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EDITORIAL

In this edition several topical issues are brought to the attention of our readers. Long-term use of hormone replacement therapy is discouraged on the basis of a large observational study of nearly a million postmenopausal women, which showed an increased incidence of fatal breast cancer. Whereas nimesulide, which has been a subject of concern due to its association with hepatic reactions, has received a favourable benefit/risk assessment by the European Committee for Proprietary Medicinal Products. A new antimalarial drug combination (chlorproguanil-dapsone) was approved by the UK Medicines and Healthcare Products Regulatory Agency (MHRA) for treating uncomplicated *Plasmodium falciparum* malaria. It is intended to be used in sub-Saharan Africa.

A European-Pacific kava strategy meeting was held in Brussels, Belgium on 25-26 August. This meeting sought to address issues on the implications of the ban on "synthetic" kava preparations on the use of natural kava products. A full report on this issue will be forthcoming later.

The first meeting of the WHO Advisory Committee for the Safety of Medicinal Products (ACSoMP) will take place in Geneva in the month of October. This is an important development since the remit of the Committee is to set a policy for WHO in the area of medicine safety and to review controversial safety issues. In December, the National Centres for Pharmacovigilance will get together in New Delhi, India for their annual meeting. Further information on this will shortly be available on the website: http://www.who-umc.org.

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SAFETY OF MEDICINES

DRUGS IN THE NEWS

ABACAVIR, LAMIVUDINE, TENOFOVIR

Virologic non-response in HIV with combination therapy

Europe, USA. The EMEA, US FDA and Swissmedic are informing physicians of reports of a high rate of early virologic non-response observed in a GlaxoSmithKline (GSK)-sponsored clinical study of therapy naïve adults receiving once daily three drug combination therapy with tenofovir (Viread), lamivudine (Epivir) and abacavir (Ziagen). The precise nature of any interaction leading to non-response is currently unknown. The Marketing Authorization Holders have been requested to further explore the nature of these interactions through *in vivo/in vitro* studies. In the meanwhile physicians are advised that,

- abacavir and lamivudine, in combination with tenofovir should not be used as a triple antiretroviral therapy when considering a new treatment regimen for naïve or pre-treated patients, particularly as a once-daily regimen
- patients currently controlled with this combination should be frequently monitored with a sensitive viral load test and considered for modification of therapy at the first sign of viral load increase.

GlaxoSmithKline has issued a 'Dear Healthcare Provider' letter for the above information. Patients about to receive or, currently on this combination therapy are advised to inform their physician immediately.

Reference:

1. *EMEA Public Statement, EMEA/20194-03, 30 Jul 2003. Available from URL: http://www.emea.eu.int*
2. *'Dear Healthcare Provider' letter from GlaxoSmithKline, 31 Jul 2003. Available from URL: http://www.fda.gov*
3. *Important Information on Human Medicines: Swissmedic, 6 Aug 2003. Available from URL: http://www.swissmedic.ch*

ACETYL-SALICYLIC ACID (PAEDIATRIC)

OTC withdrawal

Spain. The Spanish Medicines Agency has announced that, starting 20th June 2003, all paediatric OTC medicinal preparations containing salicylates/ acetylsalicylic acid (Aspirin) are being withdrawn from the market. This measure has been undertaken to prevent the use of these products in children with viral fever and thereby reduce the risk of Reye's syndrome in these children. For non-paediatric OTC products containing salicylates/ acetylsalicylic acid the Summary of Product Characteristics (SPC) will have to be modified to include the following:

- salicylates/acetylsalicylic acid – containing OTC products for adult use are contraindicated in children below the age of 16 years
- salicylates/acetylsalicylic acid – containing prescription products are contraindicated for the treatment of fever, chickenpox and viral fevers in patients below 16 years of age.

Reference:

Communication from the Spanish Pharmacovigilance System, 8 Jul 2003.

ACETYL-SALICYLIC ACID, PARACETAMOL, IRON

New packaging standards for improving child resistance

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) in the UK has announced that all products containing acetylsalicylic acid, paracetamol and iron will now be required to be in packaging that meets the new British Standard on child resistance for medicines. The new regulations will come into force on 1 October 2003 with a 2-year transitional period for products already on the market to comply. The proposal endorses an additional safeguard in keeping medicines out of children's reach and is based on a 12-week public consultation exercise involving Pharmacy Colleges, the National Health Service, Industry, Medical Colleges and other professional bodies.

Reference:

MHRA Publication, Aug 2003. Available from URL: http://medicines.mhra.gov.uk

BENZ-BROMARONE

Withdrawn due to reports of liver damage

France. Sanofi-Synthélabo has withdrawn its hyperuricaemic product benzbromarone (Desuric) in France following reports of serious liver damage associated with the product's use. Benzbromarone (Desuric) has been marketed in France since 1976, but rare reports of serious cytolytic liver damage, including fatal cases and others requiring liver transplants, have led to an unfavourable benefit/risk ratio. The company has therefore decided to stop the marketing of this product in France and to recall all stocks.

