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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This Newsletter is also available on our Internet website:
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News & Issues

This issue covers regulatory and safety information on more than thirty medicines, both old and new products. Previous warnings have been reiterated, labels updated, products withdrawn or new adverse reaction reports have been recorded, as may be the case. The feature item includes recommendations from the fourth Meeting of the WHO Advisory Committee on Safety of Medicinal Products.

In the last issue we promised to include letters from you on items that we publish in our newsletters. We are happy to bring you one such letter on a feature article from 2006. By sharing this interesting exchange we hope that we can motivate you to take a more interactive interest. We look forward to receiving your comments on any items published in this newsletter.

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Letters to the WHO Pharmaceuticals Newsletter

Aprotinin

Label updated for specific use, new safety information

Canada. Health Canada has issued a Notice to Hospitals and a Public Communication with the following information:

- Aprotinin injection is indicated for prophylactic use to reduce blood loss and the need for blood transfusion only in those patients who have an increased risk of blood loss and blood transfusion associated with cardiopulmonary bypass during coronary artery bypass grafting.
- Administration of aprotinin increases the risk of renal dysfunction, and may increase the requirement for dialysis peri-operatively. The risk is particularly high in patients with pre-existing renal impairment or those who receive aminoglycoside antibiotics or drugs that alter renal function.
- Aprotinin administration may cause fatal and nonfatal anaphylactic or anaphylactoid reactions, both with an initial (test) dose as well as with any of the components of the dose regimen. Fatal reactions have also occurred in situations where the initial (test) dose was tolerated. As a result, aprotinin should only be administered in operative settings where cardiopulmonary bypass can be rapidly initiated.
- The risk for anaphylactic or anaphylactoid reactions is increased among patients with prior aprotinin exposure, and a history of any prior aprotinin exposure must be verified before aprotinin administration. The risk for a fatal reaction appears to be greater upon re-exposure within 12 months of the most recent prior aprotinin exposure. As a result the administration of aprotinin to patients with a known or suspected previous aprotinin exposure during the last 12 months is contraindicated.

In the US the product label for aprotinin (Trasylol) has been revised to include a more focused indication for its use, and the above safety warnings and contraindications (see WHO Pharmaceuticals Newsletter No. 1, 2007).

References:

1. *Notice to Hospitals. Health Canada, 27 March 2006 (www.hc-sc.gc.ca).*
2. *Public Communication. Health Canada, 27 March 2006 (www.hc-sc.gc.ca).*

Attention deficit hyperactivity disorder (ADHD)-treatments

Patients to be notified of cardiovascular and psychiatric events

USA. The United States Food and Drug Administration (US FDA) has issued a directive that patients receiving pharmacotherapies for attention-deficit hyperactivity disorder (ADHD) must be informed of potential cardiovascular and psychiatric adverse events by the manufacturers of such drug products. Manufacturers of ADHD therapies must develop Patient Medication Guides highlighting these possible risks and advise patients of precautions that can be taken. A US FDA review of ADHD products found reports of sudden death in patients with existing heart problems and reports of stroke and cardiac arrest in adults with certain risk factors. A second US FDA review identified a slight increase in the risk of ADHD drug-related psychiatric events such as auditory hallucinations, paranoid disorders and mania.

Reference:

FDA News. U.S. Food and Drug Administration, 21 February 2007 (www.fda.gov).

Drug-eluting stents

To be used with utmost restraint

Sweden. The Swedish Medical Products Agency (MPA), in conjunction with the National Board of Health and Welfare and the Swedish Society of Cardiology, has recommended utmost restraint in the use of drug-eluting stents. The recommendation was based on the results of clinical studies, including the Swedish Coronary and Angioplasty Registry (SCAAR) study that showed increased risk of thrombosis associated with the use of drug-eluting stents. The results of the SCAAR study and four other randomized studies showed that drug-eluting stents have no advantages in terms of myocardial infarction or mortality, compared with bare-metal stents; in addition, the SCAAR study data indicated a small, long-term increased risk of these events. According to the MPA, drug-eluting stents must only be used in patients for whom no other treatment alternative exists or in patients who are at greatly increased risk of restenosis and for whom the effect of restenosis is expected to be severe.

