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: http://www.who.int/medicines

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News & Issues

This first issue of the Newsletter for the year 2006 covers the usual sections on the safety and regulatory aspects of medicines. The Feature item records the recommendations from the third meeting of the Advisory Committee on Safety of Medicinal Products. As a direct consequence of the discussions at the meeting, the Committee will propose recommendations for safety systems within the HIV/AIDS programme and design an action plan for studies focusing on specific toxicity issues associated with antiretroviral medicine use. The action plan will help deliver effective pharmacovigilance into public health programmes in countries that most need it.

WHO is announcing two new publications: *The Handbook for Good Clinical Research Practice (GCP): Guidance for Implementation* and, *The Safety of Medicines in Public Health Programmes: pharmacovigilance an essential tool.* The former will promote global standards for all clinical research studies while the latter will ultimately help each patient receive optimum therapy, and on a population basis, will help ensure the acceptance and effectiveness of public health programmes. Please write to us if you wish additional details or copies of these publications.

We are delighted to note that Portuguese translations of some of the earlier issues of the WHO Pharmaceuticals Newsletter are now available on the ANVISA website, at http://www.anvisa.gov.br/farmacovigilancia/boletim_oms/index.htm. We thank the Brazilian centre, Agência Nacional de Vigilância Sanitária (ANVISA) for taking this initiative in adding to our readership. We look forward to similar efforts from other Member States. We wish you all much happiness and good health in 2006.

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Regulatory Matters

Safety of Medicines

Feature

Alefacept

Contraindicated in HIV patients

USA. The United States labelling for alefacept (Amevive) has been revised to include new safety information, according to a 'Dear Health-care Provider' letter issued by Biogen Idec; the revised Contraindications section now states that alefacept (Amevive) should not be given to patients with HIV infection as it reduces CD4+ T lymphocyte counts that may increase disease complications or accelerate disease progression; the company says that this contraindication is consistent with the company decision not to study the drug in patients with HIV infection and psoriasis over theoretical safety concerns in this population. Other sections of the labelling for alefacept (Amevive) have also been updated to reflect additional safety information, says Biogen Idec.

Reference:
Safety information from the United States Food and Drug Administration, 9 November 2005 (http://www.fda.gov).

Beta-2 adrenoceptor agonists

Label to warn of risk of asthma

USA. The United States Food and Drug Administration (FDA) has requested manufacturers to update the labelling for the long-acting β2-adrenoceptor agonists, salmeterol/fluticasone propionate inhalation powder (Advair Diskus), formoterol inhalation powder (Foradil Aerolizer) and salmeterol inhalation powder (Serevent Diskus), to include new warnings and a Medication Guide to highlight that these drugs may increase the risk of severe asthma episodes and death when these episodes occur. The FDA says that findings from a study showed that there was an increased number of asthma-related deaths in patients receiving a long-acting β2-adrenoceptor agonist in addition to their usual asthma treatment, compared with patients receiving placebo and usual asthma treatment. Information about these risks have been included in the Medication Guide, and will be given to patients when a prescription for long-acting β2-adrenoceptor agonists is refilled or filled, says the Agency. The FDA says that long-acting β2-adrenoceptor agonists should not be the first drug used for asthma treatment, or for worsening or sudden wheezing, and should only be added if asthma is not controlled by other drugs. The FDA advises that patients should always have a short-acting bronchodilator for sudden wheezing, should contact a health-care professional immediately if wheezing worsens while using a long-acting β2-adrenoceptor agonist and should not discontinue long-acting β2-adrenoceptor agonist or asthma treatments unless they have discussed it with their health-care provider. (Also see WHO Pharmaceuticals Newsletter No. 4, 2005 for warnings from Health Canada related to beta-2 agonist bronchodilator use).

Reference:
Public Health Advisory. United States Food and Drug Administration, 18 November 2005 (http://www.fda.gov).

