No. 4, 2002

EDITORIAL

This issue is the last of the year 2002. This has been a particularly important year for us in the safety team in WHO with several publications and many international meetings highlighting the importance of safety monitoring of medicines. The annual meeting of National Centres participating in the WHO Programme, which was held in Amsterdam, was again a great success. Topics ranged from describing pharmaco-vigilance in developing countries to detailing the most recent advances in pharmacovigilance in developed countries.

One of the interesting topics at this meeting was a session on poisons centres. In this issue we are publishing an article based on the discussions during the meeting. It is clear that the aims of poisons centres and pharmacovigilance centres are very much the same and that much more collaboration is needed in this area. Future discussions will focus on how existing systems of surveillance used by the pharmaco-vigilance centres around the world may be used to further the objectives of the poisons centres.

The broad aim of this newsletter is to bring together recent information on drug safety and regulatory measures from around the world. To make this communication more effective and global, we take this opportunity to encourage our member countries and their pharmacovigilance centres to keep us posted for all recent drug safety observations and regulatory measures enforced in their countries; copies of regional adverse drug reactions newsletters, where available, would be particularly appreciated. We wish all our readers the very best in the year 2003.

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ACETYL-SALICYLIC ACID

New advice on aspirin use in children under 16

UK. The Medicines Control Agency in UK has announced that the restrictions on aspirin, excluding its use in children under the age of 12, should now be extended to include children up to 16 years of age. All aspirin products will carry a warning to this effect. The announcement is based on the advice of the Committee on Safety of Medicines (CSM) that the risk of Reye's syndrome, however small, exists also in children under the age of 16. Although the causes of Reye's syndrome (a disorder found almost exclusively in children and adolescents) are not clearly understood, aspirin use, in the presence of a fever, has been implicated. Therefore, children of this age group, particularly those with a fever, should be given other analgesics not associated with Reye's syndrome such as paracetamol and ibuprofen. Aspirin should not be given except on the advice of a doctor.

Reference:
Medicines Control Agency Statement 2002/0436, 22 Oct 2002. Available from URL: http://www.mca.gov.uk

ACETYL-SALICYLIC ACID

Warning about incorrect information on new approved uses

Canada. Health Canada has issued a public advisory warning Canadians about the incorrect information issued by Bayer Inc. on new approved uses for Aspirin. The advisory points out that the Bayer announcement is inaccurate in stating that Health Canada has approved the use of acetylsalicylic acid (Aspirin) for primary prevention, to reduce the risk of first attacks and strokes in individuals deemed to be at sufficient risk. The approved new indication applies only to the reduction of risk of a first non-fatal heart attack and does not apply to primary prevention of stroke. This indication applies only to the products Aspirin Tablets 325 milligrams and Coated Aspirin Daily Low Dose 81 milligrams and not to the whole range of acetylsalicylic acid (Aspirin) products. Bayer Inc. has issued a letter to healthcare professionals for the above correction.

Reference:
Health Canada Warnings/Advisories, 13 Aug 2002. Available from URL: http://www.hc-sc.gc.ca

CABERGOLINE AND OTHERS

Revised package inserts

Japan. Following reports of important adverse drug reactions the Japanese Pharmaceutical & Food Safety Bureau's Safety Division called for the package insert revisions for three drugs including cabergoline, methyprednisolone sodium succinate preparations with lactose additive and influenza HA vaccine. The manufacturers were required to include specific revisions for each drug by the end of September 2002. Other drugs requiring package insert revision for less important adverse reactions included tulobuterol and lafutidine.

Reference:
Pharma Japan 1808 / 26 Aug 2002.

EDARAVONE

Warnings about acute renal failure included in package insert

Japan. Acute renal failure has been added as an adverse drug reaction for the cerebral protective agent edaravone (Radicut Injection 30 mg, manufactured by Mitsubishi Pharma Corporation). The Pharmaceutical and Medical Devices Safety Information division of the Japanese Ministry of Health and Labour Welfare advised this addition on receiving reports of three deaths with acute renal failure as the suspected cause of death in patients treated with edaravone. Edaravone was launched in June 2001. About 99,000 patients have been prescribed this drug in the first year of marketing.

Reference:
Pharma Japan 1806/5 & 12 Aug 2002.

ERGOTAMINE TARTRATE AND CAFFEINE SUPPOSITORIES

Peripheral ischaemia with CYP 3A4 inhibitors

USA. FDA and Novartis have strengthened the labelling, including a new boxed warning and updates to the Contra-indications, Warnings, Pre-cautions and Clinical Pharma-cology sections of the prescribing information for ergotamine – caffeine (Cafergot) suppositories. The new information states that ergotamine use is contra-indicated with potent CYP 3A4 inhibitors such as ritonavir, nelfinavir, indinavir, erythro-mycin, calrithromycin, trole-andomycin, ketoconazole and itraconazole. This warning is based on the fact that CYP 3A4 inhibition elevates the serum levels of the ergotamine-caffeine preparations which in turn could lead to serious, life threatening vasospasm with cerebral ischaemia and/or ischaemia of the extremities. The full safety summary including the 'Dear healthcare professional letter' from Novartis may be accessed from the FDA website www.fda.gov/medwatch/Safety/2002/safety02.htm#caferg

Reference:
Email communication from Medwatch Automated Message Delivery System CDER MEDWATCH LISTSERV (MEDWATCH@CDER.FDA.GOV), 14 Nov 2002.

GAMELONIC ACID

Withdrawal of marketing authorizations

UK. The MCA has withdrawn the marketing authorization for two gamelonic acid containing derivatives (Epogam and Efamast) of primrose oil. These products were originally licensed for the symptomatic relief of atopic eczema in children (Epogam) and for the treatment of mastalgia (Efamast). The withdrawals have been made for reasons of inadequate standards of efficacy and not for reasons of safety. The Committee on Safety of Medicines (CSM) of the MCA has reviewed the relevant information on the products and has concluded that the data do not support the current standards of efficacy required for the authorization of these products as medicines for the treatment of eczema and mastalgia. While new stock of the products will not be supplied any longer, pharmacies are not required to clear old, existing stocks. Because there are no safety issues associated with these withdrawals, evening primrose oil will continue to be available in health food shops for those who wish to take a dietary supplement. Patients currently taking gamelonic acid products (Epogam, Epomast) have been advised to have their treatment reviewed at their next routine check up.

