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.

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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 amifostine (Ethyol) to strengthen warnings about the possibility of severe cutaneous reactions with the product. So far a total of 35 reactions have been reported worldwide including 11 cases of toxic epidermal necrolysis, 10 cases of Stevens-Johnson syndrome and 4 fatalities. Doctors have been provided with a list of recommended precautionary measures while using amifostine and are advised to pay special attention to any signs of rash, lesions etc on the lips, mucous membranes, palm or soles of feet; cutaneous 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, and history of cardiovascular disease. These findings suggest that patients should be monitored for cardiovascular risk factors when starting or changing their combination antiretroviral regimen. It is however noted that the overall incidence of MI remains relatively rare (126 events in 23,500 patients).

Reference:
News & Updates, 14 Feb 2003. Available from URL: http://www.druginfozone.org

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 time of reporting none of the cases had resolved. In the clinical trials which supported the registration of linezolid, the duration of exposure did not exceed 28 days. The committee suggests that the risk of persistent peripheral neuropathy should be considered when prescribing linezolid for > 28 days.

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

MINOCYCLINE

Benign intracranial hypertension

Australia. Over the past 30 years the Australian Adverse Drug Reactions Advisory Committee (ADRAC) has received 76 reports of benign intracranial hypertension, 32 of which have been associated with minocycline, including three reports in the past 6 months. All 32 patients were young (aged 12–30 years), most were receiving long-term treatment with minocycline for acne and the majority (28 patients) were female. The median time from treatment initiation to the onset of intracranial hypertension was approximately 2 months (range 2 weeks to 18 months), although one case occurred one day after the patient switched from doxycycline to minocycline. Most patients recovered within 2-12 weeks of minocycline withdrawal.

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

NEFAZODONE/ QUETIAPINE

Dispensing errors due to name confusion

USA. Bristol-Myers Squibb is advising healthcare providers in the US of dispensing errors arising from name confusion between nefazodone (Serzone) tablets, indicated for depression, and AstraZeneca's quetiapine (Seroquel) tablets, indicated for schizophrenia. The similar names, overlapping strengths (100 and 200mg), dosage form (tablets), dosing interval (twice daily) and stocking of the two products close together in pharmacies are thought to have contributed to the errors. The company warns that patients receiving either medication in error would be inadequately treated and may be at risk of adverse events. Bristol-Myers Squibb has developed a patient information leaflet to be distributed with nefazodone (Serzone), and packaging changes have been made to both products to highlight the endings of the product names.

Reference:
'Dear Healthcare Provider' letter from Bristol-Myers Squibb Company, 20 May 2002. Available from URL: http://www.fda.gov

PARACETAMOL

Advice for avoiding accidental overdose

Canada. Health Canada is advising consumers to read carefully the labels for all prescription and over-the-counter paracetamol (acetaminophen) products to avoid overdose and fatal liver toxicity. Paracetamol (acetaminophen) is a common ingredient in many popular preparations used in fever, pain, colds and flu. Often several preparations of the same brand or several medications for the same symptoms are found in one household and when used together can result in an overdose. Paracetamol is safe when used as directed. Health Canada advises consumers not to exceed the dose recommended in the label, not to use two products containing paracetamol on the same day and to exercise utmost caution while giving these products to children. In the event of an overdose, consumers must seek medical help immediately, even in the absence of obvious symptoms of overdose since early intervention is critical.

Reference:
Health Canada Warnings/Advisories, 13 Feb 2003. Available from URL: http://www.hc-sc.gc.ca

SIBUTRAMINE

Update on safety information

Canada. Health Canada has completed its review of sibutramine (Meridia) and has concluded that sibutramine (Meridia) continues to meet the requirements for sale in Canada. Sibutramine was approved for the treatment of obesity in Canada in December 2000. In 2002 Health Canada undertook a review of the safety profile of sibutramine (Meridia) following several adverse reaction reports received in Canada and elsewhere in the world. At that time the Italian Health Ministry had temporarily suspended the drug pending further investigations. The suspension has now been revoked and the drug reinstated in the Italian market. The Committee for Proprietary Medicinal Products in Europe also reassessed the drug in 2002 and concluded that the benefit/risk assessment for sibutramine containing drugs is favourable. 53 reports of adverse reactions associated with siburtramine (Meridia) use were registered with Health Canada between March and November 2002. There were no deaths reported. Health Canada advises that the adverse reaction reports are consistent with the known adverse reactions for sibutramine (Meridia) and include an increase in blood pressure and heart rate, and disturbances of the visual system such as eye pain and eye haemorrhage; patients should not take sibutramine (Meridia) while taking medications that can affect the level of serotonin in the brain, such as antidepressants; physicians should monitor patients using sibutramine (Meridia).

