WHO PHARMACEUTICALS NEWSLETTER

prepared in collaboration with the
WHO Collaborating Centre for
International Drug Monitoring,
Uppsala, Sweden

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The aim of this Newsletter is to disseminate information on the safety ***and efficacy of pharmaceutical products, based on information received from our network of "drug information officers" and other sources such as specialized bulletins and journals, as well as*** *partners in WHO. The information is produced in the form of résumés in English, full texts of which may be obtained on request from:*

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This newsletter is also available on our Internet website:
http://www.who.int/medicines

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Issues around best pharmacovigilance practices and crisis management continue to occupy us even as the medical world struggles to understand the full picture with drugs such as the coxibs. Rofecoxib was withdrawn worldwide in September 2004 and in April 2005, the United States Food and Drug Administration asked Pfizer to voluntarily withdraw valdecoxib from the market. Several regulatory agencies have responded by issuing safety information and prescribing guidelines for various COX-2 inhibitors and these are presented in this edition.

The UN Prequalification Project was launched in 2001 for providing quality assessment on a selected number of medicines for high impact diseases that are considered for purchase by several UN agencies. We have included an overview of the team's work under 'Feature' and regular updates of products which have been prequalified by WHO will appear in future issues of the Newsletter.

The World Health Assembly will take place this year from 16 to 25 May, in Geneva. The WHO Collaborating Centre for International Drug Monitoring is holding its biennial training course on Pharmacovigilance from 23 May to 3 June in Uppsala, Sweden. For those of you who will attend either of these events, we hope they will provide opportunities and incentives for promoting health care and pharmacovigilance in your countries.

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Drugs of Current Interest

Feature

Adalimumab

Updated information on haematologic events

Canada. Abbott Laboratories Limited has issued a 'Dear Health-care Professional' letter to advise of the addition of new safety information to the adalimumab (Humira, a monoclonal antibody directed against tumor necrosis factor-a) prescribing information, endorsed by Health Canada. The new safety information will also be included in the revised Canadian Product Monograph. Abbott highlights that there have been reports of serious blood dyscrasias, including leukopenia, pancytopenia and thrombocytopenia, in patients receiving adalimumab (Humira). It is not clear whether there is a causal relationship with adalimumab, and none of the reports was received in Canada. Abbott also recommends against the use of adalimumab (Humira) in combination with anakinra (an interleukin-1 antagonist), as there is a risk of severe infections. This advice stems from the observation of serious infections in patients who received anakinra concurrently with another tumour necrosis factor antagonist in clinical studies.

Reference:
'Dear Health-care Professional' letter from Abbott Laboratories Limited, 2 February 2005. Available on the internet at www.hc-sc.gc.ca

Amphetamine

Anti-ADHD preparations removed

Canada. Health Canada has suspended the marketing of amphetamine preparations (Adderall, Adderall XR) used in Attention Deficit Hyperactivity Disorder (ADHD). This directive, which came into effect on 9 February 2005 is based on 20 international reports of sudden deaths in paediatric and adult patients in association with amphetamine (Adderall, Adderall XR) use. These deaths were not associated with overdose, misuse or abuse. Fourteen deaths occurred in children, and six deaths in adults. There were 12 reports of strokes, two of which occurred in children. Health Canada is advising patients who are currently being treated with an amphetamine preparation to consult their physician immediately about use of the drug and about treatment alternatives. Health Canada is also advising that patients who are taking other drugs of the same class for the management of ADHD should not discontinue their medication but should consult their physician if they have queries or concerns. Health Canada has solicited worldwide safety data from manufacturers of other related stimulants used in the treatment of ADHD.

Reference:
Health Canada Warnings/ Advisories, 9 February 2005. Available on the internet at www.hc-sc.gc.ca

Anagrelide

Contraindicated in patients with severe hepatic impairment

USA. Shire Development Inc. is updating the prescribing information for anagrelide (Agrylin), a medication approved in the treatment of thrombocytopenia secondary to myeloproliferative disorders to reduce platelet count and the risk of thrombosis and to ameliorate associated symptoms including thrombo-haemorrhagic events. The new information advises prescribers

i. against using the product in patients with severe hepatic impairment, and

ii. to reduce the dose in patients with moderate hepatic impairment.

