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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.

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, 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

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