Reference:

Chaibriant H. Stop marketing of proprietary medical product DESURIC (Rm) (benzbromarone), 22 Apr 2003. Available from URL: http://agmed.sante.gouv.fr

EZETIMIBE

Labelling update regarding hypersensitivity reactions

USA. Merck/Schering-Plough Pharmaceuticals have issued a press release in which they note the addition of information regarding reports of hypersensitivity reactions to the labelling of their lipid-lowering agent ezetimibe (Zetia). The Adverse Reactions section of the product labelling has been updated following reports of hypersensitivity reactions, including rash and angioedema, all of which either resolved spontaneously or were successfully treated with standard therapies. In the release, Merck/Schering-Plough note that many commonly used drugs list hypersensitivity reactions, including angioedema, in the Adverse Reactions sections of their product labels, including the most widely prescribed lipid-lowering agents. They point out that, unlike other lipid-lowering drugs, clinical trials of ezetimibe (Zetia) showed no increased risk of myopathy or rhabdomyolysis.

Reference:

Merck/Schering-Plough Pharmaceuticals Media Release, 30 Jun 2003. Available from URL: http://www.merck.com

LEFLUNOMIDE

Explicit liver function monitoring directions added to label

USA. Leflunomide (Arava) labelling in the US now includes more explicit liver function monitoring directions. The label now states that at the minimum, ALT must be performed at baseline and monitored initially at monthly intervals during the first six months and then, if stable, every six to eight weeks thereafter. The label previously recommended monthly monitoring until stable without mention of the 6-month timeframe or frequency of monitoring once stable. In addition, a bolded statement on severe liver injury has been added to the Warnings section and the manufacturer (Aventis) is to issue a 'Dear Healthcare Professional' letter regarding the labelling changes.

Reference:

FDC Reports - Pink Sheet - Prescription Pharmaceuticals and Biotechnology 65: 7, 23 Jun 2003.

PAROXETINE

Unfavourable risk benefit ratio in children and adolescents

UK, Canada. New data from clinical trials of paroxetine (Seroxat) in children and adolescents received by the UK Medicines and Healthcare products Regulatory Agency (MHRA) do not show a favourable risk/benefit profile of paroxetine in this age group. According to the Committee on Safety of Medicines these data do not demonstrate efficacy in the treatment of depressive illness and show an increase in the risk of harmful outcomes, including episodes of self-harm and potentially suicidal behaviour; the risk of these outcomes appears to be 1.5−3.2 times greater in those receiving paroxetine than in those receiving placebo. The CSM has therefore advised that paroxetine should not be used in children and adolescents under the age of 18 years to treat depressive illness. The product information for paroxetine (Seroxat) is to be updated accordingly[1]. Health Canada has also advised that the product monograph for paroxetine (Paxil) be updated with similar information in Canada. Although paroxtine (Paxil) is not indicated for use in patients under 18 years of age in Canada, the off-label use of the product exists in the paediatric population. Health Canada also warns that paroxetine should not be abruptly discontinued but should be gradually tapered off to avoid discontinuation symptoms.

Reference:

1. *Letter from the Chairman of the Committee on Safety of Medicines, 10 Jun 2003. Available from URL: http://www.medicines.mhra.gov.uk*
2. *'Dear Healthcare Professional' letter from GlaxoSmithKline Inc, 10 Jul 2003. Available from URL: http://www.hc-sc.gc.ca*

SALMETEROL

Risk of life-threatening asthma episodes

USA. The US FDA is advising that all drug products containing salmeterol will now include new safety information and warnings about a small but significant number of reports of life-threatening asthma episodes or asthma related deaths in patients taking these products. Salmeterol is a long-acting bronchodilator used to treat asthma and chronic obstructive pulmonary disease (COPD). The FDA announcement follows the findings of a large safety study in the US showing a significant increase in respiratory-related death or life-threatening experience in African-American patients treated with the drug (Serevent). However, the FDA emphasizes that based on available data, the benefits of treatment with salmeterol in patients with asthma and COPD continue to outweigh the potential risks when used according to the instructions contained in the product labelling. Patients should not stop taking products that contain salmeterol, or any other medication for asthma or COPD without consulting their physicians since abrupt discontinuation of therapy can result in worsening of the disease with serious and fatal consequences.

Reference:

FDA Talk Paper, 14 Aug 2003. Available from URL: http://www.fda.gov

SOMATROPIN (rDNA ORIGIN)

Reports of fatalities in paediatric patients with Prader-Willi syndrome

USA. Pharmacia & Upjohn Company, in association with the US FDA is informing healthcare professionals about seven post marketing reports of fatalities associated with the use of growth hormone in paediatric patients with Prader-Willi syndrome. These patients had one or more of the following risk factors including severe obesity, history of respiratory impairment or sleep apnoea, or unidentified respiratory infection. In view of these observations the Contraindications section now warns that growth hormone is contraindicated in patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment. The package insert also warns about the reports of fatalities in paediatric patients with one or more of the above mentioned risk factors. The warnings section also informs that male patients (with one or more risk factors) may be at greater risk. Patients with Prader-Willi syndrome should be evaluated for upper airway obstruction before initiation of treatment and treatment with growth hormone should be discontinued if airway obstruction develops during treatment. All patients with Prader-Willi syndrome should have effective weight control, evaluated for sleep apnoea and monitored for signs of respiratory infections.