The revision follows pharmacokinetic studies that revealed an eight-fold increase in total exposure to anagrelide in patients with moderate hepatic impairment.

Reference:
'Dear Health-care Professional' letter from Shire Development Inc., January 2005. Available on the internet at www.fda.gov

Ezetimebe

Risk of myalgia, rhabdomyolysis, hepatitis, pancreatitis and thrombocytopenia

Canada. Ezetimebe (Ezetrol) is a cholesterol absorption inhibitor that is classified as a systemic drug because of the enterohepatic recirculation of one of its metabolites. Merck Frosst/Schering Pharmaceuticals have updated the product monograph for ezetimebe to include information from international post-marketing reports of rare, and in some cases serious, adverse events associated with ezetimebe use including myalgia, rhabdomyolysis, hepatitis, acute pancreatitis, thrombocytopenia and suspected interaction between ezetimebe and warfarin. The Patient Information section has been updated with signs and symptoms of hepatic, muscle, and pancreatic adverse events for which early consultation with a physician is recommended. Physicians are advised to monitor closely for adverse muscle events in all those patients who have a history of statin intolerance, to consider the diagnosis of pancreatitis in patients who develop sudden acute abdominal pain during therapy with ezetimebe and to monitor liver function before beginning ezetimebe therapy in patients being or about to be treated

with a statin; ezetimebe, in combination with a statin is contraindicated in patients with active liver disease or unexplained persistent elevations of liver transaminases. Additional International Normalized Ratio (INR) measurements are recommended in patients treated with warfarin, and in whom ezetimebe is initiated.

Reference:
'Dear Health-care Professional' letter from Merck Frosst/Schering Pharmaceuticals, 1 February 2005. Available on the internet at www.hc-sc.gc.ca

Interferon Beta-1a

Label updated with hepatic injury information

USA. Post-marketing data on Interferon Beta-1a (Avonex) show that severe hepatic injury, including hepatic failure and elevated serum hepatic enzyme levels, have been reported rarely in patients treated with Interferon Beta-1a (Avonex). In some cases these events have occurred in the presence of other drugs that have been associated with hepatic injury. Health-care professionals are advised that hepatic injury should be considered when Interferon Beta-1a (Avonex) is used in combination with other products associated with hepatic injury, or when new agents are added to the regimen of patients already on Interferon Beta-1a (Avonex). The product information has been updated to reflect the above.

Reference:
'Dear Health-care Professional' letter from Biogen Idec, 16 March 2005. Available on the internet at www.fda.gov

Lipiocis

Reports of interstitial pneumopathy

France. CIS Bio (subsidiary company of the Schering group), in agreement with the French agency for medical safety of health products (AFSSAPS) is informing health professionals that the incidence of interstitial pneumopathy associated with the use of Lipiocis® appears to be higher (2%) than initially observed in clinical trials (0.5%). Lipiocis is a radiopharmaceutical product indicated in the treatment of hepatocellular carcinomas with thrombosis of the portal vein. A total of 13 interstitial cases of pneumopathy have been reported to the French reference centre for the treatment of hepatocellular carcinomas. These diffuse infiltrative pneumopathys occur approximately a month after the injection of Lipiocis®, generally after the second injection. The clinical symptoms include the appearance of dyspnea sometimes associated with a dry cough and bilateral crepitations. The pneumopathys could lead to serious complications with a high death rate. AFSSAPS recommends that thoracic radiography must be carried out before administering Lipiocis® and if respiratory symptoms are observed. The Summary of Product Characteristics has been updated to reflect this information.

