WHO PHARMACEUTICALS NEWSLETTER

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

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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No. 5, 2004

News & Issues

As always, we bring you the latest on drug safety and regulatory information from around the world, for your information and for any action as Member States consider appropriate. We have also included a report on the workshop that was held recently in South Africa as a first step towards introducing Pharmacovigilance in HIV programmes in some African countries.

The 27th Annual meeting of representatives of countries participating in the WHO Programme for International Drug Monitoring was held in Dublin, Ireland this year. Focused surveillance methods, as a complement to spontaneous adverse drug reaction reporting system was the theme of the meeting. The sessions on drugs of current interest as well as the working group exercises were very interesting and stimulating. The recommendations from the working groups will be published in the next issue of the newsletter.

The WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) had its second meeting in October, in Geneva. New issues as well as action taken on previous recommendations were reviewed. A report from this meeting will be published in a later issue of the newsletter.

Many of our readers have expressed an interest in joining the e-list for the newsletter. We have over 400 names on the list now and are happy to include more. You can join the list by writing your e-mail details to pals@who.int.

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ANTI-DEPRESSANTS

Labels to include enhanced warnings

USA. The United States Food and Drug Administration (US FDA) has issued a statement to say that it *"generally supports the recommendations"* received from the Psychopharmacologic Drugs and Paediatric Advisory Committees regarding increased suicidality in paediatric patients receiving antidepressants. The FDA are now working to strengthen the warnings on antidepressant labelling and to increase the information provided to patients. The Advisory Committees concluded that all antidepressants studied in controlled clinical trials increased the risk of suicidal thoughts and actions in paediatric patients, and that any related warning should be applied to all antidepressants, including those that had not been studied in children. The committees thought that access to antidepressants for paediatric patients who may benefit was important; therefore, they did not recommend that the drugs be contraindicated in the US. However, they did recommend that antidepressant labelling include the results of controlled trials of the drugs in children with depression.

Reference:
Media Release, 16 September 2004. Available on the Internet at www.fda.gov

ARISTOLOCHIC ACID

To be replaced by *Stephania tetrandra* and *Inula helenium*

People's Republic of China. China's State FDA (SFDA) has banned two commonly used herbs containing aristolochic acid, a toxin reported to be linked to kidney failure and cancer. Manufacturers have been directed to replace *Aristolochia fangchi* and *Aristolochia debilis* with *Stephania tetrandra and Inula helenium respectively*, in their traditional medicine formulations by 30 September. The Provincial Drug Bureaux has been instructed to carry out inspections to ensure compliance with the ban by 31 October. Medicines found to contain either *Aristolochia fangchi* or *Aristolochia debilis* after 30 September will be treated as fake under Chinese law. By a previous order, special restrictions were imposed on four other potentially harmful aristolochic acid-containing herbs (*Fructus Aristolochiae*, *Aristolochia mollissima Hance*, *Herba Aristolochiae* and *Aristolochia tuberose)* in China; there was no outright ban on these products. Several countries withdrew aristolochic acid-containing preparations in 1981 following the demonstration of a carcinogenic potential in a three-month toxicity study in rats (see *UN Consolidated List of Products whose consumption and/or sale have been banned, withdrawn, severely restricted or not approved by governments, Eighth Issue, Pharmaceuticals*, available at http://www.un.org/esa/coordination/ecosoc/Consolidated.List.of.Products.final.pdf).

More recently, in 2001, severe adverse events among users of herbal and dietary preparations containing aristolochic acid have led to bans or consumer warnings in different parts of the world (see WHO's *Pharmaceuticals: restrictions in use and availability, April 2003*, available at http://www.who.int/medicines/library/docseng_from_a_to_z.shtml#p.

Reference:
Scrip World Pharmaceutical News No. 2985, 8 September 2004. Available on the Internet at www.scrippharma.com

ENOXAPARIN

Dosage adjustment needed in patients with renal impairment

USA. Aventis has issued a `Dear Healthcare Professional' letter advising of recent changes to enoxaparin sodium (Lovenox) prescribing information. The letter, sent out in March, was posted on the US FDA website on 17 August 2004. In the `Pharmacokinetics' section, information regarding the clearance and elimination of enoxaparin sodium in obese and low-weight patients, patients with renal impairment and patients on haemodialysis has been clarified, and new information has been incorporated regarding the distribution, metabolism and elimination of enoxaparin sodium in healthy volunteers. In addition, a `Special Populations' section has been added, with subsections for renal impairment, haemodialysis, gender, geriatric and weight considerations. The `Precautions' section has been revised, with a recommendation for dosage adjustment in patients with severe renal impairment (creatinine clearance < 30 mL/min) who have increased exposure to enoxaparin. In patients with mild or moderate renal impairment and in low-weight patients, no specific dosage adjustment is required, but careful observation for signs and symptoms of bleeding in low-weight patients is recommended. Finally, a table has been added to the `Dosage and Administration' section to clarify the recommended treatment and prophylaxis dosage regimens for patients with severe renal impairment.