Reference:
News update (What's new) available from the URL: http://www.mca.gov.uk/whatsnew/epogam.htm

GEFITINIB

Reports of interstitial pneumonia may prompt review

USA. The US Food and Drug Administration (FDA) says that the Oncologic Drugs Advisory Committee might be required to review the safety profile of the anticancer agent gefitinib (AstraZeneca's Iressa) due to reports of interstitial pneumonia among patients treated with the drug. According to the FDA as many as 125 cases of interstitial pneumonia and 39 deaths have been reported since the launch of the drug in Japan for the treatment of non-small cell lung cancer.

Reference:
Pharma Times News, 5 Nov 2002. Available from URL: http://www.ptwebcast.com/newsonline/news/051102b.htm

GEFITINIB

Revised product label to include interstitial pneumonia in the warning section

Japan. The Safety Division of the Japanese Pharmaceutical and Food Safety Bureau has directed AstraZeneca to revise the labelling of their product Gefitinib, an antineoplastic agent, to include interstitial pneumonia in the warning section of the product insert. The company has also been directed to release this Emergency Safety Information to all medical institutions and health professionals. The above order was issued in view of the number of cases of pulmonary disorders, including interstitial pneumonia that have been reported with the drug since July 2002. The company has made the necessary revision and is in the process of distributing this safety information to the appropriate health sectors.

Reference:
MHLW Press Release, 15 Oct 2002.

IMATINIB

Additional adverse reactions reported

Japan. There has been one report of a death suspected to be caused by pancytopenia or pneumonia in a patient treated with imatinib mesylate (Glivec), an orphan drug approved in the treatment of chronic myeloid leukaemia in Japan. Based on this and other reports Japan's Ministry of Health and Labor Welfare has advised the manufacturer (Novartis Pharma) to add pancytopenia, interstitial pneumonia and serious dermatological symptoms (mucocutaneous ocular syndrome, toxic epidermal necrosis, etc) to the Clinically Significant Adverse Reactions section for imatinib mesylate (Glivec). It is estimated that about 3000 patients have used imatinib mesylate (Glivec) since it was launched in December 2001.

Reference:
Pharma Japan 1802/8 July 2002.

ISOTRETINOIN

Labelling changes

USA. Roche has issued a letter to health professionals advising of several recent changes to the labelling of isotretinoin (Accutane) in the US. Based on post-marketing safety reports, aggressive and/or violent behaviours have been added to the list of events that may be caused by isotretinoin (Accutane), and prescribers are advised to exercise caution when prescribing isotretinoin (Accutane) to patients receiving systemic corticosteroids or phenytoin. In addition, a new table has been added to the boxed Contraindications and Warnings to clarify circumstances when pregnancy tests and `Accutane' Qualification Stickers are necessary. Information specific to the paediatric population has been added advising prescribers to use caution when prescribing isotretinoin (Accutane) to patients with a genetic predisposition for age-related osteoporosis or a history of childhood osteoporosis conditions, osteomalacia or other disorders of bone metabolism. It is noted that, in studies of paediatric patients treated with isotretinoin (Accutane), 29% of patients developed back pain and 22% experienced arthralgias. A statement regarding long-term

use has also been added advising that isotretinoin (Accutane) be given at the recommended doses for no longer than the recommended duration.

The changes involve the Warnings and related sections of the professional labelling, the paediatric labelling (professional and patient) and the boxed Contraindications and Warnings of the professional labelling.

Reference:

US Food and Drug Administration Internet Document, 4 Nov 2002. Available from URL: http://www.fda.gov

LEPIRUDIN

Fatal anaphylactic reactions

Europe. The European Agency for the Evaluation of Medicinal Products (EMEA) has issued a public statement that severe anaphylactic reactions have been reported in patients receiving lepirudin (Refludan). Lepirudin is a recombinant hirudin indicated as an anticoagulant in adult patients suffering from heparin-associated thrombocytopenia (HAT) type II with thrombo-embolic disease mandating parenteral antithrombotic treatment. Seven reports were received with the reactions occurring on re-exposure to lepirudin (Refludan) in six of them. Five of the patients died. In several of the reported cases the drug was prescribed outside the approved therapeutic indication. The EMEA statement reiterates the original approved indication of lepirudin (as mentioned above) and emphasises that allergic reactions including anaphylaxis could occur with the product which could be fatal in patients re-exposed to lepirudin (Refludan) in a second or subsequent treatment course. Treatment with lepirudin (Refludan) should be undertaken only in those settings where adequate medical assistance is readily available and where there is access to treatment for anaphylactic shock. Alternative treatment options should be considered in patients with previous exposure to lepirudin, other hirudins or hirudin analogues.

Canada. Berlex Canada Inc, the manufacturer of lepirudin (rDNA) for injection (Refludan), in consultation with Health Canada, has issued a letter advising health professionals of similar safety information in Canada. Revised prescribing information will be distributed once approved by Health Canada.

The WHO, Geneva issued an alert to member countries, based on the EMEA statement, detailing the risks associated with lepirudin administration.

Reference:

1. *EMEA Public Statement (EMEA/H/25175/02/Rev2/en), sent by facsimile 28 Oct 2002.*
2. *'Dear Healthcare Professional' letter from Berlex Canada Inc, 30 Oct 2002. Available from URL: http://www.hc-sc.gc.ca*
3. *WHO Information Exchange System Alert No. 107 (Drug Alerts), 29 Oct 2002. Available from URL: http://www.who.int/medicines*

MEFLOQUINE

Contraindicated for prophylaxis in patients with major psychiatric disorders

USA. FDA and Roche strengthened the Contra-indications, Warnings, Pre-cautions and Adverse Reactions sections of the product label for mefloquine (Lariam), the anti malarial drug to include the following additional information.

- Mefloquine is contraindicated in patients with active depression, a recent history of depression, generalized anxiety disorder, psychosis or schizophrenia or other major psychiatric disorders or with a history of convulsions.
- During prophylactic use, if psychiatric symptoms such as acute anxiety, depression, restlessness or confusion occur, these may be considered prodromal to a more serious event. In these cases the drug must be discontinued and an alternative medication should be substituted.

Healthcare professionals have been notified for the above additions.

