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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ACETYLSALICYLIC 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".


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.


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.


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.


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.


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**REGULATORY MATTERS**

**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

**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

**Reference:**

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

**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:**

Health Canada Warnings/Advisories, 8 May 2003.
Available from URL: http://www.hc-sc.gc.ca
pharmacist with each new prescription.

Reference:

NEFAZODONE

Regulatory status update

Republic of Turkey: 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: 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.

Reference:
1. Communication from the Division of Pharmacovigilance, Ministry of Health, Republic of Turkey, 21 March 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:

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 were resolved on discontinuation of pergolide therapy; two patients required valve replacement.

Reference:

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).

Reference:

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 may be 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:
European Medicines Agency (EMEA) has issued a public statement about an interaction between repaglinide (Novonorm/Prandin) and gemfibrozil.

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).

Reference:
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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:

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.
ANTIRETROVIRALS
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:
Available from URL: http://www.emea.eu.int

DIETHYLSTILBESTROL
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 Health 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:
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 public 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 ban on ephedra-containing products in comments submitted to the US FDA. The Association supports the FDA's proposal to limit the manufacturing and marketing of ephedra-based supplements, but believes these products should be completely banned. The president of the American Heart Association, Dr Robert O. Bonow, says that there is growing evidence that the risks of ephedra-containing supplements, which are primarily cardiovascular, far outweigh any potential benefit, and because patients have a tendency to ignore warning labels and dosage information, a complete ban is necessary to eliminate the risks.

Reference:

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:

GRAPEFRUIT JUICE

Revised advice from ADRAC

Australia. The Adverse Drug Reactions Advisory Committee (ADRAC) in Australia has revised its previous advice (WHO Pharmaceuticals Newsletters No.3, 2002 and No.1, 2003) relating to grapefruit juice interactions. The committee notes 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:

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 findings have been published in JAMA (Journal of the American Medical Association), 28 May 2003. Earlier analyses have shown increased risk of stroke and breast cancer with long-term HRT use. Several countries have reacted with new or reinforced regulations on HRT use.

Australia. Australia’s expert committee on HRT has reiterated its advice that HRT should not be used for long-term disease prevention. The committee in Australia continues to have concerns about HRT and strongly recommends that women discuss
their particular circumstances with their doctors as individual factors may affect the risks and benefits of treatment.

**Germany**. The German Regulatory Agency BfArM intends to reduce the use of hormone replacement therapies. It plans to change the product information of HRT products to include the findings from the WHI study. BfArM says that HRT should only be used for 'pronounced' menopausal problems and the duration of the treatment should be as short as possible. The product leaflet will be modified to describe the side effects of HRT in greater detail. BfArM does not recommend the use of HRT in the prevention of osteoporosis since the benefits do not outweigh the risks of stroke, thrombosis, breast cancer and other complications.

**UK**. The UK Medicines and Healthcare Products Regulatory Agency (MHRA) is currently updating all HRT product information to include appropriate warnings on the risk of stroke. The current advice in UK is that, in women who typically use HRT for the short-term treatment of menopausal symptoms, the benefits of treatment are considered to outweigh the risks. HRT is also used in the prevention of osteoporosis; women should be made aware of the increased incidence of adverse effects with long-term HRT use. The decision to use HRT should be discussed with each woman on an individual basis, taking into consideration her age, history, risk factors and personal preferences. In addition, the individual’s risks and benefits should be regularly reappraised with continued HRT use. Women on HRT should discuss their own balance of risks and benefits with their doctor.

**USA**. The US FDA's hormone therapy outreach campaign will concentrate on promoting short-term, low-dose use of HRT, according to the agency's commissioner. Because the FDA believes that long-term HRT slightly increases the risk of cardiovascular disorders and certain cancers, it now recommends that women with specific indications (e.g. hot flashes or vaginal dryness) use HRT for the shortest possible time and at the lowest possible dose. Furthermore, HRT class labelling is being amended by the FDA to reflect the increased risk of breast cancer and cardiovascular events observed with the use of conjugated estrogens/medroxy-progesterone (Prempro) in the Women's Health Initiative study conducted by the National Institutes of Health.

