate-triethylcitrate coating to control the release of morphine, there was a significant interaction with alcohol. When these capsules were put into a 20% alcohol solution, 80% of the active substance was released within 15 minutes. The EMA states that almost a full day's dose of morphine would be released all at once if a patient were to take the capsule with large drink of neat strong liquor, such as whisky or vodka. In addition, while the CHMP noted that the current product information already contra-indicates drinking alcohol when using strong opioids, it also noted some studies which show that many patients with severe pain drink alcohol while they are being treated with opioids.

Based on the above, the CHMP concluded that modified-release oral opioids using a polymethacrylate-triethylcitrate controlled-release system are highly sensitive to alcohol and that there is a risk of dose dumping if patients drink alcohol while taking them. Therefore, the Committee recommended that the marketing authorizations for these medicines should be suspended until the manufacturers have

Reference:
Press release, Questions and answers, EMA, 23 July 2010 (www.ema.europa.eu).

Octagam (intravenous immunoglobulin)

Suspension of marketing authorizations and market withdrawal due to risk of thromboembolic reaction

Europe (1). The EMA has recommended the suspension of the marketing authorizations for Octagam (human normal immunoglobulin 5% and 10%) and a recall of Octagam currently on the market in Europe. Octagam is an intravenous solution that contains human normal immunoglobulin and is used in patients who are at risk of infection, including people with primary immunodeficiency syndrome, or children born with acquired immune deficiency syndrome (AIDS). It is also used in people with certain immune disorders such as idiopathic thrombocytopenic purpura and in patients who have had a bone marrow transplant.

The Agency's Committee for