Clozapine

Blood monitoring requirements tightened

USA. Because of a significant risk of agranulocytosis with clozapine and because of the potential for very low absolute neutrophil count (ANC) and agranulocytosis, white blood cell (WBC) count monitoring is essential in patients treated with clozapine. After reviewing recommendations provided by the Pharmacological Drugs Advisory Committee (PDAC) of June 2003, the United States Food and Drug Administration (US FDA) has recommended changes to the current schedule of WBC monitoring for all clozapine users. The new labels will include the following:

- the requirement that the absolute neutrophil count (ANC) should be determined and reported along with each WBC count;
- new parameters for clozapine treatment initiation: WBC $\geq$ 3500/mm^3 and ANC $\geq$ 2000/mm$^{3;}$
- need for the initiation of monthly monitoring schedule after one year (six months weekly, six months every two weeks) of WBC counts and ANCs in the normal range (WBC $\geq$ 3500/mm^3 and ANC $\geq$ 2000/mm^3);
- addition of cautionary language to prescribers describing the increased risk of agranulocytosis in patients who are rechallenged with clozapine after recovering from an initial episode of moderate leukopenia and that these patients are now required to undergo weekly monitoring for 12 months if they are rechallenged.

In addition, the label will also include a black-box warning on the increased risk of death in elderly patients with dementia-related psychosis who are treated with an atypical antipsychotic. This reflects a class-wide label change.

Reference:
'Dear Health-care Provider' letter from Novartis, December 2005 (http://www.fda.gov).

Coagulation Factor VII a (Recombinant)

Thromboembolic events added to label

USA. Novo Nordisk Inc. has issued a 'Dear Health-care Professional' letter advising that the US labelling for the coagulation Factor VII a (Recombinant) product (NovoSeven) has been updated to include warnings about a possible increased risk of thromboembolic adverse events (AEs), and additional AE information following reports in patients with and without known coagulopathy. Novo Nordisk advises that the revised labelling includes an update to the Warnings section, which states that patients with advanced atherosclerosis, crush injury, disseminated intravascular coagulation or septicaemia, or receiving concomitant coagulants, may have an increased risk of developing thrombotic events, and that a study involving elderly non-haemophilia patients with intracerebral haemorrhage indicated that the risk of arterial thromboembolic AEs was potentially increased with the use of Factor VII a recombinant product (NovoSeven). Additionally, the Adverse Reactions section has also been updated with the product (NovoSeven)-related AE reports, including thromboembolic events, and isolated cases of allergy. Novo Nordisk advises that a causal relationship has not been established for the AEs reported.

Reference:
'Dear Health-care Professional' letter from Novo Nordisk, 23 November 2005 (http://www.fda.gov).

(Kaizen) Ephedrine Hydrochloride tablet

Not authorized as a weight-loss product

Canada. Health Canada has advised that misuse of Kaizen ephedrine HCl tablets has been associated with serious and potentially fatal adverse effects, and warns consumers not to use the oral nasal decongestant for the unauthorized indications of weight loss or increased energy; those who have used Kaizen Ephedrine HCl for these purposes, and experienced adverse effects, are advised to consult their healthcare practitioner. Health Canada says that, although there have been no specific reports associated with Kaizen Ephedrine HCl, there have been reports of adverse events associated with the use of ephedrine in combination with caffeine and other stimulants. According to Health Canada, the distributor has taken action to stop promoting the product for weight loss and as an energy booster.

Reference:
Advisory. Health Canada, 28 December 2005 (http://www.hc-sc.gc.ca).

Epoetin products

Labels to warn of severe anaemia and pure red cell aplasia

USA. The product labels for epoetin alfa (Epogen, Procrit) and darbepoetin alfa (Aranesp) have been revised following reports of antibody-mediated pure red cell aplasia (PRCA) and severe anaemia associated with erythropoietin agonists. The cases predominantly involved patients with chronic renal failure who received erythropoietin agonist by the subcutaneous route. The Warnings, Adverse Reactions, and Dosage and Administration sections of the labels have been updated accordingly, and include the following safety information:
If a patient fails to respond, or has a sudden loss of response, and an anti-erythropoietin antibody-mediated anaemia is suspected, erythropoietin agonists should be withdrawn and the manufacturer contacted to perform assays for binding and neutralising antibodies.
Erythropoietin agonists should be stopped permanently in patients with antibody-mediated anaemia.
As antibodies may cross-react, patients should not be switched to other erythropoietin agonists. The IV route of administration is recommended for patients undergoing haemodialysis.

Reference:
'Dear health-care Professional' letters from Amgen and Ortho Biotech, November 2005 (http://www.fda.gov).

