WHO PHARMACEUTICALS NEWSLETTER

prepared in collaboration with the
WHO Collaborating Centre for
International Drug Monitoring,
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The aim of this Newsletter is to disseminate information on the safety and efficacy of pharmaceutical products, based on information 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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Contents

News & Issues

More definite regulatory actions have now been taken in some countries, either for specific cyclooxygenase-inhibitors or for the non-steroidal anti-inflammatory drugs as a whole; the most recent decisions are included in this issue. A list of recently prequalified drugs is also included as part of our promise to familiarize readers with the work of the WHO prequalification team.

Preparations are under way for the Twenty-eighth Annual Meeting of Representatives of National Centres participating in the WHO International Drug Monitoring Programme, to be held in Geneva, 26 - 29 September 2005. In addition to various other collaborative features, this year's meeting will include a working group exercise on patient safety, to determine how national pharmacovigilance centres could work with the World Alliance for Patient Safety. The draft agenda for the meeting is published with this edition for your information. We hope to see many of you at the meeting.

TABLE OF CONTENTS

Regulatory Matters

Safety of Medicines

Miscellany

Albumin

Safety issues in critically ill patients

USA. The United States Food and Drug Administration (FDA) has revised its previous advice on the safety of albumin administration to patients who are critically ill, following a review of recent studies. In 1998, following the publication of a meta-analysis by the Cochrane Injuries Group, the FDA had expressed 'serious concern' about the safety of albumin administration to patients who were critically ill. The study had found that the relative risk of dying was higher with albumin than with normal saline administration in such patients; the findings were similar for patients with hypovolaemia, burns and hypoproteinaemia. In March 2005, the Blood Products Advisory Committee (BPAC) voted that the results of a randomised controlled trial (the SAFE study: Saline versus Albumin Fluid Evaluation, N Engl J Med 2004;350:2247-56), resolved the prior safety concerns raised in the Cochrane meta-analysis; in the SAFE study, the mortality rate for patients in the general ICU population was the same for those who received albumin as for those who received saline for fluid resuscitation. The FDA states that the revision of its advice is consistent with the BPAC recommendations. However, as patients with burns were excluded from the SAFE study, the relative safety of albumin cannot be determined for this group.

Reference:

Safety of albumin administration in critically ill patients. United States Food and Drug Administration, 16 May 2005 (http://www.fda.gov).

Antiretroviral agents

Caution advised against certain combinations

Canada. Bristol-Myers Squibb Canada and Gilead Sciences have issued a 'Dear Health-care Professional' letter to highlight that new clinical data show the potential for drug interactions between didanosine (delayed-release capsules enteric coated beadlets, Videx EC) and tenofovir disoproxil fumarate (Viread), with or without efavirenz (Sustiva) or nevirapine (Viramune). According to reports from recent investigator-sponsored studies, the coadministration of tenofovir and didanosine with either efavirenz or nevirapine may be associated with a potentially high virological failure rate and emergence of resistance in antiretroviral-näive adults with HIV-infection, low CD4+ cell counts and high baseline viral loads. Results of pharmacokinetic studies show that tenofovir and didanosine coadministration increases systemic didanosine exposure by 40−60%, and could potentiate didanosine-related adverse events (AEs).
The companies recommend that the coadministration of didanosine and tenofovir be undertaken with caution, that patients who are receiving both drugs be monitored carefully for continued efficacy and for AEs, and that didanosine be discontinued in patients who develop AEs associated with the drug. The companies advise that the Canadian didanosine (Videx EC) and tenofovir disoproxil fumarate (Viread) product monographs have been revised to include this information, along with recommended didanosine dosage adjustments for coadministration with tenofovir.

Reference:

'Dear Health-care Professional' letter from Bristol Myers Squibb and Gilead Sciences, Canada, 9 June 2005 (http://www.hc-sc.gc.ca).