References:
1. Letter to health professionals from Dr Laure Udin, Responsible Officer, Pharmacovigilance, AFSSAPS, 14 March 2005. Available on the internet at http://afssaps.sante.fr/htm/10/filltrpsc/lp050304.pdf
2. Modified Summary of Product Characteristics for Lipiocis. Available on the internet at http://afssaps.sante.fr/pdf/10/lipiocis.pdf

Natalizumab

Withdrawn due to serious adverse events

USA. The United States Food and Drug Administration (US FDA) has issued a public health advisory to inform patients and health-care providers that Biogen Idec has voluntarily suspended marketing of natalizumab (Tysabri) due to serious adverse event reports. The company has received two reports, one fatal and one possible case of progressive multifocal leukoencephalopathy in patients enrolled in a clinical trial who had been receiving natalizumab for multiple sclerosis for more than two years. Neither patient had any known risk factors for progressive multifocal leukoencephalopathy. On the basis of these cases, Biogen Idec is suspending dosing of the agent in clinical trials as well as voluntarily suspending marketing. At the present time, the only recommendation for patients receiving natalizumab is to discontinue its use, and for physicians to evaluate all patients who have received the agent and have signs or symptoms suggestive of progressive multifocal leukoencephalopathy.

Reference:
US FDA Public Health Advisory, 28 February 2005. Available on the internet at www.fda.gov

Olanzapine

Medication errors alert

USA. Eli Lilly & Company have issued a `Dear Health-care Professional' letter to advise of dispensing and prescribing error reports with the antipsychotic medication olanzapine (Zyprexa) and the antihistaminic preparation cetirizine (Zyrtec). Dispensing of olanzapine instead of cetirizine or vice versa has led to adverse events in patients. Such a mix-up may result in, for example, a disease relapse

in patients with schizophrenia or bipolar disorder. Factors that may contribute to the medication errors are: the first two letters of their brand names are the same, the products are usually stored near each other, both are available in 5 mg and 10 mg tablets and both have a once-daily dosing interval. Measures that have been or will be taken by Eli Lilly include changing the 10 mg ZYPREXA bottle label to ZyPREXA, for easier identification and, launching an awareness campaign focusing on the dispensing error potential.

Reference:
'Dear Health-care Professional' letter from Eli Lilly & Company, 26 January 2005. Available on the internet at www.fda.gov

Pimecrolimus/ Tacrolimus

Potential cancer risk

USA. The US FDA Division of Paediatric Drug Development has recommended that a black box warning be added to the labeling of two eczema treatments, pimecrolimus (Elidel) and tacrolimus (Protopic), to warn of potential carcinogenicity with these products. This recommendation is based on all available information regarding these agents, including animal carcinogenicity signals in mice and monkeys and post-(n = 7), skin cancer (6) and papilloma (2) with these two agents, and the division notes that the increased incidence of specific infections with pimecrolimus (Elidel) and tacrolimus (Protopic) in clinical trials provides *"additional supportive evidence of immunosuppression in paediatric patients"*. The US FDA has advised health-care professionals to prescribe the two products only as directed (minimum dose, for the shortest period of time and never in children younger than two years of age) and only after other eczema treatments have failed to work.

Reference:
US FDA Talk Paper, 10 March 2005. Available on the internet at www.fda.gov

Promethazine

Contraindicated in patients less than two years of age

USA. Wyeth Pharmaceuticals, under advice from the US FDA has updated its labels for promethazine hydrochloride (Phenergan) tablets and suppository preparations. The new labels warn against using these products in children below the age of two due to the risk of fatal respiratory depression. This advice is based on post-marketing reports of respiratory depression including fatalities associated with the

21 January 2005. Available on the internet at www.fda.gov

Qing zhisan tain shou, Li Da Dai Dai Hua, Meizitang

Presence of sibutramine

UK. The Medicines and Health-care products Regulatory Agency (MHRA) has become aware of the supply of a Traditional Chinese Medicine (TCM) slimming aid called Qing zhisan tain shou on the UK market, which contains the prescription only medicine (POM) sibutramine. The MHRA is warning consumers that sibutramine should only be prescribed under specific circumstances and requires the supervision of a registered doctor as it can cause a rise in blood pressure. Qing zhisan tain shou is supplied in a bicolour cream and brown capsule form. The capsules are contained within blister packs and presented in a white and green carton with various lettering and imagery. Two other TCM slimming products, Li Da Dai Dai Hua and Meizitang have been seized by the Netherlands' authorities and have been found to contain sibutramine. Due to the international trade in such products it is possible that these, or similar products, have found their way onto the UK