Estradiol/testosterone injection

Discontinued due to safety reasons

Canada. Sandoz Canada has advised that the estradiol/testosterone (Climacteron) injection has been discontinued because of safety concerns. The company advises that, according to published literature, women with intact uteri receiving testosterone should also receive progestogen concomitantly to prevent endometrial hyperplasia or carcinoma, and that the appropriate progestogen dosage regimen for such women who are receiving estradiol/testosterone is unknown. The company also advises that, according to published literature, estradiol/testosterone (Climacteron) may be associated with hirsutism, aggression and virilisation. Sandoz Canada recommends

that physicians and pharmacists inform users of the discontinuation, and counsel them to visit for re-evaluation and discussion of alternative hormone replacement therapy (HRT). The company says that estradiol/testosterone (Climacteron) supply will continue until stock depletion.

Reference:
Advisories, Warnings and Recalls. Health Canada, 23 November 2005 (http://www.hc-sc.gc.ca).

Ketamine

Classified as Class C drug

UK. As of 1 January 2006, Ketamine has become a controlled drug, under the Misuse of Drugs Act. This step has been taken because of its increasing misuse. In the UK it is now a Class C drug, in Schedule 4 part 1, which puts it with the majority of the benzodiazepines such as diazepam etc. However, the drug is not an internationally controlled substance.

Reference:
News & Updates. National electronic Library for Medicines, 3 January 2006 (http://www.nelm.nhs.uk).

Nevirapine

SPC to include new hepatotoxic warnings

UK. The Summary of Product Characteristics (SPC) for nevirapine (Viramune) has been updated with new hepatotoxic warnings. Female gender and higher CD4+ counts at the initiation of therapy place patients at greater risk of hepatic adverse events. Unless the benefit outweighs the risk, nevirapine (Viramune) should not be initiated in adult females with CD4+ cell counts greater than 250 cells/mm^3 or in adult males with CD4+ cell counts greater than 400 cells/mm^3. This is based on the occurrence of serious and life-threatening hepatotoxicity in controlled and uncontrolled studies. In some cases, hepatic injury has progressed despite discontinuation of treatment. It is advised that patients developing signs or symptoms of hepatitis, severe skin reaction or hypersensitivity reactions must discontinue nevirapine (Viramune) and seek medical evaluation immediately. Nevirapine (Viramune) should not be restarted following severe hepatic, skin or hypersensitivity reactions (see section on 'Problems of Current Interest' in the WHO Pharmaceuticals Newsletter No. 5, 2005 for a short article on hepatic adverse events with nevirapine).

Reference:
News & Updates. UK National electronic Library for Medicines (NeLM), 3 January 2006 (http://www.nelm.nhs.uk).

$Rh_0(D)$ Immune Globulin

Intravascular haemolysis events added to label

USA. The US labelling for $Rh_0(D)$ Immune Globulin (WinRho SDF) has been updated to include safety information regarding intravascular haemolysis in patients with immune thrombocytopenic purpura (ITP) and the potential for falsely elevated blood glucose measurements in patients receiving the product. Post-marketing surveillance of $Rh_0(D)$ Immune Globulin (WinRho SDF) has revealed rare, severe and sometimes fatal, intravascular haemolysis and potentially serious complications, which include disseminated intravascular coagulation, in patients with ITP. The updated labelling advises physicians to inform patients with ITP about the symptoms of intravascular haemolysis, and to advise them to report any of these symptoms immediately. A new Patient Information Sheet will be made available to these patients. The companies also alert health-care professionals to the potential for falsely elevated blood glucose readings in non-glucose-specific testing systems, following the administration of maltose-containing $Rh_0(D)$ Immune Globulin (WinRho SDF) liquid, and advise that only glucose-specific testing systems should be used for patients receiving $Rh_0(D)$ Immune Globulin (WinRho SDF).

Reference:
'Dear Health-care Professional' letter, from Cangene and Baxter Healthcare Corporation, 5 December 2005 (http://www.hc-sc.gc.ca).

Telithromycin

Reports of liver toxicity

Europe. The European Medicines Agency (EMEA) has made a preliminary review of cases of serious liver injury associated with the use of telithromycin (Ketek), an antibiotic used in the treatment of respiratory infections. The reported serious liver reactions started during or immediately after treatment with telithromycin (Ketek) and were, in most cases, reversible on discontinuing treatment. Further cases of liver toxicity are being reviewed by the EMEA for a full benefit/risk assessment of the product. In the meantime, the marketing authorization holder (Aventis Pharma S.A.) has been asked to include stronger warnings of liver disorders in the telithromycin (Ketek) product information. The EMEA has issued a Press Release with this update and is reminding prescribers to use telithromycin (Ketek) with caution in patients with liver impairment [(1)].