Reference:

Internet document. Swedish Medical Products Agency, 13 February 2007 (www.lakemedelesverket.se).

Interferon-1b

Not approved for idiopathic pulmonary fibrosis

USA. The US FDA has issued a Public Health Advisory about the early termination of the INSPIRE clinical study

(International Study of Survival Outcome in Idiopathic Pulmonary Fibrosis) of interferon-γ-1b (IFN-γ-1b) for idiopathic pulmonary fibrosis (IPF); the Agency says that IFN- γ-1b (Actimmune) is not approved for the treatment of IPF. An interim analysis of the INSPIRE study showed that IFN-γ-1b recipients did not benefit from the drug compared with 12.7% deaths in the placebo group; 14.5% of patients died in the IFN- γ-1b group. An independent data monitoring committee subsequently recommended early termination of the trial. IFN- γ-1b-related side effects reported in the INSPIRE trial included neutropenia, constitutional symptoms, and possibly pneumonia. The US FDA has advised patients who are receiving IFN- γ-1b to consult their doctors about whether they should continue the treatment. The Agency has also advised doctors to discuss the results of the INSPIRE trial with their patients who are receiving IFN-γ-1b for IPF, and to carefully consider whether the treatment should be continued in such patients or not.

Reference:
Public Health Advisory. U.S. Food and Drug Administration, 9 March 2007 (www.fda.gov).

Isotretinoin

Web page about dangers of online buying

USA. The US FDA notified consumers and health-care professionals of a special web page launched to warn about the dangers of buying isotretinoin online. Isotretinoin is a drug approved for the treatment of severe acne that does not respond to other forms of treatment. If the drug is improperly used, it can cause severe side effects, including birth defects. Serious mental health problems have also been reported with isotretinoin use. The new web page, www.fda.gov/buyonline/accutane, will appear in online search results for one of the brand names of isotretinoin (Accutane, Amnesteem, Claravis and Sotret). The web page warns that the drug should only be taken under the close supervision of a physician or a pharmacist, and provides links to helpful information. The new web page is in addition to special safeguards put in place by the US FDA and manufacturers of isotretinoin to reduce the risks of the drug, including a risk management programme called iPLEDGE. The aim of iPLEDGE is to ensure that women using isotretinoin do not become pregnant, and that women who are pregnant do not use isotretinoin.

Reference:
FDA Warning: Risks of buying Accutane (isotretinoin) over the Internet. U.S Food and Drug Administration, 28 March 2007 (www.fda.gov).

Metoclopramide

Increasing reports of extrapyramidal symptoms in children; paediatric use tightened

The Netherlands. Following an increase in the number of registered cases of extrapyramidal symptoms in children receiving metoclopramide, the Medicines Evaluation Board (MEB) in the Netherlands has restricted the use of metoclopramide in this population. The Board says metoclopramide should be used only in the treatment of severe nausea and vomiting of known origin, and only if treatment with other products is ineffective or is not possible. The MEB says there are better alternatives to metoclopramide. For example, domperidone is a better choice in treating post-operative nausea in children. Domperidone is also the drug of choice in treating migraines in children because the risk of extrapyramidal effects is lower than with metoclopramide. Similarly, 5-HT3 receptor antagonists (e.g. ondansetron) are the drugs of first choice in nausea due to strongly emetogenic chemotherapy because of better efficacy and fewer adverse events than with metoclopramide.

Reference:
News and Publications. The Medicines Evaluation Board, the Netherlands, 21 February 2007 (www.cbg-meb.nl/uk/nieuws).

'First-in-man' clinical trials guideline for Public Consultation

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has adapted a draft guideline for first-in-man clinical trials for potential high-risk medicinal products. This guideline has been prepared as one of the measures for minimizing the risk of serious adverse reactions of the nature that occurred during the first-in-man clinical trials of TGN1412. It gives guidance on managing the transition from non-clinical studies to first tests in humans for high-risk medicinal products.

