No. 2, 2003

EDITORIAL

As always, this issue features drug safety and regulatory information from Member States. But, equally, as always, the vast majority of the information has been collated from the 'usual' contributors. The newsletter aims to provide uniform, global and unbiased exchange of information, an objective that can be truly achieved only with the full participation of all concerned. We take this opportunity to once again request all Member States to provide us with active updates on drug safety information. WHO contact details are posted on the outside cover of the newsletter for your convenience.

In recent weeks there has been some interest in the 'old' drug thalidomide. The drug has been used in treating some of the complications in leprosy and more recently some rare forms of cancer. The feature article on thalidomide discusses some of the issues concerning the reintroduction of this drug.

At the end of March, beginning of April a training course on pharmacovigilance was held in Lusaka, Zambia. This was a training course with a difference in that the focus was on antimalarial drugs. In the months to come, this initiative will be consolidated through appropriate country support. New projects are being planned to further the concept of drug safety in public health programmes. A full report of the Lusaka training course will be available in the next issue of the newsletter.

Contents ❑

TABLE OF CONTENTS

REGULATORY MATTERS

SAFETY OF MEDICINES

DRUGS OF CURRENT INTEREST

FEATURE

ANTIHYPER-TENSIVE AGENT

Unapproved product containing prescription medicines recalled

USA. The US FDA has directed Herbsland Inc to recall an unapproved antihypertensive preparation (Ancom Anti-Hypertensive Compound Tablet) labelled to contain several prescription medicines. Herbsland Inc. is recalling all 100-tablet bottles of the preparation that contains several prescription medicines including reserpine, diazepam, promethazine and hydrochlorothiazide. The sale of this combination without a prescription poses serious health risks including sedation, depression and potentially life-threatening blood abnormalities, although no illnesses have yet been reported. Consumers are urged to stop taking this preparation and to consult their physician if they have experienced any adverse event while taking this product.

Reference:
Media Release, 17 Jan 2003.
Available from URL:
http://www.fda.gov

DESLORATADINE

Not recommended during pregnancy

Europe. The product information for desloratadine (an antihistamine) is to be revised to warn against its use during pregnancy, following a review by the European Medicines Evaluation Agency's Committee for Proprietary Medicinal Products. Desloratadine (Azomyr, Opulis, Allex, Aerius) is the major metabolite of loratadine. Although a causal relationship between hypospadias (a urogenital abnormality) and the use of products containing loratadine during pregnancy could not be confirmed or excluded, the product information for desloratadine is to be revised, as a precautionary measure, to state that its use during pregnancy is not recommended. A separate review of loratadine-containing products is ongoing.

Reports in WHO-file:
Face malformation 1, vascular malformation peripheral 1

Reference:
European Agency for the Evaluation of Medicinal Products(Committee for Proprietary Medicinal Products) December 2002 plenary meeting monthly report, 6 Jan 2003.
Available from URL:
http://www.emea.eu.int

ERGOTAMINE/ DIHYDRO ERGOTAMINE

Contraindicated with CYP3A4 inhibitors

Canada. Novartis Pharmaceuticals Canada Inc, in consultation with Health Canada, has advised healthcare providers of a new contraindication related to the concomitant use of potent CYP3A4 inhibitors with ergotamine- or dihydroergotamine mesylate-containing products following reports of serious and life-threatening cases of cerebral and peripheral ischaemia, including fatalities and amputations. CYP3A4 inhibition is known to elevate serum levels of ergotamine and dihydroergotamine mesylate and increase the risk of ergotism, characterised by vasospasm leading to cerebral and peripheral ischaemia. Potent CYP3A4 inhibitors include protease inhibitors, macrolide antibacterials and antifungal agents. While these adverse events have not been reported with less potent CYP3A4 inhibitors, Novartis warns that there is a potential risk for serious toxicity when used with ergotamine- or dihydroergotamine mesylate-containing products. The appropriate sections of the product (Bellergal Spacetabs, Cafergot suppositories and tablets, Cafergot-PB suppositories, injectable DHE and Migranal nasal spray) monographs are to be updated accordingly. The labelling for generic ergotamine- or dihydroergotamine mesylate-containing products is also expected to be updated to reflect the revised Novartis labelling. Novartis points out that the chronic daily use of ergotamine- or dihydroergotamine mesylate-containing products is not recommended and increases the risk of ergotism and rare fibrotic complications.