**Reference:**
4. Scrip No. 2827, Feb 2003

**ROFECOXIB, CELECOXIB**

**Case reports support causal association with liver toxicity**

New Zealand. The recently published IMMP (Intensive Medicines Monitoring Programme) Prescriber Update Article on COX-2 inhibitors warns that, as with other Cyclo-oxygenase (COX) – inhibitors, liver toxicity may occur with celecoxib and rofecoxib. 17 reports of hepatotoxicity were received by the IMMP as part of the monitoring of COX-2 inhibitors. In most reports, the onset time was less than three months. Three were case reports (one woman aged 85 years and two men aged 81 and 61 years age) of significant liver injury occurring in association with rofecoxib. The other case reports included other known hepatotoxic medicines. While the clinical details concerning these case reports were not complete and the clinical investigations reported were not exhaustive, it is probable that these hepatic events were related to rofecoxib. There were three other reports of similar toxicity involving celecoxib where the causal relationship was less clear due to concomitant hepatotoxic medicines including methotrexate and leflunomide. In addition, there were 8 reports of mild liver function abnormalities with celecoxib and three with rofecoxib. Two of these patients recovered following withdrawal of the COX-2 inhibitor but the outcome of the others is unknown. Dr David Coulter, Director IMMP writes that hepatotoxicity is reported infrequently in literature; the IMMP reports suggest that this type of reaction is an uncommon class effect of COX-2 specific and non specific non steroidal anti-inflammatory agents. COX-2 inhibitors should be discontinued
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in patients with signs or symptoms that suggest liver dysfunction.


ROSIGLITAZONE, PIOGLITAZONE

Adverse reactions update

Australia. The Adverse Drug Reactions Advisory Committee (ADRAC) in Australia has received 44 adverse event reports associated with rosiglitazone and 28 with pioglitazone. These include 12 reports of hepatic reactions with rosiglitazone and four with pioglitazone, and six reports of cardiac reactions with pioglitazone and 12 with rosiglitazone. The committee states that these drugs should not be used in patients with liver disease or in patients whose cardiac failure limits their physical activity, and that monitoring of liver and cardiac function is required.


SOMATROPIN

Not to be authorized for AIDS-related wasting syndrome

Europe. The European Committee for Proprietary Medicinal Products (CPMP) has ruled out granting a marketing authorization for Serono’s orphan drug somatropin (Serostim), a recombinant growth hormone for AIDS-related wasting syndrome. Doubts about the clinical relevance of the primary endpoints used in the study, the lack of long-term efficacy data under controlled conditions and concerns about the long-term safety profile are being stated as reasons for this decision. The CPMP believes that the quality, safety and efficacy data suggest an unfavourable benefit to risk balance for somatropin (Serostim).

Counterfeiting of pharmaceuticals is a worldwide phenomenon. The problem has grown over the years; international trading conditions as well as the use of sophisticated technology to mask fraudulent products make it more and more difficult to control this criminal act. Sharing of available information, a strong political will and a commitment to institute effective regulations against the counterfeiters, are some of the urgent measures needed in fighting this global menace.

Counterfeit Artesunate Antimalarial Tablets

Dr Paul Newton, Centre for Clinical Vaccinology and Tropical Medicine, Churchill Hospital, Old Road, Oxford OX3 7LJ, England, UK

Artesunate is a vital life-saving antimalarial drug, developed in China, and now used extensively in South-East Asia for the treatment of falciparum malaria. It is also commonly available from the private sector. In the late 1990s counterfeit artesunate appeared in the region and has been disseminated from Vietnam to Burma (Myanmar). In 1999-2000 up to 38 % of artesunate, labelled as manufactured by Guilin Pharma, People's Republic of China, bought in pharmacies and shops in Burma, Laos, Cambodia, Vietnam and on the Thai/Burma border contained no detectable artesunate1-2. This has led to the deaths of an unknown but substantial number of people who would otherwise have survived their malaria infection3. A simple, inexpensive Fast-Red dye test allows one to reliably check the authenticity of artesunate tablets4. The first 'generation' fakes, which bear a grey sticker rather than a true hologram, are relatively easy to distinguish from the genuine product but remain in circulation in South-East Asia.