Reference:

1. *Automated email message from CDER MEDWATCH LISTSERV (MEDWATCHLIST@CDER.FDA.GOV), 4 Oct 2002.*
2. *'Dear Doctor' letter from Roche Laboratories Inc, Sept 2002. Available from URL: http://www.fda.gov/medwatch/SAFETY/2002/lariam_deardoc.htm*

PARECOXIB

Risk of serious hypersensitivity and skin reactions

Europe. The European Medicines Evaluation Agency (EMEA) issued a public statement on parecoxib sodium (Dynastat/Rayzon/Xapit) concerning the risk of serious hypersensitivity and skin reactions. Parecoxib sodium is indicated in the short-term treatment of post-operative pain. The EMEA statement is based on the fact that serious reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme and exfoliative dermatitis as well as anaphylaxis angioedema have occurred with valdecoxib and that these reactions could also occur with parecoxib, the prodrug of valdecoxib. Some of the reactions have occurred in patients with a history of allergic type reactions to sulfonamides. The statement reflects the following:

- Physicians should note that parecoxib sodium (Dynastat/Rayzon/Xapit) is contra-indicated in patients with a history of hypersensitivity to sulfonamides.
- Patients with known allergic reactions to sulfonamides

may be prone to, and should be aware of, severe side effects with parecoxib sodium (Dynastat/Rayzon/Xapit).

Relevant changes to the prescribing and patient information for parecoxib are posted on the EMEA website.

Reference:
EMEA Public Statement (EMEA/25175/02), 22 Oct 2002. Available from URL: http://www.emea.eu.int

PAROXETINE

Change in patient leaflet wording

Ireland. The Irish Medicines Board has instructed Glaxo-Smithkline, the manufacturer of paroxetine hydrochloride (Seroxat), to replace the product at wholesale level with a new batch containing the currently approved patient information leaflet. The IMB has clarified that this is not a safety, efficacy or quality related move but only refers to a change in the patient information leaflet wording. A review by Irish and the EU Experts concluded that patient information should include a reference to suicidal behaviour and depression associated with paroxetine in the first few weeks of treatment. Patients experiencing distressing thoughts and suicidal ideations are advised to inform their physicians immediately and are advised to continue therapy for as long as recommended by their doctors.

Reference:
Seroxat Press Release, 16 Oct 2002. Available from URL: http://www.imb.ie/news

PHLEBOTONICS

Spain reassesses risk-benefit of oral vascular disorder therapies

Spain. Spanish authorities have withdrawn the marketing authorization for a number of oral vascular disorder therapies (phlebotonics) and restricted the authorised indications of those remaining on the market. These measures follow a risk-benefit reassessment of all oral vascular disorder therapies conducted by the Agencia Española del Medicamento. Products withdrawn by the agency were considered to have an unfavourable risk-benefit due to a lack of proven efficacy and included products containing diosmin, horse chestnut extract, naftazone and troxerutin. Calcium dobesilate has been restricted to the treatment of diabetic retinopathy, while all other oral vascular disorder therapies remaining on the market are now only authorised for the short-term relief (2–3 months) of oedema and other symptoms of chronic venous insufficiency.

Reference:
Spanish Medicines Agency Document (Ref 2002/09), 10 Sept 2002. Available from URL: http://www.agemed.es.

PIPER METHYSTICUM

Update on regulatory measures on kava products

Further to the update published in the WHO PN Issue No 3, 2002, the following measures have been noted worldwide on kava related withdrawals.

Singapore[1]. In January 2002 kava containing products promoted for relaxation, sleeplessness and bladder and digestive tract disorders were voluntarily withdrawn in Singapore. Although no kava-associated serious hepatic adverse events have been reported in Singapore, the Health Agency in Singapore is 'proceeding to gazette kava-kava and its active constituents as poisons under the Poisons Act' which will prohibit the importation and sale of kava-containing health products.

UK[2]. In July 2002, seven months after the voluntary withdrawal of all Piper methysticum (popular name kava) products in UK, the Committee on the Safety of Medicines (CSM) advised the Medicines Control Agency (MCA) to revoke licenses for all products containing the herbal ingredient. The banning order followed the CSM conclusion, based on available reports, that the risk-benefit ratio for products containing kava is not acceptable. The MCA is currently aware of 68 cases worldwide of liver problems suspected to be associated with kava. There have been three cases of liver toxicity in the UK suspected to be due to consumption of kava.

Australia[3]. In August 2002 Australia's medicines safety regulator, the Therapeutic Goods Administration (TGA) initiated a voluntary recall of all complementary medicines containing the herb kava. The action follows the death of a woman in Australia who used a medicine containing kava. The woman had been taking several complementary medicines, one of which contained kava. She presented with liver failure within 4 months of taking this product. The TGA will undertake a further evaluation of the use of kava to determine other regulatory measures, in addition to the voluntary recall.

Canada[4]. On 21 August 2002 Health Canada issued a warning on kava requiring a stop-sale of all kava-containing products and a recall of these products from the Canadian market. This measure comes in the wake of reports associating the use of kava with serious liver function received by Health Canada and several foreign regulatory agencies. Consumers have been advised to check the label of any herbal or food products and to discontinue the use of such products if found to contain kava. Health Canada will be establishing an Expert Advisory Panel to determine under what conditions kava might be allowed to return to the market.

Reference:
1. *Adverse Drug Reaction News 4: 3, Aug 2002.*

2. *The Pharmaceutical Journal, Pg 128, Vol. 269, 27 July 2002.*
3. *Australia's Therapeutic Goods Administration Media Release (TW20/02), 15 Aug 2002.*
4. *Health Canada Warnings and Advisories, 21 Aug 2002. Available from URL: http://www.hc-sc.gc.ca*

RABEPRAZOLE

Adverse reactions section updated

Japan. One death suspected to be caused by interstitial pneumonia in a patient treated with sodium rabeprazole (Pariet) has been reported by the manufacturer in Japan. Based on this and other related reports the Japanese Ministry of Health and Labour Welfare has advised the company to add interstitial pneumonia to the Clinically Significant Adverse Reactions section in the product insert for rabeprazole (Pariet). Rabeprazole is a proton pump inhibitor that was launched in the Japanese market in 1997 and is used by as many as 500,000 patients a year.

Reference:
Pharma Japan 1802/8 July 2002.

SERTINDOLE

Move to reintroduce

Europe. Sertindole (Serdolect) is to be reintroduced in Europe with restrictions on its use following a re-evaluation by the UK Committee on Safety of Medicines (CSM) and the European Committee of Proprietary Medicinal Products (CPMP), states an important safety message on the UK Medicines Control Agency (MCA) website. Sertindole was initially licensed in the UK in May 1996 but was withdrawn throughout Europe in 1998 due to concerns about possible risks of cardiac arrhythmias. In 2001, the CSM and the CPMP considered new preclinical and epidemiological data in their re-evaluation of the product. The European Commission decided that sertindole licenses could be reinstated across Europe but that its use would initially be restricted to patients enrolled in clinical studies in order to ensure that all patients receiving sertindole are carefully selected and monitored. The MCA and CSM will carefully monitor the safety of the reintroduction of sertindole.

