

WHO PHARMACEUTICALS NEWSLETTER



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

The aim of this Newsletter is to disseminate information on the safety and efficacy of pharmaceutical products, based on communications 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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News & Issues

Last month the World Health Organization lost its Director-General, Dr Lee Jong-wook to a cerebral stroke. He was sixty one. Dr Lee became Director-General of the World Health Organization on 21 July 2003. Before that, he had worked for more than 20 years for the Organization, first battling leprosy in the South Pacific islands, then tackling vaccine preventable diseases including polio. During his all too brief tenure as Director-General, he pioneered new ways for people to gain access to tuberculosis and HIV/AIDS medicines, making this issue a serious political objective.

Dr Lee was a "man of action", whose adventurous spirit led him to "experience more, see more, and do more," said his son Tadahiro. We keep Dr Lee's family in our prayers.

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Acetylcysteine New paediatric dosing information

USA. The United States Food and Drug Administration (US FDA) has approved acetylcysteine (Acetadote) labelling updates, which included important new information for the treatment of paracetamol overdose in paediatric patients, according to Cumberland Pharmaceuticals. The updated labelling highlights new paediatric dosing information and includes a change in the loading dose duration from 15 to 60 minutes, says the company. AJ Kazimi from Cumberland Pharmaceuticals says that studies show that cases of paracetamol poisoning in the US are on the rise with up to 70% cases occurring in children less than 19 years of age.

Reference:

Media Release. Cumberland Pharmaceuticals Inc., 6 March 2006 (<http://www.cumberlandpharma.com>).

Anabolic steroids Not to be sold as dietary supplements

USA, Canada. The US FDA has warned that the continued distribution and sale of certain unapproved drugs (Anabolic Xtreme Superdrol, Methyl-1-P) containing steroids without FDA approval could result in regulatory action against the concerned manufacturers and distributors (1). US FDA says that the products are not dietary supplements, as represented by the companies, because the active ingredients are not dietary ingredients. The products claim to be anabolic and are promoted for building muscle and increasing strength. The US FDA is concerned that consumers using these products may develop serious long-term health consequences associated with anabolic steroids including liver toxicity and testicular atrophy, gynaecomastia and infertility in

men, (masculinization) in women, short stature in children, lipid metabolism disorders, increased risk of myocardial infarction and stroke. The US FDA advises consumers to stop taking these products, and to return the products to their place of purchase. Health Canada has issued an Advisory, warning consumers not to use five products (Anabolic Xtreme Superdrol, Methyl-1-P, Ergomax LMG, Prostanozoland, and FiniGenx Magnum Liquid) containing illegal anabolic steroids as they can potentially have serious health effects (2).

References:

1. FDA News. United States Food and Drug Administration, 9 March 2006 (<http://www.fda.gov>).
2. Advisory. Health Canada, 21 April 2006 (<http://www.hc-sc.gc.ca>).

Denileukin diftitox Label to include reports of visual loss

USA. Ligand Pharmaceuticals Inc. has issued a 'Dear Health-care Professional' letter to advise of changes to denileukin diftitox (Ontak) labelling with regard to visual loss. Denileukin diftitox is indicated for the treatment of patients with persistent or recurrent cutaneous T-cell lymphoma. Ligand says that the Warnings section has been updated to advise that loss of visual acuity, usually with loss of colour vision with or without retinal pigment mottling, has been reported following denileukin diftitox (Ontak) administration. Furthermore, recovery was reported in some patients, but most reported persistent visual impairment. According to the company, the Adverse Reactions section has also been updated, and says that because these reactions are reported voluntarily from a population of uncertain size, it is not always

possible to estimate their frequency reliably, or to establish a causal relationship to drug exposure.

Reference:

'Dear Health-care Professional' letter from Ligand Pharmaceuticals Inc., 3 March 2006 (<http://www.fda.gov>).

I-Arginine Not for heart patients

Canada. According to Health Canada, patients who have previously had a heart attack should not use I-arginine supplements because of a recent study showing an increased potential risk of death when used after a heart attack (1). I-Arginine is an amino acid which is commonly used to sustain and promote healthy heart function. However a recent study published in the Journal of the American Medical Association in January 2006 suggests that I-arginine may not help improve heart and circulatory function following a first heart attack and may be associated with an increased risk of death when used after a heart attack (2). All I-arginine products are now required to carry a warning on their label reflecting this recent scientific information. Health Canada advises that for patients who have not had a previous heart attack, taking I-arginine is unlikely to present a risk and may provide benefits by helping the body repair damage to blood vessels in the heart.

