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EDITORIAL

In the previous newsletter we had appealed to the Member States for greater communication on drug safety and regulatory information. We are happy to record that Bangladesh and the Republic of Maldives have responded with some recent regulatory developments in their countries. We acknowledge the Regional Adviser's pivotal role in facilitating this information exchange.

Counterfeit medicines continue to threaten the healthcare world. Cleverly designed fake holograms of product labels and imperceptible changes to the label text make counterfeiting ever more hard to detect. In this issue, we have included an article on fake artesunate tablets, to alert readers to the level of sophistication in the world of counterfeiting.

The feature section presents an article on the workshop on pharmacovigilance that was held in Zambia in March 2003. The workshop was the first of many initiatives being planned to integrate pharmacovigilance into public health programmes.

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ACETYL-SALICYLIC ACID

MHRA confirms labelling change

UK. In a follow-up of the Medicines Control Agency's Statement on acetylsalicylic acid (Aspirin) use (WHO Pharmaceuticals Newsletter No. 4, 2002), the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) has posted, on its website, a notification that from 1 Oct 2003 all acetylsalicylic acid-containing products will be required to include the following statutory label warning: "Do not give to children under 16 years, unless on the advice of a doctor". This requirement follows an 8-week consultation process after which the Medicines Commission endorsed the advice of the UK Committee on Safety of Medicines that the warning was required. Professor Breckenridge, chairman of the Agency pointed out that there are plenty of alternative analgesic products for this age group not associated with Reye's Syndrome and that "there is simply no need to expose those under 16 to the risk, however small".

Reference:

Medicines and Healthcare products Regulatory Agency. Internet Document, 4 Apr 2003.
Available from URL:
http://www.mhra.gov.uk

ACITRETIN

Warnings of depression added to label

US. Warnings of depression, aggressive feelings and thoughts of self-harm have been added to the label of acitretin (Soriatane), a product indicated in the treatment of psoriasis. These additions follow reports linking such observations with the use of the product. However, a definite causality has not been established since other factors may have contributed to some of these events. Warnings over the drug's use in pregnancy have also been enhanced. Female patients are now required to have two negative pregnancy tests before start of therapy and must also simultaneously take two effective forms of birth control. Additionally, they must sign an agreement that they are not pregnant at start of therapy, must not get pregnant during therapy, or for three years after discontinuing treatment.

Reference:

Pharma Times News Online, 9 May 2003.
Available from URL:
http://www.pharmatimes.co.uk

ASTEMIZOLE

Withdrawn due to life-threatening ventricular arrhythmias

Spain. The Spanish Medicines Agency has withdrawn the marketing authorization for 10 medicinal products containing astemizole due to the potential of these products to produce life-threatening ventricular arrhythmias.

Reference:

Communication from the Spanish Medicines Agency, 8 Apr 2003.
Available from URL:
http://www.msc.es/agemed/csmh/notas/astemizol.asp

CAMELIA SINENSIS

Ethanolic extract products withdrawn due to hepatotoxicity

Spain, France. The French and Spanish Advisory Boards have suspended the marketing authorization of a Green Tea (Camelia Sinensis) product (Exolise), prepared from the ethanolic extract of Green Tea, due to several reports of hepatic disorders. Thirteen cases of hepatic disorders have been reported (9 in France and 4 in Spain) with this latter product (Exolise) that has been marketed by Arkopharma Laboratories in France, Belgium, Spain and the United Kingdom. All patients were women, 27 – 69 years of age, with a time to onset varying from 9 days to 5 months. 5 of the patients did not receive any other medications. Negative viral serologies were observed in 8 cases. There were 8 positive de-challenges and one positive re-challenge. The suspension order will be effective until the company provides toxicological data and additional chemical analysis of the product.

Reference:

1. *Communication from the Spanish Pharmacovigilance System, 11 April 2003.*
2. *Spanish Medicines Agency Press Release, 7 Apr 2003. Available from URL: http://www.msc.es/agemed/csmh/notas/exolise.asp*

DIETARY SUPPLEMENTS

Withdrawal of two products due to presence of sildenafil

USA. Two dietary supplement products (Vinarol from Ultra Health Laboratories Inc and Bionate Inc and Viga from Best Life International) are being voluntarily recalled by the respective companies due to the unlabeled presence of sildenafil, a prescription drug that could have serious health risks if used without medical supervision. Both products were being sold as dietary supplements, without a prescription, for increasing desire, confidence and sexual performance. Consumers who have purchased either of these products are urged to discontinue their use.

