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**EDITORIAL**

The recent regulatory and safety measures regarding the use of Selective Serotonin Reuptake Inhibitors (SSRIs) in children under the age of 18 years proves, yet again, the importance and need for post-marketing pharmacovigilance. This is particularly true for drugs with a potential for off-label use.

With just 72 countries participating as full members in the WHO International Drug Monitoring Programme, it is clear that much work remains to be done in raising awareness about drug safety among Member States. WHO HQ, along with the global experts in public health, is finalizing the document 'Pharmacovigilance in Public Health'. Once published, it is hoped that this document will demonstrate ways in which pharmacovigilance can be introduced, through public health programmes, into countries with no current facility for drug monitoring.

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The previous issue of the newsletter published the reports from two of the working groups at the Twenty-sixth Annual Meeting of National Centres held in New Delhi, December 2003. In this issue we bring you suggestions from the other two working groups, on the subject of improving adverse drug reaction reporting in member countries.

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## BENZ-BROMARONE, BENZIODARONE

### Measures following safety review

**Spain.** Following reports of hepatotoxicity, the Spanish Safety Committee reviewed the safety profile of benziodarone and benzbromarone containing medicinal products. The Committee has recommended the following regulatory measures:

1. The marketing authorizations for benziodarone (Dilafurane) and benzbromarone-allopurinol fixed dose combination products will be withdrawn.
2. Benzbromarone (Urinorm) will be brought under restricted use, to be prescribed by specialists (rheumatologists or nephrologists) in hospitals, for treating hyperuricaemia in allopurinol-intolerant patients with
  - gout polyarticular or gout tophaceous
  - renal failure
  - renal transplantation.

#### Reference:

*Press Release from the Spanish Agency for Medicines and Medical Devices (Agencia Española de Medicamentos y Productos Sanitarios), Ref: 2004/02, 10 February 2004. Available from URL: <http://ww1.msc.es/agemed>*

## EPHEDRA PRODUCTS

### To be treated as medicinal products

**Netherlands.** The Ministry of Health in Netherlands has withdrawn a draft regulation concerning the sale of food products containing ephedrine alkaloids. This means the ephedra herbal products may only be sold as medicinal products in the Netherlands. Applications for authorizing the sale of ephedra containing products as medicinal products

will be assessed by the Medicines Evaluation Board (MEB) for evidence of constant quality, safety and efficacy. European directive for traditional herbal medicinal products will soon come into force and will subsequently be incorporated into the Dutch Medicines legislation.

#### Reference:

*News and Publications from Medicines Evaluation Board, Netherlands, 18 February 2004. Available from URL: <http://www.cbg-meb.nl/uk/nieuws>*

## NEVIRAPINE

### New hepatotoxicity information added to product label

**USA, Canada.** Boehringer Ingelheim Pharmaceuticals Inc has issued a 'Dear Healthcare Professional' letter highlighting the addition of new hepatotoxicity information to the boxed warning for nevirapine (Viramune), a non-nucleoside reverse transcriptase inhibitor indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents. Information regarding risk factors for severe, life-threatening and fatal hepatotoxicity in association with nevirapine has been clarified; attention is drawn to the following:

- Women with CD4+ counts > 250 cells/mm<sup>3</sup>, including pregnant women, are at considerably higher risk of hepatotoxicity (12-fold).
- The highest risk of severe and potentially fatal hepatotoxicity is in the first 6 weeks of nevirapine treatment, but the risk continues after this time and close monitoring should be continued for the first 18 weeks of treatment.
- Hepatic injury may progress despite treatment discontinuation.

These additional recommendations follow a recent post-marketing surveillance data as well as clinical trial data analysis. Healthcare professionals are

reminded to counsel all patients that if signs or symptoms of hepatitis, severe skin reactions or hypersensitivity reactions occur they should discontinue treatment and seek medical advice immediately. Nevirapine (Viramune) should not be restarted in these patients.

#### Reference:

1. 'Dear Healthcare Professional' letter from Boehringer Ingelheim, February 2004. Available from URL: <http://www.fda.gov>
2. 'Dear Healthcare Professional' letter from Boehringer Ingelheim, 20 February 2004. Available from URL: <http://www.hc-sc.gc.ca>

## OLANZAPINE, RISPERIDONE

### New safety information regarding use in elderly patients with dementia

**Europe.** The European Agency for the Evaluation of Medicinal Products (EMA) has issued a public statement that new data from clinical trials show an increased risk of cerebrovascular adverse events and mortality in elderly patients with dementia receiving olanzapine (Zyprexa, Zyprexa Velotab, both marketed by Eli Lilly). The increase is estimated as being about three-fold for cerebrovascular adverse events and two-fold for mortality compared to placebo in this population. Health professionals are advised that:

- Olanzapine is not indicated for the treatment of dementia-related psychosis and/or disturbed behaviour.
- Because of the identified risks, patients currently receiving olanzapine for dementia related psychosis and/or disturbed behaviour should have their treatment reviewed by their physician.
- The risks identified for olanzapine cannot be excluded for other atypical or conventional neuroleptics.

