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.
# TABLE OF CONTENTS

## REGULATORY MATTERS

<table>
<thead>
<tr>
<th>Topic</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTIDEPRESSANTS</strong></td>
<td>FDA warns of paediatric suicide risk; CSM reports poor paediatric benefit/risk profile with SSRIs</td>
</tr>
<tr>
<td><strong>ATYPICAL ANTIPSYCHOTICS</strong></td>
<td>FDA requests class label change</td>
</tr>
<tr>
<td><strong>BISPHOSPHONATES</strong></td>
<td>Ocular disorders: discontinue therapy if scleritis occurs</td>
</tr>
<tr>
<td><strong>COX-2 Inhibitors</strong></td>
<td>CPMP advises stronger risk warnings</td>
</tr>
<tr>
<td><strong>DIDANOSINE/LAMIVUDINE/TENOFOVIR</strong></td>
<td>Virologic failure with once-daily triple combination therapy</td>
</tr>
<tr>
<td><strong>EFALIZUMAB</strong></td>
<td>Monitoring for thrombocytopenia recommended</td>
</tr>
<tr>
<td><strong>EPHEDRA</strong></td>
<td>Weight-loss aid ephedra to be banned</td>
</tr>
<tr>
<td><strong>LITARGIRIO</strong></td>
<td>Presence of dangerous levels of lead</td>
</tr>
<tr>
<td><strong>LORATADINE</strong></td>
<td>Not recommended during pregnancy</td>
</tr>
<tr>
<td><strong>OSELTAMIVIR</strong></td>
<td>Not indicated in patients less than one year of age</td>
</tr>
<tr>
<td><strong>PARACETAMOL</strong></td>
<td>Label to warn about liver damage with overdose</td>
</tr>
<tr>
<td><strong>STAMEN AND BELL MAGICC BULLET</strong></td>
<td>Presence of sildenafil</td>
</tr>
<tr>
<td><strong>VALGANCICLOVIR</strong></td>
<td>Not approved for CMV prevention in liver transplant patients</td>
</tr>
<tr>
<td><strong>VORICONAZOLE</strong></td>
<td>Not to be available to general practitioners</td>
</tr>
</tbody>
</table>

## SAFETY OF MEDICINES

<table>
<thead>
<tr>
<th>Topic</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTIEPILEPTICS</strong></td>
<td>ADR update from Australia</td>
</tr>
<tr>
<td><strong>BOTULINUM TOXIN TYPE A</strong></td>
<td>Place in therapy not clearly defined</td>
</tr>
<tr>
<td><strong>CELECOXIB/ROFECOXIB</strong></td>
<td>Acute temporary visual impairment</td>
</tr>
<tr>
<td><strong>DACLIZUMAB</strong></td>
<td>Increased mortality in cardiac transplant patients</td>
</tr>
<tr>
<td><strong>FLUTICASONE</strong></td>
<td>Update on adrenal insufficiency reports</td>
</tr>
<tr>
<td><strong>INTERFERON BETA</strong></td>
<td>Safety information about risk of liver injury</td>
</tr>
<tr>
<td><strong>METHADONE</strong></td>
<td>Risk of QT prolongation</td>
</tr>
<tr>
<td><strong>METHOTREXATE</strong></td>
<td>Update on pulmonary effects</td>
</tr>
<tr>
<td><strong>MIRTAZAPINE</strong></td>
<td>ADR update from Australia</td>
</tr>
<tr>
<td><strong>MORPHINE</strong></td>
<td>Accidental overdose of concentrated oral solutions</td>
</tr>
<tr>
<td><strong>NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)</strong></td>
<td>Postpartum administration may cause hypertension</td>
</tr>
<tr>
<td><strong>PERGOLIDE</strong></td>
<td>Danger of falling asleep during daily activities</td>
</tr>
<tr>
<td><strong>PYRAZINAMIDE &amp; RIFAMPICIN</strong></td>
<td>Serious liver injury with combined use in latent tuberculosis</td>
</tr>
<tr>
<td><strong>SIBUTRAMINE</strong></td>
<td>ADR update</td>
</tr>
<tr>
<td><strong>TOPIRAMATE</strong></td>
<td>Warning about metabolic acidosis</td>
</tr>
<tr>
<td><strong>WARFARIN</strong></td>
<td>Interaction with cranberry juice</td>
</tr>
</tbody>
</table>

