EDITORIAL

This first issue of the newsletter for 2003 reaches you with many good wishes and hopes of further collaboration in raising awareness in drug safety and related issues. Several activities are being planned for 2003 to promote efforts in public health and pharmacovigilance programmes. In addition, the 8th international pharmacovigilance training course will be offered in Sweden, in May 2003 and the annual meeting of the national centres for pharmacovigilance will take place in December, in India. Details of the national centres’ meeting and the International Conference of Drug Regulatory Authorities (ICDRA) are on page 10.

In this issue you will find some reports and regulatory measures for nefazodone, a drug which is currently causing concern with reports of hepatotoxicity from around the world.

The feature article reflects the difficulties with terminologies in classifying some psychoactive substances as drugs of abuse. Clearly this is an area that will continue to evolve as issues of methodology, definitions and key terms are discussed and debated upon for a global consensus.
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CISAPRIDE
Highest strength tablets being withdrawn

Australia. The Australian Prescriber (Vol. 25, No.6, 2002) advises readers that the manufacturer of cisapride has decided to withdraw the highest strength of cisapride tablets (20mg). The product information has also been revised. All patients now require measurements of renal function and ECGs before and during treatment. Follow up measures should be undertaken every three months. Concerns about cardiac arrhythmias led to restrictions being placed on the prescription of cisapride. There are few gastrointestinal conditions which require treatment with cisapride. It should only be tried if patients with gastroparesis or severe gastro-oesophageal reflux have not responded to other drugs.

Reference:

CODEINE PREPARATIONS
Products withdrawn due to problems of misuse

Malaysia. The Drug Control Authority in Malaysia has announced that liquid codeine-containing preparations will not be available after 31 December 2002. This announcement follows its decision to cancel the registration of these products due to the growing problem of codeine misuse and abuse in Malaysia.

OESTROGENS/ MEDROXY PROGESTERONE ACETATE
Boxed warning against use for the prevention of cardiovascular disease

USA. In August 2002 Wyeth Pharmaceuticals, in close cooperation with the US FDA made important revisions to the labelling of conjugated oestrogens and medroxy-progesterone preparations (WHO Pharmaceuticals Newsletter No. 4, 2002). The FDA has now carefully reviewed the results from the Women’s Health Initiative Study and has worked with Wyeth to develop a new labelling for these products (conjugated oestrogens and oestrogens and medroxy-progesterone preparations Premarin, Prempro and Premphase). The monograph for these products will now include a new boxed warning highlighting the increased risks of heart disease, heart attacks, strokes and breast cancer. The products are indicated for the following conditions:

- Treatment of moderate to severe vasomotor symptoms (such as hot flashes) associated with menopause
- Treatment of moderate to severe symptoms of vulvar and vaginal atrophy (dryness and irritation) associated with menopause. When these products are being prescribed solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
- Prevention of postmenopausal osteoporosis. When these products are being prescribed solely for the prevention of osteoporosis, approved non-oestrogen treatments should be considered; oestrogens and combined oestrogen-progesterin products should

Reference:

HERBAL
‘Woman’s Accent’ to be classified as medicinal product

UK. The Medicines Control Agency (MCA) has ruled that ‘Woman’s Accent’, an herbal product marketed in the UK, should be classified as a Medicinal Product requiring licensing. Woman’s Accent contains several ingredients such as Blessed thistle, Dong Quai, Wild Yam and Black cohosh. According to the MCA, the product was deemed to be a medicine since it claimed to relieve menstrual problems, prevent bone loss, inhibit growth of cancer cells and restore sexual function, balance progesterone and other hormone levels and to promote diuresis. These claims do not meet the criteria for exemption from licensing.

Reference:
MCA’s Final Determination issued by the Borderline Section, 30 Dec 2003. Available from URL: http://www.mca.gov.uk/ourwork/licensingmeds

MISOPROSTOL
Advice against off-label use

Malaysia. Following advice from the Malaysian Drug Control Authority, Pharmacia Corp has issued a ‘Dear Doctor’ letter advising against the off-label use of intravaginal or oral misoprostol in pregnant women for labour induction since its safety has not yet been established. In the US, the drug is approved for use with mifepristone to induce abortion in pregnancies of 49 days or less (WHO Pharmaceuticals Newsletter, No. 3, 2002).