Reference:
'Dear Healthcare Provider' letter from Novartis Pharmaceuticals Canada Inc, 30 Jan 2003.
Available from URL:
http://www.hc-sc.gc.ca

ETANERCEPT, ANAKINRA

Concurrent administration not recommended

Europe. The European Medicines Evaluation Agency (EMEA) has issued a public statement advising that the concurrent administration of anakinra (Kineret) and etanercept (Enbrel) is not authorized or recommended. The statement comes after a recently completed clinical trial sponsored by Amgen Inc demonstrated a higher incidence of serious infection and neutropenia in patients receiving concomitant anakinra and etanercept than in patients receiving either drug alone. The combined treatment did not show any additional benefit compared with etanercept therapy alone and, accordingly, the concurrent administration of anakinra and etanercept is not recommended. The EMEA notes that anakinra is indicated for the treatment of rheumatoid arthritis (RA) in combination with methotrexate, in patients with RA refractory to methotrexate alone, while etanercept is indicated for active juvenile RA and active RA or psoriatic arthritis in adults who have had an inadequate response to disease-modifying antirheumatic drugs, or in patients naive to methotrexate. The concurrent

administration of anakinra and etanercept is not a licensed use for either drug. The agency notes that the safety and efficacy of anakinra in combination with other tumour necrosis factor antagonists has not been established and therefore their combined administration is not recommended. The above EMEA statement is consistent with the earlier Health Canada warning about the increased risk of serious infections in patients treated with a combination of etanercept and anakinra (Interleukin-1 receptor antagonist, Kineret; WHO Pharmaceuticals Newsletter No.1, 2003).

Reference:
EMEA Public Statement, 5 Feb 2003. Available from URL: http://www.emea.eu.int

EDARAVONE

To be used with caution in elderly

Japan. The Safety Division for pharmaceutical products in Japan has issued a notification to the manufacturer of edaravone (Radicut) that the package insert should include 'elderly patients' in its list of people requiring cautious administration. This addition follows the high incidence of fatal reports with edaravone. The package monograph will now also have 'disseminated intravascular coagulation syndrome' added to the list of clinically significant adverse drug reactions. Edaravone is indicated for the improvement of neurological syndrome and functional disorders associated with cerebral infarction at an acute stage. The drug was launched in June 2001 and later, in 2002 renal failure was added as an adverse drug reaction following reports of 3 deaths from renal impairment in patients treated with edaravone (WHO Pharmaceuticals Newsletter No.1, 2003).

Reference:
Pharma Japan 1827/13 Jan 2003.

GEFITINIB

Recommendations from advisory committee

Japan. In October 2002 the Safety Division of the Japanese Pharmaceutical and Food Safety Bureau directed the revision of the product label to include warnings about interstitial pneumonia with gefitinib, an antineoplastic agent used in the treatment of non-small cell lung cancer (WHO Pharmaceuticals Newsletter, No.4, 2002). In addition an advisory committee was appointed to fully review gefitinib related safety issues in Japan. This committee has made the following recommendations:

1. Active dissemination of safety information to doctors; patient education for informed consent

- The company should actively offer all available information on safety and efficacy to physicians
- The doctor should explain fully to the patients the risk of fatal adverse reactions, initial symptoms of adverse reaction such as breathlessness etc before they prescribe gefitinib.

2. For use under more controlled conditions

- Gefitinib should be prescribed by doctors who have sufficient experience with lung cancer chemotherapy. The drug should be used in hospitals that can adequately treat any noxious adverse drug reactions (ADRs) that may occur with gefitinib use.
- For the first 4 weeks, treatment with gefitinib has to be given under hospital care or to patients under close observation since critical ADRs are observed during the early phase of medication.

3. New addition to package insert

- The section on 'Careful Administration' will note the need for caution in administering the drug to patients with acute lung injury, interstitial pneumonia, pulmonary fibrosis, or a medical history of such diseases since the drug could worsen the situation.

4. Information for patients

- The company should provide timely and accurate 'patient information' on the ADRs, number of reports and deaths, to help sensitize patients and their family to the ADRs and to facilitate early reporting of ADRs.

