WHO PHARMACEUTICALS NEWSLETTER

World Health Organization

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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This Newsletter is also available on our Internet website:
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NEWS & ISSUES

The New Year started on a busy note with two global meetings in February: the fifth meeting of the Advisory Committee on Safety of Medicinal Products (ACSoMP), 25-27 February 2008, and a meeting organized by WHO (HIV Department and the Department of Medicines, Policy and Standards), together with the Forum for Collaborative HIV Research, on case definitions, toxicity grading and laboratory diagnosis of adverse events related to antiretroviral (ARV)-use. Recommendations or relevant information from these meetings will be included in subsequent issues of the newsletter.

In this issue, as always, we bring you the latest regulatory decisions and safety updates for medicinal products along with information from the seventeenth meeting of the Global Advisory Committee on Vaccine Safety held in Geneva, 12-13 December 2007.

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Regulatory Matters

Safety of Medicines

Aprotinin

Programme for special access

Worldwide. Bayer temporarily suspended the marketing of aprotinin (Trasylol) worldwide until final data from the Canadian BART trial (Blood conservation using antifibrinolytics: a randomized trial in high-risk cardiac surgery patients) are available. Health Canada, the United States Food and Drug Administration (US FDA) and other regulatory authorities have been interested in working with the company to develop a programme for the use of aprotinin during the product's temporary marketing suspension. Under such a programme, physicians would be able to request aprotinin for treatment of certain surgical patients with an established medical need. Currently, aprotinin is approved for prophylactic use to reduce perioperative bleeding in patients undergoing cardiopulmonary bypass during coronary artery bypass graft surgery and who are at an increased risk for blood loss and blood transfusion requirement. Bayer, in consultation with Health Canada, has developed a process to make aprotinin available for high-risk patients where the physician believes use of aprotinin is warranted and falls within the current approved indication. The Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK has announced that limited supply of aprotinin to individual patients will be permitted under 'Special' regulations. The MHRA plans to issue further guidance following completion of the Europe-wide review of the product's benefits and risks.

Reference:
Reactions weekly 1181 p. 2; 8 December, 2007.

Atorvastatin

Advice relating to interactions and risk of hemorrhagic stroke

UK. Health-care professionals are being informed that:
- atorvastatin levels may increase when administered with drugs that inhibit its metabolism (via cytochrome P450 CYP3A4 inhibition), with an increase in the risk of side-effects; alternative non-interacting therapies should be considered if possible, and if not, then the lowest possible dose of atorvastatin must be used or atorvastatin should be stopped temporarily, if the interacting drug is only being used for a short period; and when given with certain specific drugs, atorvastatin dose should not exceed 10mg (with cyclosporine), 20mg (with clarithromycin) and 40mg (with itraconazole);
- evidence from a recent study suggests that patients with recent haemorrhagic or lacunar stroke (without coronary heart disease) may have an increased risk of haemorrhage stroke when treated with 80mg atorvastatin daily.

The product label for atorvastatin (Lipitor) has been updated with the above information.

Reference:
'Dear Health-care professional" letter from Pfizer Limited, 3 December 2007 (www.mhra.gov.uk).

Bio-identical hormone replacement therapy

No medical evidence about safety, effectiveness

USA. Seven pharmacy operations in the US that prepare so called 'bio-identical hormone replacement therapy' (BHRT) have received warnings from the US FDA that there are no medical evidence for the safety and effectiveness of these products. The US FDA is concerned that these false and unfounded claims will mislead women and health-care professionals. The pharmacy operations claim that these BHRT drugs, which contain hormones estrogen, progesterone and estriol, are superior to FDA-approved menopausal therapy drugs and that they prevent or treat serious diseases, including Alzheimer's disease, stroke, and various forms of cancer. The US FDA states that these compounded drugs (BHRT) are not approved and that the Agency's warning does not target pharmacists who practice traditional pharmacy compounding (which involves preparing a drug for an individual patient in response to a valid prescription.

Reference:
FDA News. US FDA, 9 January 2008 (www.fda.gov).