The draft guideline has been released for a two-month public consultation. Comments are invited by 23 May 2007 (see www.emea.europa.eu for details).

Reference:
Press Release. EMEA, 26 March 2007.

Miconazole

Interaction with warfarin

Finland. The use of miconazole (Daktarin) oral gel in patients receiving warfarin may lead to increased International Normalized Ratio (INR) for prothrombin time, warns Finland's National Agency for Medicines (NAM). Two cases

reported to NAM's adverse reaction database in 2005 were associated with the use of warfarin (Marevan) for auricular fibrillation and miconazole (Daktarin) oral gel. In the first, a 75-year-old woman receiving warfarin (Marevan) started treatment with miconazole (Daktarin) for an intestinal mycosis and, six days later, her INR increased from a therapeutic level to 15. In the second case, a 62-year-old woman receiving warfarin (Marevan) had a high (undetermined) INR level approximately two weeks after starting the miconazole gel (Daktarin) for candidiasis. In 2006, NAM received another report in which an 84-year-old woman, who was receiving warfarin (Marevan), developed haematuria and an increase in INR to >7 after starting treatment with the miconazole (Daktarin) oral gel. None of the patients developed serious haemorrhage and their INR levels normalized after miconazole gel was stopped and treatment was given (fresh frozen plasma, vitamin K and coagulation factor concentrate). In addition to the above cases, the national adverse reactions database has 10 non-fatal reports of interactions between warfarin (Marevan) and the miconazole (Daktarin) oral gel; all involve the potentiation of the effect of warfarin (Marevan) and some are associated with haemorrhage. NAM suggests that patients receiving warfarin should avoid the use of miconazole oral gel (Daktarin), and if alternative treatments are unavailable, INR levels should be checked frequently.

Reference:
TABU: Drug Information from the National Agency for Medicines, Finland, No. 6, 2006.

Omalizumab

Label update about anaphylaxis

USA. The US FDA has asked Genentech to add a boxed warning to the labelling for omalizumab (Xolair) to warn about possible anaphylaxis associated with the use of the drug. Anaphylaxis may include chest tightness, dizziness, pruritus, swelling of the mouth, syncope, trouble breathing and urticaria. The Agency has also requested Genentech to provide a patients 'Medication Guide' to strengthen the existing warning for anaphylaxis in the omalizumab (Xolair) label. According to the US FDA, the frequency of anaphylaxis reported in the clinical trials of omalizumab (Xolair) was about 0.1%, but the life-threatening potential and frequency of reports in the post-marketing experience of omalizumab (Xolair), and the possibility for the delayed anaphylaxis onset, have prompted the agency to recommend the boxed warning and strengthen the existing warning. The warning includes the possibility of developing anaphylaxis after any dose of omalizumab (Xolair); the anaphylaxis may be delayed up to 24 hours after administration. The US FDA has advised health-care providers to observe patients for at least two hours after an injection of omalizumab (Xolair).

Reports in WHO database:
Omalizumab (Xolair) - Anaphylactic reaction - 28

Reference:
FDA News. U.S. Food and Drug Administration, 21 February 2007 (www.fda.gov).