Reference:
Health Canada Warnings/ Advisories, 8 Feb 2003. Available from URL: http://www.hc-sc.gc.ca

SIROLIMUS

Reports of bronchial anastomotic dehiscence

Netherlands. Wyeth has issued a 'Dear Doctor' letter alerting doctors in the Netherlands about the risks of treating lung transplant patients with sirolimus. The letter says that

two centres have reported cases of bronchial anastomotic dehiscence in lung transplant recipients who started immunosuppression with sirolimus, tacrolimus and corticosteroids at the time of transplantation. At one centre, four of 15 patients developed bronchial anastomotic dehiscence while using the drug in combination with tacrolimus and corticosteroids; three of these patients died. The letter states that the safety and efficacy of sirolimus (Rapamune) in lung transplant patients as an immunosuppressive therapy has not been established and therefore such use is not recommended. It also recommends that in kidney transplant patients sirolimus (Rapamune) should be used in combination with cyclosporin and corticosteroids for 2 to 3 months and that sirolimus (Rapamune) should be continued as maintenance therapy if cyclosporin is gradually discontinued.

USA. Wyeth Pharmaceuticals in consultation with US FDA has issued a similar letter in the US informing healthcare providers of post-marketing reports of bronchial anastomotic dehiscence, including fatal cases, in de novo lung transplant recipients treated with sirolimus (Rapamune) in combination with tacrolimus and corticosteroids. The boxed Warnings section of the prescribing information for sirolimus (Rapamune) has been updated to include new information regarding reports of bronchial anastomotic dehiscence and states that the safety and efficacy of sirolimus (Rapamune) has not been established in lung or liver transplant recipients. The company points out that sirolimus (Rapamune) is indicated for the prophylaxis of organ rejection in renal transplant recipients, and is recommended for use with cyclosporin and corticosteroids.

Reference:

1. *News and Updates, 13 Feb 2003. Available from URL: http://www.druginfozone.org*
2. *'Dear Healthcare Provider' letter from Wyeth, Feb 2003. Available from URL: http://www.fda.gov*

THIOMERSAL

Further data support safety in vaccines

UK. The benefit-risk balance of thiomersal-containing vaccines remains overwhelmingly positive, states the UK Committee on Safety of Medicines (CSM). The CSM considered evidence from two recently completed UK epidemiological studies that showed no evidence of adverse developmental effects in infants exposed to the amounts of thiomersal used in existing UK vaccines. The CSM also notes that a further study in infants has shown that ethylmercury is rapidly excreted from the body after the administration of thiomersal-containing vaccines. Professor Alasdair Breckenridge, CSM Chairman, says the new studies 'reinforce CSM advice from 2001 that there is no evidence of neurological adverse effects caused by thiomersal in vaccines according to the routine UK immunisation schedule'.

Reference:

Statement from the Committee on Safety of Medicines, 21 Feb 2003. Available from URL: http://www.mca.gov.uk

TNF INHIBITORS

Safety in arthritis

USA. The FDA is reviewing the safety of Tumor Necrosis Factor (TNF) inhibitors for treating arthritis. The review is being undertaken following concerns of lymphoma associated with the TNF inhibitors. Etanercpet (Enbrel), infliximab (Remicade) and adalimumab (Humira) will be reviewed in this connection.

Reference:

News and Updates, 30 Jan 2003. Available from URL: http://www.druginfozone.org

TRAMADOL

Increasing abuse

Taiwan. The Investigation Bureau of the Ministry of Justice in Taiwan reports that tramadol has become a substance of choice for many drug abusers in Taiwan. Statistics show that the amount of tramadol seized in the country has increased sharply from 240g in 2001 to 140 kg in 2002, making tramadol the third most commonly seized drug in Taiwan last year. According to the bureau, the drug is easily trafficked by organized crime syndicates and is used by heroin addicts to ease the pain caused by withdrawal symptoms when heroin is unavailable. Tramadol is a centrally acting analgesic drug.