Atypical Antipsychotics

Risk of death in elderly patients with dementia

Canada, USA. Health Canada is advising consumers about the increased risk of death in elderly patients with dementia receiving atypical anti-psychotics (*1*). The Advisory applies to clozapine (Clozaril), risperidone (Risperdal), quetiapine (Seroquel) and olanzapine (Zyprexa) and is based on recent trials that found that elderly patients with dementia receiving atypical anti-psychotics had a 1.6-fold greater death rate than those receiving placebo. Health Canada is requesting that all manufacturers of these drugs add a warning highlighting this risk to their safety information sheets. The agency is advising patients to continue taking their medication as usual and to contact their doctor with any concerns. The US FDA has issued a Public Health Advisory highlighting the increased death rate associated with the use of atypical antipsychotics for behavioural disorders in elderly patients with dementia, and has also requested that manufacturers add a boxed warning (*2*). (See WHO Pharmaceuticals Newsletter No. 2, 2004 for similar warnings issued by the European Medicines Agency (EMEA) and the UK Committee on Safety of Medicines concerning the use of olanzapine and risperidone in the elderly population).

References:

1. 'Dear Health-care Professional' letter from Health Canada, 22 June 2005 (http://www.hc-sc.gc.ca).

2. FDA Public Health Advisory. United States Food and Drug Administration, 11 April 2005 (http://www.fda.gov).

Cyclo-oxygenase-2 (COX-2) Inhibitors

To be available under strict restrictions

New Zealand. Following the recommendations made by New Zealand's Medicines Adverse Reactions Committee (MARC), the country's Ministry of Health has decided that COX-2 inhibitors will be allowed to stay on the market, but with *"considerably stronger warnings"(1)*. New Zealand's Medicines and Medical Devices Safety Authority (Medsafe) has sent a fax to doctors and pharmacists communicating this decision, along with the following recommendations (*2*):

- COX-2 inhibitors should be contraindicated in patients with previous myocardial infarction (MI) or stroke and perioperatively for cardiac or vascular surgery, and perioperatively for major surgery in patients at high cardiovascular (CV) risk.
- Etoricoxib should be contraindicated in patients with poorly controlled hypertension.
- COX-2 inhibitors should not be used if alternatives exist, and, if used, the lowest effective dose should be used for the shortest possible duration.
- Patients should be reviewed after 2 weeks, with treatment discontinued in the absence of benefit, then reviewed every 3 months.
- Prescribers need to be aware that COX-2 inhibitors may exacerbate hypertension, cardiac failure or oedema.
- Prophylactic aspirin should not be discontinued.
- All patients at high CV risk should be informed of the risks with COX-2 inhibitors.
- Discussions regarding perioperative use of COX-2 inhibitors should be undertaken prior to surgery.

Medsafe is in the process of implementing MARC's recommendations and has asked that pharmaceutical companies continue with the voluntary moratorium on direct-to-consumer and professional advertising of COX-2 inhibitors.

References:

1. Media Release. Medsafe, 29 April 2005 (http://www.medsafe.govt.nz).
2. Alert/letter to doctors and pharmacists. Medsafe, 29 April 2005 (http://www.medsafe.govt.nz).

Cyproterone acetate and ethinylestradiol

Not to be used in contraception

Canada. Health Canada is advising consumers that the authority has reached an agreement with Berlex, manufacturer of ethinylestradiol/cyproterone (Diane-35) on revised labelling for its use in Canada.
The following warnings are included on the new package insert:

- Ethinylestradiol/cyproterone (Diane-35) must not be used in women who currently have, or have a history of, thromboembolic disorders or thrombophlebitis.
- Ethinylestradiol/cyproterone (Diane-35) should not be prescribed for contraception alone.
- Women should not use oral contraceptives during ethinylestradiol/cyproterone (Diane-35)-treatment.
- Ethinylestradiol/cyproterone (Diane-35) should be stopped 3–4 months after the complete resolution of the signs of acne.
- In some published studies, women who used ethinylestradiol/cyproterone (Diane-35) appeared to have a higher risk of blood clots than women who used combination oral contraceptives.
- Cigarette smoking increases the risk of serious cardiovascular adverse effects from ethinylestradiol/cyproterone (Diane-35), and the risk increases with heavy smoking and age (more marked in women aged ≥ 35 years).