Reference:
Medicines Control Agency. Important safety message: restricted re-introduction of the atypical antipsychotic sertindole (Serdolect). 10 Sep 2002. Available from URL: http://www.mca.gov.uk

SLIM 10

Withdrawal due to presence of undeclared substances

Singapore. 'Slim 10', an agent marketed in December 2001 as a Chinese Proprietary Medicine for slimming, was withdrawn in April 2002 after it was found to contain undeclared substances (WHO Pharmaceuticals Newsletter No. 3, 2002). In March 2002 the first report of acute hepatitis associated with 'Slim 10' was received by Singapore's Pharmacovigilance Unit and 3 other reports, 2 of hyperthyroidism and 1 of menstrual irregularities, were subsequently received, prompting an investigation by the Singapore Health Sciences Authority (HSA). The investigation revealed that 'Slim 10' contained nicotinamide, fenfluramine and thyroid gland components, and the HSA has initiated action against the parties involved in its sale and distribution. The HSA and the Expert Panel on Adverse Drug Reactions (ADRs) thank healthcare professionals for alerting them to this drug safety problem, which allowed for 'timely regulatory action'.

Reference:
Adverse Drug Reaction News 4: 1, Aug 2002.

TAMOXIFEN

Important safety information

Canada. Further to the boxed warning added to the product label by the manufacturer under advice from the US FDA (WHO Pharmaceuticals Newsletter No. 3, 2002), Health Canada has posted a message on the use of tamoxifen and the incidence of uterine malignancies, stroke and pulmonary embolism. The message was derived from the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention (NSABP P-1) study with women at high risk for breast cancer or having ductal carcinoma in situ (DCIS) receiving tamoxifen in the prevention setting. Higher incidences of uterine malignancies, stroke and pulmonary embolism were associated with tamoxifen treatment compared to that of placebo in the patient population of this study. Health Canada emphasises that the use of tamoxifen in the prevention setting is not an approved indication in Canada. The current approved indication for tamoxifen in Canada is in the treatment of breast cancer in oestrogen-receptor positive tumors where the benefits of using tamoxifen have been judged to outweigh the potential risks.

Reference:
Health Canada posting, 7 Nov 2002. Available from URL: http://www.hc-sc.gc.ca

TICLOPIDINE

Physicians urged to conduct medical tests

Japan. The Japanese Pharmaceuticals and Food Safety Bureau's Safety Division has directed the manufacturer of ticlopidine hydrochloride to send out letters to physicians urging them to conduct medical tests every two weeks, for two months, after starting ticlopidine therapy in patients. This advice issues in the wake of adverse reactions such as thrombotic

thrombocytopenic purpura (TTP), granulocytopenia and serious hepatic dysfunction, including deaths. Although these adverse reactions have already been reported by the manufacturer and the Warnings section in the product insert has been appropriately modified, this letter is being issued as an additional measure to sensitise physicians to the problem of adverse reactions with ticlopidine. 13 cases of TTP (with 5 fatalities), 35 granulocytopenia (with 6 fatalities) and 97 cases of serious hepatic dysfunction (with 6 fatalities) have been reported between July 2001 and June 2002.

Reference:
Pharma Japan 1806/5 & 12 Aug 2002.

TRASTUZUMAB

Cardiotoxicity highlighted

Norway. The Norwegian Medical Products Agency has highlighted the need for careful monitoring of patients receiving trastuzumab (Herceptin) due to the risk of cardiotoxicity associated with the drug. Trastuzumab, a monoclonal antibody used in the treatment of metastatic breast cancer, has been associated with cases of cardiotoxicity, the risk of which is greatest when trastuzumab is used in combination with anthracyclines. Patients who have previously received anthracyclines are also at risk of cardiotoxicity. Due to trastuzumab's long half-life of approximately 28.5 days, it can remain in the circulation for up to 24 weeks after treatment is stopped. In order to minimise the risk of cardiotoxicity, anthracycline-based antineoplastic therapy should be avoided for up to 24 weeks after stopping trastuzumab therapy. It is recommended that cardiac assessments are carried out prior to and during trastuzumab therapy and that discontinuation of the agent should be strongly considered in patients who develop cardiotoxicity. In light of this information, a new summary of product characteristics (SPC) has been prepared and Roche is to send letters to specialists advising them of the need for careful monitoring of patients receiving trastuzumab. The agency asks all doctors who use trastuzumab to carefully study the SPC.

Reference:
Nytt om Legemidler 25: 3, Jun 2002.

UROKINASE

Product reintroduced with important safety information update

USA. The US FDA has approved the reintroduction of urokinase (Abbokinase) for the treatment of pulmonary emboli. Abbott Laboratories has issued a 'Dear Healthcare Professional' letter advising of the reintroduction and of important changes to the product labelling. The Warnings section of the labelling has been strengthened to include post-marketing reports of anaphylaxis and class information regarding potential cholesterol embolsation, and the 'Adverse Reactions' section now incorporates safety information from both Abbott's clinical trials and post-marketing experience. Urokinase (Abbokinase) has been approved solely for use in the lysis of massive pulmonary emboli and pulmonary emboli accompanied by unstable haemodynamics.

Reference:
Food and Drug Administration. 2002 Safety alert - Abbokinase (urokinase), 10 Oct 2002. Available from URL: http://www.fda.gov

CLOZAPINE

Close monitoring for cardiac events emphasized

UK. The association between clozapine (Clozaril) and myocardial disease is well recognised. However, the findings of a recent re-evaluation of serious clozapine-associated adverse cardiac events has resulted in a strengthening of warnings regarding clozapine use. The Committee on Safety of Medicines (CSM) and the Medicines Control Agency (MCA) advise that patients in whom persistent tachycardia develops should be closely monitored, and that clozapine should be discontinued if myocarditis or cardiomyopathy is suspected. They stress that patients who develop clozapine-induced myocarditis or cardiomyopathy should not be re-exposed to clozapine.

Reports in WHO file:
Myocarditis 171, cardiomyopathy 232

Reference:
Current Problems in Pharmacovigilance [Online] 28: 8, Oct 2002.
Available from URL:
http://www.mca.gov.uk.

CORTICO-STEROIDS

Risk of adrenal suppression in paediatric population

UK. The Committee on Safety of Medicines (CSM) and the Medicines Control Agency (MCA) remind prescribers of the risks of adrenal suppression in children receiving inhaled corticosteroids. Adrenal suppression is a dose-related class effect of all inhaled corticosteroids and prescribers are strongly advised not to exceed the paediatric licensed dosages. They are reminded that, because of its greater potency, fluticasone should normally be used at half the dose of budesonide or beclomethasone.