Reference:
'Dear Healthcare Professional' letter from Aventis, March 2004. Available on the internet at www.fad.gov

INFLIXIMAB

Label to reflect haematological and neurological events

USA. Centocor has issued a `Dear Healthcare Professional' letter advising of changes to the USA infliximab (Remicade) label, following post-marketing reports of haematological and neurological events. A `Warning on Haematological Events' has been added to the label to advise of reports of neutropenia, leukopenia, thrombocytopenia and pancytopenia, some of which were fatal. The `Warning on Neurological Events' has also been updated to detail cases of Central Nervous System (CNS) manifestation of systemic vasculitis. In addition, pericardial effusion, neutropenia, and cutaneous and systemic vasculitis have been added to the `Adverse Reaction' sections of infliximab prescribing information. Physicians are advised that they should consider discontinuation of infliximab in patients who develop significant adverse CNS reactions or haematological abnormalities. Infliximab is a biological therapeutic product indicated in the treatment of rheumatoid arthritis and Crohn's disease.

Reference:
'Dear Healthcare Professional' letter from Centocor, 11 August 2004. Available on the Internet at www.fda.gov

LEVOTHYROXINE

Changes to regulatory status

Canada. Health Canada's Therapeutic Products Directorate (TPD) has issued a notice to manufacturers advising that products containing levothyroxine sodium or digoxin will now be regulated as new drugs, in order to ensure that products are "*adequately assessed at the pre-approval stage and appropriately monitored throughout their life-cycle on the market*"[1]. The move follows an evaluation of these drugs by the TPD, which determined that levothyroxine and digoxin possess characteristics that could lead to *"serious therapeutic failures and/or adverse drug reactions"*, if not properly managed.

Meanwhile, in the United States of America, the American Thyroid Association (ATA) Alliance for Thyroid Protection Education has issued a press release to warn patients who take levothyroxine not to change their brand of medication without consulting their physician, following a decision by the US FDA to approve generics as equivalent to branded levothyroxine preparations[2]. The ATA Alliance expresses concern over the methodology that the US FDA has used to determine bioequivalence, and the fact that the decision was made without input from clinical endo-crinologists. They also advise that levothyroxine has a narrow toxic to therapeutic ratio, and that excessive or inadequate levels of the hormone could have significant clinical consequences.

Reference:
1. Health Canada Internet document, 9 July 2004. Available on the Internet at www.hc-sc.gc.ca
2. ATA Alliance for Thyroid Education Media Release, 13 July 2004. Available on the Internet at www.thyroid.org

PHU CHEE / LIN CHEE / ACTIVE RHEUMA PLUS

Banned due to presence of undeclared glucocorticoids

Norway. The Norwegian Medicines Agency (NoMA) has banned the sale of two herbal medicines, Phu Chee and Lin Chee/Active Rheuma plus, that were found to contain high doses of undeclared dexamethasone (Phu Chee) and prednisolone (Lin Chee/Active Rheuma plus). NoMA has received reports of serious adverse reactions to these herbal medicines. Physicians from a hospital in northern Norway have reported that several patients receiving Phu Chee or Lin Chee/Active Rheuma plus developed symptoms similar to those observed with prolonged use, or high doses, of glucocorticoids, along with subsequent withdrawal symptoms. Laboratory analysis has shown that Phu Chee contains dexamethasone 0.4–0.5mg per tablet and Lin Chee/Active Rheuma plus contains an unknown quantity of prednisolone. As the recommended dosage of Phu Chee was 3–9 tablets/day, patients could have been exposed to a daily dexamethasone dose of 1.2–4.5mg. The number of patients who have taken these drugs is unknown, but over the last two years, they have been mostly used by patients with rheumatoid arthritis and arthrosis. NoMA has sent a letter to all of the distributors' customers, with warnings about use and rapid discontinuation of the herbal medicines, as well as advice to see a doctor.

Reference:
Communication from the Pharmacovigilance section, Norwegian Medicines Agency, August 2004.

PHENYLPROP-ANOLAMINE

Banned in the Republic of Korea

The Republic of Korea. On 1 August, 2004, the Korean Food and Drug Administration (KFDA) banned the production and sale of about 170 prescription and over-the-counter cold remedies containing phenylpropanolamine (PPA). The ban follows the conclusions of a Korean study that PPA-containing drugs may be associated with strokes. PPA-containing products were withdrawn in several countries following the publication of an

article (New England Journal of Medicine, 2000; 343: 1826-32) that reported a risk of haemorrhagic stroke associated with the use of PPA. (Also see WHO Pharmaceuticals Newsletter No. 4, 1996).

