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EDITORIAL

In addition to the regular articles on regulatory decisions and safety issues, in this edition, you will find a small item on the use of praziquantel. This describes an important advance in the treatment of schistosomiasis for pregnant women and women of child-bearing age with the recommendation that praziquantel can be used in these populations provided adequate monitoring takes place. This is a major challenge to pharmacovigilance programmes wherever schistosomiasis is endemic.

In the last issue of the newsletter we published an article on the use of metamizole sodium in Brazil. Some of our readers have expressed reservations about the article. We reiterate that the article on metamizole does not, in any way, reflect WHO's position on the drug. The intention was to open a debate on the need for continued monitoring of older generic drugs and to remind our readers of the necessity always to compare safety with similar products on the market. We now invite specific comments to the article and would be pleased to publish those and other concerns in the next issue of our newsletter.

We also wish to bring to your attention the upcoming events: the Annual Meeting of National Centres in Amsterdam and the Regional training course on pharmacovigilance in Canberra. We hope to see many of you at one of these events.

Lastly, we are holding a one-day workshop on "The Impact of Regulation on the Safe use of Drugs". This will be held immediately prior to the International Conference of Drug Regulatory Authorities (ICDRA) in Hong Kong in June 2002. A full report of this will be published in the next edition of this newsletter.

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ACARBOSE

Revised precautions for Acarbose and others

Japan. Korosho Japan has ruled that the package inserts for acarbose, zafirlukast and vincristine sulfate should be appropriately revised to reflect the serious adverse drug reactions (ADRs) being reported with these drugs. The precautions section in the package insert for acarbose (Glucobay) will now include the statement that acarbose can cause serious hepatic function disorders such as fulminant hepatitis. Hepatic function tests are advised once a month during the first six months after starting treatment with the drug and at longer but regular intervals thereafter. Hepatic function disorders and jaundice are to be added as serious ADRs in the package insert for zafirlukast (Accolate) while 'bone marrow depression' and 'interstitial pneumonia' will be in the precautions section for vincristine sulfate (Oncovin).

Reference:
Pharma Japan No. 1785: 11, 4 Mar 2002.

CYPROTERONE WITH ETHINYL-ESTRADIOL

Risk of venous thromboembolism

New Zealand. Cyproterone-containing estrogen pills (Diane-35/35D, Estelle-35/35D) are used to treat conditions caused by an excess of the hormone androgen, e.g. pronounced acne. These pills provide oral contraception as well. In a letter to doctors, midwives and pharmacists, the Medicines Adverse Reactions Committee (MARC) for New Zealand has advised that the risk of venous thromboembolism (VTE) with oral contraceptives (OCs) containing cyproterone acetate and ethinylestradiol is at least as great as that with third generation OCs. The Centre for Adverse Reactions Monitoring in Dunedin, New Zealand has received 18 reports of VTE, including 15 of pulmonary embolism, in women taking cyproterone-ethinylestradiol pills. MARC reminds practitioners that cyproterone-ethinylestradiol combination pills are indicated only in women for the treatment of androgen-dependent diseases (including pronounced acne) and polycystic ovary syndrome and for oral contraception in these women. All patients currently on these medicines should be reviewed at their next visit (or repeat prescription) for the appropriateness of this therapy. Both new and current patients should be fully advised of the risks of VTE and be informed of the symptoms of VTE and situations of increased risk. The advice from MARC is based on a study in the Lancet (2002) and other previously published smaller studies. Medsafe has also updated the June 2000 patient leaflet on OCs and blood clots to include the above information.

