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EDITORIAL

We are pleased to report that the first meeting of the newly established Advisory Committee on Safety of Medicinal Products was held in October. This meeting was very productive and a number of recommendations as published in this issue were made. A statement was made by this Committee recommending the need to incorporate pharmacovigilance in the WHO strategy to provide antiretrovirals to three million people by 2005. The feature article emphasizes the urgency in evolving a safety strategy for herbal issues as these remain largely un-addressed.

Representatives from WHO attended the International Conference on Harmonization (ICH) expert working group meetings in November, in Osaka, as observers. The document Pharmacovigilance Planning, which describes the link between pre- and post-marketing surveillance will now be circulated to Member States for comments. The 26th Annual Meeting of the National Centres participating in the International Drug Monitoring Programme will be held in December, in India. The meeting will focus on ADR reporting and how it can be improved. A detailed report of this meeting will appear in one of the later issues.

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Reference:

Communication from ANMAT, 19 Aug 2003. Available from URL: http://www.anmat.gov.ar

BICALUTAMIDE

Withdrawn due to accelerated deaths

Canada, UK. Following discussions with Health Canada, AstraZeneca has issued a `Dear Health Care Professional' letter recommending that, due to a trend towards accelerated deaths, clinicians discontinue use of bicalutamide (Casodex) 150mg in patients with localised prostate cancer otherwise managed by watchful waiting (i.e., therapy initiated only if signs or symptoms of disease progression occur). Approval was granted in November 2002 for bicalutamide 150mg as immediate therapy in some patients with localised prostate cancer for whom surgery or radiation was inappropriate. Health Canada has now withdrawn this approval after reviewing data from a planned second analysis of the Early Prostate Cancer trial programme that show a trend towards accelerated deaths in patients with localised prostate cancer who received bicalutamide 150mg, compared with those who received placebo (196 [25.2%] deaths vs 174 [20.5%] deaths; hazard ratio 1.23; 95% CI 1−1.5). Based on this data, along with the absence of factors suggesting a high risk of disease progression in patients with localised prostate cancer otherwise managed by watchful waiting, AstraZeneca has recommended that bicalutamide 150mg be discontinued in such patients. Patients taking bicalutamide 50 mg/day for metastatic prostate cancer are not affected by this new information[(1)]. The Committee on Safety of Medicines in the UK has advised that for patients with localized prostate cancer, the balanced risk benefit of bicalutamide is unfavourable and the product is no longer licensed for the treatment of this condition. Other approved uses are not affected. Patients receiving bicalutamide for localized prostate cancer should be reviewed at the earliest opportunity and treatment discontinued[(2)].

References:

1. *Health Canada Warnings and Advisories, 18 Aug 2003. Available from URL: http://www.hc-sc.gc.ca*
2. *Communication from the Committee on Safety of Medicines, 28 Oct 2003. Available from URL: http://www.mhra.gov.uk*

DACLIZUMAB

Warning about hypersensitivity reactions, increased mortality in cardiac transplant study

USA. The US prescribing information for daclizumab (Zenapax) has been updated to include two new warning statements regarding increased mortality seen in a cardiac transplant study and hypersensitivity reactions. Roche Pharmaceuticals has issued a 'Dear Healthcare Professional' letter informing prescribers of the updates. The addition of information to the 'Warnings' section of the product label regarding increased mortality reflects the findings of a randomised, double-blind, placebo-controlled trial of daclizumab (Zenapax) for the prevention of allograft rejection, in which 434 cardiac transplant recipients received concomitant cyclosporin, mycophenolate mofetil and corticosteroids. In the study, increased mortality was seen at 6 and 12 months in patients receiving daclizumab (Zenapax) compared with those receiving placebo (7% vs 5% and 10% vs 6%, respectively). Some of the increased mortality appeared to be related to a higher incidence of severe infection. Other sections of the product (Zenapax) labelling affected by the addition of this information have also been updated. Current information relating to the risk of hypersensitivity reactions has also been added to the 'Warnings' section, which states that severe, acute (onset within 24 hours) hypersensitivity reactions including anaphylaxis have been observed both on initial exposure and following re-exposure to the product. Permanent discontinuation of daclizumab is advised in the event of a severe hypersensitivity reaction.