Reference:

1. *Medwatch Safety Alert, 4 Apr 2003. Available from URL: http://www.fda.gov/medwatch/SAFETY/2003/vinarol.htm*
2. *Medwatch Safety Alert, 23 May 2003. Available from URL: http://www.fda.gov/medwatch/SAFETY/2003/vinarol.htm*

HUA FO

Presence of tadalafil

Canada. Health Canada is warning consumers not to use Hua Fo VIGOR-MAX Tablets, a Chinese Herbal product that contains tadalafil. Tadalafil is a prescription drug approved for sale for male erectile dysfunction in the UK, Germany, Sweden, Denmark, Finland, New Zealand, Australia and Singapore. It is not approved for sale in Canada. Inappropriate use of tadalafil could cause severe adverse reactions. Tadalafil should not be used by individuals who are taking any medication or other products containing nitrates: concurrent use could result in the development of potentially life-threatening low blood pressure. Also, tadalafil should not be used by patients with severe renal or hepatic insufficiency. Health Canada issued a previous warning in February 15, 2002 (WHO Pharmaceuticals Newsletter No. 2, 2002) concerning Hua Fo when it was found to contain sildenafil. At the time, Health Canada required the importer to remove the product from the shelves. Health Canada is again directing the importer to remove Hua Fo VIGOR-MAX from the market and has issued a Customs Alert to stop its further importation.

Reference:
Health Canada Warnings/ Advisories, 27 May 2003. Available from URL:
http://www.hc-sc.gc.ca

IODINE

Some products contain more than the RDA

Canada. Health Canada is advising consumers against using some products containing iodine (SEAVITE Premium Atlantic Kelp Blend and SEAVITE Premium Atlantic Kelp tablets) since these products, when consumed according to the label instructions, can provide 25 times the recommended daily allowance (RDA) of iodine for adults; this could lead to serious adverse health consequences. The RDA for iodine ranges from 90 micrograms per day for children aged 1-8 years to 150 micrograms per day for adults. Excessive iodine intake could lead to thyroid disorders and in turn to heart problems. Three reports of serious adverse events have been associated with the use of these products; one patient required hospitalisation. The excessive iodine can manifest itself as an under- or over-active thyroid. Individuals especially sensitive to the toxic effect of excess iodine include children of all ages, pregnant women, foetuses and newborns of breast feeding women and those under previous or current supervision for thyroid disease. Individuals taking amiodarone, a prescription drug for treating heart rhythm disorders may also be at increased risk. Health Canada warns that concerned consumers should talk to their healthcare provider.

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

LEVODOPA/ CARBIDOPA

New warning about somnolence and sudden onset sleep

UK. Bristol Myers Squibb has revised the Summary of Product Characteristics (SPC) for their levodopa/carbidopa (Sinemet) preparation to include new warnings about somnolence and sudden onset of sleep. The 'Special Warnings and Precautions for Use' section (Section 4.4) has been changed to include a warning that states that levodopa has been associated with somnolence and sudden onset of sleep. Patients must be advised to exercise caution and refrain from driving, if affected. A reduction in dose or discontinuation of treatment may be considered. The sections on 'Effects on ability to drive and use machines' and 'Undesirable effects' (sections 4.7 and 4.8) have been modified to reflect these additions.

Reference:
Drug Info Zone, UK Medicines Information Service, 28 May 2003. Available from URL:
http://www.druginfozone.nhs.uk

LINDANE

Additional warnings and medication guide added to label

USA. The US FDA has issued a Public Health Advisory concerning the use of topical formulations of lindane lotion or shampoo for the treatment of scabies and lice, which announces significant updates to the product labelling. The labelling changes include the addition of a new boxed warning which emphasises that lindane is only indicated as a second-line treatment for scabies and lice in patients who are intolerant of, or unresponsive to, other therapies. It also provides updated safety information regarding the potential risks of adverse effects associated with use and misuse of the products, and states that lindane lotion or shampoo is contraindicated in premature infants, is not recommended for use in infants and should be used with caution in patients who weigh less than 50kg (110 pounds). The new warning also advises practitioners that, if itching continues after a single treatment, reapplication of lindane lotion or shampoo is not appropriate. The advisory states that lindane packaging sizes will be limited to 1 and 2 ounces to minimise the potential for patients to apply the product in excess and to minimise reapplication, and that pharmacists should only dispense sufficient lindane for a single application (< 2 fluid ounces). A medication guide informing patients of the risks associated with lindane products and providing instructions for the appropriate use of the drug must now be dispensed by the

pharmacist with each new prescription.

