

WHO PHARMACEUTICALS NEWSLETTER

prepared in collaboration with the
WHO Collaborating Centre for
International Drug Monitoring,
Uppsala, Sweden

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The aim of this Newsletter is to disseminate information on the safety and efficacy of pharmaceutical products, based on information received from our network of "drug information officers" and other sources such as specialized bulletins and journals, as well as partners in WHO. The information is produced in the form of résumés in English, full texts of which may be obtained on request from:

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Many countries in Africa are introducing combinations of antiretrovirals as a part of WHO's strategy to provide antiretroviral treatment to an additional three million people by 2005. Most of the needed first-line drugs are also available as multi-source generics. As with many of the newly registered products there is still limited experience with the operational use of antiretroviral drugs in general, especially in the different developing country settings. It is imperative that measures should be undertaken not only to guarantee the quality of the products but also to ensure proper monitoring of their safety and efficacy.

A workshop course is being organized by WHO in Pretoria, South Africa from 1 to 10 September for HIV/AIDS programme managers and officials responsible for pharmacovigilance in eight African countries (Kenya, Malawi, Mozambique, Nigeria, South Africa, Uganda, United Republic of Tanzania and Zambia). The programme for this workshop is included on page 8 of this issue.

The Annual Meeting of the National Centres participating in the WHO Programme for International Drug Monitoring will take place in October, in Dublin. The theme of this meeting is "Pharmacovigilance and focused surveillance methods" (draft agenda on page 10). This will be followed by the annual meeting of the International Society of Pharmacovigilance, also in Dublin. We hope to see many of you at one or both of these meetings.

We have now established a list of e-mail addresses for electronic mailing of the newsletter to our readers. You can join this list by sending your e-mail details to pals@who.int.

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ALOSETRON

Risk management plan to remain in place

USA. The risk management plan for alosetron (Lotronex) should not be altered until further safety and efficacy data have been collected, according to the United States Food and Drug Administration's (US FDA) Drug Safety and Risk Management Advisory Committee. GlaxoSmithKline's alosetron (Lotronex) was withdrawn in 2000 following reports of gastrointestinal (GI) complications and, in November 2002, was relaunched under a restricted marketing and distribution plan. Since this re-introduction, physician prescribing of alosetron (Lotronex) appears to be limited, which GlaxoSmithKline contends is due to physician reluctance to sign the forms required under the plan. However, the Committee argues that altering the risk management plan is unacceptable, and that the prescribing community needs to be better educated regarding the alosetron risk management plan.

Reference:

FDA Advisory News and Information, 10 May 2004. Available on the Internet at www.fdaadvisorycommittee.com

ANTIDEPRESSANTS

Health Canada-endorsed safety information

Canada. "Dear Healthcare Professional" letters have been issued by the manufacturers of seven selective serotonin reuptake inhibitors (SSRIs) and other newer antidepressants, in conjunction with Health Canada, highlighting important safety information regarding potential behavioural and emotional changes. A new Class warning has been incorporated into the labelling for mirtazapine (Organon's Remeron RD/Remeron),⁽¹⁾ fluvoxamine (Solvay Pharma's Luvox),⁽²⁾ venlafaxine (Wyeth Pharmaceutical's Effexor/

Effexor XR),⁽³⁾ sertraline (Pfizer's Zoloft),⁽⁴⁾ paroxetine (GlaxoSmithKline's Paxil),⁽⁵⁾ fluoxetine (Eli Lilly's Prozac)⁽⁶⁾ and citalopram (Lundbeck's Celexa).⁽⁷⁾ The Class warning highlights results of placebo-controlled clinical trials in paediatric patients, which suggest that, compared with placebo, use of SSRIs and other newer antidepressants may be associated with behavioural and emotional changes, including an increased risk of suicidal ideation and behaviour. However, due to small numbers and variability in placebo groups, the relative safety profiles of different agents cannot be reliably determined. Additional data in both paediatric and adult patients include reports of severe agitation-type events including akathisia, agitation, disinhibition, emotional lability, hostility, aggression and depersonalisation, with events sometimes occurring within several weeks of treatment initiation. The warning advises close monitoring for suicidal ideation or other suicidal behaviour in all patients. In addition, it is advised that treatment with these agents, with the exception of fluoxetine, should not be discontinued abruptly due to the risk of discontinuation symptoms; discontinuation should instead be gradual. For fluoxetine, plasma levels of fluoxetine and norfluoxetine decrease gradually at the conclusion of therapy, making tapering unnecessary in most patients.⁽⁶⁾