Reference:

1. *Prescriber Update Article – Letter to Doctors/Midwives/ Pharmacists about VTE with cyproterone-containing OCs, Mar 2002. Available from URL: http://www.medsafe.gov.nz*
2. *Medsafe Patient Information Leaflet on oral contraceptives and blood clots, Mar 2002. Available from URL: http://www.medsafe.gov.nz*
3. *Lancet 359: 1085-1101, 2002.*

ENOXAPARIN SODIUM

Important changes to injection product labelling

USA. FDA and Aventis Pharmaceuticals have strengthened the Warnings and Precautions sections of the prescribing information for enoxaparin sodium (Lovenox) injection. Healthcare professionals are informed that the use of this injection is not recommended for thromboprophylaxis in patients with prosthetic heart valves. This warning follows reports of prosthetic heart valve thrombosis in patients who had received enoxaparin. Some of these patients were pregnant women in whom thrombosis led to maternal and foetal deaths. Pregnant women with prosthetic heart valves may be at higher risk for thromboembolism. A paragraph has been added to the 'teratogenic effects' subsection regarding reports of congenital anomalies including cerebral anomalies, limb anomalies, hypospadias, peripheral vascular malformation, fibrotic dysplasia and cardiac defect in infants born to women who received enoxaparin during pregnancy. The non-teratogenic effects subsection has also been revised to indicate that pregnant women receiving anti-coagulants, including enoxaparin, are at increased risk for bleeding; hemorrhage can occur at any site and may lead to death of mother and/or foetus. Pregnant women and women of child-bearing potential should be apprised of the hazard to the foetus and the mother if enoxaparin is administered during pregnancy.

Reference:
'Dear Healthcare Professional' letter by Aventis Pharmaceuticals, Feb 2002. Available from URL: http://www.fda.gov/medwatch/SAFETY/2002

HERBAL DIETARY SUPPLEMENTS (PC-SPES & SPES)

Adulteration with prescription only medicines precipitates regulatory action

Canada, Ireland, USA. PC-SPES and SPES are herbal medicines manufactured by Botanic Lab in the USA. The two products are marketed as 'herbal

dietary supplements' for 'prostate health' and for 'strengthening the immune system' respectively. These are sold through the internet, by mail and phone order as well as through various distributors and healthcare professionals. An analytical report from the California Department of Health, USA showed that samples of PC-SPES and SPES were adulterated with warfarin and alprazolam respectively. The Canadian medicines regulatory authority has also reported similar contamination. Warfarin is an anticoagulant (blood-thinning agent) which can cause serious bleeding, particularly if taken with other medications without prior supervision while alprazolam is a prescription only medicine used in the treatment of anxiety. In view of these reports Health Canada, the Irish Medicines Board and the State Health Director of California, USA have all warned consumers to immediately stop using these two products and to consult their health-care practitioners. Botanic Lab has also informed consumers of these laboratory findings and has issued a product recall of all lots of PC SPES pending further reports from additional testing of PC SPES in both commercial as well as academic laboratories.

Reference:

1. *Warning from the Office of Public Affairs, California Department of Health Services, 7 Feb 2002. Available from URL: http://www.fda.gov/medwatch/SAFETY/2002*
2. *'Dear customer' letter from Botanic Lab, 8 Feb 2002. Available from URL: http://www.fda.gov/medwatch/SAFETY/2002*
3. *Health Canada Warnings/Advisories, 8 Feb 2002. Available from URL: http://www.hc-sc.gc.ca*
4. *Current News and IMB Statements, 15 Feb 2002. Available from URL: http://www.imb.ie/*

HUA FO

Sildenafil detected in tablets

Canada. Health Canada has analysed and detected the presence of sildenafil in Hua Fo Tablets, an unapproved herbal product that claims to enhance sexual function. Sildenafil is a prescription-only drug approved for the treatment of male erectile dysfunction. Health Canada is warning consumers not to use Hua Fo Tablets since the use of sildenafil without medical supervision could cause severe adverse reactions such as potentially life-threatening low blood pressure in the presence of concurrent treatment with other medications such as nitrates. Although to date no adverse reactions have been reported to Health Canada involving the use of Hua Fo, consumers who have used Hua Fo are nevertheless being advised to contact their physicians. Health Canada has issued this warning to advise consumers, healthcare professionals and the provincial ministries of health of the safety issues related to the use of Hua Fo. Hua Fo is manufactured in China by Guizhou Ribulo Medical Industry Inc. and sold in Canada by Shenlong Company. Health Canada is also working with the importer of the product to ensure its removal from the market.