5. Strengthening of safety measures by the company

- The company is required to conduct research into the mechanism of induction of interstitial pneumonia and have a committee of experts discuss the results.
- The company will put in place a coordinated method of data collection for serious ADRs, and a program for a prospective trial to clarify the risk factor of interstitial pneumonia and acute lung injury with gefitinib.

Reference:
Communication to WHO from the Ministry of Health, Labour and Welfare, Japan, March 2003.

INTERFERON BETA-1A

Label revised to reflect new safety information

USA. The US FDA has asked Biogen to change the Warnings, Precautions, Adverse Reactions, Patient Information, and Clinical Studies sections of the prescribing information for Interferon beta-1a (Avonex) to include important new safety information. A cautionary note regarding use in patients with depression and other severe psychiatric symptoms, post-marketing reports of depression, suicidal ideation and/or

development of new or worsening of pre-existing psychiatric disorders including psychosis, and reports of anaphylaxis, pancytopenia, thrombocytopenia, autoimmune disorders of multiple target organs, and hepatic injury manifesting itself as elevated serum enzyme levels and hepatitis have been added to the labelling. A three-year study with interferon beta-1a (Avonex) showed that the drug is effective in the early treatment of multiple sclerosis (MS). On January 31 the FDA approved its use as an early treatment in MS and the clinical study data which formed the basis for the FDA decision is now included in the Clinical Studies section.

Reference:

'Dear Healthcare Professional' letter from Biogen, 7 March 2003. Available from URL: http://www.fda.gov

INTRAVENOUS FIBRINOLYTICS

Statement against use in diabetics removed

Europe. The Committee for Proprietary Medicinal Products (CPMP) has directed that the product insert for intravenous (IV) fibrinolytics should no longer include the statement contra-indicating the use of these products for treating myocardial infarction in diabetics or in those with diabetic retinopathy. Currently all IV fibrinolytics are contraindicated for use in patents with diabetic haemorrhage retinopathy in all EU member states. However the CPMP has approved the removal of this restriction after reviewing clinical trial data, published data and pharmacovigilance data-bases; the committee's analysis has shown that the benefit of increased survival and reduced cardiac morbidity in these patients far outweighs the risk of intraocular haemorrhage.

Reference:

CPMP Position Statement, 20 Feb 2003. Available from URL: http://www.emea.eu.int

METRODIN HP

Withdrawn due to risk of vCJD

UK. Metrodin High Purity (HP), a product used in the treatment of infertility and manufactured from urine sourced from Italy, is being withdrawn in the UK by the Committee on Safety of Medicines (CSM), following confirmation of a case of variant Creutzfeldt-Jakob Disease (vCJD) in Italy. The withdrawal of Metrodin HP is based on the precautionary principle that products manufactured using human urine from a country where at least one case of vCJD has been confirmed should not be used whenever practicable. This principle initially related only to human blood plasma but following a publication reporting the presence of an abnormal prion protein in the urine of CJD patients, the CSM advised that the same principle should apply to urine (see under 'Plasma / Urinary Medicinal Products). The chairman of the CSM, Professor Alasdair Breckenridge, says that after careful consideration the CSM advised that even a theoretical risk such as that associated with Metrodin HP was unacceptable given that there are alternative treatments, but he stressed that there have been no reported cases of the transmission of CJD via urine or products derived from urine.

Reference:

Medicines Control Agency Media Release, 10 Feb 2003. Available from URL: http://www.mca.gov.uk

OESTROGEN/ PROGESTOGEN

FDA proposes HT class labelling to include WHI data

USA. The US FDA has issued a letter to manufacturers of oestrogen- and progestogen-based hormone therapy (HT) products requesting that all hormone therapy labelling be updated to incorporate the findings of the Women's Health Initiative (WHI) study. The FDA has requested the labelling changes following an analysis of the WHI data, which showed an increased risk of breast cancer and cardiovascular disease with Wyeth's conjugated oestrogens/ medroxyprogesterone product (Prempro) compared with placebo. The FDA's labelling recommendations include the addition of a black box warning concerning the increased risk of cardiovascular disease and breast cancer, and revised indications for postmenopausal osteoporosis and vulvar/vaginal atrophy. Manufacturers had until early March to submit data to the FDA to justify exemptions to the proposed class labelling. The proposed labelling states that, in the absence of comparable data, the risks identified in the WHI study should be assumed to be similar for other doses and combinations of oestrogens and progestogens and that, because of the risks, oestrogens with or without progestogens should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals.