## DRUGS OF CURRENT INTEREST

<table>
<thead>
<tr>
<th>Topic</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotics - metabolic effects</td>
<td></td>
</tr>
<tr>
<td>Lapdap – a threat or an opportunity?</td>
<td></td>
</tr>
<tr>
<td>Venlafaxine and severe respiratory disorders</td>
<td></td>
</tr>
</tbody>
</table>

## FEATURE

Improved ADR Reporting: Report from Working Groups at the Twenty-sixth Annual Meeting of National Centres, WHO International Drug Monitoring Programme, 8-10 December 2003
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:

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 Lily), 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:
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, cladronic 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 cladronic 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:

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.


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:

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.


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 pseudoephedrine 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.

OSEL TAMIVIR
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:

PARACETAMOL
Label to warn about liver damage with overdose

India. The Drugs Controller General of India (DCGI) has asked all manufacturers of paracetamol formulations to include a label warning that an overdose may damage the liver. The directive follows a similar 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 paracetamol preparations are available in the Indian market.

Reference:

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:

VALGAN-CICLOVIR
Not approved for CMV prevention in liver transplant patients

USA. Valganciclovir (Valcyte) has not been approved for the prevention of cytomegalovirus (CMV) infections in liver transplant recipients, states a `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:

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.

Reference:
Midland Therapeutic Review & Advisory Committee Verdict on Voriconazole, VS03/11, October 2003. Available from URL: http://mtrac.co.uk
ANTIEPILEPTICS
ADR update from Australia

Australia. The Australian Adverse Drug Reactions Advisory Committee (ADRAC) reports on the analysis of 40-month data from the ongoing Australian Pregnancy Register for Women on Antiepileptic Medication. Out of a total of 403 pregnancy outcomes in women receiving antiepileptic drugs, 87% resulted in a healthy live birth and 6.5% had a foetal malformation. The rate of foetal malformation was significantly greater for first trimester valproic acid exposure (16%) than for exposure to all other antiepileptic drugs (2.4%). In addition, the mean daily dose of valproic acid was greater in those with foetal malformations than in those without (1975mg vs 1128mg). The Committee points out that a recently published Finnish study also showed an association between in utero valproic acid exposure, as well as carbamazepine and oxcarbazepine exposure, and foetal malformation. The Committee says that, in pre-pregnancy planning for women taking antiepileptic drugs, prescribers should review medication with the aim of maximising seizure control while minimising the risk of foetal malformation.

Reference:

BOTULINUM TOXIN TYPE A
Place in therapy not clearly defined

Scotland. The Scottish Medicines Consortium (SMC) has completed its assessment of clostridium botulinum toxin type A (Botox) and have advised NHS Boards and Area Drug and Therapeutic Committees (ADTCs) that clostridium botulinum toxin A is not recommended for use within NHS Scotland for adult patients with focal spasticity of the wrist and hand that is associated with stroke. In their press statement the SMC state that clostridium botulinum toxin A produces a localised reduction in muscle tone in patients with post-stroke hand and wrist spasticity and may improve disability. However, the place in therapy was not clearly defined nor was the economic case proven.

Reference:

CELECOXIB/ROFECOXIB
Acute temporary visual impairment

New Zealand. The Intensive Medicines Monitoring programme (IMMP) in New Zealand has presented evidence of acute severe temporary visual disturbance with celecoxib and rofecoxib, two of the new selective anti-inflammatory cyclooxygenase-2 (COX-2) inhibitors. Monitoring of the two drugs was started in December 2000 and at the time this material was presented to the British Medical Journal, the IMMP had received seven reports of visual disturbance with these drugs; the authors report that four of the seven patients had an onset time of one week or less. One patient regularly had problems for a few hours after each dose. Inflammatory arthritis in one and increased risk of vasculitis or arterial thrombosis in another could have affected observations in two of the patients; however, according to the authors, the rapid recovery excludes vascular embolism or thrombosis in these patients; the ages of the patients also suggest that the impairment was not confined to the elderly. The authors propose inhibition of the synthesis of prostaglandins, with an ultimate effect on retinal blood, as a likely mechanism for the visual impairment with these drugs. Visual disturbances have also been reported with conventional non-selective COX inhibitors.

