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EDITORIAL

It was good seeing many of you in India during the Twenty-sixth Annual Meeting of the National Centres participating in the WHO International Drug Monitoring Programme. The working groups at the meeting debated on system differences and ways in which countries could learn from each other for improved reporting of adverse drug reactions. No doubt this last meeting will set the agenda for activities in pharmacovigilance for the current year. Implementing the suggestions into practice, in real terms, will be a challenge. Preparations are in full swing for the ICDRA meeting to be held in Spain 16-19 February 2004. A pre-ICDRA satellite workshop on counterfeit drugs will address important questions and problems pertaining to fake - drugs the world over. We are in the process of revising the National Information Officers List; we are happy to note that many of the Member States have already responded with updated information and we hope to hear from the others before the turn of the month. And last, but not least, we wish all our readers a very happy new year in 2004.

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ANTI-DEPRESSANTS

FDA warns of paediatric suicide risk; CSM reports poor paediatric benefit/risk profile with SSRIs

USA, UK. The United States Food and Drug Administration (FDA) has issued a Public Health Advisory alerting healthcare professionals to reports of suicidal ideation and suicide attempts in clinical trials of antidepressants in paediatric patients with major depressive disorder (MDD)[1]. Preliminary data from 20 placebo-controlled trials involving the eight antidepressants citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline and venlafaxine suggest an excess of reports of suicidality in paediatric patients assigned to some of these drugs compared with those assigned to placebo. The FDA has completed a preliminary review of such reports and determined that additional data and analysis, and a public discussion of available data is needed. The FDA emphasises that there have been no reports of completed suicides associated with the use of these antidepressants. It also notes that the data were adequate to establish effectiveness in paediatric MDD only for fluoxetine (Prozac). Prescribers are reminded that all antidepressant labelling includes a warning about the possibility of suicide attempts inherent in MDD and that, close supervision of high-risk patients should accompany initial drug therapy.

The UK Committee on Safety of Medicines (CSM) has advised that, based on the review by the Expert Working Group, the balance of risks and benefits for the treatment of major depressive disorder (MDD) in under 18s is judged to be unfavourable for the Selective Serotonin Reuptake Inhibitors (SSRIs) sertraline, citalopram and escitalopram and un-assessable for fluvoxamine; only fluoxetine (Prozac) has been shown to have a favourable balance of risks and benefits in this age group[2]. The CSM had earlier also issued a warning that paroxetine and venlafaxine, two other SSRIs, should not be used in treating MDD in children and adolescents under the age of 18 years. In adults the benefits of treatment are considered to outweigh the risk for all SSRIs. None of the above mentioned drugs have ever been licensed for use in depressive illness in under-18s although their use in MDD in this population is known. Although fluoxetine does not have a marketing authorisation for MDD in the UK in under-18 year olds, the CSM has considered the clinical trial data and advised that the balance of risks and benefits is favourable. However, the decision to prescribe fluoxetine (or one of the other SSRIs in a patient who might be intolerant to fluoxetine) should only be made with specialist advice and after careful consideration of all available information. For those under 18 MDD patients, who are currently on an SSRI, the treatment must be gradually tapered off in order to avoid precipitating sudden-withdrawal reactions.

References:

1. *FDA Talk Paper T03-70, 27 October 2003. Available from URL: http://www.fda.gov*
2. *'Dear Colleague' letter from Chairman CSM, via Pubic Health Link, 10 December 2003. Available from URL: http://medicines.mhra.gov.uk*