However, two further sophisticated 'generations' of counterfeit artesunate, labelled as produced by ‘Guilin Pharma’, have recently been found in Laos and Cambodia with new, convincing and very well crafted but fake holograms attached to the blisterpacks (see figures below). Also see www.shoklo-unit.com).5. The second 'generation' hologram is a true hologram and only appears to differ from the genuine hologram in the shape of mountain outline and the lack of the microscopic legend 'Guilin Pharma' printed below the 'waves'. The printing on the blisterpack is not clear. All have the same code, and manufacture and expiry dates (code '00902' and manufacture and expiry dates of '09/00' and '09/03', respectively).

The third generation hologram has a mountain outline similar to the genuine Guilin product but lacks the microscopic legend 'Guilin Pharma' printed below the 'waves'. The printing on the blisterpack is crisp and similar to that on the genuine product, bearing the code '010901' with manufacture and expiry dates of '09/01' and '09/04', respectively. It is likely however that artesunate with these 2nd and 3rd 'generation' fake holograms have or will be made with different dates and codes. All 'artesunate' blisterpacks with the 2nd and 3rd generation fake holograms were negative for artesunate by the Fast-Red Dye Test and contained no artesunate on HPLC analysis. It is feared that counterfeit artemisinin blisterpacks bearing the new sophisticated fake holograms are widely distributed in Asia, and perhaps Africa, but because of their similarity to the genuine product they are unrecognised by pharmacists, health staff and patients. There are also reports of fake intramuscular artemether, used to treat patients with severe falciparum malaria, labelled as produced by Kunming Pharmaceuticals (Kunming, PRC) in Burma (Myanmar) (New Light of Myanmar, Rangoon, Myanmar; electronic edition, 9th November 2001). There is an urgent need for action and we hope that this information might prompt interventions to combat this under recognised serious public health problem.

Reference

Genuine artesunate hologram

Counterfeit artemisnien hologram – 2nd generation

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DRUGS OF INTEREST

Haematologic toxicity of two glycopeptides: vancomycin and teicoplanin

All reactions reported to the World Health Organization Monitoring Centre in Uppsala through the end of 2001 were analysed for the two drugs.

Erythropoiesis had the most adverse reactions reported from the United States (n=28), France (n=14), United Kingdom (n=9) and Australia (n=8). Of those associated with vancomycin (n=60), various types of anaemia accounted for 33 with 18 examples of pancytopenia but in 10, myelosuppression was demonstrated. For teicoplanin (n=9) much less experience existed with almost all being accounted for by pancytopenia (n=7).

Platelet and haemostatic disorders were once again most commonly reported from the United States (n=139), France (n=54) and Australia (n=27). Venous thrombosis was infrequent with bleeding accounting for most of the reports. For vancomycin the surprisingly common finding was thrombocytopenia (n=148) followed by purpura from other causes (n=30) and then ecchymotic haemorrhage (n=23). For teicoplanin (n=54), almost all were due to thrombocytopenia (n=49).

Leucocyte associated adverse reactions were most frequent from the United States (n=214), Austria (n=57), Germany (n=42) and United Kingdom (n=23). For vancomycin (n=508), leucopenia (n=229) was followed by granulocytopenia (n=81) and this progressed to agranulocytosis (n=78) with eosinophilia (n=75) and leucocytosis (n=34) being less common.

There are unaccountable differences in prescribing practices between the various countries and the longer period of vancomycin availability and usage explains the relatively high incidence in side effects when compared to teicoplanin. Another shortcoming is the lack of information from many parts of the globe where there is either no reporting or follow-up of outcome in serious complications such as aplasia, agranulocytosis or thrombocytopenia. This limits the value of their data. Additionally, without detailed case records on such issues as the level to which platelets fell and the response after withdrawing antibiotics, recommendations are difficult.