Reports in WHO-file: Allergic reaction 3, anaphylactoid reaction 2

Reference:

'Dear Healthcare Professional' letter from Roche Pharmaceuticals, Aug 2003. Available from URL: http://www.fda.gov

DANAZOL

Use restricted to second-line therapy in endometriosis

UK. The use of danazol (Danol) has been restricted to second-line therapy in endometriosis and benign fibrocystic breast disease, as a result of safety and risk-benefit assessments suggesting that it may increase the baseline risk of ovarian cancer in patients being treated for endometriosis. The following indications have been removed from the Danol Summary of Product Characteristics (SPC): gynaecomastia, pre-operative thinning of the endometrium prior to surgery, dysfunctional uterine bleeding

presenting as menorrhagia to control excessive blood loss and to control dysmenorrhoea, control of benign, multiple or recurrent breast cysts in conjunction with aspiration.

Reference:
News & Updates, UKMi, 10 Sept 2003. Available from URL: http://www.druginfozone.nhs.uk

LEVACETYL-METHADOL

Product to be withdrawn due to adverse cardiac events; safer alternatives to be adopted

USA. Roxane Laboratories is to discontinue the sale and distribution of levacetylmethadol (Orlaam) Oral Solution 10 mg/mL in the US due to increasing reports of severe adverse cardiac events. Since the product (Orlaam) was introduced in 1995 for the management of opioid dependence, Roxane has received 15 reports of QT interval prolongation, eight of torsade de pointes and six of cardiac arrest, as well as reports of arrhythmias, syncope and angina. These reports led to the removal of levacetylmethadol (Orlaam) from the European market in March 2001 and extensive changes to the US package insert in April 2001. With less toxic treatment alternatives available, the company now believes that the risks of levacetylmethadol (Orlaam) use no longer outweigh its benefits. The product will be discontinued after the current inventory is depleted, which is estimated to occur in early 2004.

Reference:
'Dear Healthcare Professional' letter from Roxane Laboratories Inc, 23 Aug 2003. Available from URL: http://www.fda.gov

MOROCTOCOG ALFA

Reports of lack of effect in prophylaxis patients

Canada. Wyeth Canada is informing physicians of changes to the Precautions and Adverse Reactions sections of the product monograph for moroctocog alfa (Refacto, Recombinant Anti-haemophilic Factor). Moroctocog alfa (Refacto, Antihaemophilic Factor Recombinant) has been licensed in Canada since 2002 and is indicated for the control and prevention of haemorrhagic episodes and for routine and surgical prophylaxis in patients with haemophilia A. Reports of lack of effect, mainly in prophylaxis patients, have been received during the clinical trials and in the post-marketing setting with this product (Refacto, Antihaemophilic Factor) in Canada. The lack of effect and/or low factor VIII recovery has been reported in patients with inhibitors and also in patients who had no evidence of inhibitors. The lack of effect has been described as bleeding into target joints, bleeding into new joints, other bleeding or a subjective feeling by the patient of new onset bleeding. The product insert now reflects these observations and advises that, in view of these reports of less than expected therapeutic effect, it is important to individually titrate and monitor each patient's dose of moroctocog alfa (ReFacto), particularly when initiating treatment, to ensure an adequate therapeutic response.

Reference:
'Dear Healthcare Professional' letter from Wyeth Canada, 30 Sept 2003. Available from URL: http://www.hc-sc.gc.ca

NEFAZODONE

Sale discontinued due to adverse hepatic events

Canada. On 27 November 2003 Bristol-Myers Squibb Canada will discontinue the sale of nefazodone (Serzone-5HT2), indicated for the symptomatic relief of depressive illness. This decision follows several reports of hepatotoxicity associated with nefazodone use. Since its introduction in 1994, nefazodone has been temporally associated with hepatic adverse events such as jaundice, hepatitis and hepatocellular necrosis in patients receiving therapeutic doses. As of December 2002 there were 51 Canadian reports of hepatotoxicity ranging from no symptoms to transplantation, suspected to be associated with nefazodone use. Cases of liver injury have occurred as early as a few weeks after initiation of therapy or after continuous use for up to three years. Physicians are advised to arrange alternate therapies before 27 November 2003 for their patients currently on nefazodone and to consult the product monographs for both nefazodone and the chosen alternate antidepressant before making the switch.