Reference:
FDA Talk Paper, 28 March 2003. Available from URL: http://www.fda.gov

NEFAZODONE

Regulatory status update

Republic of Turkey[1]. The Directorate General of Pharmaceuticals and Pharmacy has decided to suspend the license for nefazodone hydrochloride preparations (Serzone) held by Bristol Myers Squibb Drugs Inc in Turkey. This decision has been taken in view of the latest data received by the Turkish Ministry of Health as well as worldwide developments that suggest acute hepatic failure associated with nefazodone use. A variety of other antidepressant agents are available in the market and can be used effectively in its place. Procedures to stop further prescription and withdrawal of nefazodone (Serzone) from the market have been initiated.

Singapore[2]. Since nefazodone, indicated for the treatment of depression, was licensed in Singapore in 1997, the Pharmacovigilance Unit has received one local adverse drug reaction (ADR) report of mildly elevated ALT levels associated with nefazodone. Up to December 2002, 28 reports of liver failure, including 15 which resulted in death, associated with nefazodone had been received worldwide. In Singapore the package insert for nefazodone (Serzone) has been amended to include warnings relating to the risk of hepatic adverse events and a 'Dear Healthcare Professional' letter was issued in February 2002 to inform physicians of these amendments.

Reports in WHO-file:
Liver and biliary system disorders 474

Reference:

1. *Communication from the Division of Pharmacovigilance, Ministry of Health, Republic of Turkey, 21 March 2003*
2. *Adverse Drug Reaction News (Singapore), 5:1, Feb 2003.*

NIMESULIDE

Paediatric preparations banned in Bangladesh

Bangladesh. The manufacture, distribution, sale and use of all dosage forms of nimesulide paediatric preparations were recently officially banned in Bangladesh. The banning of adult dosage forms of nimesulide preparations is now under active consideration of the Directorate of Drugs Administration of Bangladesh. A nation wide survey of reports of adverse effects with nimesulide is being conducted before taking a final decision with the adult usage formulations. Importation of nimesulide raw material has already been discontinued in order to discourage further manufacture of nimesulide preparations in the country.

Reference:
Communication to WHO, Geneva, from Director, Directorate of Drugs Administration, Ministry of Health and Family Welfare, Bangladesh, 11 Jun 2003.

PERGOLIDE MESYLATE

Risk of cardiac valvulopathy

Canada. A 'Dear Healthcare Professional' letter regarding pergolide mesylate (Permax) and the risk of cardiac valvulopathy has been issued by Eli Lilly Canada Inc and Draxis Health Inc. During post-marketing surveillance, a small number of individuals have been identified as developing cardiac valvulopathy involving one or more valves during pergolide therapy. In some cases, symptoms of valvulopathy resolved on discontinuation of pergolide therapy; two patients required valve replacement. Although a causal relationship has not been established, the 'Warnings' section of the product monograph is to be updated accordingly. The company has sent out a similar letter to healthcare professionals in the USA earlier in the year, in February 2003 (WHO Pharmaceuticals Newsletter No.2, 2003).

Reports in WHO-file:
Cardiomyopathy 4

Reference:
'Dear Healthcare Professional' letter from Draxis Health Inc and Eli Lilly Canada Inc, 14 Apr 2003. Available from URL: http://www.hc-sc.gc.ca

REPAGLINIDE

Contraindicated with gemfibrozil

Europe. The European Medicinal Products Evaluation Agency (EMEA) has issued a public statement about an interaction between repaglinide (Novonorm/ Prandin), a medicine used to lower blood sugar in diabetic patients, and gemfibrozil, a lipid-lowering agent. The blood glucose lowering effect of repaglinide maybe markedly enhanced and prolonged when administered together with gemfibrozil, with an increased risk of severe hypoglycaemia. The Agency has received 5 reports of serious adverse hypoglycaemic episodes in patients using repaglinide and gemfibrozil at the same time. Therefore, the EMEA's Committee for Proprietary Medicinal Products (CPMP) has decided to contraindicate the concomitant use of these two drugs. Patients already receiving repaglinide and gemfibrozil should be reviewed and put under alternative combination treatment with close monitoring of diabetic status. The repaglinide Summary of Product Characteristics (SPC) and the product package leaflet have been appropriately modified to reflect the above mentioned contraindication.

Reference:
EMEA Public Statement (EMEA/11700/03), 21 May 2003. Available from URL: http://www.emea.eu.int

RISPERIDONE

Prescribing information updated to reflect cardiovascular adverse events

USA. Janssen Pharmaceutica Inc has issued a 'Dear Healthcare Provider' letter in the US advising of changes to the prescribing information for risperidone (Risperdal). The 'Warnings' section of the prescribing information for risperidone has been updated to include information regarding cerebrovascular adverse events following reports of stroke and transient ischaemic attack, including fatalities, in trials of risperidone in elderly patients with dementia-related psychosis. In four placebo-controlled trials there was a significantly higher incidence of cerebrovascular adverse events in patients treated with risperidone (Risperdal) compared with patients treated with placebo. Prescribers are reminded that risperidone is not indicated for the treatment of dementia.