Reports in WHO-file: celecoxib-230; rofecoxib-244

Reference:

DACLIZUMAB
Increased mortality in cardiac transplant patients

Canada. Hoffmann-La Roche Limited has issued a notice to hospitals regarding important new safety information for daclizumab (Zenapax). A cardiac transplant study, conducted to determine if daclizumab reduced the incidence of acute rejection, found an increased 6- and 12-month mortality rate in patients who received daclizumab, compared with those who received placebo, in combination with cyclosporin, mycophenolate mofetil and corticosteroids. In some cases, investigators prescribed concomitant polyclonal antilymphocyte globulin therapy to protect patients who may be receiving placebo. However, due to the blinded nature of the study, some patients received both daclizumab and polyclonal antilymphocyte globulin therapy, and this over immunosuppression may explain most of the elevated mortality, as well as the increased incidence of infection seen in patients who received daclizumab. The letter also contains information on severe acute hypersensitivity reactions, including anaphylaxis, which have been observed with daclizumab (Zenapax), both on initial exposure and on re-exposure. The Canadian Product Monograph will be revised to include statements related to both the increased mortality in the cardiac transplant study and to updated information regarding hypersensitivity reactions. A similar letter was also sent out by the company to health...
professionals in the USA, under advice from the FDA (see WHO Pharmaceuticals Newsletter No.5, 2003).

Reference:

FLUTICASONE
Update on adrenal insufficiency reports

Canada. From January 1996 to the end of September 2002, Health Canada received nine reports of suspected adrenal insufficiency associated with inhaled fluticasone. In comparison, they did not receive any reports associated with inhaled budesonide or beclomethasone during this time. Of the nine reports associated with fluticasone, five involved children aged 4–13 years and, where specified, dosages ranged from 250 to 110 µg/day. In four of the cases, the fluticasone dosage was more than 1000 µg/day. Health Canada reminds clinicians that increasing the dosage of inhaled corticosteroids above a certain limit has minimal benefit and increases the risk of systemic adverse effects. Furthermore, the Canadian asthma consensus guidelines recommend that the minimum effective dose required to maintain control should be used. Health Canada also recommends that patients and parents should be advised of the risk and signs and symptoms of adrenal suppression associated with inhaled corticosteroids, and cautions of the risk of serious adverse reactions if they stop treatment abruptly.

Reference:

INTERFERON BETA
Safety information about risk of liver injury

Canada. Health Canada, in consultation with Biogen Idec Canada, Berlex Canada and Serono Canada is informing health professionals that serious liver injury (e.g. hepatitis) has been reported with beta-interferon therapy for the treatment of multiple sclerosis in a clinical setting; there were three cases of liver failure needing liver transplantation. Rare but serious liver injury occurred mostly in the early months of therapy but also in patients on therapy beyond one year. Physicians should perform periodic liver function tests, particularly in the early months of therapy; dose reduction should be considered if serum ALT (alanine aminotransferase) increases five times above baseline levels. Patients should be made aware of the signs and symptoms of liver injury including yellowing of the skin or eyes (jaundice), nausea and vomiting, easy bruising of the skin, diffuse itching and abdominal pain; patients experiencing any of these symptoms should contact their physician immediately. Product monographs are being revised to provide physicians and pharmacists with this updated safety information regarding liver injury.

Reference:

METHOTREXATE
Update on pulmonary effects

UK. Following a review of the available data regarding methotrexate use and pneumonitis, the UK Committee on Safety of Medicines (CSM) has advised that patients be informed of the risk of pneumonitis associated with methotrexate use and to seek medical attention if they develop indicative symptoms, that prescribers monitor patients for symptoms, and that if pneumonitis is suspected methotrexate be withdrawn and corticosteroids given. By 25 April 2003, the CSM had received 90 UK reports of parenchymal lung disorders through the Yellow Card Scheme; the reports included 52 of pneumonitis, 21 of pulmonary fibrosis, five of
interstitial lung disease and three of interstitial pneumonitis; the outcome in 17 reports was fatal.