Reference:
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only be considered for women with significant risk of osteoporosis that outweighs the risks of the drug.

Healthcare providers are advised to prescribe oestrogen and combined oestrogen with progestin at the lowest dose and for the shortest duration, consistent with treatment goals. The FDA has also requested all other manufacturers of oestrogen and oestrogen plus progestin combination products to make similar labelling changes to their products.

Reference:

PALIVIZUMAB
Label to clarify risk of anaphylaxis, hypersensitivity reactions

USA. MedImmune Inc has made several recent changes to the prescribing information for palivizumab (Synagis) used in the prevention of serious lower respiratory tract disease caused by Respiratory Syncytial Virus (RSV) in paediatric patients at higher risk of RSV disease. The Warnings section has been modified to note that very rare cases of anaphylaxis (< 1 case per 100,000 patients) have been reported following re-exposure to palivizumab (Synagis); rare severe acute hypersensitivity reactions have also been reported on initial exposure or re-exposure to palivizumab. The section advises that therapy with palivizumab should be permanently discontinued if severe hypersensitivity reaction occurs and re-administration should be undertaken with a lot of caution in the case of milder hypersensitivity reactions. In the event of anaphylaxis or severe allergic reactions appropriate medications (e.g. epinephrine) should be administered with appropriate supportive care. The Overdose section of the prescribing information has also been modified to reflect post-marketing data which suggest that, within a single RSV season, adverse events following a sixth or greater dose of palivizumab are similar in character and frequency to those after the initial 5 doses.

Reports in WHO file:
Anaphylactic shock 1, anaphylactoid reaction 2

Reference:

PIPER METHYSTICUM
Regulatory update from Malaysia

Malaysia. The Malaysian Adverse Reactions Advisory Committee (MADRAC) reports that the Drug Control Authority (DCA) in Malaysia has decided to extend its December 2001 withdrawal of products containing acetone-extract kava to include all products containing kava. Regulatory decisions on kava products taken elsewhere in the world may be referred to in previous issues of the WHO Pharmaceuticals Newsletter.

Reference:

RIBAVIRIN
Package inserts revised for co-administration with interferon α-2b

Japan. The Safety Division of the Pharmaceutical and Food Safety Bureau (Ministry of Health, Labour and Welfare, MHLW) in Japan has directed Schering Plough, manufacturer of capsules, to revise the product insert for ribavirin (Rebetol) to reflect the possibility of cerebral haemorrhage when co-administered with interferon α-2b (Intron A) in the treatment of hepatitis C. This directive, issued in September 2002, was based on 4 cases (including one death) of intracerebral haemorrhage and 1 death due to subdural haemorrhage reported at the time. Since then the MHLW has received 11 more reports of intracerebral haemorrhage. The co-administration of ribavirin (Rebetol) and interferon α-2b (Intron A), as a more effective treatment of hepatitis C, received formal approval in November 2001. It is estimated that by now about 26,000 patients have received this therapy. The revisions to the package insert will reflect that cerebral haemorrhage has been reported in patients concurrently receiving ribavirin and interferon α-2b, that the risk of cerebral haemorrhage is high in patients with hypertension and diabetes, and that the drugs should be administered with caution in patients with a present or past history or a family history of hypertension and/or diabetes and in patients with impaired glucose tolerance. Similar revisions will be made in the package insert for interferon α-2b (Intron A) as well.

Reference:

TRADITIONAL MEDICINES
Several Chinese medicines withdrawn due to presence of prescription and pharmacy-only components

New Zealand. The Medicines Safety Authority of the Ministry of Health in New Zealand (Medsafe) is ordering the withdrawal of several traditional Chinese medicines sold as herbal remedies since they have been found to contain scheduled

Available from URL:
http://www.fda.gov
medicines and toxic substances. Products to be withdrawn include

- Guan Xin Su He capsules, Long Dan Xie Gan Wan Pills, Zhiyuan Xinginkeli sachets – all containing aristolochic acid which has been linked to severe kidney damage and urinary tract cancer
- Wei Ge Wang tablets – containing prescription medicine sildenafili
- Sang Ju Gan Mao Pian tablets – containing pharmacy-only medicines diclofenac (a non-steroidal anti-inflammatory agent) and chlorpheniramine (an antihistamine)
- Yen Qiao Jie Du Pian capsules – containing chlorpheniramine, diclofenac and paracetamol
- Niu Huang Jie Du Pian tablets – containing 4% arsenic
- Xiaoke Wan pills – containing glibenclamide, a prescription-only hypoglycaemic agent
- Shuen Feng cream – containing ketoconazole, a prescription antifungal agent
- Dezhong Rhinitis drops – containing ephedrine hydrochloride.