Reference:
'Dear Healthcare Provider' letter from Janssen Pharmaceutica Inc, 16 Apr 2003. Available from URL: http://www.fda.gov

TELITHROMYCIN

Aggravation of myasthenia gravis

Europe. The European Medicinal Products Evaluation Agency (EMEA) has issued a public statement regarding the use of telithromycin (Ketek) in patients with myasthenia gravis. Recent reports, including one fatal case, indicate an association between telithromycin and myasthenia gravis exacerbation with respiratory failure. Within a few hours of telithromycin intake, exacerbation of muscle weakness, dyspnoea, or severe respiratory failure has occurred in patients with myasthenia gravis; the mechanism for this exacerbation is unknown. The EMEA points out that telithromycin use is not recommended in patients with myasthenia gravis unless no therapeutic alternative exists and that patients with myasthenia gravis taking telithromycin should be advised to immediately seek medical attention if their symptoms worsen. The telithromycin (Ketek) Patient Leaflet and the Summary of Product Characteristics have been amended to reflect this safety information.

Reference:
EMEA Public Statement (EMEA/8837/03), 23 Apr 2003. Available from URL: http://www.emea.eu.int

Pan Pharmaceuticals Limited, Australia: Manufacturing Licence Suspended

The Australian Therapeutic Goods Administration has suspended Pan Pharmaceuticals' Licence to manufacture medicines, for a period of six months, following several safety and quality violations by the company. The WHO has issued a worldwide alert (Alert No. 108, available from URL: http://www.who.int/medicines/library/qsm/drugalert/alert108.pdf) to notify member states about the Australian decision.

The Republic of Maldives has responded to the WHO alert notification by adding Pan Pharmaceuticals' products to the list of drugs withdrawn in the country.

ANTIRETRO-VIRALS

Benefit/Risk balance remains strongly positive for combination antiretroviral therapy

Europe. The Committee for Proprietary Medicinal Products (CPMP) has issued a public statement that the benefit/risk balance of combination antiretroviral treatment (CART) remains strongly positive in HIV infected patients. The statement follows an analysis of the results of studies undertaken by various groups to address questions concerning the prevalence and especially, the incidence of long-term cardiovascular and metabolic complications associated with CART. The CPMP holds that the long-term cardiovascular effect of CART has not been conclusively demonstrated and therefore concerns about the risk of cardiovascular disease should not lead to the withholding of CART when indicated for HIV-patients; ongoing studies of long-term cardiovascular complications should be continued for an extended follow-up time, at least till January 2005 to provide more conclusive results.

Reference:
CPMP Public Statement, EMEA/CPMP/2383/03, 25 Apr 2003. Available from URL: http://www.emea.eu.int

CYPROTERONE ACETATE & ETHINYL-ESTRADIOL

Update on risk of venous thromboembolism

Canada. The combination product of cyproterone and ethinylestradiaol (Diane-35) is prescribed in the treatment of androgen related conditions such as severe acne or hirsutism in women. As with all estrogen/progestogen combination products, the combination of cyproterone and ethinylestradiol (Diane-35) is associated with an increased risk of venous thromboembolism. This product is therefore contraindicated in women with thrombophlebitis, thromboembolic disorders or a history of these conditions. Some published studies suggest that users of this combination product (Diane-35) may have an elevated risk of venous thromboembolic events compared to users of combination oral contraceptives. The combination of cyproterone and ethinylestradiol (Diane-35) should not be prescribed for the sole purpose of contraception. And, during treatment with this combination, other oral contraceptives should not be used. This information has been sent to all healthcare professionals by Berlex Canada Inc, in consultation with Health Canada.

Reports in WHO-file:
Thromboembolism 3, thrombosis 43

Reference:
'Dear Healthcare Professional' letter from Berlex Canada Inc, 10 Apr 2003. Available from URL: http://www.hc-sc.gc.ca

DIETHYL-STILBESTROL

Gynaecological and obstetric complications after *in utero* exposure

Canada. The Marketed Health Products and Therapeutic Products Directorates of Health Canada have drawn attention to a recent letter issued to prescribers in France by the French regulatory agency (AFSSAPS), now posted on the Heath Canada website, regarding the risks of gynaecological and obstetric complications in women exposed to diethylstilbestrol *in utero*. In France, between 1948 and 1976, approximately 200 000 pregnant women received diethylstilbestrol (Distilbène; Stilboestrol-Borne) treatment, which at the time was indicated to prevent miscarriage and pregnancy-related bleeding. The number of children born of these pregnancies, now aged 25−52 years, is estimated to be around 160 000 and problems related to *in utero* diethylstilbestrol exposure are therefore expected to occur until around 2015.