Reference:
Current Problems in Pharmacovigilance, September 2003. Available from URL:
http://www.mca.gov.uk

MIRTAZAPINE
ADR update from Australia

Australia. In the October issue of the Australian Adverse Drug Reactions Bulletin, the Australian Adverse Drug Reactions Advisory Committee (ADRAC) highlights adverse reactions associated with the antidepressant drug mirtazapine. ADRAC has received a total of 253 adverse drug reaction (ADR) reports associated with mirtazapine, including potentially serious reports of seizures (n = 16) and blood dyscrasias (15). Other mirtazapine-associated ADRs reported to ADRAC include oedema (n = 33), anxiety/agitation (24), myalgia/arthritis (24), sedation (23) and skin reactions (20). In addition, a prescription event monitoring (PEM) study conducted in England involving over 13,000 patients found drowsiness/sedation and malaise/lassitude to be the most frequent mirtazapine-associated ADRs occurring in 5.8% and 2.8% of patients, respectively. However, although two cases of blood dyscrasias were identified in this study, there were no cases of seizures.

Reference:
Australian Adverse Drug Reactions Bulletin Vol 22, No. 5, October 2003. Available from URL:

MORPHINE
Accidental overdose of concentrated oral solutions

USA. Accidental overdose of concentrated oral morphine solutions has resulted in serious adverse events and deaths, according to a ‘Dear Healthcare Professional’ letter issued by Elan Pharmaceuticals in the United States. In most cases, oral morphine solutions that were ordered in mg were mistakenly interchanged for mL, resulting in a 20-fold overdose. Elan distributes three concentrated oral solutions containing morphine 20 mg/mL (Roxanol, Roxanol-T and Roxanol 100). In order to prevent medication errors, the company has requested that prescribers write prescriptions for oral morphine solutions clearly stating the required concentration of oral solution, the intended morphine dose in mg and the corresponding volume in mL.

Reference:
‘Dear Healthcare Professional’ letter from Elan Pharmaceuticals, October 2003. Available from URL:
http://www.fda.gov

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)
Postpartum administration may cause hypertension

Australia. The Adverse Drug Reactions Advisory Committee (ADRAC) has recently received six reports of hypertension or hypertensive crisis in women following the postpartum administration of NSAIDs (indometacin, ibuprofen or diclofenac). Four of the women had a history of pre-eclampsia, one of whom died of hyper-tensive crisis and intracranial haemorrhage after undergoing a Caesarian section. The other two women, including one who experienced an eclamptic seizure, had no prior history of hypertension. Only two of the women were receiving anti-hypertensive therapy at the time of the adverse event. The committee suggests that the severe hypertension in the reported cases may have been caused by the patients underlying condition, but that it is plausible that NSAID administration made a significant contribution. ADRAC advises careful monitoring of blood pressure in women (with a history of pre-eclampsia or essential hypertension) administered NSAIDs in the postpartum period.

Reference:
Reactions 980: 2, 6 December 2003.

PERGOLIDE
Danger of falling asleep during daily activities

USA. Eli Lilly and Company, in consultation with FDA is advising healthcare professionals that patients treated with pergolide mesylate (Permax) have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles which sometimes resulted in accidents. Pergolide mesylate (Permax) is an adjunctive treatment to levodopa/carbidopa in the management of Parkinsonism and somnolence is a common occurrence with this drug. In the current observations some patients did not have warning signs such as excessive drowsiness and report being alert immediately prior to the event. Many clinical experts believe that falling asleep while engaged in activities of daily living always occur in a setting of pre-existing somnolence, although patients may not give such a history. Eli Lilly is therefore advising that before initiating therapy with pergolide mesylate (Permax) patients should be advised of the potential to develop drowsiness and specifically asked about factors that may increase the risk such as concomitant sedating medications or the presence of sleep disorders; the drug should be discontinued if a patient develops significant daytime sleepiness or episodes of falling asleep during activities such as conversations, eating etc. If a decision is made to

WHO Pharmaceuticals Newsletter No. 1, 2004 • 7
continue peroglide mesylate (Permax), patients should be advised not to drive and to avoid other potentially dangerous activities.