Patients are advised to inform their doctor if they currently have, or have a history of, blood clots, myocardial infarction, stroke or chest pain.

References:

Advisories and Warnings. Health Canada, 12 May 2005 (http://www.hc-sc.gc.ca).

Donepezil

Warning of rhabdomyolysis

Japan. The Ministry of Health, Labour and Welfare in Japan has added a new warning on the possibility of rhabdomyolysis associated with the use of donepezil (Aricept), an acetylcholinesterase inhibitor drug. The Ministry enforced this action following the death of a 70 year-old man with Alzheimer's disease and other complications who was treated with this drug. The warning advises that treatment should be halted if muscle pain, elevated urine/blood myoglobin levels or acute kidney failure are detected.

Reference:

Scrip World Pharmaceutical News No. 3067, 29 June 2005 (http://www.scripnews.com).

Drotrecogin alfa (activated)

Only for use in high-risk patients

Europe. The EMEA's Committee for Medicinal Products for Human Use (CHMP) has recommended drotrecogin alfa (Xigris) be used only in high-risk patients (that is patients at a high risk of death from sepsis associated with acute organ dysfunction) and when therapy can be started within 24 hours of organ failure. Additionally, the committee has recommended that drotrecogin alfa (Xigris) be used only by experienced doctors in institutions skilled in the care of patients with severe sepsis, and that the agent should not be used in patients with single organ dysfunction, especially if they have had recent surgery. It may be recalled that some months ago Eli Lilly had issued letters to health professionals in Canada and in the US warning about a higher mortality in patients treated with drotrecogin alfa compared to placebo (see WHO Pharmaceuticals newsletter No. , 2005).

Reference:
EMEA's post-authorisation summary of opinion for Xigris, EMEA/138447/2005, 21 April 2005 (http://www.emea.eu.int).

Efavirenz

Reports of neural tube defects

USA. Bristol-Myers Squibb has issued a `Dear Health-care Provider' letter advising of a change in the pregnancy category for efavirenz (Sustiva) from Category C (risk of fetal harm cannot be ruled out) to D (positive evidence of fetal risk), following four retrospective reports of neural tube defects (three cases of spina bifida cystica and one of Dandy Walker syndrome) in infants born to women who received efavirenz in their first trimester of pregnancy. Bristol-Myers Squibb warns that, prior to initiation of efavirenz (Sustiva), women of child-bearing potential should undergo pregnancy testing. The company also recommends that women receiving efavirenz (Sustiva) should avoid pregnancy, and that efavirenz (Sustiva) should be used during the first trimester only "*if the potential benefit justifies the potential risk to the fetus*".

Reference:
'Dear Health-care Provider' letter from Bristol-Myers Squibb Company, March 2005 (http://www.fda.gov).

Efalizumab

Immune mediated haemolytic anaemia

USA. Genentech has issued a new warning regarding events of immune-mediated haemoltyic anaemia associated with efalizumab-use, indicated in the treatment of severe plaque psoriasis in adult patients (18 years or older). According to Genentech, two cases of haemolytic anaemia were observed in efalizumab (Raptiva) clinical trials; two additional cases were reported in the postmarketing setting. In its letter to health-care providers Genentech has stated that a causal relationship between efalizumab (Raptiva) and these events has not been established but cannot be excluded and that health-care providers should discontinue treatment if haemolytic anaemia occurs.

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

Galantamine

Death in subjects with mild cognitive impairment

USA. The prescribing information for galantamine (Reminyl) has been updated to reflect the results of two randomised placebo-controlled clinical trials in which 13 of 1026 patients with mild cognitive impairment receiving galantamine (Reminyl) died, compared with 1 of 1022 patients who received placebo. Ortho-McNeil Neurologics Inc. has issued a `Dear Health-care Professional' letter to advise that the results of these trials have been added to the Precautions section of the Reminyl Prescribing Information. In this letter, Ortho-McNeil Neurologics Inc. notes that galantamine (Reminyl) is approved only for the treatment of mild to moderate Alzheimer's disease.