The UK Committee for Safety of Medicines has issued a similar communication for another atypical antipsychotic agent, risperidone as well as for olanzapine. A meta-analysis of randomized placebo-controlled clinical trials in elderly patients with dementia has shown that, compared with placebo, the risk of stroke with risperidone is, approximately, three times higher. The CSM has advised that the magnitude of risk of stroke is sufficient to outweigh likely benefits with either drug in the treatment of behavioural disturbances associated with dementia and is a case for concern in any patient with a high baseline risk of stroke.

#### References:

1. EMEA Public Statement, EMEA/CPMP/856/04Final, 9 March 2004. Available from URL: <http://www.emea.eu.int>
2. 'Dear Health Professional' letter from Chairman, Committee on Safety of Medicines, 9 March 2004. Available from URL: <http://www.medicines.mhra.gov.uk>

## PAROXETINE

### Prescribing advice for use in adults

**UK.** Further to an earlier communication that Selective Serotonin Reuptake Inhibitors (SSRIs) have poor benefit-risk profile in children and adolescents, the Committee for Safety of Medicines (CSM) has reviewed clinical trial data on the use of paroxetine (Seroxat) in adults and has made the following recommendations:

1. Paroxetine should be prescribed at the recommended dose, (20 mg daily for the treatment of depression, social anxiety disorder (SAD), generalised anxiety disorder (GAD) and post traumatic stress disorder (PTSD); 40 mg daily in obsessive compulsive and panic disorders).
2. Patients currently being successfully treated with a high dose should be

continued on that dose to the end of the planned course of treatment.

3. A change of treatment should be considered for patients currently being treated with a higher than recommended dose if they are not doing well.
4. There is evidence that attempts to escalate the dose rapidly are associated with an increased incidence of adverse events.
5. Adverse events that occur soon after starting therapy may be difficult to distinguish from the underlying condition. There is evidence that increasing the dose in this situation may be detrimental.
6. Any cessation of treatment with paroxetine should not be abrupt but should proceed by a gradual downward titration.

In an earlier communication, CSM had advised that paroxetine as well as several other SSRIs have unfavourable benefit-risk profiles for paediatric and adolescent use (WHO Pharmaceuticals Newsletter No. 1, 2004).

#### Reference:

'Dear Colleague' letter from Chairman, Committee on Safety of Medicines, 11 March 2004. Available from URL: <http://www.info.doh.gov.uk>

## RITONAVIR & FLUTICASONE

### Concomitant use should be avoided

**Canada.** GlaxoSmithKline Inc, in consultation with Health Canada, has issued a 'Dear Healthcare Professional' letter to advise that the concomitant use of ritonavir and fluticasone propionate should be avoided unless the potential benefits outweigh the risks of systemic corticosteroid effects. According to the letter, results of a drug interaction study in healthy volunteers show that ritonavir can greatly

increase plasma concentrations of fluticasone propionate, leading to markedly reduced serum cortisol levels. In addition, the letter notes that there have been post-marketing reports of clinically significant drug interactions in patients receiving concomitant ritonavir and fluticasone propionate, leading to systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. Canadian Product Monographs for fluticasone propionate (Flonase, Flovent and Advair) and ritonavir (Kaletra, Norvir) will be modified to incorporate the above information.

#### Reference:

'Dear Healthcare Professional' letter from GlaxoSmithKline, 22 January 2004. Available from URL: <http://www.hc-sc.gc.ca>

## TERBINAFINE

### Label to include possibility of hepatic disorders

**Japan.** The monograph for the oral antifungal preparation, terbinafine (Novartis Pharma's Lamisil) has been revised to include statements on the possibility of hepatic disorders and insufficiency, including jaundice and hepatitis. Since these disorders are observed to occur within the first two months of therapy, monthly monitoring is advised during this period and periodically thereafter. The revised warnings section also refers to the possibility of pancytopenia, thrombopenia, agranulocytosis, Stevens-Johnson and Lyell syndromes and rhabdomyolysis occurring with terbinafine treatment. Topical, oral and once daily-spray formulations of terbinafine (Lamisil) are available in Japan and are indicated for several dermal and systemic fungal infections, including athlete's foot and *Candida*.