The New Zealand Director General of Health has issued a Public Statement asking people to stop taking these products and to seek medical advice from their physicians. Medsafe has requested all importers and distributors of traditional Chinese medicines to cease all distribution and sale of these products, withdraw them from retail outlets and to ensure that other products they sell do not contain scheduled medicines. Medsafe has also written to all general medical practitioners alerting them to these products, outlining risks associated with their use and providing advice on appropriate management of people exposed to these drugs.

**Reference:**

Available from URL: [http://www.medsafe.govt.nz](http://www.medsafe.govt.nz)

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**VALDECOXIB**

**Label revised to reflect hypersensitivity reactions and skin reactions**

**USA.** Pharmacia and Pfizer have updated the Warnings section in the product monograph of valsartan tablets (Bextra) to include hypersensitivity reactions (anaphylactic reactions and angioedema) and skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis and erythema multiform as possible adverse reactions with the product. The Contraindications section advises that valsartan (Bextra) should not be given to patients who have demonstrated allergic-type reactions to sulfonamides. These updates are based on post-marketing surveillance reports of such reactions occurring with valsartan (Bextra) in patients with or without a history of allergic-type reactions to sulfonamides. In the US, valsartan (Bextra) is indicated for the relief of signs and symptoms of osteoarthritis and adult rheumatoid arthritis, and for the treatment of primary dystmenorrhoea.

**Reports in WHO file:**

- Face oedema 1, oedema peripheral 1

**Reference:**


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**ZAFIRLUKAST**

**Product label updated with specific patient-management recommendations**

**Canada.** Based on post-marketing surveillance reports AstraZeneca Canada Inc has made specific changes to the product monograph of zafirlukast (Accolate), indicated in the prophylaxis and chronic treatment of asthma in adults and children of 12 years age and above. The Warnings section (Hepatic Effects) now advises that zafirlukast (Accolate) should be discontinued immediately following signs or symptoms of liver dysfunction, without waiting for further confirmation of hepatotoxicity. If liver function tests (serum ALT) are consistent with hepatic dysfunction, zafirlukast (Accolate) therapy should not be resumed. And, if no other attributable cause exists for the hepatotoxicity, the patient should not be re-exposed to the product. Zafirlukast is not recommended for patients with hepatic impairment including hepatic cirrhosis. Further, the Adverse Reactions section gives the additional information that cases of symptomatic hepatitis (with or without hyperbilirubinemia) without other attributable cause and rarely, hyperbilirubinemia without other elevated liver function tests have been reported, especially in women, with 40mg/kg of the drug. In most, but not all cases, the symptoms abated and liver enzymes returned to normal or near normal after discontinuing treatment; in rare cases the situation progressed to liver failure.

The company has also issued a public advisory with the information that patients being treated with zafirlukast (Accolate) should consult their physicians about symptoms they may experience such as nausea, fatigue, loss of appetite, flu-like symptoms, pain on the right side of stomach, below ribs, yellow colouring of eyes, etc.

**Reference:**

SAFETY OF MEDICINES

CYPROTERONE ACETATE
Not authorized for sole purpose of contraception

Canada. In a recent advisory issued in December 2002 Health Canada has reiterated the following important safety concerns on the use of cyproterone acetate (Dianette). Prescribers are reminded that:

- Cyproterone acetate (Dianette) is not indicated for use solely as an oral contraception
- Cyproterone acetate (Dianette) is a treatment for severe acne in women who have not responded to oral antibiotics, or for moderately severe hirsutism
- The treatment should be withdrawn 3 to 4 cycles after the treated condition has completely resolved
- The incidence of venous thromboembolism in cyproterone acetate users is higher than that in women who use low-dose oestrogen combined oral contraceptives
- Women who have severe acne or hirsutism may have an inherently increased cardiovascular risk