Reference:

News and Updates, 23 Jan 2003. Available from URL: http://www.druginfozone.org

TRAMADOL

ADR update

Australia. During the 4 years that tramadol (Tramal) has been available in Australia, the Australian Adverse Drug Reactions Advisory Committee (ADRAC) has received 354 reports of adverse events associated with its use. The most common reactions include nausea, vomiting, sweating, dizziness, rash, tremor and headache, but ADRAC has also received reports of more serious adverse reactions such as confusion, hallucinations, convulsions, serotonin syndrome, increased blood pressure, hypersensitivity, hepatic reactions and five reports of an interaction between tramadol and warfarin leading to decreased prothrombin activity. The committee notes that the concomitant use of other drugs may have contributed to the cases of convulsions and serotonin syndrome.

Reference:

Australian Adverse Drug Reactions Bulletin 22, Feb 2003.

Presented below are brief analyses of adverse drug reaction (ADR) data for two well known drugs, benazepril and rosiglitazone, from the ADR database of the WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden (the UMC). Dr David Clark from the University of Otago, Dunedin, New Zealand warns about the need to be alert to rare but serious adverse reactions such as agranulocytosis while prescribing ACE inhibitors and Dr Warren Curt Appel from Canada advises that associations of hemiparesis with rosiglitazone should be considered but in the context of other contributory factors.

Benazepril and agranulocytosis: a possible rare adverse reaction involving ACE inhibitors as a class

Eight case reports (5 female and 3 male) submitted to the WHO-UMC, involving benazepril in association with agranulocytosis (including the terms neutropenia and granulocytopenia) were reviewed.

Of those with onset of treatment and detection of reaction dates specified (3 cases), 1 indicated onset of the reaction the same day as commencing treatment, 1 case was noted 2 months after starting treatment and 1 after 8 months of starting treatment with benazepril. It is recognized that the disease onset is insidious and it may take time before diagnosis. Thus in spite of the small numbers and variability, drug causality remains possible. In most of the cases, the patients had been administered one or more concomitant medications that were also listed as suspected drugs.

Dechallenge and rechallenge:
'Definite improvement' was reported following cessation of benazepril treatment (dechallenge) in 2 cases and in 4 cases dechallenge was either not specified or 'not known'. In the remaining 2 cases the patient died while on treatment. No information on rechallenge was provided for 3 of the remaining cases, there was 'no rechallenge' in 2 cases and it was 'unknown' in 1.

Outcome:
Outcome was specified in 6 of the 8 cases: one of the remaining 2 was 'unknown' and the other 'not specified'. In 3 of these cases the patients 'recovered without sequelae', in 1 case the patient had 'not yet recovered' and the other 2 cases reported death (see above). One of these recorded 'drug might be contributory' and the other 'unrelated to drug'.

Comment:
The WHO-UMC reports are inconclusive and do not justify a warning alone. However, agranulocytosis is listed as a recognised rare reaction in major sources of drug information. In its monograph on benazepril, the Physician's Desk Reference states that "Another angiotensin-converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression".

Drugdex, in a 'Drug Consults' monograph on ACE inhibitor-induced neutropenia, gives an incidence of less than 0.1%. The monograph indicates that "in patients with renal dysfunction (serum creatinine greater than 1.6 milligrams/deciliter), but without collagen-vascular disease the risk of neutropenia is 0.2%" and that "the incidence increases to between 3.7% to 7.2% when both these conditions are present. It also states that "although the large majority of reports involve captopril, cases involving both enalapril and lisinopril with clinically significant responses are available". Drugdex also indicates that ACE inhibitor product labelling in the US contains a general class warning for drug-induced agranulocytosis.

The reports submitted to the WHO-UMC involving benazepril in association with agranulocytosis do not negate, nor do they strengthen the evidence for agranulocytosis as a rare adverse reaction associated with ACE inhibitors. However, because ACE inhibitors are a very widely used class of drug, it is important that prescribers remain aware of this rare, but potentially serious adverse effect and in particular of the increased risk of agranulocytosis if prescribing an ACE inhibitor to patients with collagen-vascular disease and renal impairment.