Reference:
'Dear Healthcare Professional' letter from Bristol-Myers Squibb Canada, 2 Oct 2003. Available from URL: http://www.hc-sc.gc.ca

NIMESULIDE

Product under 'special pharmacovigilance'

Argentina. The food, drug and medical devices agency in Argentina, ANMAT, has directed that nimesulide should be brought under the category of products under 'special pharmacovigilance'. This category includes those drugs that are put under high alert and scrutiny for adverse reactions. Manufacturers are obliged to report all adverse effects associated with nimesulide use. (For other related information on nimesulide, see WHO Pharmaceuticals Newsletter No. 2, 3 & 4, 2002; 3 & 4, 2003).

Reference:
Disposicion de ANMAT no 4087/03, 6 Aug 2003.

OSELTAMIVIR

Adverse reactions section to include acute renal failure, thrombocytopenia, leucopenia

Japan. The Pharmaceuticals and Food Safety Bureau's Safety Division has advised that acute renal failure, leucopenia and thrombocytopenia should be added as clinically significant adverse reactions to the product insert of oseltamivir (Tamiflu) indicated in the treatment of influenza. These additions are based on reports associating oseltamivir (Tamiflu) use with acute renal failure and acute hepatitis. It is recommended that patients be carefully observed upon onset of acute renal failure and appropriate measures taken immediately if any abnormalities occur. In case of leukopenia and thrombocytopenia, the drug should be discontinued.

Reference:
Pharma Japan 1859, 8 Sept 2003.

PHENYLPROPAN-OLAMINE

New warnings on cardiovascular risks to be added

Japan. The Ministry of Health, Labour and Welfare (MHLW) has asked manufacturers of products containing phenylpropanolamine (PPA) to include new warnings on cardiovascular risks. The move follows several reports of cerebral haemorrhage and other problems associated with the use of PPA containing products. Around 170 products, mostly OTC cough and cold preparations containing PPA, are available in Japan. Although a US study published in 2000 suggested a link between PPA and haemorrhagic stroke, the Japanese government did not impose use restrictions at the time since the US study observations were based on a much higher dose (150 mg) used in appetite suppressants and diet aids compared with the more conservative maximum daily dose of 100 mg in the OTC preparations in Japan; appetite suppressants are not approved in Japan. The PPA products in Japan already carry warnings about the potential risk in people with a history of high blood pressure or other cardiovascular problems. Despite these, there have been several adverse drug reaction reports necessitating the current move by MHLW to include stricter warnings on possible side effects, including cerebral haemorrhage. The MHLW has not restricted sales but is encouraging manufacturers to develop non-PPA products. (Also see WHO Pharmaceuticals Newsletter No. 4, 1996).

Reference:
Scrip World Pharmaceutical News No. 2876, 15 Aug 2003.

SOMATROPIN

Refused approval for use in AIDS-related wasting syndrome

Europe. The Committee for Proprietary Medicinal Products (CPMP) in Europe has once again refused to approve the use of Serono's somatropin (Serostim) in treating AIDS-related wasting syndrome (cachexia). The company's application was similarly turned down earlier in the year. The CPMP said it was unable to identify a target population for somatropin (Serostim) treatment because of the heterogeneity of the study group in terms of body composition and antiviral options. A lack of long-term efficacy data, concerns over the safety profile following repeated administration in AIDS patients and doubts about the clinical relevance of the primary endpoints are also cited as reasons for the refusal. The US FDA has accorded full approval for using somatropin (Serostim) in cachexia.