Carbamazepine

SJS/TEN more common in patients with HLA-B*1502

USA. Risk of carbamazepine-related Stevens Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) is significantly increased in patients positive for the HLA-B*1502 allele, according to the US FDA. This information has been added to the product label and in the revised boxed warning. The Agency says that the HLA-B*1502 allele occurs exclusively in patients with Asian ancestry including South Asian Indians. Screening for this allele should be performed for most patients of Asian ancestry before carbamazepine initiation and the drug should not be started in those who test positive for HLA-B*1502 allele unless the expected benefit clearly outweighs the increased risk. SJS and TEN risk may also be increased in patients who test positive for HLA-B*1502 and receive other antiepileptic drugs that have been associated with these disorders. Despite the risk being low in patients who test negative for this allele, SJS and TEN can still develop in this group, says the Agency. In more than 90% of carbamazepine recipients, SJS and TEN develop within the first few months of drug initiation; therefore, the risk is low in patients who test positive for HLA-B*1502 allele but have been receiving carbamazepine for more than a few months.

Reports in WHO Individual Case Safety Reports (ICSR) database:
Toxic epidermal neerolysis 45 (1997 – 2007)
Stevens Johnson syndrome 1180 (1969 - 2007).

Reference:
FDA Alert. US FDA, 12 December 2007 (www.fda.gov).

Edetate disodium

Fatalities due to medication errors or unapproved use

USA. The US FDA has issued a Public Health Advisory about important safety information concerning the use of edetate disodium (marketed as Endrate and generic products).
The Agency advises that adults and children have died after receiving edetate disodium instead of edetate calcium disodium, or when edetate disodium has been administered for `chelation therapies' and other uses not approved by the US FDA. The Agency notes that, because edetate disodium and edetate calcium disodium have very similar names and are commonly referred to as only `EDTA', they are easily mistaken for each other. The US FDA is currently reviewing the benefit/risk profile of edetate disodium, and has issued important safety considerations to be observed in the interim. In particular, the US FDA recommends that hospitals evaluate their need to stock edetate disodium in their pharmacies. The Agency also advises that adults and children who receive treatment for lead poisoning should only be given the edetate calcium sodium form of `EDTA'. Other recommendations include that the abbreviation `EDTA' should not be used when prescribing or dispensing an order for either of these drugs, and prescribers should consider including the indication for use on prescribing orders.

Reference:
Public Health Advisory. US FDA, 16 January 2008 (www.fda.gov).

Ethinylestradiol/ norelgestromin birth control patch

Label to include risk of VTE

USA. The US FDA has approved additional changes to the label for the ethinylestradiol/ norelgestromin transdermal contraceptive patch [Ortho Evra Contraceptive Transdermal (Skin) Patch] to include the results of a new epidemiological study that found that users of the birth control patch were at higher risk of developing serious blood clots, also known as venous thromboembolism (VTE) than women using oral contraceptive pills. The patch was studied in women aged 15-44. These recent findings support an earlier study that also said that women in this group were at higher risk for VTE (see WHO Pharmaceuticals Newsletter No. 5, 2006). The Patch releases ethinyl estradiol (an estrogen hormone) and norelgestromin (a progestin hormone) through the skin into the blood stream. Women using the product will be exposed to about 60 per cent more estrogen than if they were using typical birth control pills containing 35 micrograms of estrogen.

Increased levels of estrogen may increase the risk of side effects, including VTE.

Reference:
FDA News. US FDA, 18 January 2008 (www.fda.gov).

Lumiracoxib

Withdrawn

New Zealand. Lumiracoxib [Prexige] has now been withdrawn from the New Zealand market (see WHO Pharmaceuticals Newsletters Nos. 5 and 6, 2007 for withdrawals in other countries.) Medsafe, the medicines and medical devices safety authority in New Zealand has reviewed the latest safety data for lumiracoxib and found reports of liver damage associated with prolonged use of low-dose lumiracoxib. The Agency has advised current lumiracoxib users to stop taking the drug and to consult their doctor if they develop nausea, vomiting, stomach pains, loss of appetite, yellowing or pruritus of skin, or dark urine.