Reference:

Health Canada Warnings/Advisories, 15 Feb 2002. Available from URL: http://www.hc-sc.gc.ca

INTERFERON ALFA 2B, RECOMBINANT

Safety related labelling change

USA. Schering Corporation, the manufacturer of interferon alfa 2b (Intron A) has issued a letter to health professionals informing them of safety related labelling changes to the product information for all alpha interferons. The change includes the addition of a boxed warning stating that neuropsychiatric, autoimmune, ischemic and infectious disorders may be aggravated in patients taking interferon alfa 2b (Intron A). The revised warning also includes specific requirements for monitoring these patients for life-threatening adverse events. Patients with persistently severe or worsening signs or symptoms of the above mentioned conditions should be withdrawn from therapy. In many but not all cases these disorders are expected to resolve after stopping therapy.

Reference:

'Dear Health Professional' letter from Schering Corporation, 14 Mar 2002. Available from URL: http://www.fda.gov/medwatch/SAFETY/2002

KAVA-KAVA

Further investigations into Piper methysticum and liver injury

New Zealand, Canada, Ireland, USA. Further to the precautionary warnings issued by the regulatory authorities in Germany, Switzerland, UK and USA (Pharmaceuticals Newsletter No. 1, 2002), the following actions have been recorded on the use of Kava.

16 January 2002: The New Zealand Ministry of Health has stated that it is looking into concerns expressed by overseas authorities about a reported link between kava consumption and liver damage in some people. In New Zealand Kava is mostly consumed as a natural drink whereas in Europe it is consumed as a pre-packaged dietary supplement. Since factors other than kava consumption may have caused liver damage, it is difficult to draw a definite cause-effect relationship with the present evidence in New Zealand. However the ministry has been working closely with the Australia New Zealand Food

Authority (ANZFA) since it became aware of this issue in early January to gather relevant information and is awaiting further information from Europe before reaching a conclusion on whether any action is warranted.

16 January 2002: Health Canada has advised consumers not to use any product that contains kava although no cases of liver toxicity have been reported in Canada with Kava. Health Canada is conducting a comprehensive safety assessment of kava and will take further action, if required, on completion.

4 February 2002: The Irish Medicines Board in consultation with the industry initiated a voluntary withdrawal of all products containing kava from the Irish market with immediate effect although the Medical Director at IMB stated that the current data are confounding. The IMB based its withdrawal on similar actions by other EU Member States.

25 March 2002: The US FDA is advising consumers of the potential of liver injury with the use of kava-containing dietary supplements. Persons who have liver disease or liver problems, or persons who are taking drug products that can affect the liver have been advised to consult a physician before using kava-containing supplements. Consumers who use kava-containing dietary supplements and who experience signs of illness associated with liver disease should also consult their physician. The FDA has also issued a letter to health-care professionals informing them of the consumer advisory and has urged consumers and their health-care professionals to report any cases of liver and other injuries that may be related to the use of kava. In the meanwhile the FDA will continue to investigate the relationship, if any, between the use of dietary supplements containing kava and liver injury.

Reference:

1. *Media Release, 16 Jan 2002. Available from URL: http://www.ndp.govt.nz/media*
2. *Health Canada Warnings / Advisories, 16 Jan 2002. Available from URL: http://www.hc-sc.gc.ca*
3. *Current News and IMB Statements, 4 Feb 2002. Available from URL: http://www.imb.ie/*
4. *Consumer Advisory, 25 Mar 2002. Available from URL: http://www.cfsan.fda.gov/*
5. *'Dear Healthcare Professional' letter by US FDA, 25 Mar 2002. Available from URL: http://www.cfsan.fda.gov/*

NEFAZODONE

New black box warning to report rare cases of liver failure

USA. Due to reports of rare cases of nefazodone (Serzone)-associated liver failure leading to transplant and/or death, a black box warning has been added to the product information in the US, according to a 'Dear Healthcare Practitioner' letter posted on the FDA's website. The warning is based on the postmarketing experience of >7.2 million US patients, and includes the following information.