References:

1. "Dear Healthcare Professional" letter from Organon Canada Ltd. Available on the Internet at www.hc-sc.gc.ca
2. "Dear Healthcare Professional" letter from Solvay Pharma, May 2004. Available on the Internet at www.hc-sc.gc.ca
3. "Dear Healthcare Professional" letter from Wyeth, 26 May 2004. Available on the Internet at www.hc-sc.gc.ca
4. "Dear Healthcare Professional" letter from Pfizer Canada Inc., 26 May 2004. Available on the Internet at www.hc-sc.gc.ca
5. "Dear Healthcare Professional" letter from GlaxoSmithKline Inc.,

May 2004. Available on the Internet at www.hc-sc.gc.ca

6. "Dear Healthcare Professional" letter from Eli Lilly Canada Inc., 18 May 2004. Available on the Internet at www.hc-sc.gc.ca
7. "Dear Healthcare Professional" letter from Lundbeck Canada Inc., 26 May 2004. Available on the Internet at www.hc-sc.gc.ca

BUPROPION

Labelling updated to include class warning

Canada. Following discussions with Health Canada, Biovail Pharmaceuticals has advised of bupropion-associated behavioural and emotional changes in a "Dear Healthcare Professional" letter. Bupropion is marketed in Canada as the antidepressant Wellbutrin SR and the smoking cessation drug Zyban, and a Class warning regarding behavioural and emotional changes, including risk of self-harm, has been added to the labelling of both products. This warning applies to both paediatric and adult patients, although neither of these products is indicated for use in patients aged <18 years.

Reference:

"Dear Healthcare Professional" letter from Biovail Pharmaceuticals, 8 June 2004. Available on the Internet at www.hc-sc.gc.ca

CLOZAPINE

Labelling to include updated patient safety registry information

Canada. Health Canada's Marketed Health Products Directorate and Therapeutic Products Directorate have issued a letter to health-care providers to highlight upcoming revisions to the Canadian Product Monographs for clozapine products. The revisions are to strengthen labelling and to address ongoing issues surrounding patient consent regarding sharing of information between

clozapine registries that contain monitoring information of patients receiving clozapine as a risk mitigation strategy to address the risk of agranulocytosis. The revisions emphasize the following points:

- switching from one brand of clozapine to another is only to be done by pharmacists after obtaining a new, registry specific patient registration form completed by the prescribing physician
- physician to inform patients about potential sharing of information between clozapine registries, and to document patient consent
- regarding sending of mandatory laboratory results, the physician is responsible only for informing the laboratory of where to send haematological results
- weekly neutrophil and WBC count monitoring for four weeks at the end of treatment is only necessary with complete cessation of clozapine treatment.

Reference:

"Dear Healthcare Professional" letter from Health Canada Therapeutic Products Directorate, 23 June 2004. Available on the Internet at www.hc-sc.gc.ca

DEXTROPROPOXYPHENE/ PARACETAMOL

Prescribing reminder

UK. Due to the established toxicity in overdose and poorly defined clinical value of the pain reliever dextropropoxyphene/paracetamol (Co-proxamol), the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK is reminding physicians to observe the following:

- restrict the number of tablets prescribed and avoid prescribing dextropropoxyphene/ paracetamol (Co-proxamol) to patients at risk of self-poisoning or with a history of alcohol abuse
- advise patients that the medication is for their use only and can be dangerous

when taken with alcohol or central nervous system (CNS) depressants and that unused tablets should be destroyed or returned to a pharmacy

- inform patients that they should receive a patient information leaflet and ask for one if they do not

According to the MHRA the rationale for the extensive use of the combination of dextropropoxyphene (32.5mg) and paracetamol (325mg) (Co-proxamol) is not evidence based; dextropropoxyphene is a weak analgesic and combining it with paracetamol has not been shown to have greater efficacy than full strength paracetamol. This combination product (Co-proxamol) is currently under review and is the subject of a public request for information.