Reference:
Current Problems in Pharmacovigilance 28: 7, Oct 2002.

CYPROTERONE

More incidence of venous thrombo-embolism than with low-estrogen preparations

UK. Cyproterone (Dianette) is indicated for women with hirsutism, or acne which is refractory to other treatments. The Committee on Safety of Medicines (CSM) and the Medicines Control Agency (MCA) remind prescribers that cyproterone is not authorised for the sole purpose of oral contraception, and they note the increased incidence of venous thromboembolism in 'Dianette' users compared with users of oral contraceptives with a low estrogen content.

Reports in WHO file:
Venous thrombosis 11, thromboembolism 1

Reference:
Current Problems in Pharmacovigilance [Online] 28: 9-10, Oct 2002.
Available from URL:
http://www.mca.gov.uk.

EPOETIN ALFA

Pure red cell aplasia

Australia. The Australian Adverse Drug Reactions Advisory Committee (ADRAC) has received 12 reports of pure red cell aplasia (PRCA) associated with the use of epoetin alfa (Eprex) in patients with renal failure. The patients were aged from 28–76 years and the duration of epoetin alfa use, where known, was from 4–13 months. The committee notes that the antierythropoietin antibodies which develop in epoetin alfa-induced PRCA are known to cross-react with all other erythropoietin products, including darbepoetin (Aranesp), which was released in Australia in November 2001. It is not known whether PRCA will develop in patients receiving darbepoetin alone. The sponsor of epoetin alfa (Eprex) has recently issued a 'Dear Healthcare Professional' letter, recommending that epoetin alfa (Eprex) be administered intravenously to reduce the risk of antibody formation. ADRAC says that suspected cases of PRCA should be confirmed by antibody testing and/or bone marrow examination. In such cases, epoetin alfa should be discontinued and patients should be switched to another therapy but not to another erythropoietin.

Reports in WHO file:
Pure red cell aplasia 39

Reference:
Australian Adverse Drug Reactions Bulletin 21: 11, Aug 2002.
Available from URL:
http://www.health.gov.au.

OESTROGENS AND MEDROXY-PROGESTERONE

New information to provide prescribing guidance

USA. Wyeth Pharmaceuticals in consultation with the US FDA has issued a letter to healthcare professionals about important safety update in the labelling of conjugated estrogens/ medroxyprogesterone acetate tablets (Prempro, Premphase) and conjugated oestrogen tablets USP (Premarin). The labelling changes reflect new data, primarily from the Women's Health Initiative (WHI). Several sections have been modified including the Indications and Usage, Contraindications, Warnings, Precautions and Dosage and Administration sections. The letter notes that the product indications remain the same. However, because of the potential of increased risks of cardiovascular events, breast cancer and venous thrombo-embolic events, use of these conjugated products should be limited to the shortest duration consistent with the treatment goals and risks for the individual

woman and should be periodically re-evaluated. When used solely for the prevention of postmenopausal osteoporosis, alternative treatments should be carefully considered. Wyeth Pharmaceuticals has also issued a patient information leaflet summarizing the major risks and benefits of treatment with conjugated oestrogen tablets (Premarin).

Reference:

1. *'Dear Healthcare Professional' letter from Wyeth Pharmaceuticals, 28 Aug 2002. Available from URL: http://www.fda.gov/medwatch/SAFETY/2002/premarin_deardoc.pdf*
2. *Patient Information leaflet. Available from URL: http://www.fda.gov/medwatch/SAFETY/2002/premarin_PPI.pdf*

GLITAZONES

Update on adverse drug reactions in Canada

Canada. The oral thiazolidinedione drugs rosiglitazone (Avandia) and pioglitazone (Actos) have been associated with a number of reports of adverse events in Canada between their time of marketing in March and August 2000, respectively, and March 2002, according to a report in the Canadian Adverse Drug Reaction Newsletter. During this time, a total of 282 suspected adverse reactions to rosiglitazone have been reported to Health Canada. Of these reports, 134 were considered serious. There were 60 reports of cardiovascular disorders, including 36 reports of heart failure, and 16 reports of liver and biliary diorders; 10 reports had a fatal outcome. For pioglitazone, 29 reports of suspected adverse reactions have been received, 24 of which were considered serious including 8 reports of cardiovascular disorders (4 of heart failure), 1 report of liver and biliary disorders and 1 report with a fatal outcome. It is noted that, although people with type 2 diabetes are at increased risk of heart failure, diabetic patients receiving glitazones appear to be at greater risk of heart failure than diabetic patients not using glitazones. In order to minimise the risk of serious adverse events, physicians are reminded to follow all the recommendations and monitoring guidelines listed in the product information, which lists serious hepatic impairment and acute heart failure as contraindications for the use of rosiglitazone and pioglitazone.

Reference:

Canadian Adverse Drug Reaction Newsletter 12: 2-3, July 2002.

INDAPAMIDE

Reports of hyponatraemia

Australia. Since the release of indapamide in the mid 1980s, the Australian Adverse Drug Reactions Advisory Committee (ADRAC) has received 164 reports of hyponatraemia associated with its use, making it the most commonly reported cause of hyponatraemia in the 30-year history of ADRAC. Of the 164 reports of hyponatraemia, 68 reports also described hypokalaemia. Most patients were elderly (88% were aged ≥65 years) and the majority were women (82%). In 75 of 129 cases with a documented serum sodium level, the level was ≤120 mmol/L. ADRAC notes that indapamide is also available in combination with perindopril (Coversyl Plus). Despite the lower dose of indapamide in this product compared with the standard indapamide tablet (1.25 vs 2.5 mg), there have been 5 reports of hyponatraemia associated with 'Coversyl Plus' in the first 5 months of 2002. The Committee recommends that indapamide be prescribed with caution, and that serum sodium levels should be measured promptly if the patient displays any change in conscious or mental state.

Reports in WHO file: Hyponatraemia 474

Reference:

Australian Adverse Drug Reactions Bulletin 21: 11, Aug 2002. Available from URL: http://www.health.gov.au.