Reference:

Hormone therapy class labelling uses Wyeth template; appeals due by March. FDC Reports - Pink Sheet - Prescription Pharmaceuticals and Biotechnology 65: 21-22, 13 Jan 2003.

PERGOLIDE MESYLATE

Labelling change to reflect development of cardiac valvulopathies

USA. Eli Lilly and Company, in cooperation with the US FDA, has issued a 'Dear Healthcare Professional' letter advising of changes to the labelling for pergolide (Permax), used in the treatment of Parkinson's disease, to reflect safety information relating to the risk of cardiac valvulopathy. Post-marketing surveillance has identified a small number of reports of cardiac valvulopathy in patients

receiving pergolide. Although a causal relationship has not been established, pathological assessment of the valves surgically removed in these cases was consistent with valvulopathy seen in association with the use of other ergot alkaloid drugs. The Warnings section of the package insert for pergolide (Permax) has been modified and now states that there have been reports of cardiac valvulopathy involving one or more valves in patients receiving pergolide and that, in some cases, symptoms or manifestations of cardiac valvulopathy improved after pergolide was discontinued.

Reports in WHO-file:
Cardiomyopathy 4, heart valve disorders 4

Reference:
'Dear Healthcare Professional' letter from Eli Lilly and Company, 25 Feb 2003. Available from URL: http://fda.gov/medwatch/SAFETY/2003/permax.htm

PLASMA/ URINARY MEDICINAL PRODUCTS

Danger of variant Creutzfeldt-Jacob Disease

UK. The Committee on Safety of Medicines (CSM) has advised that no human plasma or urine used in the production of medicines should be sourced from a country with one or more endogenous cases of variant Creutzfeldt-Jacob Disease (vCJD). The CSM continually reviews the safety of medicines that are prepared from human and animal materials, particularly with respect to any potential risk from transmissible spongiform encephalopathies (TSEs). In 1998 the CSM, taking into account the number of vCJD reported in the UK, recommended that human blood plasma sourced from the UK should not be used to prepare medicines. Later this restriction was extended to also include plasma from all other countries where at least one endogenous case of vCJD (indigenous to that country) had been reported. Still later the same precautionary principle was extended to urine-derived products since the abnormal prion protein was detected in the urine of patients with TSEs. The CSM advises that where possible plasma and urine should be sourced from countries with no or low risk of BSE and that that plasma pools for fractionation and urine used for the manufacture of medicines should be restricted to a single country of origin. Use of plasma derived products in medicines should be limited and where available, recombinant alternatives should be used.

Reference:
CSM Safety Review, Feb 2003. Available from URL: http://www.mca.gov.uk

SALMETEROL

Potential risk of fatal asthma episodes

USA. GlaxoSmithKline (GSK) has advised healthcare professionals of important safety information regarding the use of salmeterol (Serevent) in patients with asthma after interim analysis of a large salmeterol safety study suggested a potential association between salmeterol and an increased risk of life-threatening asthma episodes or asthma-related deaths. GSK has consequently decided to discontinue the study. The Salmeterol Multicenter Asthma Research Trial (SMART) was designed to assess the safety of salmeterol following concerns about the safety of regular use of short- and long-acting β2-agonists in asthma management. In addition to their regular asthma medication, patients enrolled in the study received salmeterol 42 µg twice daily or placebo for 28 weeks. Although interim analysis of data available on 25,858 patients did not show any significant differences between treatment groups in the risk of respiratory-related events or deaths, there was a non-significant trend towards serious asthma-related events or deaths in patients treated with salmeterol. Among African-American patients, the risk of both respiratory- and asthma-related events or deaths was significantly higher with salmeterol than with placebo, although GSK notes that the African-American group had more severe asthma at baseline. In addition, in the total population of patients not receiving inhaled corticosteroids at baseline, the risk of asthma-related death was significantly higher in those taking salmeterol than in those taking placebo. Further analysis of data from the study is ongoing and GSK is working with the US FDA to review potential changes to the labelling for salmeterol (Serevent) to reiterate and reinforce guidance on appropriate and safe prescribing. In accordance with these guidelines, the company recommends that patients receiving salmeterol should also receive effective asthma control medication, such as inhaled corticosteroids. It also says that the findings of the SMART study may be consistent with a β2-agonist class effect.