ATYPICAL ANTI-PSYCHOTICS

FDA requests class label change

USA. The FDA has sent a letter to six manufacturers of atypical antipsychotics requesting updated product labelling to include additional information on hyperglycaemia and diabetes mellitus (see also section on Drugs of Current Interest). The letter has been sent to the makers of olanzapine (Zyprexa; Eli Lilly) clozapine (Clozaril; Novartis), risperidone (Risperdal; Janssen), quetiapine (Seroquel; AstraZeneca), ziprasidone (Geodon; Pfizer) and aripiprazole (Abilify; Bristol Myers Squibb). The requested labelling states that, all patients treated with atypical antipsychotics should be monitored for symptoms of hyperglycaemia and that, those that develop such symptoms undergo fasting glucose testing. It also advises that diabetic patients or, those with risk factors for diabetes, who start taking atypical antipsychotics be monitored for worsening glucose control. The FDA states in the letter that "increased attention to the signs and symptoms of diabetes mellitus may lead to earlier detection and appropriate treatment, and thus may reduce the risk for the most serious outcomes". It recognises that the relationship between atypical antipsychotic use and hyperglycaemia-related adverse events is not fully understood, but notes that epidemiological studies suggest an increased risk. Also noted in the labelling is that the assessment of any relationship between atypical antipsychotics and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes in patients with schizophrenia, and by the increasing incidence of diabetes in the general population. But not all accept a class effect. Pfizer has stated that its atypical antipsychotic ziprasidone has not been associated with an increased risk of diabetes and that it intends to work closely with the FDA to review the requested class label change. Pfizer says that evidence from clinical trials has consistently shown that ziprasidone has a weight-neutral profile and that it does not adversely affect patients' levels of insulin, cholesterol, triglycerides or blood glucose.

Reference:

Reactions 970: 2, 27 September 2003.

BIS-PHOSPHONATES

Ocular disorders: discontinue therapy if scleritis occurs

Canada. In the October 2003 issue of the Canadian Adverse Reaction Newsletter, ocular disorders associated with bisphosphonates are discussed.

Bisphosphonates can rarely cause serious ocular adverse effects, as suggested by international data from spontaneous adverse reaction reporting systems. Pamidronic acid has been associated with ocular inflammation, including uveitis, nonspecific conjunctivitis, episcleritis and scleritis, and similar ocular adverse effects have been reported with alendronic acid, clodronic acid, etidronic acid and risedronic acid. Up to 28 Feb 2003, Health Canada has received 27 reports of bisphosphonate-associated ocular and visual disorders; 13 of these reports involved alendronic acid, five involved etidronic acid, six involved pamidronic acid, and three involved risedronic acid. To date, there have been no reported cases of ocular disorders associated with clodronic acid or zoledronic acid in Canada. Health Canada recommends that patients who experience visual loss or ocular pain during bisphosphonate therapy should be referred to an ophthalmologist, and that if scleritis occurs, bisphosphonate therapy must be discontinued. They add that more than one ocular adverse effect may occur at the same time and, in some cases, the bisphosphonate may need to be discontinued for the ocular inflammation to resolve.

Reference:
Canadian Adverse Reaction Newsletter Vol 13, Issue 4, October 2003. Available from URL: http://www.hc-sc.gc.ca

COX-2 Inhibitors

CPMP advises stronger risk warnings

Europe. The European Committee for Proprietary Medicinal Products (CPMP) has finalised a EU-wide review of the cyclooxygenase-2 (COX-2) inhibitor substances celecoxib, etoricoxib, parecoxib, rofecoxib and valdecoxib. The review was initiated by France in July 2002 due to gastrointestinal and cardiovascular safety concerns. The CPMP has concluded that the benefit-risk balance for these drugs remains positive for the target populations. However, the Committee recommends that the product label should be strengthened with additional warnings, in particular recommending caution in patients with underlying gastrointestinal and cardiovascular risks. The Committee also recommends adding (or modifying) warnings concerning the risk of severe skin and hypersensitivity reactions.

Reference:
EMEA Press Release EMEA/CPMP/5732/03/Final, 20 November 2003. Available from URL: http://www.emea.eu.int

DIDANOSINE/ LAMIVUDINE/ TENOFOVIR

Virologic failure with once-daily triple combination therapy

Europe. A high rate of early virologic failure and emergence of nucleoside/nucleotide reverse transcriptase inhibitor resistance-associated mutations occurred in a clinical study of once-daily triple combination therapy comprising didanosine enteric coated beads (Videx), lamivudine (Epivir) and tenofovir disoproxil fumarate (Viread).