USA. The FDA has issued a Public Health Advisory [(2)] referring to an article in the

Annals of Internal Medicine that reports three patients with serious liver toxicity following administration of telithromycin (Ketek). All three patients developed jaundice and abnormal liver function; one recovered, one required a transplant and the third died. The FDA is evaluating the issue of liver toxicity associated with telithromycin-use and, in the meantime, has provided the following recommendations to health-care providers and patients:

- Health-care providers should monitor patients taking telithromycin for signs or symptoms of liver problems. Telithromycin should be stopped in patients who develop signs or symptoms of liver problems.
- Patients who have been prescribed telithromycin and are not experiencing side effects such as jaundice should continue taking their medicine as prescribed unless otherwise directed by their health-care provider.
- Patients who notice any yellowing of their eyes or skin or other problems like blurry vision should contact their health-care provider immediately.
- As with all antibiotics, telithromycin should only be used for infections caused by a susceptible microorganism. Telithromycin is not effective in treating viral infections, so a patient with a viral infection should not receive telithromycin since they would be exposed to the risk of side effects without any benefit.

References:

1. Press Release (EMEA/29386/2006). European Medicines Agency, 27 January 2006 (http://www.emea.eu.int).

2. Public Health Advisory. United States Food and Drug Administration, 20 January 2006 (http://www.fda.gov).

Baclofen

Adverse reactions due to device related issues

Canada. Health Canada has received 21 reports of adverse reactions suspected to be associated with intrathecal baclofen (Lioresal) from 1 January 1992 to 30 June 2005, according to the latest issue of the *Canadian Adverse Reaction Newsletter*. Ten reports implicated the surgically implanted baclofen pump system; five of these reports involved problems with the catheter system and five reports involved suspected improper pump preparation leading to an inadvertent baclofen bolus dose, resulting in coma. Health-care professionals are advised to consider device-related issues when assessing the need for baclofen dose adjustments.

Reference:
Canadian Adverse Reaction Newsletter, October 2005, 15(4):1.

Clarithromycin

Study reports fatal cardiac events

USA. The FDA has alerted health-care professionals to a study in Denmark that has found increased mortality from cardiac problems in heart disease patients treated with clarithromycin compared with those who received placebo will be determined as more information becomes available.

Reference:
FDA Alert for Health-care Professionals, December 2005 (http://www.fda.gov).

Colchicine

Dosage decreased for better safety

New Zealand. The New Zealand Medicines and Medical Devices Safety Authority, Medsafe has advised prescribers of revised dosage advice for colchicine, as the use of high colchicine doses "is no longer appropriate" because of dose-related serious adverse effects, according to a Prescriber Update article. This advice coincides with the introduction of a colchicine 0.5 mg tablet (Colgout).

Medsafe also advises that:

- colchicine is now limited to second-line treatment for acute gout, when non-steroidal anti-inflammatory drugs (NSAIDs) are contraindicated, lack efficacy or have unacceptable adverse drug effects;
- the dosing interval has increased from two to three hourly to six hourly, the maximum daily colchicine dose is 2.5 mg in the first 24 hours and the maximum cumulative dose should not exceed 6 mg over four days;
- other treatments should be considered in elderly patients

initial symptoms of colchicine-associated toxicity include nausea, vomiting and diarrhoea, and usually occur 2–12 hours after ingestion; if toxicity does occur, patients should discontinue colchicine immediately and seek medical advice.

Reference:
*Prescriber Update, December 2005, 26(2) (*http://www.medsafe.govt.nz*).*

Corticosteroids (Topical)

Reports of facial damage

New Zealand. The New Zealand Centre for Adverse Reactions Monitoring has received 14 reports of facial skin damage associated with the use of potent topical corticosteroids, according to a `Prescriber Update' article. The reports included telangiectasia, abnormal pigmentation, rosacea, perioral dermatitis, skin atrophy and striae, and were primarily associated with mometasone (Elocon), although the authors note that all topical corticosteroids used on the face carry a risk of facial skin damage, especially the more potent ones. The authors remind prescribers and patients that the use of topical corticosteroids on the face should be limited to ≤ two weeks; prescribers are advised to give clear instructions to