Reference:

Medicines and Healthcare products Regulatory Agency (MHRA) News, 30 June 2004. Available on the Internet at www.mhra.gov.uk

DOMPERIDONE

Not to be used to increase milk production in women

USA. The Food and Drug Administration (FDA) is warning breastfeeding women not to use domperidone to augment lactation because of safety concerns. The agency is concerned with the potential public health risks associated with domperidone.

Domperidone is not approved in the US for any indication. Some women who breastfeed and/or pump breast milk are purchasing this drug from compounding pharmacies in the US and from sources in foreign countries. The FDA has issued warning letters to the pharmacies that compound domperidone containing products and to firms that supply domperidone to pharmacies in the US. Although domperidone is approved in several countries outside the

US to treat certain gastric disorders, it is not approved in any country for enhancing breast milk production in lactating women. Worldwide there have been several published reports and case studies of cardiac arrhythmias, cardiac arrest and sudden death in patients receiving an intravenous form of domperidone that has been withdrawn from the market in a number of countries. In several countries where the oral form is still marketed, labels for the product contain specific warnings against use of domperidone by breastfeeding women and note that the drug is excreted in breast milk that could expose a breastfeeding infant to unknown risks.

Reference:

FDA Talk Paper, 7 June 2004. Available on the Internet at www.fda.gov

LEFLUNOMIDE

Update on interstitial lung disease

Canada. Aventis Pharma Inc. have issued a "Dear Healthcare Professional" letter highlighting important safety information regarding reports of interstitial lung disease associated with leflunomide. The letter advises that leflunomide, indicated for the treatment of active rheumatoid arthritis in adults, has been associated with rare spontaneous reports of interstitial lung-disease, reported in 0.19 per 1000 person-years' exposure. In a Japanese post-marketing surveillance programme involving 3658 patients receiving leflunomide, interstitial lung disease was reported in 0.8% of patients, with 29 cases of interstitial pneumonitis, 11 of which had a fatal outcome. Causality assessment was complicated in these cases due to the presence of confounding factors such as pre-existing lung disease and/or previous or concomitant use of other disease-modifying

antirheumatics known to be associated with interstitial lung disease. The "Precautions", "Adverse Reactions" and "Information for the Consumer" sections have been updated with this safety information. (See also WHO Pharmaceuticals Newsletters Nos. 9/10, 1998; 2&3, 2001; 1, 2003; 4, 2003).

Reference:

"Dear Healthcare Professional" letter from Aventis Pharma Inc., 21 June 2004. Available on the Internet at www.hc-sc.gc.ca

ROSUVASTATIN

Higher dose and predisposing factors linked with rhabdomyolysis

Europe, USA, Canada.

AstraZeneca has revised the package insert for rosuvastatin (Crestor) for use in the 25 Member States of the European Union. The revised insert includes new prescribing information regarding the maximum dose of rosuvastatin (Crestor). These changes were advised by the UK Medicines and Healthcare products Regulatory Agency and Committee on Safety of Medicines, following a Europe-wide review of safety information regarding the association between rosuvastatin use and rhabdomyolysis. The new information advises the following:

- all patients to start on 10mg once daily, only increased to 20mg if necessary after 4 weeks
- 40mg dose contraindicated in patients with predisposing risk factors for muscle toxicity
- specialist supervision recommended when 40mg given, with this dose only necessary for a minority of patients.

Patients currently receiving the 40mg dose, who have not already been seen by a specialist, are advised to have

their treatment reviewed at their next routine appointment. Following these measures in Europe, the US FDA has issued a public advisory for rosuvastatin, advising that many of these recommendations are "already captured in the FDA approved labelling for rosuvastatin (Crestor)", with this labelling including a specific section titled Myopathy/ Rhabdomyolysis. The FDA is not proposing to change the rosuvastatin (Crestor) labelling following the recent review, but wishes to "re-emphasize to physicians the importance of carefully following the recommendations in the current product label".