Reference:
Reactions weekly, 1184: 4, 12 January 2008.

Modafinil

Life-threatening skin and other serious hypersensitivity reactions

Canada. Shire Canada Inc. has issued a `Dear Health-care Professional' letter to advise of new warnings regarding modafinil (Alertec) and severe skin reactions, serious hypersensitivity reactions and psychiatric adverse effects. The Product Monograph has been updated to advise that modafinil can cause life-threatening skin and other serious hypersensitivity reactions. It states that severe cutaneous adverse reactions such as toxic epidermal necrolysis, Stevens-Johnson syndrome and drug rash with eosinophilia and systemic symptoms (DRESS) have occurred in both adults and children receiving modafinil. Furthermore, angioedema, anaphylactic reaction and multi-organ hypersensitivity reactions, involving at least one fatal case, have been reported in association with the drug. The revisions also include warnings that modafinil is not approved for use in paediatric patients, and can cause psychiatric symptoms. Patients are advised to stop taking modafinil and seek medical attention immediately if they experience a skin rash, sores in the mouth, blisters and skin peeling, swelling of the face, eyes, lips, tongue or throat, difficulty swallowing or breathing, or a hoarse voice.

Reports in the WHO ICSR database:
1997 - 2007

Allergic reaction	*6*
Anxiety	*41*
Nervousness	*46*
Depression	*33*
Insomnia	*45*
Somnolence	*43*
Dermatitis exfoliative	*1*

Reference:
'Dear Heath-care Professional Letter' from Shire Canada Inc. 18 December 2007 (www.hc-sc.gc.ca).

Nonoxynol 9 OTCs

To include warning about lack of protection against HIV and other STDs.

USA. The US FDA has directed manufacturers of over-the-counter (OTC) stand-alone vaginal contraceptive and spermicidal products containing the chemical ingredient nonoxynol 9 (N9) that these products should have a warning that N9 does not provide protection against infection from HIV or other sexually transmitted diseases (STDs). Stand-alone spermicides include gels, foams, films or inserts containing N9 and are used for contraception. The US FDA also requires that the labels for these products warn that N9 can irritate the vagina and rectum, which may increase the risk of contracting HIV/AIDS from an infected partner.

Reference:
FDA News. US FDA, 18 December 2007 (www.fda.gov).

Rosiglitazone

New warnings and contraindications in Europe

Europe. The European Medicines Agency (EMEA) has recommended updating the product information for rosiglitazone-containing antidiabetic medicines with the following:

- a new warning that the use of rosiglitazone in patients with ischaemic heart disease and/or peripheral arterial disease is not recommended;
- a new contra-indication stating that

rosigltazone must not be used in patients with an acute coronary syndrome, such as angina or some types of myocardial infarction. When rosiglitazone was first introduced in the European Union in 2000, it was contraindicated in patients with a history of cardiac failure (see WHO Pharmaceuticals Newsletter No. 3, 2007). The current updates are the result of a re-assessment of the benefits and risks of rosiglitazone and pioglitazone (another antidiabetic medicine) in 2007. A boxed warning on the risks of heart failure was added for all thiazolidine class of antidiabetic drugs (which includes rosiglitazone) in the US in 2007 (see WHO Pharmaceuticals Newsletter No. 4, 2007).

Reference:
Press Release. EMEA, 24 January 2008 (www.emea.europa.eu).

Sargramostim

Liquid formulation withdrawn due to increasing adverse reaction reports

Leukine) ever since the liquid formulation was changed to include edetate disodium (EDTA). Health-care professionals are requested to immediately stop using the liquid sargramostim (liquid leukine) and to return any unused vials. Bayer is assuring health professionals that it will establish a special access program for the currently marketed lyophilized sargarmostim (lyophilized Leukine, 250mcg) which does not contain EDTA. Bayer will reformulate liquid sargramostim (liquid Leukine), to eliminate EDTA from the formulation.

Reference:
'Dear Health-care Professional' letter from Bayer HealthCare Pharmaceuticals, 23 January 2008 (www.fda.gov).