Reference:

PYRAZINAMIDE & RIFAMPICIN
Serious liver injury with combined use in latent tuberculosis

USA, Canada. The American Thoracic Society and the Centers for Disease Control and Prevention (CDC) recommend that the combined regimen of pyrazinamide and rifampicin should not be offered as a first-line treatment to persons with latent tuberculosis infection (LTBI). This advice follows a recent CDC report describing high rates of hospitalisation and death from liver injury following the combined use of these two drugs in LTBI patients. The CDC advises the use of alternative recommended regimens in LTBI. Health Canada has made a similar announcement, based on the CDC findings and directives.

Health Canada advises that recommendations for the treatment of active TB remain unchanged.

Reference:
1. MMWR 52(31): 735-739, 8 August 2003. Available from URL: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5231a4.htm

SIBUTRAMINE
ADR update

UK. An update on suspected adverse drug reactions reported in association with sibutramine (Reductil) is presented in the September 2003 issue of the bulletin: Current Problems in Pharmacovigilance. Since sibutramine was licensed in Europe in May 2001, approximately 130 000 patients in the UK have been prescribed the agent. The most commonly reported adverse reactions include headache, hypertension, tachycardia, palpitations, chest pain, dizziness, insomnia, depression, anxiety and minor gastrointestinal symptoms. Prescribers are reminded of the recommended protocol blood pressure (BP) and heart rate (HR) monitoring in patients receiving sibutramine, and that treatment should be discontinued in patients who have a persistent increase in resting HR of ≥ 10 beats/min or BP of ≥ 10 mm Hg.

Reference:

TOPIRAMATE
Warning about metabolic acidosis

USA. Ortho-McNeil is informing healthcare professionals that topiramate can cause hyperchloremic, non-anionic gap metabolic acidosis (decreased serum bicarbonate). Topiramate is indicated as an adjunctive treatment of partial-onset seizures, generalized tonic-clonic seizures and seizures associated with the Lennox-Gastaut syndrome in adults and children two years of age and older. Decreases in serum bicarbonate occur soon after initiation of topiramate but can occur at any time during treatment. Conditions (renal disease, severe respiratory disorders, status epilepticus, diarrhoea, surgery) or drugs that predispose to acidosis may be additive to the bicarbonate lowering effects of topiramate. Chronic untreated metabolic acidosis may increase the risk for nephrolithiasis or nephrocalcinosis, and may also result in rickets in paediatric patients and/or osteoporosis with an increased risk for fractures. Hyperventilation, fatigue and anorexia or in more severe situations cardiac arrhythmias or stupor may be some of the symptoms of acute or chronic metabolic acidosis. Physicians are advised to measure baseline and periodic serum bicarbonate during topiramate therapy. If metabolic acidosis develops and persists, a dose reduction should be considered or, the drug should be discontinued with gradual dose reduction. If the patients need to be retained on therapy even in the wake of persistent acidosis, an additional alkali treatment should be considered.

Reference:

WARFARIN
Interaction with cranberry juice

UK. The Committee on Safety of Medicines (CSM) has drawn attention to a possible interaction between warfarin and cranberry juice. Since 1999 the CSM has received five reports of a possible interaction between warfarin and cranberry juice leading to changes in the International Normalized Ratio (INR) values. One case was fatal and involved a man whose INR increased to more than 50 six weeks after he started drinking cranberry juice; he died of gastrointestinal and pericardial haemorrhage. Two other patients experienced increased INRs when taking cranberry juice; one patient stabilised following a reduction in warfarin dosage and the other's INR normalised after cranberry juice was stopped. A fourth patient experienced an unstable INR, and a decreased INR was reported in another patient. The CSM notes that the interaction is biologically plausible through inhibition of cytochrome P450 by flavonoids in cranberry juice and suggest that, until the possible
interaction is investigated further, it would be prudent for patients taking warfarin to limit or avoid drinking cranberry juice.