The European Agency for the Evaluation of Medicinal Products (EMEA) has issued a public statement regarding the results of this 24-week clinical study, in which virologic failure occurred in 91% of 24 HIV-infected treatment-naive patients receiving a once-daily regimen of didanosine, lamivudine and tenofovir disoproxil fumarate. The EMEA notes that the precise nature of the interactions leading to this non-response is unknown and the EMEA's Committee for Proprietary Medicinal Products has requested that the marketing authorisation holders explore these interactions. While investigations are ongoing, the EMEA advises the following precautionary measures:

- When considering a new treatment regimen, tenofovir in combination with didanosine and lamivudine should not be used, particularly as a once-daily regimen.
- Patients well controlled on this combination should be frequently monitored and considered for treatment modification if signs of virologic failure emerge.
- Patients receiving or about to receive a regimen including didanosine, lamivudine and tenofovir in combination should inform their physician immediately.

The EMEA points out that similar recommendations were made on 30 July 2003 regarding the once-daily triple therapy with abacavir, lamivudine and tenofovir. A WHO alert (WHO Drug Alert 109, available from URL http://www.who.int/medicines/library/) was also issued for the above information.

Reference:
EMEA Public Statement EMEA/CPMP/5094/03, 22 October 2003. Available from URL: http://www.emea.eu.int

EFALIZUMAB

Monitoring for thrombocytopenia recommended

USA. Labelling for efalizumab (Raptiva) should require monitoring of platelet counts to

minimise the risk of thrombocytopenia, the US FDA's Dermatologic & Ophthalmic Drugs Advisory Committee has recommended, reports The Pink Sheet. Although the Committee agreed that the overall risk-benefit ratio of efalizumab for the treatment of psoriasis is favourable, members noted that data suggest an association between the agent and the development of clinically significant thrombocytopenia, and that there are reservations regarding the lack of long-term safety data available, particularly for the detection of cancers and serious infections. In clinical trials, 8 of 2762 (0.3%) efalizumab recipients experienced platelet counts of less than 50 000/mm, five of whom were hospitalised with thrombocytopenia. In addition, 7 of 1620 (0.4%) efalizumab-treated patients were diagnosed with serious infections after first exposure to the agent, and 20 (of 1784 subject-years) developed non-melanomatous skin cancer. Genentech is to discuss the potential labelling implications for efalizumab with the FDA.

Reference:
FDC Reports – The Pink Sheet – Prescription Pharmaceuticals and Biotechnology 65: 27-28, No. 38, 22 September 2003.

EPHEDRA

Weight-loss aid ephedra to be banned

USA, Jordan. The FDA has announced that it is to ban the weight-loss aid ephedra due to safety concerns that the product can cause heart attacks and stroke. Ephedra is an adrenaline-like stimulant that can have potentially dangerous effects on the heart. The FDA has reports of 155 deaths of people who took ephedra and more than 16,500 complaints in its records. However, the agency has allowed an exemption for practitioners of Chinese medicine with many years of experience in using ephedra in treating ailments ranging from asthma to fevers. The Jordan Food and Drug Administration has withdrawn a herbal product (Magic Herb), used to promote weight loss, on the grounds that it contains ephedra. Jordanians have been alerted not to buy or use the product. This decision was based on the US FDA's website information about the unreasonable risk in using food supplements containing ephedra or ephedrine.

References:
1. *News & Updates from Drug Info Zone, 2 January 2004. Available from URL: http://www.druginfozone.nhs.uk*
2. *Communication from Jordan Pharmacovigilance Centre, 19 January 2004.*

LITARGIRIO

Presence of dangerous levels of lead

USA. The FDA has issued a warning to the public not to use 'Litargirio' for any health-related or personal purposes as the powder contains dangerous levels of lead (up to 79%). This warning follows a health alert issued by the Rhode Island Department of Health after it was discovered that several children undergoing treatment for lead poisoning had been using 'Litargirio' as a deodorant, and their blood lead levels only began to decrease after they stopped using 'Litargirio'.

The FDA says that 'Litargirio' powder is manufactured by Roldan, Ferreira, and possibly by other laboratories in the Dominican Republic, and it is used particularly by people from the Dominican Republic. The product has been used as a deodorant, foot fungicide, treatment for burns and wound healing, and for other purposes as a traditional remedy, despite having no proven health benefits. According to the FDA, the high concentration of lead in 'Litargirio' poses health risks when used in contact with the skin or ingested and this risk is particularly serious in children in whom it may cause permanent neurological damage. The FDA has advised the public to stop using 'Litargirio' immediately, to place any unused product in a sealable container or plastic bag and contact their local sanitation/waste department regarding disposal, and to thoroughly wash hands and other body parts or household surfaces that have come into contact with the powder. They also recommend that children or pregnant/nursing women who have used 'Litargirio' should be tested for lead poisoning.

