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.

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No 1, 2009

This, the first issue for the year, brings you information on safety updates and regulatory decisions announced between late 2008 and mid-January 2009. We have also included the results of a survey conducted in 2006 by the WHO Collaborating Centre for Drug Statistics Methodology, Oslo, on the user community and applications of the ATC/DDD methodology.

We wish you all a very productive year in 2009 and thank you for your interest in the newsletter.

Printed by the WHO Document Production Services, Geneva, Switzerland

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Regulatory Matters

Safety of Medicines

Feature

Botulinum toxin type A

Possible risk of toxin spreading to distant parts of the body

Canada. Health Canada has issued safety update related to botulinum toxin type A products (BOTOX ®, BOTOX Cosmetic ®), about the risk of the toxin spreading to other distant parts of the body. Possible symptoms include muscle weakness, swallowing difficulties, pneumonia, speech disorders and breathing problems, and can be fatal. Health Canada says that it has worked with the manufacturer to revise the labelling of these products, noting that there are no medically confirmed cases of distant toxin spread in Canada. It also advises the public using the products to seek immediate medical care if swallowing, speech or breathing disorders arise.

Reference:
Advisories, Warnings and Recalls, Health Canada, 13 January 2009 (www.hc-sc.gc.ca).

Fentanyl transdermal patches

Changes to dosage conversion guideline

Canada. Manufacturers of all fentanyl transdermal patches have made changes to the dosage conversion guidelines and analgesic equivalency table of opioids in the Canadian Product Monographs for Fentanyl Transdermal Systems, according to Health Canada. With regard to the dosage conversion guidelines, the conversions from IM/IV morphine and IV hydromorphone to the fentanyl transdermal patch have been revised. In addition, the analgesic equivalency table has been revised to remove some data including those referring to IM meperidine, which is because the drug causes central nervous system toxicity if used by the parenteral route chronically. They also warned that serious or life-threatening hypoventilation can result if appropriate dose conversions are not used.

(See WHO Pharmaceuticals Newsletter No. 5 & 6, 2008 for adverse event reports following overdose with use of fentanyl patches in UK.)

Reference:
Advisories, Warnings and Recalls, Health Canada, 2 January 2009 (www.hc-sc.gc.ca).

Magnesium oxide

New warning about hypermagnesaemia

Japan. In September 2008, the Ministry of Health, Labour and Welfare (MHLW), Japan requested relevant pharmaceutical companies to amend the package inserts of magnesium oxide, to describe hypermagnesaemia and its initial symptoms in the "Clinically Significant Adverse Reactions" section, as well as to explain that serum magnesium levels should be periodically measured, especially when the drug is administered over long term. This action followed the review of 15 cases of hypermagnesaemia associated with magnesium oxide, including two fatal cases, reported to MHLW from April 2005 to August 2008. (Magnesium oxide is used as a laxative and as an antacid.)

Reference:
Pharmaceuticals and Medical Devices Safety Information No.252, November 2008, MHLW, Japan (www.pmda.go.jp/english/).

Nitrous oxide

Risk of neurological and haematological toxic effects

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) has alerted that prolonged use of nitrous oxide, a medical gas used widely in surgical anaesthesia, may lead in rare cases to megaloblastic anaemia and myelopathy due to inactivation of vitamin B12.

According to the Agency, neurological toxic effects occurred after a single exposure to nitrous oxide during general anaesthesia, in patients with vitamin B12 deficiency. Health-care professionals have been advised to consider assessment of vitamin B12 levels before nitrous oxide anaesthesia in people with risk factors for deficiency.

Reference:
Drug Safety Update, MHRA, Volume 2, Issue 5, December 2008 (www.mhra.gov.uk).

Oral sodium phosphate products

New alert on acute phosphate nephropathy

USA. The United States Food and Drug Administration (US FDA) issued an alert notifying health-care professionals and consumers of the risk of acute phosphate nephropathy associated with the use of oral sodium phosphate products (OSP) for bowel cleansing prior to colonoscopy or other procedures.

The US FDA is requiring the manufacturer of the two OSPs (Visicol and OsmoPrep), that are available by prescription only, to add a Boxed Warning to the labelling for these products, as well as to develop and implement

a risk evaluation and mitigation strategy (REMS), which will include a Medication Guide. The Agency recommends that in light of that risk, over-the-counter laxative OSP products should not be used for bowel cleansing.

Reference:
FDA Alert, US FDA, 11 December 2008 (*www.fda.gov*).

Rituximab and efalizumab

Risk of progressive multifocal leukoencephalopathy

UK (1). MHRA has issued safety advice about progressive multifocal leukoencephalopathy (PML) associated with the monoclonal antibodies rituximab and efalizumab. The Agency says that there have been reports of 76 cases of confirmed or suspected PML in patients treated with rituximab and two cases of PML in patients treated with efalizumab. Rituximab is indicated in combination with methotrexate for adults with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other antirheumatic drugs. Efalizumab is indicated for the treatment of adults with moderate to severe chronic plaque psoriasis who have failed to respond to, or are intolerant of, other systemic therapies.

The MHRA has advised that patients should be monitored regularly for neurological symptoms or signs that might suggest PML and that if PML is suspected, treatment must be suspended until PML has been excluded.

The Summaries of Product Characteristics are being updated.

Canada (2). Health-care professionals have been warned about the risk of serious infections, including PML, in patients receiving efalizumab (Raptiva). There have been reports of serious bacterial, viral, fungal and opportunistic infections, including two fatal cases in the United States of John Cunningham virus infection with PML in patients treated with efalizumab for plaque psoriasis, according to Health Canada. According to the Agency, if a patient develops a serious infection, efalizumab should be discontinued and appropriate treatment should be instituted.