Pentavalent rotavirus (W179-9) vaccine

Label updated with information on intussusceptions and haematochezia

USA. The US FDA is notifying health-care providers and the public about 28 post-marketing reports of intussusception following the administration of live, oral, pentavalent rotavirus W179-9 vaccine (RotaTeq). Intussusception is a serious and potentially life-threatening condition that occurs when the intestine gets blocked or twisted. RotaTeq is indicated for the prevention of rotavirus gastroenteritis. It is not known how many of the 28 cases are vaccine-related and how many may have occurred by coincidence. The US Vaccine Adverse Event Reporting System (VAERS) received these reports between 3 February 2006 (when RotaTeq was licensed for use in the US) and 31 January 2007. Intussusception occurred after dose 1, dose 2 and dose 3 of the vaccine, and approximately 50% of cases occurred 1–21 days postvaccination (range 0–73 days). Surgical repair was necessary in 16 infants while the remaining infants had reduction of the intussusception by contrast or air enema.
The US FDA noted that the number of the rotavirus (W179-9) vaccine (RotaTeq)-associated intussusception cases reported to date does not exceed the expected number based on annual background rates of 8–43 cases per 100 000 for an unvaccinated population of infants aged 6–35 weeks. However, the agency acknowledged that vaccine adverse events are not always reported and that there may be additional unreported cases of intussusception following vaccination. Currently, there are two large-scale postmarketing studies being conducted by Merck & Co. (involving about 44 000 infants) and the US Centers for Disease Control and Prevention's Vaccine Safety Data Link (involving approximately 90 000 infants).
The US prescribing information for rotavirus (W179-9) vaccine) (RotaTeq) has been updated to reflect the above information.

Reference:
FDA Public Health Notification. U.S. Food and Drug Administration (Center for

Biologics Research and Evaluation), 13 February 2007 (www.fda.gov).

Methotrexate dosage errors

The Belgian Drug Monitoring Centre has received notification of two cases of severe adverse events resulting from dosage errors associated with methotrexate. In the first case, a patient misunderstood the dosage and took six 2.5 mg tablets of methotrexate a day for two weeks, instead of six tablets a week, for rheumatoid arthritis. In the second case, a patient took three 2.5 mg tablets of methotrexate a day for one week, instead of one tablet a day, for psoriasis, on a friend's advice. Both patients were hospitalized for diarrhoea and mucositis, and one developed pronounced bone marrow depletion.

The Belgian Drug Monitoring Centre says that confusion may arise when a drug does not have to be taken every day. Such errors have been reported with mefloquine for malaria prevention with, for example, one dose being taken daily instead of weekly. Unusual dosages are also seen with some bisphosphonates: weekly for risedronic acid (Actonel Hebdomadaire) and alendronic acid (Fosamax

Pergolide

Risk of heart valve damage; to be removed from the market

USA (1). Manufacturers have volunteered to remove pergolide drug products from the market due to the risk of serious damage to the heart valves of patients treated with these products. Pergolide is a dopamine agonist and is used with levodopa and carbidopa to manage the symptoms of Parkinson's disease. The US FDA notes that new studies confirm old data associating pergolide with increased chance of regurgitation (back-flow of blood) of the mitral, tricuspid and aortic valves of the heart. Valve regurgitation is a condition in which valves do not close tightly, allowing blood to flow backward across the valve. Symptoms include shortness of breath, fatigue and heart palpitations. Valvular heart disease was first described in association with pergolide in 2002. In 2003 the product label was updated to include valvulopathy to the warnings section. Then in 2006, the warning was upgraded to a black box warning because of new data concerning risks of heart valve damage. The Agency advises that the products being removed include two generic versions of pergolide manufactured by Par and Teca and a proprietary version (Permax) manufactured

an Investigational New Drug (IND) application for those few patients who are currently receiving pergolide and who cannot be successfully switched to other available treatments.

Canada (2). Heath Canada has informed that it is currently evaluating the new data on the risk of heart problems associated with pergolide treatment. When completed, results of the review will be communicated to the public and to health-care providers. Heath Canada stresses that patients should not stop taking their medication without consulting their physician since sudden discontinuation of pergolide may have serious consequences for the patient.

References:

1. FDA News. U.S. Food and Drug Administration, 29 March 2007 (www.fda.gov).
2. Information Update. Health Canada, 31 March 2007 (www.hc-sc.gc.ca).

Pioglitazone

Fractures in females

USA. Takeda Pharmaceuticals and the US FDA notified health-care professionals of recent safety data concerning pioglitazone-containing products. The results of an analysis of the manufacturer's clinical trial database of pioglitazone showed more reports of fractures in female patients taking pioglitazone