In the Canadian Adverse Drug Reactions Monitoring Programme (CADRMP) database, there are eight Canadian post-market cases of rhabdomyolysis associated with rosuvastatin. Five cases occurred with rosuvastatin 40mg daily, two cases have occurred at the 10mg usual recommended daily dose and for the remaining case the dose was not specified. The involved patients all had one or more pre-existing risk factors for statin induced myotoxicity. AstraZeneca, under advice from Health Canada has warned health-care professionals to be cautious when prescribing rosuvastatin in patients with pre-existing risk factors or concomitant medications which pose an increased risk for statin induced myopathy or rhabdomyolysis.

Reference:

1. Medicines and Healthcare products Regulatory Agency News, 9 June 2004. Available on the Internet at www.mhra.gov.uk/news
2. US FDA Public Health Advisory, 9 June 2004. Available on the Internet at www.fda.gov
3. "Dear Healthcare Professional" letter from AstraZeneca, 15 June 2004. Available on the Internet at www.hc-sc.gc.ca

SULPHUR HEXAFLUORIDE

Use in echocardiography suspended

Europe. Use of sulphur hexafluoride (SonoVue) in echocardiography has been temporarily suspended by the EMEA pending further evaluation of the agent's risk/benefit profile.

The EMEA has issued a public statement to inform health-care professionals that SonoVue

- should not be used in echocardiography
- is contraindicated in patients with known heart disorders
- is still indicated for use in non-cardiac imaging
- should be given under close medical supervision with supervision continued for ≥30 minutes after administration.

This regulatory action comes after reports of adverse events including severe hypotension, bradycardia, cardiac arrest and acute myocardial infarction, most of which occurred in patients undergoing echocardiography in the context of an idiosyncratic hypersensitivity reaction. Three fatalities occurred in patients with severe coronary artery disease. The EMEA will continue to review information relating to the safety of SonoVue and will take further action as appropriate. The labelling for the agent has been updated accordingly.

Reference:

EMA Public Statement, 19 May 2004. Available on the Internet at www.emea.eu.int

ATYPICAL ANTIPSYCHOTICS

Reports of diabetes

Australia. Australia's Adverse Drug Reactions Advisory Committee (ADRAC) has received reports of hyperglycaemia associated with four of the atypical antipsychotics: clozapine, olanzapine, quetiapine and risperidone (for details see Table 1). In the ADRAC reports, the median age at diabetes onset for olanzapine was 42 years (range 30–56) and for clozapine was 38 years (17–70). Median time to onset of diabetes was 13 months (range 2 days to 4 years) for olanzapine and 25 months (20 days to 8 years) for clozapine. Of the 19 reports of diabetes with olanzapine, olanzapine was the sole suspected agent in 17, and of the 52 reports with clozapine, clozapine was the sole suspected agent in 49. In some of the reports received by ADRAC,

recovery followed withdrawal of the antipsychotic but in others, continuing antidiabetic treatment was required.

Reference:

Australian Adverse Drug Reactions Bulletin Vol. 23, No. 3, June 2004. Available on the Internet at www.tga.gov.au

ATYPICAL ANTIPSYCHOTICS

ADR update from Finland

Finland. Finland's National Agency for Medicines has reviewed common antipsychotic-associated reactions reported to its adverse drug reaction (ADR) registry, and found that the atypical antipsychotics "*do not appear to be without adverse effects*". During the 30-year period covered by Finland's ADR registry, a total of 974

antipsychotic-associated ADRs have been reported, 564 of which have been received since 1994. Clozapine was the suspected drug in 484 reports, with adverse events including leucopenia, granulocytopenia and agranulocytosis, often with infectious signs, and was the suspected drug in 22 fatalities (see Table 2 for other antipsychotics). Since 1994, as use of the newer atypical antipsychotics has replaced use of conventional antipsychotics, the majority of reports, even after clozapine (n = 306), involved these newer agents (risperidone [n = 65], olanzapine [45] and quetiapine [36]) and, even with the increasing use of these newer agents, there were still reports of serious adverse events (see Table 3).

Reference:

TABU: Drug Information from the National Agency for Medicines, Finland, 2: 50-52, 2004.