The Canadian Product Monograph will be updated to include a boxed warning on the risk of serious infections, including PML.

(See WHO Pharmaceuticals Newsletter No. 5 & 6, 2008 for warnings of PML in the USA as well as reports on rituximab and efalizumab in VigiBase)

References:
(1). Drug Safety Update, MHRA, Volume 2, Issue 5, December 2008 (www.mhra.gov.uk).
(2). Advisories, Warnings and Recalls, Health Canada, 22 January 2009 (www.hc-sc.gc.ca).

Tacrolimus

Risk of serious medication errors

Netherlands (1). The Dutch Medicines Evaluation Board (MEB) has announced the receipt of reports of medication errors that could result in severe adverse events with the use of two products (Prograf and Advagraf) containing the immunosuppressant tacrolimus.

The marketing authorization holder has sent a letter to health-care professionals to draw their attention to the products' different dosing schedules: twice daily for immediate-release (Prograf) and once daily for prolonged-release (Advagraf).

UK (2). The MHRA has emphasized that the two products containing the immunosuppressant tacrolimus (Prograf and Advagraf) are not interchangeable and should not be substituted without careful therapeutic monitoring.

According the Agency, as of 10 December 2008, medication errors in prescribing, dispensing and administration with the two products (Advagraf and Prograf) have been reported in seven European (EU) countries and most reports were from the UK. Some of these errors have led to serious adverse reactions, including acute rejection of transplanted organs.

The Agency reminded health-care professionals of the correct dosing schedules for these products. Changes to the product information and labelling are planned to come into effect by April 2009.

References:
(1). News, Human Medicines, MEB, 10 December 2008 (www.cbg-meb.nl).
(2). Drug Safety Update, MHRA, Volume 2, Issue 6, January 2009 (www.mhra.gov.uk).

Toremifene

New contraindication in patients at risk of prolonged QT intervals

Europe. The European Medicines Agency (EMEA) has advised against the use of toremifene in patients at risk of prolonged QT intervals and other heart problems including electrolyte disturbances

(particularly hypokalaemia), clinically relevant bradycardia, clinically relevant heart failure with reduced left-ventricular ejection fraction, and a history of symptomatic arrhythmia. Toremifene is used to treat hormone-dependent metastatic breast cancer in postmenopausal women.

This recommendation is based on a review of toremifene by EMEA's Committee for Medicinal Products for Human Use (CHMP), which was conducted because of concerns that the medicine could cause QT prolongation. The CHMP has concluded that although the overall benefits of toremifene are greater than its risks, the use should not be allowed in patients with QT-prolongation or other heart problems. Additionally, it was recommended that toremifene should not be used together with other medicines known to prolong the QT-interval.

The EMEA is advising physicians to prescribe toremifene according to this updated product information.

References:

1. Press Release, EMEA, 22 January 2009 (www.emea.europa.eu).
2. Alert No. 120, Information Exchange System, WHO, 23 January 2009 (www.who.int/medicines).

Bevacizumab

Eye inflammation reported with unauthorized use

Canada. Health-care professionals have been informed of new safety information concerning off-label use of bevacizumab (Avastin) in the ophthalmology setting. Bevacizumab is authorized for intravenous administration in the treatment of patients with metastatic carcinoma of the colon or rectum in combination with fluoropyrimidine based chemotherapy.

The company says that it has been made aware of a number of cases of eye inflammation, endophthalmitis, blurred vision, and floaters, some of which are Toxic Anterior Segment Syndrome, in patients who were administered bevacizumab (Avastin) intravitreally.

It also says that in 2008, there was no unusual reporting pattern associated with bevacizumab (Avastin) distributed in Canada when used for the authorized indication.

***Reference**:*
Advisories, Warnings and Recalls, Health Canada, 16 December 2008 (www.hc-sc.gc.ca).

& Flu Fighter tablets and Nyal Cold & Flu Fighter tablets) contain the herbs *Andrographis paniculata* (Andrographis), *Sambucus nigra* (Elderberry), *Salix alba* (White willow) and *Valeriana officinalis* (Valerian).

TGA has advised consumers using these products to stop their use immediately and to consult their doctor if they have concerns.

Reference:
Health alert, TGA, 19 December 2008 (www.tga.gov.au).

Icodextrin, intravenous immunoglobulins, galactose and d-xylose

Possible interference with non-glucose-specific glucose meters

Canada. Health Canada is warning about the possible interference of some medical products with certain blood glucose meters. According to the Agency, medical products which contain or are metabolised into maltose, galactose and xylose may induce falsely elevated blood glucose readings of non-glucose-specific glucose monitoring systems, because

Canada has recommended using glucose-specific monitoring systems in hospitals.

(See WHO Pharmaceuticals Newsletter No. 5 & 6, 2008 for warning of interaction between icodextrin and glucose monitoring devices in the USA.)

Reference:
Advisories, Warnings and Recalls, Health Canada, 15 December 2008 (www.hc-sc.gc.ca).

Local anaesthetic with postoperative infusion pumps

Reports of articular chondrolysis

Canada. Health Canada has encouraged health-care professionals to refrain from using postoperative pain pumps for continuous intra-articular infusion of local anaesthetics, particularly with epinephrine, for pain management after shoulder surgery. Bupivacaine is commonly used with the pumps, and a combination of bupivacaine and epinephrine is also used, with the epinephrine inducing vasoconstriction and slowing down the absorption of bupivacaine.

As of July 2008, Health Canada received eight incident reports of