- The reported rate of liver failure associated with nefazodone is approximately 1 case per 250,000-300,000 patient-years.*
- Nefazodone is not recommended for use in patients with acute liver disease or elevated baseline aminotransferase levels, which can complicate patient monitoring.
- Patients should be advised to be vigilant for symptoms or signs of liver dysfunction, and to seek advice from their physician should any become apparent.
- Nefazodone should be withdrawn in patients who exhibit signs or symptoms of liver failure, or if evidence of hepatocellular injury develops. Furthermore, such patients should be assumed to be at increased risk of developing liver injury if nefazodone is restarted, and therefore this should not be considered.

Additional information is included in the appropriate sections of the labelling for nefazodone.

** 3-4 times greater than the estimated background rate*

Reference:

'Dear Healthcare Practitioner' letter from Bristol-Myers Squibb, 9 Jan 2002.
Available from URL: http://www.fda.gov.

ORAL CONTRACEPTIVES

Risk of cervical cancer with long-term use in women with high risk type of HPV

UK. The Chief Medical Officer from the UK Department of Health has issued an urgent communication to all Health Professionals with the following information: A recent study published in the Lancet (2002), although not conclusive, strengthens the evidence that oral contraceptives (OCs) may contribute to the development of cervical cancer in women with high risk type human papilloma virus (HPV). The study reports an association between increasing risk of cervical cancer and increasing duration of use of OCs (3 fold increase in risk following 5-9 years of OC use versus 4 -fold increase after 10 or more years of OC use) in women with HPV. HPV is a sexually transmitted infection. There are more than 80 HPV viruses, only a few of which are associated with an increased risk of cervical cancer. With the current evidence it is difficult to state whether it is the use of OCs, sexual activity, the type of HPV or the duration of HPV infection which is/are the main precipitating factor(s) for cervical cancer. Furthermore, the original

studies were carried out in women from developing countries with no adequate cervical screening programme. While cervical screening is not perfect, between 80% and 90% of cervical abnormalities can be detected and treated in women who attend regular screening programmes. The communication therefore advises that all sexually active women, especially those on long-term OCs, be encouraged to have regular cervical smears. The benefits of using OCs outweigh the risks in the vast majority of women who use them.

Reference:

1. *Urgent Communication from Chief Medical Officer, 27 March 2002. Available from URL: http://www.mca.gov.uk*
2. *Lancet 359: 1085-1101, 2002.*

PAROXETINE

Withdrawal symptoms can be severe

USA. The US FDA published a new product warning for paroxetine regarding the severe withdrawal symptoms of the kind that could lead to dependence. Withdrawal symptoms such as bad dreams, paraesthesia and dizziness can occur in up to 7% of patients. The warning mentions anecdotal reports of agitation, sweating and nausea and tells doctors to consider restarting treatment if symptoms become intolerable. Welcoming the FDA safety warning Dr Peter Haddad, consultant psychiatrist for Salford's Mental Health Service NHS Trust has stated that there is a danger of misdiagnosis and inappropriate investigation of the symptoms following paroxetine withdrawal. For example, severe dizziness can easily be diagnosed for labyrinthitis. Patients should be warned not to stop taking their antidepressants suddenly; doctors should taper the dose at the end of treatment, keeping a close watch for withdrawal symptoms.