Reference:
1. *FDA Talk Paper, 23 Jan 2003. Available from URL: http://www.fda.gov*
2. *'Dear Healthcare Professional' letter from GlaxoSmithKline, 28 Jan 2003. Available from URL: http://www.fda.gov*

SERTRALINE

Contraindicated with pimozide

Canada. Pfizer Canada Inc in consultation with Health Canada is advising health professionals against the concomitant use of sertraline hydrochloride (Zoloft) and pimozide since their interaction could result in elevated plasma levels of pimozide. Elevation of blood pimozide levels could result in

QT interval prolongation and serious arrhythmias including Torsade de Pointes. This safety alert is consistent with the prescribing information for sertraline released by Pfizer Inc in consultation with the US FDA in November 2002 (WHO Pharmaceuticals Newsletter, No. 1, 2003). Sertraline is used to relieve symptoms of depression, panic disorder or obsessive-compulsive disorder and pimozide is used in the treatment of Tourette's syndrome.

Reference:

1. *'Dear Healthcare Professional' letter from Pfizer Canada Inc, 28 Feb 2003. Available from URL: http://www.hc-sc.gc.ca*
2. *Health Canada Warnings/ Advisories, 5 Mar 2003. Available from URL: http://www.hc-sc.gc.ca*

AMANTADINE, OSELTAMIVIR, ZANAMIVIR

NICE guidance for use in flu treatment.

UK. The National Institute for Clinical Excellence (NICE) advises that amantadine should not be used in the treatment of flu and that neither zanamivir nor oseltamivir should be used to treat flu-like symptoms in individuals who are otherwise healthy. When the number of people with flu reaches a high enough level, zanamivir may be used to treat flu-like symptoms in those patients who are at risk of developing complications. These two drugs are recommended for treating flu-like illness in at-risk adults. Oseltamivir is recommended to treat flu-like illness in at-risk children above the age of one year. NICE recommends that adequate monitoring schemes should be in place to quickly spot the outbreak of influenza at the very beginning.

Reference:
News & Updates, 26 Feb 2003. Available from URL: http://www.druginfozone.nhs.uk

AMIFOSTINE

Warning about severe skin reaction

Europe. Schering Plough Pharmaceuticals is amending the labelling of its cytoprotectant reactions occurring at a site distinct from the injection or the irradiation site should be investigated and amifostine therapy should be suspended immediately. Amifostine is used to prevent some of the side effects of chemotherapy or radiation therapy in cancer patients.

Reference:
Scrip, 2824, 19, 2003.

ANTIRETRO-VIRALS

Increased risk of MI

Australia, Europe, USA. A large prospective observational study involving 23,500 HIV-infected patients drawn from 11 different sites in the US, Australia and Europe has shown that there is a 27% increased risk of myocardial infarction (MI) in these patients for each year of highly active antiretroviral therapy (HAART) exposure, up to 7 years. The subjects received combination antiretroviral treatment that included a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor. Exposure to HAART for less than one year was associated with an MI incidence of 2.2 per 1000 person and increased to 6.4 MIs per 1000-person years with exposure of 6 years or longer. MI risk was not linked with any particular antiretroviral agent. Other independent risk factors for MI included age, current smoking,

CELECOXIB, ROFECOXIB

Neuropsychiatric events

Australia. Acute neuro-psychiatric reactions may be a class effect of the COX-2 inhibitors, according to the Australian Adverse Drug Reactions Advisory Committee (ADRAC). ADRAC has received 142 reports of acute neuro-psychiatric reactions associated with celecoxib (Celebrex) and 49 reports associated with rofecoxib (Vioxx). The most common reactions associated with celecoxib were confusion (23 reports), somnolence (22) and insomnia (21), while the most common reactions associated with rofecoxib were confusion (16) and hallucinations (11). In many cases the onset of the event occurred within 24 hours of the first dose of the drug, although some cases occurred following re-exposure.

Reference:
Australian Adverse Drug Reactions Bulletin 22, Feb 2003.

LINEZOLID

Peripheral neuropathy

Australia. The Australian Adverse Drug Reactions Advisory Committee (ADRAC) has received four reports of persistent peripheral neuropathy in patients treated with the antibacterial agent linezolid (Zyrox) for 6–9 months; at the