Rosiglitazone – hemiparesis association

The UMC database contains a number of cases with the association between rosiglitazone and hemiparesis. For the high level term "paralysis", which includes paresis, hemiparesis, hemiplegia and paralysis, there are 12 such cases. Cases date from 1999-present in the database. Total ADRs for rosiglitazone = 9082.

These twelve cases comprise 8 males and 4 females with an average age of 65.9 years (range 34-77). Country of origin of these cases:

Country	Germany	Switzer-land	UK	USA
Number of cases	6	1	1	4

Rosiglitazone is an oral anti-diabetic agent. It is a member of the group of drugs known as thiazolidinediones, a new group of drugs called "insulin sensitizers". Rosiglitazone specifically targets insulin resistance, which is thought to be central to the development of type 2 diabetes and some of the complications of the disease. Rosiglitazone is approved as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus either as

monotherapy or in combination with metformin or a sulfonylurea. Rosiglitazone is not indicated for combination therapy with insulin; combined use increases the risk of heart failure or oedema[1].

Combination therapy is evident in 11 of the subject cases. It is possible that cases of hemiparesis (and similar disorders) represent a severe neurological deficit such as occurs with cerebrovascular events. In fact, other cases in the data set for rosiglitazone include the terms cerebral haemorrhage (2), and various cerebrovascular disorders [cerebral infarct (5), cerebral ischaemia (3) and cerebrovascular disorders general (26)].

By comparison, pioglitazone, another thiazolidinedione, shows 8 cases of "paralysis", (hemiparesis 2, hemiplegia 1, paralysis 3, and paresis 2). Cases are all from the USA. There are 4 males, 4 females with an average age of 64.4 years (range 50-73). The total number of ADRs for pioglitazone is 14,832, dating from 2000 to present. In addition, there are 11 cases of cerebrovascular disorder and 8 cases of cerebral infarct.

In contrast, for the more traditional anti-diabetic drug metformin, there are 12 cases of "paralysis" listed from 1995. These cases represent 6 males, 6 females, with an average age of 63.6 years (range 42-79). The total number of ADRs for metformin from 1969 to present is 13,654.

In order to understand a possible mechanism for these events, a diabetologist at the Ottawa Health Sciences hospital was consulted. He provided the following observations:

Both severe hyperglycemia as well as hypoglycemia could lead to neurological insult. Rosiglitazone on its own does not produce hypoglycemia, but could do so if used in conjunction with a sulfonylurea or insulin (it would not do so when used with metformin). Its use with insulin has also been associated with fluid retention and congestive heart failure, which might also potentially affect circulation to the brain if there was a severe cardiac output deficit.

Thiazolidinedione-induced oedema has been described recently in a publication by Niemeyer and Janney[2]. Considering the relatively high prevalence of cardiovascular disease among diabetic patients, it is likely that a number of cerebrovascular events will be seen in this population. The following table outlines various types of ADRs that are of interest in this context for the three comparison drugs.

Drug/ADR	Rosiglitazone (1999-2003)	Pioglitazone (2000-2003)	Metformin (1969-2003)
Coma	21	18	98
Diabetic/hypoglycemic coma	4	3	23
Hyperglycemia	188	316	301
Hypoglycemia	180	181	388
Oedema	274	243	36
General/peripheral oedema	541	234	58
Cardiac failure (incl. L/R)	311	186	89
Cardiomegaly	41	31	10
Cerebrovascular disorders	26	11	35
Cerebral infarct/ischaemia	8	8	1
Transient Ischaemic Attack	7	2	3
Cerebral haemorrhage	2	0	2
Hemiparesis	7	2	6
Paralysis	5	3	8
Paresis	2	2	1
TOTAL ADRs	9082	14,832	13654

Thus, although hemiparesis in association with rosiglitazone may not constitute an important signal per se, factors that may contribute to development of neurological insult, such as oedema and cardiac failure seem to have been reported more frequently with this drug than with comparison anti-diabetic drugs. If this association is to be followed, it should be in the context of contributory factors.