Reference:
Antipsychotics - metabolic effects  
Dr David Coulter, IMMP, New Zealand  
Patients with schizophrenia usually require life-long treatment with antipsychotics from a young age. The centre for the Intensive Medicines Monitoring Programme (IMMP) in New Zealand has received reports of weight gain, hyperglycaemia, dyslipidaemia and hypertension with antipsychotics, all of which are risk factors for myocardial infarction, stroke and sudden death. In some patients, the changes have been severe. These metabolic effects occur with fairly high frequency (either singly or in combination) and are a concern in the long-term management of patients with schizophrenia. Some of the reports in the IMMP records include drugs such as clozapine (hyperglycaemia, n = 16; weight gain n = 9; dyslipidaemia n = 7, ages 23 – 49 years, onset time 1–7 years; hypertension n = 10) and olanzapine (hyperglycaemia, n = 3; weight gain, n = 16; dyslipidaemia n = 3, ages 29, 35, 44, onset time 1–13 m). Reports have also been received of pancreatitis, probably also associated with the dyslipidaemia. The WHO database has 124 reports of dyslipidaemia with clozapine, 50 with olanzapine, 8 with quetiapine and 43 with risperidone. The risk of ischaemic heart disease, problems associated with diabetes mellitus and other related morbidity means that the benefit harm ratio becomes less favourable. These problems need to be more widely appreciated and considered carefully in therapeutic management. There may be significant differences between the atypical antipsychotics in their potential to produce abnormal metabolic effects.

Lapdap – a threat or an opportunity?  
Dr Alex Dodoo, Ghana  
Lapdap is a fixed dose combination (chlorproguanil-dapsone) antimalarial developed specifically for use in sub-Saharan Africa. It was registered for use initially in the UK and has subsequently been launched in several African countries. Unlike medicines in use in the developed economies of the world where adequate monitoring systems exist, Lapdap is being introduced into countries with poorly developed or non-existent monitoring systems. This may pose a threat to public health, particularly as the contraindication for Glucose-6-Phosphate Dehydrogenase (G6PD) enzyme deficiency, which is prevalent in Africa, is not indicated on the product label for these countries. While the Lapdap situation is worrying, the discussions around Lapdap may present an opportunity for resource-poor countries to develop unique systems for monitoring drugs in use in their settings.

Given that drug development is disease-driven and that some diseases are more prevalent in certain geographic regions than in others, it is imperative to make sure that these regions have the capacity to monitor the safety of drugs that will be specifically introduced for their use. A well-developed adverse drug reaction (ADR) monitoring system, designed to address adverse reactions specific to drug-use in resource poor settings, should be in place even as disease-specific drugs are being introduced into these countries. That alone can ensure the rapid detection of ADR-problems in these settings. Several sub-Saharan African countries have absolutely no drug safety monitoring systems. These countries also have the additional problem of unscrupulous drug promotion, direct to consumer advertising and the presence of sub-standard and counterfeit drugs. There is, therefore, an urgent need to establish pharmacovigilance programmes as well as improve public education in these countries. Each country should examine its own needs and priorities and adopt a system that takes into consideration the existing facilities, personnel and other resources.

Venlafaxine and severe respiratory disorders  
Dr E.P. van Puijenbroek  
Dr A.C. van Grootheest  
Netherlands Pharmacovigilance Centre, Lareb  
Venlafaxine is a serotonin and noradrenaline reuptake inhibitor approved for marketing in 1994. The Netherlands Pharmacovigilance Centre has received four reports of severe pneumonia occurring during therapy with venlafaxine. Two reports concerned eosinophilic pneumonitis and two reports that of non-eosinophilic pneumonitis. The mechanism for both eosinophilic and non-eosinophilic pneumonitis is unknown. Drug-induced infiltrative lung disease is an established, although infrequent, complication of serotonin reuptake inhibitors (SSRIs). Pneumonia has been documented also in relation to paroxetine and fluoxetine, two well-known SSRIs. The WHO database has 592 reports of respiratory disorders observed during venlafaxine therapy. Given the available evidence, it may be concluded that a causal relationship between the use of venlafaxine and severe respiratory disorders is likely. As the use of this drug continues to increase, physicians should be made aware of this life-threatening but fully reversible complication.
Improved ADR Reporting: Report from Working Groups at the Twenty-sixth Annual Meeting of National Centres, WHO International Drug Monitoring Programme, 8-10 December 2003