#### Reference:

*Scrip World Pharmaceutical News* No. 2923, 4 February 2004. Available from URL: <http://www.scrippharma.com>

## ANALGESICS

### Campaign on safe use of over-the-counter pain relief

**USA.** The United States Food and Drug Administration (US FDA) has launched a national education campaign to advise consumers on the safe use of over-the-counter (OTC) pain relief products. The campaign focuses on OTC pain relievers and fever reducers containing paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, ibuprofen, naproxen sodium and ketoprofen. The FDA notes that, although these medications are safe when used as directed, they can cause serious problems when used by people with underlying health problems or those receiving certain other medications. The campaign will provide advice on how to avoid the concomitant use of multiple medications that contain the same active ingredients, outline health conditions that increase risk and highlight the risk of liver damage associated with paracetamol and the risk of stomach bleeding and kidney disorders associated with NSAIDs. The campaign will include an OTC pain reliever brochure distributed through pharmacies, a newspaper article, a reprint of an FDA Consumer magazine article entitled 'Use Caution With Pain Relievers' and public service advertisements in magazines. The FDA is considering labelling changes to further increase the safe use of products containing paracetamol and NSAIDs, and is reviewing various labelling proposals that better reflect the latest scientific knowledge about OTC oral pain relievers.

**Reference:**

*FDA News, 22 January 2004.*  
Available from URL:  
<http://www.fda.gov>

## ANTI-DEPRESSANTS

### Under-18 patients receiving SSRIs/SNRIs to consult physicians

**Canada.** Health Canada is advising Canadians that patients under 18, who are currently being treated with an antidepressant belonging to the class of Selective Serotonin Reuptake Inhibitors (SSRIs) or Selective Noradrenalin Reuptake Inhibitors (SNRIs) should consult their treating physicians to confirm that the benefits still outweigh the potential risks with these drugs. Health Canada has also requested that the manufacturers of these drugs should provide a thorough review of the worldwide safety data for these drugs when used in children under 18 years of age. These recommendations follow worldwide safety concerns that suicidal ideations and suicide attempts were observed in clinical trials of antidepressants in paediatric patients with major depressive disorder. It may be recalled that the United States Food and Drug Administration as well as the UK Committee on Safety of Medicines had both issued related advice on the use of SSRIs in this age group (see WHO Pharmaceuticals Newsletter No. 1, 2004). Health Canada notes that the use of SSRIs and SNRIs in paediatric patients is not approved in Canada and that the use of these drugs in this population is as such the responsibility of the prescribing physicians.

**Reference:**

*Health Canada Warnings/Advisories, 2 February 2004.*  
Available from URL:  
<http://www.hc-sc.gc.ca>

## ATYPICAL ANTI-PSYCHOTICS

### Increased risk of obesity and type II diabetes

**USA.** The American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologist and the North American Association for the Study of Obesity have issued a joint statement about the increased risk of obesity and type II diabetes in patients receiving atypical antipsychotic medication. The statement names olanzapine (Lilly's Zyprexa) and clozapine (Novartis's Clozaril/Leponex) as the worst culprits for promoting weight gain, increasing diabetes risk and worsening lipid profile and puts the two newest drugs, aripiprazole (Bristol-Myers Squibbs Abilify) and ziprasidone (Pfizer's Geodon) in the best light. Physicians should preferably use atypicals with the least effect on blood glucose and body weight; body-mass index, plasma glucose and lipid profile should be measured at the time of starting therapy and throughout treatment. In addition, physicians should consider switching patients to atypical antipsychotics with the least metabolic effects if they gain more than 5% of their initial body weight or have a worsening of glycaemia or dyslipidaemia during treatment (also see section on Drugs of Current Interest in WHO Pharmaceuticals Newsletter No. 1, 2004).

**Reference:**

*Scrip World Pharmaceutical News No 2922, 30 January 2004.*  
Available from URL:  
<http://www.scrippharma.com>

## CILOSTAZOL

### Not recommended for treating intermittent claudication

**Scotland.** The Scottish Medicines Consortium (SMC) has completed its assessment of cilostazol and has rejected its use in the treatment of intermittent claudication. The SMC has concluded that although cilostazol is more effective than placebo in enabling greater, pain-free walking, it has limited effects on quality of life and is substantially more expensive than its competitors. The SMC has also expressed concerns over issues of clinical effectiveness, including potential for several major drug interactions with antiplatelet therapy.