Table 1. Antipsychotic-associated diabetes

	Clozapine	Olanzapine	Risperidone	Quetiapine
Diabetes	52	19	3	3
Impaired glucose metabolism	55	13	4	2
Weight increase	51	66	17	1
Total reports	2826	922	510	144

Table 2. Antipsychotic-associated ADRs over 30-years

Antipsychotic	Number of reports
Chlorpromazine	75
Risperidone	71
Olanzapine	52
Haloperidol	43
Thioridazine	39
Quetiapine	38

Table 3. Serious events since 1994

Event	Number of reports
Neuroleptic malignant syndrome	45
Heart disorders	44
Blood dyscrasias	32
Milk secretion/hyperprolactinaemia	29
Liver disorders	28
Oedema	11
Extrapyramidal symptoms	10
Seizures	8
Tardive dyskinesia	7
Death	27

BISPHOSPHONATES

Reports of ocular disorders

Australia. The Australian Adverse Drug Reactions Advisory Committee (ADRAC) reports that inflammatory ocular disorders appear to be a rare adverse effect of bisphosphonates. To date, there have been 28 cases of bisphosphonate-associated ocular inflammation reported to ADRAC, including uveitis (13 reports), iritis (6), scleritis/episcleritis (7) and optic neuritis (2). The median time to onset of these reactions was 3 weeks, but ranged from 2 days to >3 years. Of the 21 patients who had a documented outcome, 15 had recovered at the time of report submission, four were improving (although one required a trabeculectomy) and one had reduced visual acuity. In a recent report, an elderly man with low bone mineral density of the hip developed uveitis three weeks after risedronic acid 35mg once weekly was initiated. He developed eye pain again after restarting risedronic acid and this pain recurred after he switched to alendronic acid 70mg once weekly. According to ADRAC reports and the literature, ocular inflammation has only been associated with alendronic acid, pamidronic acid, risedronic acid and zoledronic acid. ADRAC speculates that the risk may be higher with IV bisphosphonates, but that number of reports may relate to usage. It may be recalled that the Canadian Adverse Reaction Newsletter (Vol. 13, Issue 4, October 2003) discussed similar reports of ocular reactions with bisphosphonates; Health Canada recommended discontinuing bisphosphonate therapy if scleritis occurred during treatment (WHO Pharmaceuticals Newsletter No. 1, 2004).

Reports in WHO file:
Bisphosphonates and Vision disorders: 556

Reference:
Australian Adverse Drug Reactions Bulletin Vol. 23, No. 2, April 2004.

DIETHYL-STILBESTROL

Still causing problems decades later

Australia. The latest Australian *Adverse Drug Reactions Bulletin* highlights a number of health issues occurring today associated with the use of diethylstilbestrol to prevent miscarriage more than three decades ago.

In 1971, a clear association between diethylstilbestrol and adenocarcinoma of the vagina in females exposed to the agent *in utero* was identified, with the lifetime incidence estimated at approximately 1 per 1000. Since this time, a number of other diethylstilbestrol-associated adverse events in females exposed to the agent *in utero* have been identified:

- vaginal/cervical adenosis (reported incidence up to 90%)
- histological/structural reproductive tract abnormalities (incidence from 18% to 58%)
- cervical/vaginal dysplasia
- increased infertility rates
- increased pregnancy complication rates.

In addition, a small increase in the rate of breast cancer in women who received diethylstilbestrol has been reported, and males exposed to the agent *in utero* have an increased incidence of epididymal cysts.

Reference:
Australian Adverse Drug Reactions Bulletin Vol. 23, No. 3, June 2004.
Available on the Internet at www.tga.gov.au

MERCAPTAMINE, MERCAPTOPURINE

Medication errors due to name confusion

UK. Three reports of serious medication errors due to confusion between mercaptamine and mercaptopurine, both of which are 50mg in strength, have been received by the UK Medicines and Healthcare

products Regulatory Agency (MHRA). The Agency reminds health-care professionals to be aware that alphabetized lists of medicines may have changed, and to be careful when selecting medicines to avoid such errors. The MHRA notes that this error has the potential to have a serious outcome as mercaptopurine is used mainly to treat acute leukaemia whereas mercaptamine has anaemia and leukopenia as side effects.