Reference:
'Dear Health-care Professional' letter from Ortho-McNeil Neurologics Inc., 31 March 2005 (http://www.fda.gov).

Hydromorphone hydrochloride

To be withdrawn for safety reasons

USA. The FDA has advised Purdue Pharma to suspend the sales and marketing of hydromorphone hydrochloride (Palladone) controlled-release capsules in the US, as co-ingestion of the drug with alcohol may cause severe adverse effects, such as depressed breathing, coma and even death. The FDA is not aware of any reports of life-threatening adverse effects in patients drinking alcohol while receiving hydromorphone, which has been for sale in the US since January 2005. However, the results of a recent company-sponsored

pharmacokinetic (PK) study show that the co-ingestion of alcohol affects hydromorphone hydrochloride's controlled-release mechanism, which may lead to the rapid release of hydromorphone and result in high peak plasma hydromorphone concentrations; during the co-ingestion of hydromorphone and 4% alcohol, some subjects developed almost twice the peak plasma hydromorphone concentration observed with the ingestion of hydromorphone hydrochloride and water. Based on available data, the agency has concluded that the overall hydromorphone hydrochloride (Palladone) risk/benefit profile is unfavourable because of this potentially fatal interaction.

The FDA advises health-care providers, who have prescribed hydromorphone hydrochloride, to contact patients who are affected, to advise them not to use hydromorphone with concomitant alcohol, and to prescribe an appropriate substitute. Patients receiving hydromorphone hydrochloride (Palladone) are advised to contact their physician to discuss alternative treatment, including immediate-release hydromorphone, and to avoid alcohol, or medicines containing alcohol, on the days that they take hydromorphone. The FDA recommends that unused hydromorphone hydrochloride (Palladone)-capsules should be flushed down the toilet for safe

anticoagulation in patients with heparin induced thrombocytopenia (HIT) and associated thromboembolic disease in order to prevent further thromboembolic complications. As of April 25, 2005, the product monograph has been updated with the following information:

- Serious thrombotic events can occur in HIT patients. Caution should be exercised in the timing of drug administration during the transition period between discontinuing parenteral anticoagulation therapy, such as lepirudin (REFLUDAN) , and starting oral anticoagulation.
- Coumarin derivatives should only be initiated when platelet counts are normalizing. The intended maintenance dose should be started with no loading dose. To avoid prothrombotic effects when initiating coumarin, lepirudin (REFLUDAN) should be continued for 4 to 5 days and discontinued when the International Normalized Ratio (INR) stabilizes within the desired target range.

In a letter to health professionals, Berlex Canada Inc. writes that 'coumarin therapy be avoided during acute HIT and only be initiated after a substantial recovery of the platelet count has occurred

Mitoxantrone

Label to reflect risks of cardiotoxicity

USA. Mitoxantrone (Novantrone) is approved for use in patients with secondary progressive, progressive relapsing, or worsening relapsing-remitting multiple sclerosis. In the US, mitoxantrone (Novantrone) label has been revised to state that cardiac monitoring should be performed at baseline, and before every dose of mitoxantrone, in patients with multiple sclerosis receiving the drug. The revisions follow post-marketing reports that show diminished cardiac function in patients occurring early on in treatment with the product. The Boxed Warning, Warnings, and Dosage and Administration sections of the label have been revised.

Reference:
'Dear Health-care Professional' letter from Serono, April 2005 (http://www.fda.gov).

NSAIDs

Black box warning for both prescription and OTC products

USA. FDA has requested that sponsors of all non-steroidal anti-inflammatory drugs (NSAID) make labelling changes to their products. The FDA has recommended label changes for both the