Reference:
Health Canada
Warnings/Advisories, 23 Dec 2002.
Available from URL: http://www.hc-sc.gc.ca

EPOETIN ALFA
Subcutaneous administration and PRCA

UK. In June 2002 Janssen Ortho Inc, Canada, issued a letter (WHO Pharmaceuticals Newsletter No. 2, 2002) that warned health professionals against the subcutaneous (SC) administration of epoetin alfa (Eprex) in patients with chronic renal failure (CRF) since it could precipitate pure red cell aplasia (PRCA) in these patients. More recently, in December 2002 the UK Committee on Safety of Medicines issued a warning letter with the following additional information:

- Recommended storage conditions for epoetin alfa (between 2 and 8 degrees Celsius) should be adhered to at all times. This stipulation is considered relevant in light of the apparent association between epoetin alfa, PRCA and un-met storage conditions.
- In other approved indications there is no evidence of an increased risk of PRCA and epoetin alfa (Eprex) may be administered subcutaneously.

Norway. The Norwegian Medical Agency has also alerted physicians to the occurrence of epoetin alfa-related PRCA and to a corresponding labelling change that recommends epoetin alfa (Eprex) be given by the IV route in patients with CRF. They note that in Norway to date only one case of PRCA related to SC use of epoetin alfa has been reported.

Malaysia. The Malaysian Adverse Reactions Advisory Committee (MADRAC) has received one report of PRCA that occurred in a patient 2 months after starting epoetin alfa (Eprex) treatment.

Reference:

ETANERCEPT
Usage with recombinant IL-1Ra increases incidence of serious infections

Canada. Amgen Canada Inc, in consultation with Health Canada is warning health professionals about the increased risk of serious infections in patients treated with a combination of etanercept and recombinant human interleukin-1 receptor antagonist (IL-1Ra, Kineret) than in patients treated with etanercept alone. This warning is based on a recently completed clinical trial in the United States that compared the efficacy and safety of etanercept alone with etanercept plus IL-1Ra (Kineret) in patients with rheumatoid arthritis. The trial demonstrated that:

- Patients receiving concurrent IL-1Ra and etanercept had a higher incidence of serious infections than patients receiving etanercept alone
- The combination had no therapeutic benefit over treatment with etanercept alone
- Amgen Canada Inc, in accordance with Health Canada, will amend the Canadian Prescribing Information to include these observations.

Reference:

ETANERCEPT AND INFlixIMAB
Possible association with lymphoproliferative disorders

USA. A review of MedWatch reports by the FDA and National Cancer Institute suggests that etanercept and infliximab may be associated with lympho-
proliferative disorders. Between November 2001 and September 2002 68 cases of lymphomas, ‘possibly or probably’ associated with these two drugs, were reported to the FDA through the adverse event reporting system. 26 reports were received earlier, between May 1999 and 2000; 18 of these reports involved treatment with etanercept and lymphoma was diagnosed a median of 8 weeks after starting therapy. According to the researchers, while definitive conclusions may not be drawn at this stage, the fact that the latent period was quite similar to that associated with lymphomas that develop with immuno-suppressive therapy for patients who receive organ transplants, further implicates these products. The researchers also found that, in two patients, one treated with etanercept and the other with infliximab, there was regression of their lymphoma once treatment was discontinued. They advise that patients should be monitored for ‘spontaneous remission’ after withdrawal of the agent to see if cytotoxic chemotherapy can be avoided, patients’ clinical conditions permitting.


FLUOROQUINOLONES
Reports of tendon disorders
Australia. Until December 2002, 112 cases of fluoroquinolone-associated tendon disorders had been filed with the Australian Adverse Drug Reactions Advisory Committee (ADRAC). 30 cases involved tendon rupture. Ciprofloxacin was the drug involved in most cases (100 cases) followed by norfloxacin (9 cases) and one case for each of gatifloxacin, enoxacin and moxifloxacin. In the 106 cases for which age was reported, 73 patients were over 60 years of age and 20 were in their fifties; 47 patients were receiving concomitant oral corticosteroids. ADRAC reminds prescribers that increasing age and concomitant usage of corticosteroids are established risk factors for fluoroquinolone-associated tendon disorders.