Reference:

'Dear Healthcare Professional' letter from Pharmacia EndocrineCare, 30 May 2003. Available from URL: http://www.fad.gov

TIROFIBAN

Advice against off-label use

Malaysia. The Drug Control Authority (DCA) in Malaysia has directed the manufacturer of tirofiban (Aggrastat) to issue a 'Dear Doctor' letter advising health professionals against the off-label usage of tirofiban (Aggrastat) injection. This advice follows reports of fatal outcomes occurring with the use of tirofiban with heparin during cardiopulmonary bypass in patients who previously experienced heparin-induced thrombocytopenia type II reactions.

Reference:

Malaysian News. Available from URL: http://www.bpfk.gov.my

TOPIRAMATE

Risk of oligohidrosis and hyperthermia

USA, Canada. Ortho-McNeil Pharmaceutical Inc in the USA and Janssen-Ortho Inc in Canada are warning healthcare professionals about rare reports, primarily in children, of oligohidrosis (decreased sweating) and hyperthermia in patients treated with topiramate (Topamax). Most cases occurred in association with exposure to elevated temperatures and/or energetic activity. The prescribing information for topiramate (Topamax) has been updated to reflect these reports. Oligohidrosis and hyperthermia may have potentially serious sequelae and may be preventable by prompt recognition of symptoms and appropriate treatment. Patients on topiramate therapy should be closely monitored for signs of decreased sweating and increased body temperature, and when topiramate is prescribed with other drugs such as carbonic anhydrase inhibitors and anticholinergics that can predispose patients to heat-related disorders.

Reports in WHO-file:
Sweating decreased 9, hyperpyrexia 3, hyperpyrexia malignant 1

Reference:

1. *'Dear Healthcare Professional' letter from Ortho-McNeil, 09 Jul 2003. Available from URL: http://www.fda.gov*
2. *'Dear Healthcare Professional' letter from Janssen-Ortho Inc, 11 Jul 2003. Available from URL: http://www.hc-sc.gc.ca*

ATYPICAL ANTI-PSYCHOTICS

Reports of hypertension

New Zealand. The Intensive Medicines Monitoring Programme (IMMP) in New Zealand has led to the identification of associations between atypical antipsychotics and hypertension. A total of 572 case reports involving atypical antipsychotics were analysed and hypertension was identified as a possible adverse drug reaction (ADR). Hypotension, a known side effect, was reported in 19 cases, compared with 13 cases of hypertension, involving clozapine (n = 10), risperidone (2) and quetiapine (1). The two most severe cases occurred with risperidone: two women, aged 53 and 54 years, received risperidone 1 and 0.5 mg/day, respectively, for 3 days before experiencing increases in blood pressure (BP) to 190/110 and 210/110mm Hg, respectively; both patients recovered shortly after risperidone discontinuation. In the 11 other cases, patients aged 15–66 years developed marked increases in BP with systolic pressures of 140–170mm Hg and diastolic pressures of 95–120mm Hg. In all but one case, BP elevation occurred within 1 month of starting treatment. 4 of the 13 patients were receiving concomitant SSRIs. According to the Director of the programme, Dr David Coulter "the evidence

BOTULINUM A

Patients misled over safety

USA. The US FDA has raised objections that the web advertising or the product information in print for botulinum A toxin preparation (Botox) as posted by the company (Allergan) has insufficient information on the unwanted side effects that could result in patients treated with the product for cosmetic purposes. FDA is of the opinion that the advertisements pertaining to the product are false and misleading because they falsely identify the product as a cosmetic treatment, fail to reveal material facts about the product use and minimise the risk information presented. The advertising does not make it clear that more than four in ten people treated with the product suffer some form of side effect. The most common side effects of the treatment are headache and nausea; the product has also been linked with respiratory infection and 'flu syndrome', as well as temporary drooping of the eyelids.

Reference:
News & Updates, 27 Jun 2003. Available from URL: http://www.druginfozone.nhs.uk

CHELIDONIUM MAJUS

Statement to advise use under supervision

available evidence linking ingestion of *C.majus* with moderate to severe, reversible acute hepatitis in a relatively small number of individuals worldwide. The mechanism underlying the hepatotoxic effect needs to be elucidated. Pending further information, the Therapeutic Goods Administration (TGA) has advised healthcare professionals to be vigilant to signs of liver toxicity associated with the use of Chelidonium-containing medicines. *C.majus* (Greater celandine) has been traditionally used to treat a range of conditions including liver disorders and is available internationally.

Reference:
Therapeutic Goods Administration Alert (Complementary Medicines), 07 Aug 2003. Available from URL: http://www.health.gov.au

CYCLO-OXYGENASE (COX)-2 INHIBITORS

Reports of hepatotoxicity

New Zealand. Seventeen reports of hepatotoxicity have been received as part of the IMMP (Intensive Medicines Monitoring Programme) monitoring of selective COX-2 inhibitors, including three reports of significant liver injury in patients aged 85, 81 and 61 years, who