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The Return of Thalidomide: New Uses and Renewed Concerns

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History

Thalidomide or α-(N-phthalimido) glutarimide was marketed in 1957 for morning sickness and nausea and soon became the 'drug of choice to help pregnant women'. It went into general use by the following year and was widely prescribed in Europe, Australia, Asia, Africa and the Americas[1]. Allegedly, the drug was harmless and a lethal dose could not even be established[2]. However, in the early 1960s, in what might be described as the worst case of pharmaceutical oversight, the drug was found to be associated with a congenital abnormality causing severe birth defects in children born of women who had been prescribed this drug during pregnancy. More than 10, 000 cases of birth defects were reported in over 46 nations following thalidomide exposure. Children were born with missing (amelia) or abnormal (phocomelia) legs, arms, feet and hands; spinal cord defects; cleft lip or palate; absent or abnormal external ears; heart, kidney, and genital abnormalities; and abnormal formation of the digestive system. It is estimated that 40% of thalidomide victims died within a year of birth[3]. Today there are approximately 5000 thalidomide survivors[1]. The 'thalidomide syndrome' triggered a world wide response. Safety monitoring systems were set up to prevent this tragedy ever happening again and the drug was taken off the market in many countries in 1961.

Thalidomide in Leprosy

A few years later, however, the drug thalidomide was reintroduced as treatment for a complication of leprosy called erythema nodosum leprosum (ENL). Although the evidence was not fully established, very soon the drug was heralded as the drug of choice for the management of ENL reactions in leprosy and regulatory authorities granted exemption from licensing requirements to enable doctors to obtain limited supplies of thalidomide under strictly controlled circumstances for use in named patients. Thalidomide's effectiveness in minimizing symptoms of ENL was mainly due to its antipyretic action. Its effectiveness in controlling neuritis, the major cause of permanent disabilities in leprosy, was limited.

Several controlled studies done in the 70's have demonstrated that **prednisolone** is more effective in controlling ENL and associated neuritis[4-6]. In addition, it was demonstrated that **clofazimine**, an anti-leprosy drug introduced on a small scale in the early 60's had anti-inflammatory action[7,8]. Studies showed that clofazimine is the drug of choice for the management of chronic, recurrent ENL reactions, as it had both anti-reaction and anti-leprosy effect. Moreover, while almost all patients given thalidomide relapsed after discontinuation of the drug, none of the patients treated with clofazimine for ENL reactions relapsed[9-11]. The drug clofazimine is now a component of the multidrug therapy (MDT), introduced by WHO in 1981 as the standard treatment for leprosy. The presence of clofazimine in the combination has significantly reduced the frequency and severity of ENL reactions world-wide[12,13].

Today ENL reaction is a rare complication, limited to a small proportion of multibacillary patients. Most of the ENL reactions are mild in nature and do not require any specific treatment except with some analgesics/antipyretics. In those suffering ENL associated neuritis, the drug of choice is prednisolone. For chronic recurrent reactions the drug of choice is clofazimine.

Thalidomide in other indications

The above points clearly demonstrate that there is no place for thalidomide in leprosy. But very often this disease is used as an entry point to reintroduce thalidomide for a multitude of other indications. Millions of treatments are being prescribed annually and almost all of it is for non-leprosy conditions including cancer treatment and use in HIV. There are limited trials demonstrating the efficacy of thalidomide in other conditions[14,15]. Each condition must be evaluated in its own right and there must be put in place stringent restrictions on its availability. In addition there must be a monitoring system in place. There is no justification in extrapolating data from monitoring systems for leprosy to other conditions. The medical community that support the use of thalidomide for other conditions should make their own case for the drug. They cannot base it on the leprosy studies which are anything but exhaustive.

In conclusion

Today, a large number of thalidomide babies continue to be born each year[16-18] possibly reflecting regulatory insufficiency and widespread use under inadequate supervision. In Brazil, which has more than 1000 registered thalidomide victims, the last officially known case was born in 1995[19,20]. There is evidence that second generation babies with similar deformities are being born to thalidomide victims[21,22]. In the US, Celgene Corporation has had FDA approval to market the drug since 1998 for the cutaneous manifestations of moderate to

severe erythema nodosum leprosum. In Europe, the US company Pharmion Corp and French rival Laphal have both secured orphan drug status for thalidomide and have applied to market the drug as a therapy for multiple myeloma and for ENL in the EU. The EU is currently holding discussions on the re-launch of thalidomide. Whatever the outcome of the EU discussions, it cannot be over emphasized that any potential benefit with thalidomide must be balanced with the known toxicity and the accompanying ethical and legal constraints on its use. Experience has shown that it is virtually impossible to develop and implement a fool-proof surveillance mechanism to combat misuse of thalidomide.

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