GRAPEFRUIT JUICE
Specific reports of drug interactions
Australia. The Australian Adverse Drug Reactions Advisory Committee (ADRAC) has received 14 reports, as on December 2002 describing possible drug interactions with grapefruit juice. Most of the reports involve interactions with dihydropyridine calcium channel antagonists (5 reports) and HMG-CoA reductase inhibitors (statins, 5 reports). The committee reminds prescribers that several drug classes may interact with grapefruit juice and that patients receiving these drugs should be made aware of this possibility. Earlier, in June 2002, Health Canada had issued a similar warning about the possible interaction of grapefruit juice and that patients receiving these drugs should be made aware of this possibility. Earlier, in June 2002, Health Canada had issued a similar warning about the possible interaction of grapefruit juice with certain drug substances, affecting their metabolism, leading to higher plasma concentrations of these drugs with serious and even life threatening consequences (WHO Pharmaceuticals Newsletter No. 3, 2002).


INDOMETACIN
Case report
Malaysia. The Malaysian Adverse Reactions Advisory Committee (MADRAC) has received one case report of a woman who developed a rectovaginal fistula complicated by faecal incontinence following the use of intravaginal indomethacin for labour suppression. She subsequently required anal sphincter and rectovaginal fistula repair.


LEFLUNOMIDE
Update on ADR reports
Canada. Between 29 March 2002 and 31 May 2002 Health Canada received 99 reports of suspected adverse reactions associated with leflunomide (Arava), 79 of which were serious and four of which had a fatal outcome. The reports included haematological reactions (20), hepatic and biliary reactions (11) and respiratory reactions (11). In addition, 15 reports involved the concomitant use of leflunomide and methotrexate, a combination associated with increased toxicity and not approved in Canada. Healthcare professionals are reminded of the possibility of severe adverse reactions to leflunomide and that these risks may be increased with concomitant methotrexate use; strict monitoring of liver and bone marrow function is recommended for all leflunomide recipients.


MICONAZOLE
Interaction with warfarin
Australia. The Australian Adverse Drug Reactions Advisory Committee (ADRAC) has received 18 reports involving drug interactions between...
SAFETY OF MEDICINES

miconazole oral gel (Daktarin oral gel) and warfarin with a resultant increase in INR (International Normalized Ratio) values. In 17 cases this involved a clinically significant increase in INR with values ranging between 7.5 and 18 and occurred within 1-2 weeks of starting miconazole. Withdrawal of one or both drugs was necessary in most cases; at least nine patients required vitamin K and five required treatment with fresh frozen plasma. Since miconazole is available without a prescription, both pharmacists and physicians are reminded to be vigilant to the possibility of such an interaction.

Reference:

SERTRALINE

New prescribing information to advise against concomitant use with pimozide

USA. Pfizer Inc, under advice from USFDA is informing healthcare professionals about a change in the prescribing information for sertraline hydrochloride (Zoloft) tablets and oral concentrate. This advice was issued after a study showed that concomitant administration of sertraline hydrochloride (Zoloft, 200 mg) in patients given a single dose of pimozide (2 mg) increased the plasma concentration of pimozide by about 40%. The mechanism of this interaction remains unknown. According to Pfizer, given the narrow therapeutic index of pimozide and the fact that the interaction occurred with a low dose of pimozide, concomitant administration of sertraline (Zoloft) and pimozide should be contraindicated. The Contraindications and Precautions sections for sertraline have been appropriately modified to reflect this new information. Sertraline (Zoloft) is indicated for the treatment of major depressive disorder, panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder and premenstrual dysphoric disorder and pimozide in the treatment of Tourette’s syndrome.