Compared with the general population, men who were exposed to diethylstilbestrol *in utero* have an increased risk of pathologies affecting the urogenital system, including epididymal cysts, testicular abnormalities and abnormalities of the urinary meatus. The primary complications seen in women exposed to diethylstilbestrol *in utero* are clear cell adenocarcinoma of the vagina or cervix, and structural, morphological and functional abnormalities involving the vagina, cervix, uterus and fallopian tubes; some of these pathologies can result in fertility problems and obstetric complications.

The letter advises that if *in utero* diethylstilbestrol exposure is suspected the patient should be referred to a specialist and should consult a gynaecologist annually. All pregnancies in women exposed to diethylstilbestrol should be treated as high risk, although the majority will have normal outcomes.

Reference:
Important drug safety information from Health Canada, 18 Mar 2003. Available from URL: http://www.hc-sc.gc.ca

EPHEDRA

Moves to reduce risks of ephedra-containing products

USA. In the US, the Department of Health and Human Services (HHS) has announced plans to take action regarding the potentially serious risks associated with ephedra-containing dietary products. Ephedra is a naturally occurring substance derived from the

Chinese herbal Ma Huang. It is an adrenaline-like stimulant that can have potentially dangerous effects on the nervous system and heart. On the basis of new evidence in the medical literature and in adverse event reports, there are reasons for the heightened concern that dietary supplements containing ephedra may present a significant and unreasonable risk of illness and injury.

Under the Dietary Supplement Health and Education Act of 1994, FDA does not review dietary supplements for safety and efficacy before they are marketed but the law allows the FDA to prohibit the sale of a dietary supplement if it 'presents a significant or unreasonable risk'. In order to assess these risks, the HHS and FDA will

- seek rapid pubic comment on the new evidence on health risks associated with ephedra
- seek rapid public comment on whether the currently available evidence presents a 'significant or unreasonable risk of illness or injury'
- seek rapid public comment on a strong new warning label for ephedra products
- immediately execute a series of actions against ephedra products making unsubstantiated claims.

The American Heart Association has also called for a ignore warning labels and dosage information, a complete ban is necessary to eliminate the risks

Reference:

1. *Department of Health and Human Services Media Release: 28 Feb 2003. Available from URL: http://www.fda.gov*
2. *American Heart Association Media Release, 3 Apr 2003. Available from URL: http://www.americanheart.org*

FLUTICASONE PROPIONATE

Reports of adrenal crisis

Australia. Adverse Drug Reactions Advisory Committee (ADRAC) in Australia has received 10 reports of inhaled corticosteroid-associated adrenal crisis. Eight cases involved children aged 3–10 years who had received fluticasone propionate (Flixotide) 250–1500 µg/day; in six cases, the daily dose was > 500µg, the upper limit recommended by The Thoracic Society of Australia and New Zealand and by The National Asthma Council in Australia, before referral to a respiratory physician. The committee notes that higher fluticasone propionate doses may not confer greater efficacy and prescribers are reminded that "inhaled corticosteroids should be given at the lowest effective dose and reviewed regularly".

Reports in WHO-file:
Adrenal insufficiency 100

Reference:

that, although there have been no reports of significant clinical problems occurring when grapefruit juice and medication ingestion are separated by more than a few hours, grapefruit juice has the potential to have an interacting effect for up to 3 days after ingestion. ADRAC now considers that "the safest course is to avoid grapefruit and its juice altogether when taking medicines that interact". Statins and calcium channel blockers are some of the classes of drugs reported to interact with grapefruit juice.

Reference:

Australian Adverse Drug Reactions Bulletin 22: 8, Apr 2003.

HORMONE REPLACEMENT THERAPY (HRT)

Risk of dementia

As part of the Women's Health initiative (WHI) study, the Women's Health Initiative Memory Study (WHIMS) sought to evaluate the effect of oestrogen plus progestogen hormone replacement therapy (HRT) on the risk for dementia and mild cognitive impairment in women. HRT appears to increase the risk of dementia and mild cognitive impairment, doubling the risk of dementia in women over the age of 65. The effect on dementia became apparent after one year of treatment and continued throughout the 5-year duration of the study. These