Nevertheless, as information accumulates, it is prudent for users of these products to be aware of the very widespread, and increasing range of haematologic adverse drug reactions.
WHO Training Workshop on Pharmacovigilance: Basic Introduction and Specifics for Malaria Programmes

24 March – 2 April 2003, Lusaka, Zambia

Because of increasing levels of resistance to antimalarial drugs several endemic countries are in the process of introducing combinations of artemisinin derivatives as 1st-line or 2nd-line treatment of malaria. South Africa has introduced artemether/lumefantrine (Coartemâ) as 1st-line treatment of malaria in 2001 and Zambia has started phased deployment of this drug at the end of 2002, also as 1st-line treatment. Zanzibar and Burundi have adopted artesunate + amodiaquine as 1st-line treatment and the new treatment policy will be implemented in 2003. Mozambique has recently adopted amodiaquine + sulfadoxine/pyrimethamine as 1st-line treatment and artemether/lumefantrine (Coartemâ) as 2nd-line treatment and implementation may start in late 2003. Both the Democratic Republic of Congo and Rwanda are considering a policy change to artemisinin-based combinations in the near future.

As with all newly registered products, there is still limited experience with large-scale operational use and safety of these drugs in special population groups, such as infants, pregnant women, patients with malnutrition and HIV/AIDS. Unfortunately in most malaria endemic countries, particularly in Africa, pharmacovigilance is not yet implemented by the public sector, and post-marketing surveillance by the pharmaceutical sector is not functioning. The introduction of artemisinin combination therapies (ACTs) provides an opportunity to establish pharmacovigilance of antimalarial drugs in these countries. While initially the monitoring activities will focus on antimalarial drugs only, it is expected that over time the system will be strengthened with the support of WHO to include safety monitoring of all drugs.

It was with this background in mind that WHO convened a workshop of malaria managers and officials responsible for pharmacovigilance from five African countries introducing artemisinin-based combination therapies, notably Burundi, Democratic Republic of Congo, Mozambique, Zambia and Zanzibar. A total of 18 participants were exposed to the basic methods and skills for drug safety monitoring, with the aim of introducing a common system of pharmacovigilance of new antimalarial treatments, with access to the WHO database and international expertise, and to initiate plans for early implementation in the respective countries.

The programme of the training workshop aimed to present the best accepted international standards as promoted by WHO (24-28 March 2003); and the examplary experience with large-scale operational use and safety of these drugs in special population groups, such as infants, pregnant women, patients with malnutrition and HIV/AIDS. Unfortunately in most malaria endemic countries, particularly in Africa, pharmacovigilance is not yet implemented by the public sector, and post-marketing surveillance by the pharmaceutical sector is not functioning. The introduction of artemisinin combination therapies (ACTs) provides an opportunity to establish pharmacovigilance, based on the best accepted international standards as promoted by WHO (24-28 March 2003); and

Part II – Country-specific adaptation of the general WHO protocol of artemisinin-based combination therapies, practical aspects and planning (29 March – 2 April 2003)

The training workshop was designed by WHO/EDM and WHO/MAL (HQ& AFRO) in close collaboration with the WHO Collaborating Centre for International Drug Monitoring (Uppsala Monitoring Centre). The following tutors were actively engaged in planning and teaching activities: Mr S. Olsson, Sweden, Dr Ushma Mehta, South Africa, Dr David Coulter, New Zealand, Dr Alex Dodoo, Ghana. The following WHO Secretariat provided facilitation: Dr A. Bosman, WHO/MAL, Dr M. Couper, WHO/EDM, Dr T. Sukwa, AFRO/MAL and Dr F. Masaninga, WHO Office in Zambia. Overall support from the WHO’s Representative Office and the National Malaria Malaria Control Centre of the Central Board of Health of Zambia helped to make the workshop successful.

Each of the five participating countries developed draft guidelines and plans of action for pharmacovigilance which will be presented to the Ministry of Health of the respective countries. WHO will provide technical support to countries for early implementation, monitoring and evaluation.

It is hoped that the workshop can be used as a prototype for other diseases of public health importance.
The third annual meeting of the International Society of Pharmacovigilance (ISoP) will be held in Marrakesh, Morocco, 8-11 October 2003. A wide range of scientific topics will be covered under the conference theme of ‘Pharmacovigilance in Clinical Practice’. Abstracts for both oral and poster presentations are invited. The closing date for submission of abstracts is 15 July 2003. All registrations will have to be made online, through the website: www.isop2003.org. This site provides full details of scientific and social programmes, registration fees, accommodation and other relevant information. Two parallel pre-conference courses will also be offered on ‘Compliance in Pharmacovigilance’ and on ‘How to write a paper for peer-reviewed journals’. Separate registration is required for attending the pre-conference courses.