ISOTRETINOIN

Avoiding teratogenicity

New Zealand. The first New Zealand case of embryopathy was recently reported to the Centre for Adverse Reaction Monitoring (CARM). The woman had been taking isotretinoin 40 mg/day for three months when she became pregnant. Antenatal ultrasound showed no abnormalities but the child was born with typical retinoid embryopathy including heart, ear and oesophageal malformations. Based on this, the NZ Medicines and Medical Devices Safety Authority (Medsafe) has issued a Prescriber Update Article, once again reminding that effective contraception is recommended for all women of childbearing age for whom isotretinoin is a treatment option. Physicians are advised to counsel all female patients about the very significant risk of teratogenicity. They should verify patient's sexual history, irrespective of age, race or religious beliefs, conduct a pregnancy test in women of childbearing age and provide appropriate advice on effective contraception.

USA. Roche Laboratories, in consultation with US FDA has added a new table to clarify those circumstances where pregnancy tests are required in women in whom isotretinoin (Accutane) treatment is an option.

The World Health Organisation database has 691 reports of foetal disorders associated with isotretinoin, including 35 of multiple malformations.

Reference:

1. *Prescriber Update Articles, Aug 2002. Available from URL: http://www.medsafe.govt.nz/profs/Puarticles/teratogen.htm*

2. *Letter from Roche Laboratories, Sept 2002.*
   Available from URL:
   http://www.fda.gov/medwatch/SAFETY/2002/accutane_deardoc_10-2002.htm

LEVOFLOXACIN

Reports of tendinopathy

Belgium. The Belgian Pharmacovigilance Centre has received 161 reports of levofloxacin (Tavanic) - associated tendinopathy, including 68 reports of tendon rupture, since the drug was marketed in 2000 through to 16 April 2002. The average age of patients with levofloxacin-associated tendinopathy was 69 years and about half were receiving concomitant corticosteroid treatment. The average time between the start of levofloxacin treatment and the development of tendinopathy and tendon rupture was 8.4 and 10 days, respectively, with tendon rupture occurring within 48 hours in some cases. The centre notes that, although data from spontaneous reports are insufficient for risk comparisons, the number of cases of tendon disorders reported in association with levofloxacin to date is much higher than that for ciprofloxacin (22 cases), norfloxacin (8), ofloxacin (63) and pefloxacin (16), all of which have been on the market for > 10 years. The most common indications for which levofloxacin was prescribed in patients who experienced tendon rupture were acute or chronic bronchitis (32%) and chronic obstructive pulmonary disease (28%); the pharmacovigilance centre reminds its readers that the outpatient prescription of levofloxacin is only justified for the treatment of community-acquired pneumonia in patients allergic to β-lactams. The centre stresses the importance of advising patients for whom levofloxacin treatment is found necessary to contact their doctor if tendon pain occurs, and points out that the increased risk associated with age and the presence of simultaneous corticosteroid therapy should be considered.

Reports in WHO file:
Tendon disorders 888

Reference:
Folia Pharmacotherapeutica 29: 63, July 2002.

OESTROGEN-ONLY HRT

Potential risk of ovarian cancer following prolonged use

New Zealand. On 17 July 2002 the Ministry of Health, New Zealand issued a Media Release in response to the United States Cancer Institute (NCI) study examining the risk of ovarian cancer in women using oestrogen – only hormone replacement therapy (HRT). The Ministry advises that women taking oestrogen-only HRT should discuss with their doctors the risks and benefits of long-term treatment with oestrogen at their next visit since the NCI study, although not conclusive, does suggest that there may be a small increase in the chance of developing ovarian cancer for women who have taken oestrogen only HRT for 10 or more years (6 per 10,000 women per year in those using oestrogen-only HRT continuously for 10 years as against 4 in 10,000 per year for women of a similar age not taking any form of HRT). Further, according to the press release, the study was conducted on patients first treated in 1970's using higher-doses than are used nowadays. It is therefore difficult to extrapolate the findings to present day, low-oestrogen HRT users. Nor is there adequate evidence to issue new prescribing advice on Oestrogen-only HRT. Nevertheless the study is further proof that prolonged use of any form of HRT should only take place on the basis of a careful assessment of the risks and benefits for each individual.

Oestrogen-only HRT is different from the combination HRT that was the subject of Women's Health Initiative study as only one hormone (oestrogen) is used. In New Zealand, oestrogen-only HRT is predominantly used only by women who have had a hysterectomy and is used less commonly than combination HRT (oestrogen and progesterone).

Reference:
New Zealand Ministry of Health Media Release, 18 July 2002.
Available from URL:
http://www.medsafe.govt.nz/hot/media/oestrogenonlyhrt.htm

OMEPRAZOLE

Interaction with clozapine

New Zealand. The Intensive Medicines Monitoring Programme (IMMP) in New Zealand has received three reports of elevation of clozapine levels when omeprazole was co-prescribed in patients already stabilised on clozapine. Seizures occurred in two of the cases; clozapine was withdrawn for four days in one and omeprazole was discontinued and clozapine dose was reduced in the other; both patients recovered with these measures. The IMMP director writes that these reports suggest that the addition of omeprazole may cause elevated plasma levels of clozapine and dose-related adverse effects. The mechanism for this interaction is not clear. However, the CYP 3A4 enzyme system might be involved since both drugs are substrates for this hepatic enzyme. Prescribers are advised to consider this potential interaction and check plasma clozapine levels if concomitant omeprazole therapy is required.

Reference:
Prescriber Update 23(3):39, 2002.
Available from URL:
http://www.medsafe.govt.nz/profs/Puarticles/ClozOmep.htm

ORAL CONTRA-CEPTIVES

Ectopic pregnancy following emergency oral contraceptive failure

New Zealand. In pregnancies occurring following progestogen-only emergency oral contraceptive (OC) failure, the possibility of ectopic pregnancy should be considered warns a Prescriber Update article recently posted on the New Zealand Medsafe website. This may occur by the same mechanism by which pregnancies in women using daily progestogen-only OCs are more likely to be ectopic than pregnancies in users of other contraceptive methods. The Centre for Adverse Reactions Monitoring (CARM) has received 3 reports of ectopic pregnancy following the use of progestogen-only emergency OCs and prescribers are reminded to advise women about the possibility of ectopic pregnancy following failure of progestogen-only emergency OCs. Women should seek prompt medical attention if, following use of a progestogen-only emergency OC, amenorrhoea or any other symptoms suggestive of pregnancy occur.

Reference:

Internet Document , 21 Oct 2002. Available from URL: http://www.medsafe.govt.nz

QUETIAPINE

Potential for medication error

Canada. AstraZeneca has alerted healthcare professionals that the antipsychotic drug quetiapine (Seroquel) and the antidepressant drug nefazodone (Serzone 5HT2) have similar-sounding proprietary names; this could result in name-confusion and dispensing errors. At the time the company had received one report of such a medication error. A similar alert was sent to healthcare professionals in the USA and the letter was posted on the US FDA website in May 2002.