Reference:
Korean News Media, August 2004.

RIFAMPICIN/ PYRAZINAMIDE

Revised advice

France. Revised recommendations on the use of combination rifampicin and pyrazinamide for latent tuberculosis in patients receiving infliximab (Remicade) have been issued by the French regulatory authority, l'Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS), following reports of cases of serious and sometimes fatal hepatitis. AFSSAPS advises that the combination of rifampicin and pyrazinamide should be avoided and that the combination of rifampicin and isoniazid be used instead or, alternatively, isoniazid alone in elderly patients, in patients with cirrhosis or in the event of toxicity.

Reference:
French Health Products Safety Agency, 20 August 2004. Available on the Internet at http://afssaps.sante.fr

ZIPRASIDONE

Updated prescribing information

USA. Pfizer has issued a `Dear Healthcare Practitioner' letter advising of changes to the US prescribing information for ziprasidone (Geodon). The changes, which were made in accordance with a request by the US FDA, warn of an increased risk of hyperglycaemia and diabetes mellitus associated with atypical antipsychotics. The new warning acknowledges reports of hyperglycaemia associated with atypical antipsychotics, and recommends monitoring for symptoms of hyperglycaemia in all patients receiving atypical antipsychotics, including ziprasidone. However, the letter notes that ziprasidone was not included in the epidemiological studies that suggested an increased risk of hyperglycaemia in patients receiving atypical antipsychotics, and that there have been few reports of hyperglycaemia or diabetes associated with the agent. The letter points out that fewer patients have received ziprasidone treatment, and it is not known if this limited experience is the reason for the small number of such reports. The new prescribing information recommends fasting blood glucose testing for patients who develop symptoms of hyperglycaemia during ziprasidone treatment and patients with risk factors for diabetes mellitus, and regular monitoring for worsening glucose control in patients with an existing diagnosis of diabetes mellitus.

Reference:
'Dear Healthcare Practitioner' letter from Pfizer Global Pharmaceuticals, August 2004. Available on the Internet at www.fda.gov

BEVACIZUMAB

Increased risk of thromboembolic events

USA. Bevacizumab (Avastin), used in combination with intravenous 5-fluorouracil-based chemotherapy, is indicated for first-line treatment of patients with metastatic carcinoma of the colon or rectum. Recently Genentech Inc. issued a `Dear Healthcare Provider' letter warning of an increased risk of serious arterial thromboembolic events associated with bevacizumab (Avastin). In the letter, Genentech notes that there is evidence of an association between bevacizumab use and an increased risk of stroke, transient ischaemic attacks, myocardial infarction, angina, and fatal arterial thrombotic events. They advise that patients who experience an arterial thromboembolic event during bevacizumab treatment should discontinue the drug permanently. Genentech is currently revising the package insert for bevacizumab (Avastin) to include detailed information regarding arterial thomboembolic events.

Reference:
'Dear Healthcare Provider' letter from Genentech Inc, 12 August 2004. Available on the Internet at www.fda.gov

CLOPIDOGREL

Reports of haemorrhagic events

Australia. The Australian Adverse Drug Reactions Advisory Committee (ADRAC) warns prescribers of the risk of haemorrhagic events with clopidogrel (Plavix, Isocover), especially when given in combination with other drugs known to cause bleeding. ADRAC has received 460 adverse drug reaction reports associated with clopidogrel, and a total of 130 reports (28%) described haemorrhagic events, 18 of which were fatal. These included patients who received clopidogrel alone (n = 27), in combination with aspirin (27), or with one (25) or two or more (63) anticoagulants, thrombolytics, platelet inhibitors or NSAIDs. In addition, ADRAC has received 80 reports of blood dyscrasias, including one report of thrombotic thrombocytopenic purpura, involving disseminated platelet aggregation. Allergic cutaneous reactions have also been reported in association with clopidogrel (141 reports to ADRAC). Clopidogrel is an anti-platelet agent used for the reduction of atherosclerotic events.

Reports in WHO-file:
Purpura thrombopenic thrombotic 46

Reference:
Australian Adverse Drug Reactions Bulletin, 23: 14-15, No. 4, 2004.

