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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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FEATURE

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Highest strength tablets being withdrawn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)[1]. 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[2]. 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[3].

Reference:

1. *Australian Prescriber 25, No.6, 2002. Available from URL: http://www.australianprescriber.com*
2. *Australian Prescriber 23:93, 2000. Available from URL: http://www.australianprescriber.com*
3. *Australian Prescriber 24:110-2, 2001. Available from URL: http://www.australianprescriber.com*

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Products withdrawn due to problems of misuse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.

Reference:

Cough preparations containing codeine. Berita Ubat-ubatan 19:5, Aug 2002.

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:

MADRAC News, Berita Ubat-ubatan 19:8-9, Aug 2002.

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-progestin products should

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:

1. *FDA Press Release, 8 Jan 2003. Available from URL: http://www.fda.gov*
2. *'Dear Healthcare Professional' letter from Wyeth Pharmaceuticals, 6 Jan 2003. Available from URL: http://www.fda.gov*

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 Overdosage 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:

'Dear Healthcare Professional' letter from MedImmune Inc, 26 Nov 2002. Available from URL: http://www.fda.gov

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:

MADRAC News, Berita Ubat-ubatan 19:8-9, Aug 2002.

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:

1. *Pharma Japan 1812/23, Sept 2002.*
2. *MHLW Press Release, 15 Oct 2002.*

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

medicines and toxic substances. Products to be withdrawn include

- Guan Xin Su He capsules, Long Dan Xie Gan Wan Pills, Zhiyuan Xinqinkeli sachets – all containing aristolochic acid which has been linked to severe kidney damage and urinary tract cancer
- Wei Ge Wang tablets – containing prescription medicine sildenafil
- 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:

Media Release, 21 Jan 2003. Available from URL: http://www.medsafe.govt.nz

VALDECOXIB

Label revised to reflect hypersensitivity reactions and skin reactions

USA. Pharmacia and Pfizer have updated the Warnings section in the product label for valdecoxib 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 Contra-indications section advises that valdecoxib (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 valdecoxib (Bextra) in patients with or without a history of allergic-type reactions to sulfonamides. In the US, valdecoxib (Bextra) is indicated for the relief of signs and symptoms of osteoarthritis and adult rheumatoid arthritis, and for the treatment of primary dysmenorrhoea.

Reports in WHO file:
Face oedema 1, oedema peripheral 1

Reference:

'Dear Healthcare Professional' letter from Pharmacia Corporation and Pfizer Inc, 13 Nov 2002. Available from URL: http://www.fda.gov

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[1]. 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[2] 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:

1. *'Dear Healthcare Professional' letter from AstraZeneca Canada Inc, 7 Oct 2002 (posted on website on 18 Dec 2002). Available from URL: http://www.hc-sc.gc.ca*
2. *'Public Advisory' from AstraZeneca Canada Inc, 18 Dec 2002. Available from URL: http://www.hc-sc.gc.ca*

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 ooestrogen 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 epoein 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:

1. *Communication from Chairman, Committee on Safety of Medicines, UK, (Ref. CEM/CMO/2002/17), 12 Dec 2002. Available from URL: http://www.info.doh.gov.uk*
2. *Harg P, Buajordet I, Madsen S. Eprex: should be administered intravenously in order to reduce the risk for erythroplasia. Nytt om Legemidler 25: 8, Nov 2002.*
3. *MADRAC News, Berita Ubat-ubatan 19:8-9, Aug 2002.*

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:

'Dear Healthcare Professional' letter from Amgen Canada Inc, 17 Dec 2002. Available from URL: http://www.hc-sc.gc.ca

ETANERCEPT AND INFLIXIMAB

Possible association with lympho-proliferative 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 dis-continued. 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.

Reference:
Arthritis Rheum 46:3151-3158, 2002.

FLUORO-QUINOLONES

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.

Reference:
Australian Adverse Drug Reactions Bulletin 21:15, Dec 2002. Available from URL: http://www.health.gov.au

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 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).

Reference:
Australian Adverse Drug Reactions Bulletin 21:14, Dec 2002. Available from URL: http://www.health.gov.au

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 indometacin for labour suppression. She subsequently required anal sphincter and rectovaginal fistula repair.

Reference:
MADRAC News, Berita Ubat-ubatan 19:8-9, Aug 2002.

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 in-cluded 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.

Reference:
1. *McMorran M. Adverse reactions to natural health products. Canadian Adverse Reaction Newsletter 12: 1-2, Oct 2002.*
2. *Loorand-Stiver L, Murty M. Leflunomide (Arava): haematologic, hepatic and respiratory reactions. Canadian Adverse Reaction Newsletter 12: 2-3, Oct 2002.*

MICONAZOLE

Interaction with warfarin

Australia. The Australian Adverse Drug Reactions Advisory Committee (ADRAC) has received 18 reports involving drug interactions between

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:
Australian Adverse Drug Reactions Bulletin 21:14-15, Dec 2002. Available from URL: http://www.health.gov.au

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 hydochloride (Zoloft, 200 mg) in patients given a single dose of pimozide (2 mg) increased the plasma concen-

disorder, panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder and premenstrual dysphoric disorder and pimozide in the treatment of Tourette's syndrome.

Reference:
Letter from Pfizer Inc, Nov 2002. Available from URL: http://www.fda.gov

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

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.

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

Reference:
Health Canada Advisory, 26 Nov 2002. Available from URL: http://www.hc-sc.gc.ca

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