Reference:

'Dear Healthcare Professional' letter from AstraZeneca, 31 Oct 2002. Available from URL: http://www.hc-sc.gc.ca

QUININE

Reports of thrombocytopenia

Australia. Since 1972, the Australian Adverse Drug Reactions Advisory Committee (ADRAC) has received 198 reports of thrombocytopenia associated with quinine, 4 of which had a fatal outcome. In 17 of the 20 reports received since the beginning of 2000, patients had platelet counts of 0−14 × 109/L; most of these patients required hospitalisation and treatment with platelet transfusions, corticosteroids or immuno-globulin. The committee notes that, in most cases, platelet levels normalise within 1 week of quinine withdrawal. As quinine-induced thrombocytopenia occurs via an immune-based mechanism, ADRAC says that patients who have developed this reaction should subsequently avoid all products containing quinine, including drinks such as tonic water. The committee also reminds prescribers that quinine is no longer recommended for the treatment of nocturnal cramps; the US FDA withdrew nocturnal cramps as an indication for all quinine products in 1995 due to a lack of evidence of efficacy, and the Australian Medicines Handbook advises against its use for this indication.

Reports in WHO-file:
Thrombocytopenia 392

Reference:

Australian Adverse Drug Reactions Bulletin 21: 10, Aug 2002. Available from URL: http://www.health.gov.au.

RISPERIDONE

Safety update in elderly dementia patients

Canada. Janssen-Ortho Inc, in consultation with Health Canada has advised health professionals of new safety information for the use of risperidone (Risperdal), an antipsychotic medication, in elderly, dementia patients. The manufacturer has notified doctors and pharmacists of reports of strokes and stroke-like events in elderly patients with dementia taking risperidone (Risperdal). Worldwide exposure to risperidone (Risperdal) in elderly, dementia patients is approximately 2.5 million patient years. From this patient population there have been 37 reports of strokes or stroke-like events (1 in Canada), including 16 deaths (1 in Canada). Generally, there appears to be an increased risk of strokes and stroke-like events in the elderly population. Physicians are advised to reassess the risks and benefits of the use of risperidone (Riperdal) in elderly patients, taking into account risk predictors for stroke in the individual patient. Patients or their caregivers should be counselled to inform their doctors of past and present medical history, including history of stroke and to immediately report all signs and symptoms of potential strokes such as sudden weakness or numbness in the face, arms or legs, and speech or vision problems.

Reference:

1. *'Dear Healthcare Professional' letter from Janssen-Ortho Inc, 11 Oct 2002. Available from URL: http://www.hc-sc.gc.ca*
2. *'Important Drug Safety Update for Consumers' from Janssen-Ortho Inc, 17 Oct 2002. Available from URL: http://www.hc-sc.gc.ca*

STATINS

Precautions will minimise risk of myopathy

UK. According to the Medicines Control Agency (MCA), the overwhelming beneficial effects of the statins clearly outweigh the low risk of myopathy. However, precautions that must be taken in order to minimise the risk of myopathy include the strict adherence to dosage instructions, identification of patients with an increased risk of myopathy, making patients aware of the risks of myopathy and of the importance of promptly reporting any potential signs or symptoms, and stopping treatment if creatine kinase levels become elevated.

Reference:

Current Problems in Pharmacovigilance 28: 8-9, Oct 2002. Available from URL: http://www.mca.gov.uk.

NIMESULIDE

Further to our earlier report (WHO Pharmaceuticals Newsletter No 3, 2002) on Spain's decision to temporarily suspend the product and, in response to the recent interest in the drug we present below some background information on nimesulide.

Nimesulide is a non-steroidal anti-inflammatory analgesic and antipyretic drug (NSAID). It is a selective cyclooxygenase – 2 (COX –2) enzyme inhibitor and is effective in the treatment of a wide range of inflammatory and painful conditions including osteoarthritis, extra-curricular disorders such as tendonitis and bursitis, post-operative pain and primary dysmenorrhoea.

Nimesulide was first marketed in Italy in 1985 and since then has been launched in about 50 countries around the world. The drug is off-patent and is marketed by a variety of firms. Several adverse reactions were reported with nimesulide during the latter half of 1998 and the early months of the year 1999[1-3].

In Portugal, in 1999, following a risk-benefit assessment, a core SPC (Summary of Product Characteristics) was approved for nimesulide. Therapeutic indications were restricted to osteoarthritis, extra-articular rheumatic conditions, post-operative and/or post-traumatic pain and inflammation, oral/ dental inflammatory conditions and dysmenorrhoea. The core SPC also stated that

- Nimesulide should not be used for periods longer than 7 days in the treatment of acute pain
- Use in patients with hepatic failure is contraindicated
- Liver function should be monitored in patients with previous history of hepatic injury
- Precaution is needed when nimesulide is used with other drugs that may cause hepatic injury

The Portuguese marketing authorizations for paediatric nimesulide formulations were suspended in March 1999[1,2].

The Register of Adverse Reactions of the Finnish National Agency for Medicines (NAM) for the year 2000 shows that the majority of adverse drug reactions (ADRs) among non-steroidal anti-inflammatory drugs were associated with nimesulide; over half of the reports were associated with liver reactions[4]. According to NAM's research director Dr Erkki Palva, so far 109 reports of adverse events (66 of which related to liver toxicity) and one fatality have been reported since the drug received marketing authorization in Finland in 1997[5]. Finland has temporarily suspended the sale, supply and distribution of nimesulide products while NAM and the concerned firm continue to investigate[6]. The European Medical Products Evaluation Agency (EMEA) has also initiated a safety procedure to establish causality with nimesulide. In May 2002 the Spanish Regulatory Authority temporarily withdrew nimesulide products from the Spanish market pending conclusions from the EMEA evaluation[7].

Nimesulide was authorised in Ireland in 1995. The potential for hepatic effects with nimesulide has been an on-going concern to the Irish Medicines Board (IMB) which reviewed the drug's safety in 1999 and updated the prescribing information at that time to reflect concerns of hepatotoxicity. Following the IMB's review in 1999 the concerned company in Ireland was requested to perform post-marketing authorization studies to address the safety issues with nimesulide. The interim data provided by the company on 1,212 patients indicate that, at this stage there is no apparent difference in the safety profiles of nimesulide, diclofenac and ibuprofen[8].