Reference:
Media Release, 2 October 2003. Available from URL: http://www.fda.gov

LORATADINE

Not recommended during pregnancy

Europe. The European Committee for Proprietary Medicinal Products (CPMP) has finalised a EU-wide review of loratadine that was initiated by Sweden due to safety concerns of hypospadias in new-born boys born to mothers receiving loratadine during pregnancy. The CPMP has concluded that a causal relationship could neither be confirmed nor excluded. However, the Committee advises that as a precautionary measure the product information for loratadine should be revised to state that the use of loratadine during pregnancy is not recommended; combinations of loratadine and pseudoephedrine should be contraindicated in pregnancy since pseudo-ephedrine decreases maternal uterine blood flow. A similar parallel review for desloratadine could neither establish nor exclude a causal relationship with hypospadias; the CPMP has advised against using this drug also in pregnancy.

Reference:
EMEA Press Release EMEA/CPMP/5732/03/Final, 20 November 2003. Available from URL: http://www.emea.eu.int

OSELTAMIVIR

Not indicated in patients less than one year of age

USA. Roche Laboratories Inc, in consultation with US FDA, is advising healthcare professionals that oseltamivir (Tamiflu), indicated in the treatment of uncomplicated acute illness due to influenza, should not be used for either treatment or prophylaxis of influenza in children under one year of age. This warning is being issued because a single dose of 1000 mg/kg oseltamivir phosphate (about 250 times the recommended dose in children) in juvenile rats resulted in the death of 7-day old rats; the deaths were associated with levels of oseltamivir phosphate in the brain approximately 1500 times those seen in adult animals. It is likely that these high exposures were related to an immature blood-brain barrier. The clinical significance of these preclinical data to human infants is uncertain. Given the uncertainty in predicting the exposures in infants with immature blood-brain barriers, it is recommended that oseltamivir (Tamiflu) not be administered to children younger than one year of age. The company is in the process of updating the product monograph with the above information.

Reference:
'Dear Healthcare Professional' letter from Roche Laboratories Inc

recommendation by the non-prescription drug advisory committee of the US FDA to have a more explicit warning on all packs of paracetamol OTC preparations about the possibility of liver toxicity caused by overdose with the drug. More than half a dozen parcetamol preparations are available in the Indian market.

Reference:
Scrip World Pharmaceutical News No. 2906, 28 November 2003. Available from URL: http://www.scrippharma.com

STAMEN AND BELL MAGICC BULLET

Presence of sildenafil

Canada. Health Canada has warned against use of the health products Stamen and Bell Magicc Bullet after both were found to contain sildenafil. Neither product has been approved by Health Canada for sale, nor are they labelled to contain sildenafil. Health Canada has received one report of an adverse reaction to Stamen but no reports relating to Bell Magicc Bullet. Health Canada is currently working with the distributors to remove the products from the market and advises consumers, who have used the products and have concerns, to contact their physicians or health care providers.

Reference:

`Dear Healthcare Professional' letter issued by Roche Laboratories, Inc. Following completion of a randomised clinical trial, valganciclovir has been approved for the prevention of CMV infections in high-risk kidney, heart and kidney-pancreas transplant patients. However, valganciclovir has not been approved for this use in liver transplant patients due to a higher incidence of overall CMV disease and of tissue-invasive CMV disease in patients receiving valganciclovir compared with those receiving ganciclovir (19% vs 12% and 14% vs 3%, respectively).

Reference:
'Dear Healthcare Professional' letter from Roche Laboratories Inc, 30 September 2003. Available from URL: http://www.fda.gov

VORICONAZOLE

Not to be available to general practitioners

UK. Voriconazole is an alternative anti-fungal agent for the treatment of serious invasive fungal infections. The Midland and Therapeutic Review and Advisory Committee (MTRAC) has stated that voriconazole is more likely to be prescribed only in secondary care and that there is little experience with voriconazole. In view of the above observations the Committee has decided that it is not appropriate for general practitioners to prescribe this drug.