**Reference:**

*Press Statement from Scottish Medicines Consortium, 8 March 2004. Available from URL: <http://www.scottishmedicines.org.uk>*

## CYPROTERONE

### Hepatotoxicity with high doses

**Australia.** Over the years the Australian Adverse Drug Reactions Advisory Committee (ADRAC) has received 105 reports of adverse reactions associated with high-dose cyproterone therapy. Of these reports, 32 are related to adverse liver effects. All except one of the hepatic reactions involve male patients, 56-92 years of age, being treated for prostate cancer. Time to onset of liver dysfunction ranges from four days to four years. Where liver function tests are available, the majority indicate the presence of cholestatic hepatitis, but some show marked elevation of hepatocellular enzymes; ten patients died, nine due to hepatic failure. Severe hepatic reactions have not been reported to ADRAC with the use of low dose (1-2 mg) cyproterone. ADRAC advises that while cyproterone -

induced hepatotoxicity is rare, it can be life-threatening or fatal and that it would be reasonable to monitor liver function intermittently in patients taking long-term high-dose cyproterone.

**Reference:**

*Australian Adverse Drug Reactions Bulletin, Vol. 23, No.1, February 2004. Available from URL: <http://www.tga.gov.au>*

## ESTROGEN

### Estrogen-alone trial of WHI study halted

**USA.** The National Institutes of Health in the USA has halted the estrogen-alone arm of the Women's Health Initiative (WHI) Study since the data indicated that estrogen-alone did not affect (neither increased nor decreased) heart disease, the principal question being evaluated in the study. On the other hand, estrogen alone appeared to increase the risk of stroke and decrease the risk of hip fracture. The US FDA will now assess the data to determine whether these data support additional labelling changes for postmenopausal hormone therapy. The estrogen plus progestin trial of the WHI study was discontinued in July 2002 after 5.6 years of follow-up because of increased risk of breast cancer. The memory sub-study of WHI (WHIMS) was also halted in May 2003 after the data showed an increased risk of probable dementia in women 65 years of age or older. FDA continues to advise that postmenopausal women, who use, or are considering using estrogen or estrogen plus progestin hormone therapy, should regularly discuss their hormone therapy benefits and risks with their healthcare providers.

**Reference:**

*FDA Talk Paper, 2 March 2004. Available from URL: <http://www.fda.gov>*

## ISOTRETINOIN

### Tighter prescribing regulations to be considered

**USA.** An FDA panel of experts will soon begin reviewing new data that show that current safety measures, to ensure that isotretinoin (Roaccutane) is not used by pregnant women, are ineffective. Women are supposed to have two negative pregnancy tests before starting therapy and monthly tests during treatment. Strict prescribing restrictions were imposed by the manufacturer of isotretinoin (Roaccutane by Roche) in 2002. However, although the number of prescriptions dispensed has decreased by 23%, 120 pregnant women have reportedly taken the drug even after the implementation of the prescribing restrictions.

**Reference:**

*News & Updates, Drug InfoZone, UK Medicines Information Service, 26 February 2004. Available from URL: <http://www.druginfozone.nhs.uk>*

## LEFLUNOMIDE

### Worsening of respiratory symptoms

**Japan.** Sixteen cases of pulmonary problems, including five deaths, have been reported in Japan in patients taking leflunomide (Aventis Pharma's Arava). The company has now issued a warning letter to doctors, hospitals, pharmacists and wholesalers. Leflunomide (Arava) is a disease modifying anti-rheumatic preparation. 10, 20 and 100 mg tablet formulations of the product were approved in Japan in the year 2003. By 26 January 2003, 3412 Japanese patients had taken the product (Arava) and interstitial symptoms were seen in 16 cases, nine of whom developed more serious interstitial pneumonia or pulmonary fibrosis; five of the nine patients died. Problems due to lung disorders were determined as

the cause of death in three patients while a clear causality could not be established in the other two deaths. Aventis is examining the reports to determine exact causality and any possible influence from drug-drug interactions or other factors. In the meantime it is recommended that leflunomide (Arava) should not be used in patients with a prior history of interstitial pneumonia or pulmonary fibrosis or in those with respiratory symptoms.