Nimesulide has never been marketed in some countries such as the USA and Australia. In South East Asia the drug enjoys variable regulatory status. For example, in Thailand, only the tablet form of the drug is available; the suspension form was voluntarily withdrawn. In India, both tablet and gel forms have been available for almost 10 years. Although some hepatic adverse reactions have been reported with nimesulide to the Indian National Pharmaco-vigilance Centre, exact causality assessment is difficult since the patients were also using other analgesics at the time.

The Drug Controller General of India (DCGI) has asked manufacturers of nimesulide to submit the complete reports of Adverse Drug Reaction within a month[9,10].

Nimesulide is marketed in Brazil as a prescription drug. The drug is available as tablets, paediatric suspensions, suppositories and paediatric drops.

Reference:

1. *Nimesulide ADR controversy in Portugal. Scrip 1999, No.2406:8.*
2. *Portugal suspends paediatric nimesulide. Scrip 1990, No.2431:20.*
3. *Israel nimesulide suspension inquiry. Scrip 1999, No.2434:23.*
4. *ADR News of National Agency for Medicines (TABU 2.2001), p.46. Available from URL: http://www.nam.fi/uploads/english/tabu_eng_2001*
5. *As reported by Reuters Health, London, 20 March 2002. Available from URL: http://dispatch,mail-list.com/archives/hbv_research*
6. *Press Release from Finnish National Agency for Medicines, 15 March 2002. Available from http://www.namfi/english/news*
7. *WHO Pharmaceuticals Newsletter No.3, 2002.*
8. *Irish Medicines Board Drug Safety Newsletter, Issue 15, July 2002.*
9. *National Pharmacovigilance Centre (India) Newsletter, vol.1, No.1, Dec 1999.*
10. *News Item in Daily Excelsior, New Delhi, 30 Oct 2002. Available from URL: http://www.dailyexcelsior.com/02oct31*

Poisons Centres and Adverse Drug Reaction Reporting - opportunities for greater collaboration

Lesley Onyon, International Programme on Chemical Safety (IPCS)

Discussion on potential collaboration between poisons units and adverse drug reaction reporting (ADR) centres got off to a good start at the WHO Annual Meeting of National Centres participating in the WHO Programme for International Drug Monitoring, in October 2002.

At the molecular level, the human body makes no distinction between pharmaceuticals, pesticides and other exogenous chemicals - each has the potential to interact with the same metabolic pathways and mechanisms for gene transcription.

This fundamental fact is often overlooked in day-to-day work. Sophisticated and separate regulatory arrangements exist for the registration and use of pharmaceuticals, pesticides and other chemicals in commercial use. Getting to grips with these systems can be so daunting that it is too easy to lose sight of what we have in common.

The IPCS provides an international focal point for poisons information, prevention and management. These activities are at the heart of IPCS which is a co-operative programme of the WHO, the International Labour Organization (ILO) and the United Nations Environment Programme (UNEP). IPCS is designed to establish the scientific basis for the assessment of risk to human health and the environment from exposure to chemicals and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The establishment and strengthening of poisons centres is one of the priorities adopted by Governments in the follow-up and implementation of recommendations of the United Nations Conference on Environment and Development, held in Rio de Janeiro in 1992. This Conference, otherwise know as the Earth Summit, provides in Agenda 21, Chapter 19, the blueprint for the environmentally sound management of chemicals at international, regional and national levels.

IPCS objectives for poisons information, prevention and management

- To promote the development of poisons centres in countries that do not have them.
- To strengthen existing centres.
- To provide information and training.
- To provide tools to facilitate the collection of internationally-harmonized human data. E.g. INTOX Databases Management System.
- To improve the evidence base for medical assessment and management of chemically exposed persons.
- To strengthen the global poisons centre network, providing mutual assistance and support, and developing a global surveillance and response system for toxic outbreaks.

In a survey conducted in 2000, 285 poisons centres had been established in 43% of WHO Member States. However there were differences in the facilities provided and the extent of the country covered by a particular poisons centre. In 2002, it was estimated that a further 8 countries had newly established a poisons centre and 9 had strengthened their existing capacity by opening new centres within the country or upgrading existing facilities. Additional 8 countries had started work to develop new centres.

The effort necessary to establish a poisons centre is high. Given that the infrastructure and professional resources needed for the establishment of national adverse drug reaction reporting (ADR) centres are similar, there is potential value in joining forces to establish new centres and strengthen others, particularly in small countries where resources are limited. Indeed, when the countries where ADR monitoring centres and poisons centres are located is examined it can be seen that there are relatively large number of countries with both types of centres (sometimes combined) e.g. Tanzania, France, Uruguay, but there are others where countries have either poisons centres or ADR centres. This is true in the Americas and Eastern and Central Europe. There are still others where neither type of centre exists.

As well as capacity building activities there are other issues where ADR and poisons centres have common interests. IPCS has recently established a human data initiative to ensure that the best use is made of existing human data for risk assessment purposes. Poisons centres are often uniquely placed to monitor the pattern, incidence and severity of exposures to chemicals and to detect new trends and emerging patterns of human health effects. In this area there are opportunities for poisons centres to learn from the systems used for surveillance by ADR monitoring centres.

The IPCS Human Data Initiative also provides an opportunity to refine and help develop new methodological

approaches for risk assessment. Clinical data collected from poisons centre treatment units can be used to provide the basis for in-depth risk assessments and to validate some of the traditional approaches used to extrapolate from animal toxicity tests to predict human responses. One example of this would be to refine the use of uncertainty factors used to establish margins of safety in risk assessment.

Many of these methodological issues are also relevant to understanding adverse drug reactions. The experience gained from the development and application of genomic technologies for designing safer medicines provides another opportunity for collaborative work. In toxicology there is a growing awareness of genomics as a potential tool for risk assessment and for improving knowledge and approaches for the identification of susceptible human sub-population groups.

The Uppsala Monitoring Centre (UMC, WHO Collaborating Centre for International Drug Monitoring) will hold its eighth international pharmacovigilance training course in Uppsala, Sweden from 12-23 May 2003. The course aims to support the development of programmes for spontaneous adverse reaction reporting and will benefit healthcare professionals (physicians, pharmacists, nurses) engaged or, soon to be engaged in the practical operation of programmes for spontaneous adverse reaction reporting in a hospital, regulatory or industry setting.

Application forms and course details may be downloaded from the UMC website http://www.who-umc.org. or by writing to Ms Anneli Lennartsson at

the Uppsala Monitoring Centre
Stora Torget 3
S-753 20 Uppsala
Sweden

Completed application forms should reach the UMC before 10 March 2003.