Reference:

British Medical Journal 324: 260, 2 Feb 2002.
Available from URL: http://bmj.com

SODIUM PHOSPHATES ORAL SOLUTION

Risk of electrolyte shift if maximum dose is exceeded

Canada. Sodium Phosphates Oral Solution has been marketed in Canada since 1987 as a laxative for the relief of occasional constipation. The product is also used as part of a bowel-cleansing regimen in preparing patients for surgery or for colonoscopy, etc. From 1987 up to October 31, 2001 the Canadian Adverse Drug Reaction Monitoring Program had received 10 domestic reports of serious electrolyte disturbances (hypocalcaemia, hyperphosphatemia, hypernatremia, hypokalemia and acidosis), dehydration, renal failure and tetany in patients ingesting more than 45 ml of the solution, in patients at medical risk and/or in patients using multiple purgatives for bowel preparation. In view of these reports, Johnson & Johnson o Merck Consumer Pharmaceuticals and Pharmascience Inc., in consultation with Health Canada have each issued a letter to all health professionals with information related to the safe use of sodium phosphates oral solution. The identification, characterization and management of drug-related adverse events is dependent on the active participation of health care professionals in adverse drug reaction reporting programmes. Healthcare professionals are requested to report any suspected adverse reactions in patients receiving sodium phosphates oral solution directly to Johnson & Johnson o Merck Consumer Pharmaceuticals (Fleet® Phospho-Soda®)or to Pharmascience Inc.

Reference:

1. *'Dear Healthcare Professional' letter by Johnson & Johnson o Merck Consumer Pharmaceuticals, Canada, 15 Mar 2002. Available from URL: http://www.hc-sc.gc.ca*
2. *'Dear Healthcare Professional' letter by Pharmascience Inc. Canada, 18 Mar 2002. Available from URL: http://www.hc-sc.gc.ca*

TAMOXIFEN

Prevention in breast cancer versus risks of thromboembolic events

UK. Tamoxifen is already a widely used hormonal treatment for women following treatment for early and advanced breast cancer. Now, in addition to its use as a treatment in cancer, preliminary results from the International Breast Cancer Intervention Study (IBIS) provide evidence also for the use of tamoxifen to 'prevent' breast cancer in healthy women at high risk. The results so far show that the incidence of breast cancer was reduced by one-third in women at high risk, compared to women taking a placebo. The study also indicated, however, that tamoxifen can increase the risk of thromboembolism, particularly during and immediately after major surgery o r periods of immobility. The UK Department of Health has sent out an urgent communication with the above information to all directors of public health. The key messages in the communication may be summarised as under:

1. It is clear that the benefits for women being treated for breast cancer with tamoxifen far outweigh the risks. It is important that women taking the drug as a treatment continue to do so as there is overwhelming evidence that tamoxifen saves life among women with breast cancer. There is evidence of some increase in risk from thromboembolism with tamoxifen, especially during and immediately after major surgery or periods of immobility. Patients

should be made aware of the symptoms of venous thrombo-embolism and if they have any sudden onset of breathlessness they should consult their doctor immediately.

2. The IBIS study gives evidence of the preventative action of tamoxifen in breast cancer. However this is not a use of tamoxifen that has yet been licensed except in the context of a trial.

3. A full analysis of all trials needs to be carried out to consider whether the benefits of preventative action outweigh potential risks.

Reference:

Urgent Communication from Chief Medical Officer, 27 Mar 2002. Available from URL: http://www.mca.gov.uk

ZIPRASIDONE HCl

Warnings and contraindications sections strengthened

USA. The US FDA and Pfizer have strengthened the Warnings and Contraindications sections of the ziprasidone (Geodon) prescribing information to inform healthcare professionals of the particular drugs or types of drugs that are contraindicated with ziprasidone. The revisions are being made only to clarify existing information in the package insert. The earlier contraindications section included a list of seven drugs contraindicated with ziprasidone and stated that this list of drugs was 'not a complete list'. Not all physicians, pharmacists and pharmacy databases interpreted this language as intended. Some may have considered certain drugs excluded from the contraindication while others may have believed that, irrespective of the level of documentation, any drug associated with QT-prolongation was contraindicated with ziprasidone. Pfizer and FDA agreed that there was a need to provide greater clarity around the particular drugs or types of drugs that are contraindicated with ziprasidone. The key sections that have been changed in the label now clearly state that an additive effect of ziprasidone and other drugs that prolong the QT interval cannot be excluded. Therefore, ziprasidone should not be given with dofetilide, sotalol, quinidine, other class Ia and III anti-arrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol, or tacrolimus. Ziprasidone should be avoided in combination with other drugs that are known to prolong QTc interval. Additionally, clinicians should be alert to the identification of other drugs that have been consistently observed to prolong the QTc interval. Such drugs should not be prescribed with ziprasidone. Ziprasidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias.