Reference:

TAMOXIFEN

Increased risk of stroke, pulmonary embolism and uterine cancer

Canada. Health Canada has issued important safety information regarding tamoxifen and the incidence of uterine malignancy, stroke and pulmonary embolism. This follows the recent publication of information derived from the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention study, in which women at high risk of breast cancer or with ductal carcinoma in situ received tamoxifen for breast cancer prevention. In the study population, the incidence rates for uterine malignancy, stroke and pulmonary embolism were up to 3 times higher with tamoxifen than with placebo. Health Canada has emphasized that the use of tamoxifen for breast cancer prevention is not an approved indication in Canada. However, in the approved indication for the treatment of breast cancer in oestrogen receptor positive tumours, the benefits of using tamoxifen have been judged to outweigh the potential risks. However, physicians and patients should discuss the risks and benefits prior to starting treatment with tamoxifen. Patients who are taking tamoxifen should immediately report to their doctor symptoms of weakness or numbness of the face, arms or legs, and problems with speech or vision which may indicate stroke; leg swelling, chest pain or shortness of breath which may indicate blood clots; and abdominal pain or abnormal vaginal bleeding which may indicate cancer of the uterus. Patients should inform their doctor if they have had a history of stroke or stroke-like events, blood clots or uterine cancer.

Reference:

Reports in WHO files:
Uterine carcinoma 43, uterine fibroid 46, uterine neoplasm 25

Reference:
WHO Pharmaceuticals Newsletter No. 1, 2003 • 6
NEFAZODONE

Nefazodone (Serzone, Serzonil, Nefadar, Dutonin, Rulivan) is an antidepressant with a structure and mechanism of action distinct from that of selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants. The product has been marketed worldwide since 1994. An estimated 11 million people have been prescribed this drug so far.

As with many other newer antidepressants, hepatobiliary adverse reactions have been associated with nefazodone usage. In its September 2000 meeting the Medicines Adverse Reactions Committee (MARC) in New Zealand noted that a rate of hepatic reactions of 3.9/1000 had been recorded for nefazodone with the New Zealand Intensive Medicines Monitoring Programme (IMMP). At that time 235 reports of nefazodone-associated hepatic reactions had been filed with the WHO database for adverse drug reactions. Based on this MARC recommended asking the sponsor company to update the data sheet by dropping the comment that a causal association between nefazodone and increased liver enzymes and hepatitis had not been established.

From the time the drug was introduced in Canada (1994) to July 24, 2002 a total of 123 reports of nefazodone-related adverse biliary reactions were registered with Health Canada. Health Canada, in July 2001, issued a public advisory related to the risk of severe liver injury associated with the use of nefazodone. It also directed the manufacturers of various nefazodone preparations (Serzone-SHT2, Lin-Nefazodone and Apo-Nefazodone) to issue letters to health professionals recommending that patients be counselled about the risk of hepatotoxic effects before the initiation of nefazodone therapy and that close monitoring be undertaken should signs of hepatotoxicity or abnormal liver aminotransferase or bilirubin levels develop during treatment.

Nefazodone was registered in Sweden in 1995, and was later taken off the market in 2002 when the company (Bristol-Myers Squibb, BMS) voluntarily withdrew the product from Sweden amidst concerns of hepatic adverse reactions. The Netherlands Medicine Assessments Board announced in November 2002 that it would investigate nefazodone (Dutonin) and hepatic effects reported with the drug. Shortly after, in a December 2002 letter to the Dutch Medicines Evaluation Board (CBG), BMS announced that it would voluntarily stop selling nefazodone in Netherlands after April 2003; the company also planned to notify Danish authorities of a similar withdrawal in Denmark in the near future. More recently, on 8 January 2003, the company announced its plan to stop selling nefazodone in all European countries while continuing to market it outside of Europe.

In addition to reports of hepatotoxicity, post-marketing reports of priapism, frequent hypotension (though not severe) and occasional episodes of frank syncope have been recorded with nefazodone. Drug interactions are important considerations as well. Nefazodone is metabolized by (and is an inhibitor of) the CYP4503A4 enzyme. Thus, other drugs that inhibit CYP4503A4 (ketoconazole, erythromycin, and itraconazole) may delay nefazodone clearance. In contrast, drugs such as carbamazepine and rifampin may increase nefazodone clearance by inducing CYP4503A4. Nefazodone is contraindicated in patients taking astemizole, terfenadine or cisapride.

To date there are 449 reports of nefazodone-related hepatic reactions in the WHO ADR database. The bulk of the ADR data on nefazodone (as with most drugs) comes from spontaneous reporting, a system that is inherently limited by, among other factors, a tendency to underreport. To that extent, this figure might not be very representative of the actual nature of the problem. Nefazodone will remain a molecule of interest and vigilance, at least in those countries where it will continue to be available.