Reference:
Information to Healthcare Professionals, MHRA, 30 April 2004.
Available on the Internet at www.mhra.gov.uk

METHADONE

Risk of QT prolongation

Sweden. In a recent publication, the Swedish Medical Products Agency (MPA) draws attention to the risk of QT interval prolongation and *torsade de pointes* with methadone treatment, and advises against testosterone use in patients receiving methadone.

The MPA notes that, earlier this year, the Swiss drug regulatory authority informed nations within the European pharmacovigilance collaboration of reports of adverse cardiac reactions with methadone, with seven reports of *torsade de pointes*, six of which involved QT interval prolongation, and 14 other reports of QT interval prolongation. A subsequent review revealed five cases of *torsade de pointes* in Denmark and three in France, with two reports of sudden death in England and one of ventricular fibrillation in Spain. The MPA points out that when administered once daily, methadone trough concentrations should be 200–400 ng/mL, and that this should be verified, especially in elderly patients. The MPA advises caution in patients at increased risk for QT interval prolongation, and that an ECG should be recorded as a control for all patients when the dosage

exceeds 150mg/day and if other risk factors for QT interval prolongation are present. (Also see WHO Pharmaceuticals Newsletter No. 1, 2004.)

Reference:

Swedish Medical Products Agency document (Swedish), 1 June 2004. Available on the Internet at www.mpa.se

PARECOXIB

Associated with renal impairment

Australia. Parecoxib can cause renal impairment, with multiple doses associated with a greater risk, according to a report in the Australian Adverse Drug Reactions Bulletin. In Australia, parecoxib is only approved for a single perioperative dose for postoperative pain, due to concerns about the safety of multiple doses. To date, Australia's Adverse Drug Reactions Advisory Committee (ADRAC) has received 20 reports of parecoxib-associated adverse reactions, 13 of which involved renal impairment, including four cases of acute renal failure. In six of these cases, patients had received multiple doses of parecoxib, up to five, but the other seven had received only one dose. However, two of these seven patients had risk factors.

Reference:

Australian Adverse Drug Reactions Bulletin Vol. 23, No. 3, June 2004. Available on the Internet at www.tga.gov.au

possibly symptoms of a withdrawal syndrome. A US FDA advisory committee has recommended that the potential risks of *in utero* SSRI-exposure should be described in patient labelling. The proposed precaution states that "neonates exposed to SSRI/SNRI late in 3rd trimester have developed AE requiring prolonged hospitalization, respiratory support, tube feeding. AE may arise immediately upon delivery". The FDA is also proposing class labelling of SSRIs and SNRIs on *in utero* exposure to be added to the pregnancy section.

Reference:

Reactions Weekly (Adis International), No. 1007, 26 June 2004.

TESTOSTERONE

Not to be used as a cure for impotence

Sweden. The Swedish Medical Products Agency (MPA) advises against testosterone treatment for impotence in patients receiving methadone. Such treatment, which has been recommended in Internet advertising, can produce abnormally high testosterone levels and carries a risk for increased plasma lipid levels, cardiovascular damage and activation of latent prostate cancer. The MPA points out that, even under sustained methadone treatment, testosterone levels return to normal, with restoration of normal sexual function generally within 1–2 years.

product may be associated with serious adverse effects, including death. The capsules contain synephrine, which is similar to ephedrine and may have similar adverse effects, including hypertension and cardiovascular toxicity. Health Canada has previously advised consumers against the use of ephedrine-containing products, especially those containing caffeine and other stimulants, and ThermoNex also contains high levels of caffeine as well as other agents which increase the effects of synephrine.

Reference:

Health Canada Warnings/Advisories, 28 May 2004. Available on the Internet at www.hc-sc.gc.ca

TNF- α ANTAGONIST

Treatment associated with tuberculosis

Sweden. Between 2000 and 2003, the Swedish Medical Products Agency (MPA) received 13 reports of tuberculosis (TB) in patients receiving tumour necrosis factor (TNF)- α antagonist treatment, with an additional two reports of atypical mycobacterial infection. The ages of the patients in these cases ranged from 32 to 94 years, with infection developing within 12 months' treatment in six patients and after more than 12 months in five patients (duration

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https://www.yunbaogao.cn/report/index/report?reportId=5_30045