Reference:
PharmaTimes News Online, 5 Sept 2003. Available from URL: http://www.pharmatimes.com

TERFENADINE

Withdrawn due to ventricular arrhythmias

Argentina. As of 19 August 2003, the Food, Drug and Medical Devices agency in Argentina, ANMAT, has withdrawn the marketing authorization for all products containing terfenadine. This measure follows associations of life-threatening ventricular arrhythmias with terfenadine. (Also see WHO Pharmaceuticals Newsletter No. 3&4, 5&6, 1998; 5&6, 9&12, 1999 for previous withdrawals).

Reference:
Communication from ANMAT, 19 Aug 2003. Available from URL: http://www.anmat.gov.ar

VALSARTAN

Reports of interstitial pneumonia

Japan. The Pharmaceuticals and Food Safety Bureau's Safety Division has advised that interstitial pneumonia should be added to the list of adverse reactions associated with the use of the antihypertensive valsartan (Diovan). The product insert will now warn that interstitial pneumonia-associated symptoms such as fever, cough, dyspnoea and abnormalities in chest X-rays may occur with the use of valsartan (Diovan). If such symptoms are observed following treatment with valsartan, the drug should be discontinued and appropriate measures such as adrenocorticosteroid hormone administration should be initiated.

Reference:
Pharma Japan 1859, 8 Sept 2003.

ROFECOXIB/ CELECOXIB

GI adverse effects

Australia. A significant number of cases of GI adverse effects associated with rofecoxib and celecoxib have been reported to the Adverse Drug Reactions Advisory Committee (ADRAC), many involving elderly patients with known risk factors. However, 16 reports of celecoxib-associated peptic ulcer and 16 of celecoxib- and 5 of rofecoxib - associated GI haemorrhage occurred in patients aged less than 60 years with no stated risk factors. The Committee points out that 'the serious events reported to ADRAC suggest that selective COX-2 inhibitors should be treated with similar caution to other NSAIDs'.

Reference:
Australian Adverse Drug Reactions Bulletin 22: 15, No. 4, Aug 2003.

HRT

CPMP to re-evaluate risk-benefit

France. The French Regulatory Agency AFFSSAPS, in collaboration with the European Medicines Evaluation Agency, will re-evaluate the risk-benefit profile of hormone replacement therapy (HRT) in order to see how the results of the Million Women study might be incorporated into the body of knowledge for HRT. As reported

LEVETIRACETAM & LOPINAVIR/ RITONAVIR

Potential for dispensing errors

USA. UCB Pharma, in collaboration with the US FDA is warning healthcare professionals about the potential for dispensing errors with levetiracetam (Kepra) and lopinavir/ritonavir (Kaletra) products on account of their similar sounding trade names. Levetiracetam (Kepra) is an antiepileptic, while lopinavir/ ritonavir is an antiretroviral. Physicians are requested to spell the drug names correctly and to write clearly as can be easily read and understood by the person filling the prescription. And, where appropriate, the intended use should also be indicated; patients should be advised to carefully counter-check all medications they receive at the pharmacy and to immediately contact the pharmacist for any observed discrepancies.

Reference:
'Dear Healthcare Professional' letter from UCB Pharma Inc, Sept 2003. Available from URL: http://www.fda.gov

MEFLOQUINE HYDRO-CHLORIDE

Issuance of medication

consumer language to summarize information in the professional package insert, including the approved indication and major adverse events. Healthcare professionals are advised to provide this guide to anyone who is given mefloquine hydrochloride (Lariam) for the prophylaxis of malaria. The guide is intended only for travellers who are taking mefloquine hydrochloride (Lariam) to prevent malaria and may not apply to patients who are sick with malaria and who are taking the product to treat malaria.

Reference:
'Dear Healthcare Professional' letter from Roche Laboratories, Sept 2003. Available from URL: http://www.fda.gov/medwatch

REPAGLINIDE & GEMFIBROZIL

Risk of hypoglycaemia with concomitant use

Canada. Novo Nordisk Canada Inc. has informed healthcare professionals that the concomitant use of repaglinide and gemfibrozil is now contraindicated, following the publication of a study in healthy volunteers demonstrating a markedly enhanced blood glucose-lowering response to repaglinide (GlucoNorm) with concomitant gemfibrozil. The Company says that these findings indicate a potential risk of severe and prolonged hypoglycaemia and it has