Reference:
5. Reuters News, as reported on UK Medical Information (UKMI) website http://www.druginfozone.org
Drugs of Abuse: Problems of Data Collection, Definitions and Liability Assessment

Tokuo Yoshida, Quality Assurance and Safety: Medicines, Essential Drugs and Medicines Policy, WHO

The 1969 WHO Expert Committee Report on Drug Dependence defines *drug abuse* as a ‘persistent or sporadic excessive drug use inconsistent with or unrelated to acceptable medical practice’. Drugs of abuse are controlled internationally by the United Nations. WHO, within this system, determines the abuse liability (likelihood of abuse) and *therapeutic usefulness* of psychoactive substances and proposes their addition to, removal from or transfer to appropriate lists of controlled substances. Since 1949, through its Expert Committee on Drug Dependence, WHO has reviewed more than 400 substances. WHO is also involved in the process of developing guidelines to improve the prescribing of controlled drugs, with the aim of preventing dependence and abuse.

*Abuse liability* assessment requires relevant data. Despite recent methodological advancement in laboratory studies, actual abuse is often hard to predict based only on laboratory test results in both animals and humans. Epidemiological data, however, are very scarce. Only a small number of countries with adequate resources have a data collection system in place for abused drugs, through information collected via drug abusers seeking treatment. Surveys for measuring drug abuse are expensive and not possible in countries with resource restraints. In these prevailing conditions of limited and scarce drug-abuse data, information from the WHO Collaborating Centre for International Drug Monitoring in Sweden has been of significant value. This centre, popularly known as the Uppsala Monitoring Centre (the UMC) maintains an adverse drug reactions database of therapeutic drugs from as many as 70 countries from around the world. WHO Adverse Drug Reaction Terms (WHO-ART) such as *drug abuse*, *drug dependence*, *withdrawal syndrome* etc make this facility sensitive enough to detect dependence liability in therapeutic use.

However, in spite of the obvious advantages, data interpretation and reporting of abuse related ADR data are not without complications. Confusion in terminology is rather common; the most frequent of confusions is about the relationship between *withdrawal syndrome* and *drug dependence*. The modern definition of drug dependence requires neither withdrawal nor tolerance, since an individual can become dependent on a drug without necessarily developing tolerance or demonstrating withdrawal symptoms upon discontinuation of the drug. However, excessive emphasis on this can lead to the opposite misconception that withdrawal is unrelated to dependence. When an individual has difficulty in managing the need for repeated doses of the drug to feel good or to avoid feeling bad, the person is considered "dependent" on the drug. Therefore, severe withdrawal can (but not always) lead to dependence.

The SSRIs (Selective Serotonin Reuptake Inhibitors) provide a useful case-study in understanding issues of dependence liability assessment for drugs acting on the central nervous system. It is stated that, although withdrawal reactions may occur on stopping therapy, the available pre-clinical and clinical evidence do not suggest that SSRIs cause dependence (EMEA/CPMP/2775/99). However, such a conclusion may only be drawn after a careful review of the significant number of ‘drug dependence’ reports for SSRIs received by the ADR monitoring system and, not on the basis of the terminology discussion that withdrawal reactions by themselves are insufficient to imply dependence.

The use of a different term *discontinuation syndrome* to replace the conventional expression *withdrawal syndrome* is adding more confusion to this debate. However, whether the reactions are called *discontinuation syndrome* or *withdrawal syndrome*, the terminology would have no influence on the person’s need for repeated doses of the drug. Rather, it is the severity of the reactions to drug discontinuation that will determine the need for repeating the doses of the drug to avoid feeling bad. This example indicates the need for continued efforts to clarify the meaning of key terms used in pharmacovigilance.
• The 26th Annual Meeting of Representatives of the National Centres participating in the WHO International Drug Monitoring Programme is scheduled to be held in New Delhi, India 8-10 December 2003. This will be preceded by a pre-meeting workshop on ‘Pharmacovigilance-promoting drug safety through collaboration’, 5-6 December 2003 in Mumbai, organized by the WHO Special Centre for Pharmacovigilance, India, in collaboration with the World Health Organization.

• The 11th International Conference of Drug Regulatory Authorities (ICDRA) will be held 15-18 February 2004 in Madrid, Spain.