LAMOTRIGINE

Interaction with hormonal contraceptives

Canada. GlaxoSmithKline Inc, in consultation with Health Canada, has issued a 'Dear Healthcare Professional' letter with the following safety information for the antiepileptic drug, lamotrigine (Lamictal):

- A recent study has demonstrated that concomitant use of hormonal contraceptives with lamotrigine may significantly decrease serum lamotrigine levels.
- GSK has received a limited number of post-marketing reports of break-through seizures, unexpected pregnancies and of menstrual bleeding disorders occurring with the concomitant use of lamotrigine and hormonal preparations.
- Dose adjustments may be needed to counter the interactive effects on serum drug levels. A maintenance dose of lamotrigine may need to be increased by as much as two-fold in women starting or currently taking oral contraceptives and who are not also taking carbamazepine, phenytoin, phenobarbital, primidone or rifampin. On the other hand, the maintenance dose of lamotrigine may need to be decreased by as much as 50% if oral contraceptives are stopped in patients who are not also taking carbamazepine, phenytoin, pheno-barbital, primidone or rifampin.
- Women patients currently being treated with lamotrigine should be advised not to start or stop their oral contraceptives without consulting their physician.
- Although not formally evaluated, similar adjustments may be needed for women receiving lamotrigine in combination with hormonal contraceptives or hormonal replacement therapy.
- Women receiving lamotrigine along with oral contraceptives or other hormonal preparations should notify their physician immediately if they experience changes in their menstrual pattern.

Reference:
'Dear Healthcare Professional' letter from GlaxoSmithKline Inc, September 2004. Available on the Internet at www.hc-sc.gc.ca

NITRO-FURANTOIN

Risk of lung toxicity with long-term use

Australia. Of the 576 reports of suspected adverse drug reactions to nitrofurantoin (Macrodantin, Furadantin, Ralodantin) received by the Australian Adverse Drug Reactions Advisory Committee (ADRAC), 142 (25%) reports described pulmonary toxicity, 40 of which were associated with long-term use of the drug. The reports of pulmonary toxicity

with long-term use of nitrofurantoin were consistent with interstitial pneumonitis or pulmonary fibrosis and commonly had presenting symptoms of dyspnoea or cough, although some hypersensitivity symptoms were also reported. The ratio of females to males was 7:1, the median age was 70 years (range 47–90), the doses used were 50–300 mg/day and the longest time to onset was 16 years. Of the 40 reports, two patients died after developing pulmonary toxicity and 12 had recovered at the time of reporting. Some reports described indications of persistent lung damage. The ADRAC advises that the risk of pulmonary toxicity should be considered when nitrofurantoin treatment is extended for ≥ 6 months, especially in elderly patients, and that nitrofurantoin should be discontinued if pulmonary symptoms occur.

Reports in WHO-file:
Respiratory system disorders 3178

Reference:
Australian Adverse Drug Reactions Bulletin, 23: 15, No. 4, August 2004.

RITUXIMAB

Possible association with Hepatitis B reactivation

Canada. Hoffman-La Roche Limited has issued a `Dear Healthcare Professional' letter advising of a possible association

therapy, and approximately one month after administration of the last dose; fulminant hepatitis, liver failure and death were reported in some patients. The letter advises that patients at high risk of HBV infection should be screened before starting rituximab therapy, and that both HBV carriers and patients who have recovered from HBV infection should be closely monitored during, and up to one year after rituximab therapy. It is suggested that rituximab, and any concomitant anti-neoplastic therapy, be discontinued in patients who develop HBV reactivation.

Reference:
'Dear Healthcare Professional' letter from Hoffmann-La Roche Limited, 27 July 2004. Available on the Internet at www.hc-sc.gc.ca

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)

Potential adverse effects in neonates

Canada. Health Canada has issued an advisory highlighting potential adverse effects of SSRIs and other newer antidepressants in neonates following *in utero* exposure. This advisory, which applies to bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, paroxetine, sertraline and

Patients are warned against stopping their medication without consultation, and are advised to discuss treatment options with their doctor (see WHO Pharmaceuticals Newsletter No. 4, 2004, for related information from the US FDA).

Reference:
Health Canada Warnings / Advisories, 9 August 2004. Available on the Internet at www.hc-sc.gc.ca

WARFARIN

Interaction with fluoroquinolones

Canada. A total of 57 reports of suspected coagulation disorders associated with concomitant fluoroquinolone and warfarin treatment had been received by Health Canada as of 15 January this year (see table for details). In these 57 reports, 46 patients were aged ≥ 60 years and six were aged < 60 years, with age not reported in the remaining five cases. Forty-nine of the reports were considered to be serious, 16 involved adverse reactions which led to hospital admission and four patients, aged 70–90 years, died. In these reports, values of International Normalized Ratio or INR values as high as 50 were reported and, in 15 of the reports, INR had been stabilized with warfarin before the addition of the fluoroquinolone. Health Canada notes that the interaction is labelled in the official Canadian product