The Twenty-sixth Annual Meeting of the National Centres participating in the WHO International Drug Monitoring Programme was held in December, in New Delhi, India. Members present at the meeting were assigned to one of four working groups (A, B, C and D), with all working groups focusing on one common issue: Improving Adverse Drug Reaction (ADR) Reporting. In general, the working groups represented countries with advanced, moderately developed or no systems for drug safety monitoring. We present a summary of the recommendations from the four groups in two parts: recommendations for working groups A & B are presented in this issue and those from working groups C & D will be presented in the next issue of the newsletter.

Group A

This group discussed the impact of education and feedback on reporting habits.

Education
The group recommended that there should be post-graduate training to improve reporting and that pharmacovigilance programmes should form part of the accreditation criteria. Consultant physicians should be encouraged to fill in spontaneous reporting forms when they come across ADRs during ward rounds. This will act as a positive reinforcement to medical students. Case reports should be published in easily accessible journals. The Regional/National Pharmacovigilance Centres should develop websites that are easy to understand and contain straightforward guidelines in a simple language.

Feedback
Personal feedback including acknowledgement of reports and brief comment or communication on reports was considered important in stimulating reporting habits; a new spontaneous reporting form should be included with each letter of acknowledgement. A more general version of acknowledgement would be to include the reports in drug bulletins and journals. A somewhat different approach would have to be followed in providing feedback to consumers; it should involve general statements which are balanced and avoid discussion of specific causal relationship, with a call on patients to contact their physicians if they suspect an ADR or in cases of doubt.

DISCUSSION: Countries with established pharmacovigilance systems already have a culture of reporting. Education is therefore important to create a culture of reporting in those countries where pharmacovigilance systems are new or poorly established. Towards this, websites are useful but have resource implications. It may not be possible to allocate sufficient time for pharmacovigilance teaching in the undergraduate curriculum. However, pharmacovigilance can be tagged onto other areas dealing with medicines and their safety. It is vital to stress the importance of feedback and where possible, allow a public dissemination of discussions that go on between a patient and his/her physician without classifying them as ‘privileged’ information.

Group B

This group examined the sources of case reports in various countries to get an idea of where most reports come from.

In all countries most reports come from physicians. Industry is also a big source of reports in several countries. Mandatory reporting by healthcare professionals is not always effective; perhaps it is time to focus on creating a ‘culture’ of reporting. Consumer reporting could provide valuable information on ADRs related to OTC as well as traditional and complementary medicines. Consumer reports may not be thorough but are nevertheless important. The group called for consumer reporting either directly to the National Centre or, preferably through physicians or, to the National Regulatory Authority, as might be appropriate. A different approach might be essential for each country since organizational differences exist across countries, for example, the presence (or absence of) regional reporting centres in addition to a national pharmacovigilance centre in some, the same centre functioning as the focal point for pharmacovigilance as well as poisons related information in some others, etc.

However, there is a need to be wary of media attention on consumer reports. Further, consumers should be dissuaded from the mistaken notion that they can get compensation by reporting suspected ADRs. The quality of consumer reports can be improved through appropriate education of consumers, to identify true ‘ADRs’ as opposed to expected side effects. Towards this, Patient Information Leaflets (PILs) should provide relevant, concise and precise patient information; the product inserts provided by companies under the directives of drug regulators are often cumbersome in being too ‘thorough’ and confusing. PILs should strive to have a balance between highlighting potential problems and stating the obvious, in a language that the general population can easily understand.

Ultimately, for pharmacovigilance to be more effective, it should be seen as an
amalgamation of two activities – regulatory activity and clinical practice. The frequency of reporting to the WHO ADR database could well affect the timeliness of identifying important signals and subsequent regulatory action, if any.

Final recommendations by the group were as follows:

a) Emphasize reporting by health professionals as an important source of signals.

b) Develop mechanisms for consumer reporting.

c) Provide information to patients through patient information leaflets.

d) Educate public health workers on ADR reporting.

e) Expedite reporting to the WHO global ADR database.