**References:**

1. *Scrip World Pharmaceutical News No. 2922, 30 January 2004. Available from URL: <http://www.scrippharma.com>*
2. *The Lancet, Vol. 363, No. 9407, 07 February 2004. Available from URL: <http://www.thelancet.com>*

## SEROTONERGIC AGENTS

### Update on reports of serotonin syndrome

**Australia.** Serotonergic agents (several antidepressants, antiparkinsonism drugs, antimigraine agents etc.) increase serotonergic activity. Excessive central and peripheral serotonergic activity can lead to serotonin syndrome, autonomic and neuromuscular dysfunctions and behavioural changes. Symptoms of the syndrome include confusion, convulsions, hypertension, hallucinations etc. The Australian Adverse Drug Reactions Advisory Committee (ADRAC) has so far received 161 reports of serotonin syndrome. The majority of these reports described the concomitant use of two or more serotonergic agents, in particular SSRIs (68 reports), tramadol (29), moclobemide (23), venlafaxine (18), tricyclic antidepressants (18) and St John's Wort (8). 61 reports included patients receiving a single agent: SSRIs (40 reports), moclobemide (5), venlafaxine (5) and tramadol (5). In the majority of the reports, the signs and symptoms developed within 24 hours of the addition of

another serotonergic agent or an increase in dose of an agent. Recovery was documented in 85% of the cases where the outcome upon withdrawal of the drug(s) was known. ADRAC advises that patients receiving serotonergic drugs should be made aware of the risks and symptoms of serotonin syndrome.

**Reference:**

*Australian Adverse Drug Reactions Bulletin, Vol. 23, No.1, February 2004. Available from URL: <http://www.tga.gov.au>*

The previous issue of this newsletter featured the recommendations made by two of the working groups (Group A and Group B) on ways and means of improving adverse reaction (ADR) reporting in countries. Here are the reports from the other two groups (C and D), as presented at the Twenty-sixth Annual Meeting of the National Centres participating in the International Drug Monitoring Programme.

## Group C

Group C presented their work as a mini-research topic entitled 'Improved reporting and pharmacovigilance centres: a case study'.

### Aim

To explore the feasibility of:

- i) obtaining useful qualitative data (in terms of education in pharmacovigilance reporting) and
- ii) obtaining recommendations for improved education in reporting, from a disparate group of health professionals with diverse international backgrounds.

The method employed was interactive discussion among the group of healthcare professionals and the recording and analysis of data received.

### Results

The main problems identified involved structures (systems) for pharmacovigilance, the role-players and incentives and disincentives. Resources available for pharmacovigilance, feedback, education and legal issues were all identified as potential problem areas which could be exploited to improve reporting.

### Recommendations:

- Link reporting to Continuous Medical Education/Continuous Professional Development points. Increase introduction of pharmacovigilance into

curricula of different role-players.

- Facilitate appropriate training in, and use of awareness information (print and electronic).
- Co-opt media to serve the cause of pharmacovigilance.
- Learn from disciplines that use qualitative research as their primary evidence dataset (e.g., social sciences).
- Determine the right mix of quantitative/qualitative approaches in fine-tuning the science of pharmacovigilance.
- Learn marketing skills from, e.g., advertising industry.

**Discussion:** Modelling the behaviour of people is an incredibly powerful way of changing attitudes. When a senior person stops a ward round to fill an ADR report it is extremely powerful and will live forever in the memory of junior personnel.

## Group D

Group D examined how to improve the quantity and quality of reports in countries with 'young', newly initiated pharmacovigilance programmes, analysing the reasons for the lack of success of pharmacovigilance in some of the other countries and suggesting possible interventions. The group looked at sources of reports (with a special discussion on donated drugs), discussed the impact of education and the role of academic institutions on reporting habits and then went on to examine reporting in an organizational context, both local and international, with some comments on impact/outcome evaluation.

Most countries start targeting doctors for reporting before bringing in other healthcare providers into the system. Public health workers are also involved in some countries, though some with a structured system avoid

reports from healthcare workers on the grounds that their knowledge-base is not strong enough for ADR reporting.

The supportive strategies that could be used for improving reporting were explored and key suggestions included:

- Introducing a system that accepts reports from all possible sources, as a first step, to get the programme going and later fine-tuning to improve the quality of reports;
- Using the lay media to sensitize health professionals and the public towards reporting;
- Providing incentives, in the form of feedback to reporters (especially on the outcome of the evaluation);
- Including pharmacovigilance in both pre- and post-graduation curriculum and providing 'Continuing Medical Education' points for pharmacovigilance;
- Enforcing mandatory time-bound reporting by industry;
- Encouraging generic manufacturers to outsource pharmacovigilance to specialist consultancy firms;
- Using marketing methods developed in commercial sectors to promote reporting;
- Providing a catalogue/bibliography on published studies on pharmacovigilance;
- Sharing information in medical records.

**Discussion:** Pharmacovigilance is particularly important where Drug Regulatory Agencies are weak and control of drug distribution is poor because it can help improve the effectiveness and safety of products within the system.