Reference:

Letter from Pfizer, Mar 2002. Available from URL: http://www.fda.gov/medwatch/SAFETY/2002

ALENDRONATE

Case reports of pancreastitis with alendronic acid suggest a link?

Canada. Six case reports of pancreatitis associated with alendronic acid therapy have been received by the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) between the time the agent was launched in Canada (December 1995) and August 2001, according to an article in the Canadian Adverse Drug Reaction Newsletter. The article notes that, based on these cases, it is difficult to establish a causal relationship between alendronic acid and pancreatitis, as the case reports contain limited data. However, in one of the case reports, the patient had been receiving alendronic acid monotherapy for 13 days when pancreatitis developed, and the complication resolved after she discontinued the drug. Furthermore, that patient did not have any additional risk factors for pancreatitis. In the remaining case reports, the onset of symptoms of pancreatitis after initiation of alendronic acid therapy ranged from 48 days to several years (data not provided for 2 patients), and the patients were elderly and female where such data were provided. One woman died, and her death was reported to be possibly drug related. The article calls for the continued reporting of other Committee (ADRAC) has received 31 reports of fatal adverse events associated with amiodarone use. 17 of these involved pulmonary events, including pulmonary fibrosis (8 reports) and pulmonary infiltration (5). The committee warns that pulmonary toxicity associated with amiodarone use can develop rapidly. It suggests that amiodarone be used at the lowest effective dose, and that the development of dyspnoea or non-productive cough in patients receiving amiodarone should be investigated immediately.

Reference:
Australian Adverse Drug Reactions Bulletin 21: 2, Feb 2002.

ANTIRETROVIRAL THERAPY (ART)

Lipodystrophy syndrome with ART under-reported in Canada

Canada. Antiretroviral therapy (ART)-related lipodystrophy syndrome is 'highly under-reported' in Canada, according to a report in the Canadian Adverse Drug Reaction Newsletter. In the article, a working case definition of lipodystrophy syndrome is described as one with at least 1 metabolic abnormality and at least 1 clinical feature, in addition to no AIDS-defining event or other serious condition, or the use of anabolic steroids, the 4 cases of ART-associated lipodystrophy syndrome that met the working definition, 3 were associated with the protease inhibitors indinavir, saquinavir and ritonavir, and the remaining report was associated with stavudine. The patients included 3 men and 1 woman, and were aged 33-56 years. The clinical features of lipodystrophy syndrome included lipodystrophy (2 patients), fat disorder (2) and enlarged abdomen (1), and metabolic abnormalities included hyperglycaemia (2), hypertriglyceridaemia (2) and diabetes mellitus (1). The article points out that the prevalence of lipodystrophy syndrome during highly-active antiretroviral therapy has been reported by retrospective studies to be between 17 and 84%. As the incidence of lipodystrophy syndrome is therefore clearly under-reported to Health Canada, the Therapeutic Products Directorate has implemented a project to promote the reporting of adverse drug reactions in patients with HIV infection.

Reference:
Canadian Adverse Drug Reaction Newsletter 12(1): 3 - 4, Jan 2002.

ARISTOLOCHIA

Safety update from Oman

Sultanate of Oman. The Directorate General of Pharmaceutical Affairs & Drug Control (DGPA&DC) in the Sultanate of Oman has made a decision to