Reference:

1. Advisory. Health Canada, 16 May 2006 (<http://www.hc-sc.gc.ca>).
2. Schulman SP et al. I-Arginine therapy in acute myocardial infarction. *The Journal of the American Medical Association*, 2006, 295: 58-64.

Pegaptanib sodium

Reports of anaphylaxis/anaphylactoid reactions

USA. The US Prescribing Information for pegaptanib injection (Macugen) has been amended following rare, US postmarketing reports of anaphylaxis/anaphylactoid reactions associated with intravitreal pegaptanib administration. Pegaptanib sodium injection (Macugen) is indicated for the treatment of neovascular (wet) age-related macular degeneration. The updated product label advises that pegaptanib (Macugen) is contraindicated in patients with known hypersensitivity to pegaptanib or other excipients in the product, and that a patient's medical history should be evaluated for hypersensitivity reactions prior to performing the intravitreal procedure; updates to the Precautions and Adverse Events sections have also been made to highlight the reports of anaphylaxis/anaphylactoid reactions. The companies (OSI) Eyetech Inc. and Pfizer Inc. say that a direct link between pegaptanib or the various medications, and the anaphylaxis/anaphylactoid cases, which include angioedema, has not been established (see WHO Pharmaceuticals Newsletter No. 2, 2006 for Health Canada - endorsed safety information on pegaptanib).

Reference:

'Dear Health-care Professional' letter from (OSI) Eyetech Inc. and Pfizer Inc., 6 March 2006 (<http://www.fda.gov>).

Bowel cleansing oral sodium phosphates

Risk of renal damage

USA. The US FDA has issued an alert that acute phosphate nephropathy, a type of acute renal failure, is a rare but serious adverse event associated with the use of oral sodium phosphates (OSP) for bowel cleansing. According to the Alert, acute phosphate nephropathy has been documented in 21 patients who used an OSP solution and in one patient who used an OSP tablet; older individuals, those with kidney disease or decreased intravascular volume, and those using medicines that affect renal perfusion or function (diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and possibly nonsteroidal anti-inflammatory drugs) are at higher risk of acute phosphate nephropathy.

Reference:

FDA Alert. United States Food and Drug Administration, May 2006
(<http://www.fda.gov>).

Glucosamine products

86 reports to date in Sweden

Sweden. The Swedish Adverse Drug Reactions Database contains 86 reports of suspected adverse reactions associated with glucosamine products from 2001 until February 2006, according to the Swedish Medical Products Agency. The Agency says that the majority of these cases were reported after 2002, when the first glucosamine product, Artrox, was approved as a drug. According to the Agency, there are now just over 10 glucosamine products approved in Sweden, including

Artrox, Glucosine, Glukosamin Copyfarm and Glukosamin Pharma. According to the Agency, previously unknown adverse reactions of particular interest included the following: angioedema (n = 2), urticaria (1), colitis (2), gastric/duodenal ulcer (3), oedema/lower limb oedema (3), dizziness (4), arthralgia (2), bronchial asthma/bronchial asthma aggravated (3), diabetes aggravated (2) and hypercholesterolaemia (2). There were also three cases of an increased effect of warfarin during concomitant treatment with glucosamine products.

(Reports in WHO database: All reactions - 645).

Reference:

Three year adverse reaction follow-up of glucosamine products as drugs. Swedish Medical Products Agency, 21 April 2006
(<http://www.moa.se>).

Isotretinoin

Suspected association with vascular disorders

Canada. Health Canada has received 29 domestic reports of suspected isotretinoin (Accutane)-associated vascular disorders between the time the drug was marketed in Canada (1983) and 31 December 2005, according to an article in the *Canadian Adverse Reaction Newsletter*. Eleven of the cases were reports of myocardial infarction, thromboembolic disorders and stroke, which are not included in the Canadian Accutane product monograph, say the authors. These reactions occurred in four men and seven women, aged 15–48 years, who had received mean doses of isotretinoin 40–80 mg/day for four days to four months before reaction onset. At last follow-up, eight of the patients had recovered (one with sequelae), one had not yet recovered and outcomes were

unknown for the remaining two patients.

(Reports in WHO database: Vascular disorder - 26).

Reference:

Canadian Adverse Reaction Newsletter, April 2006, 16(2): 3.

Mifepristone

Two additional sepsis deaths

USA. Danco Laboratories has informed the US FDA of two additional deaths following medical abortion with mifepristone (Mifeprex), according to an US FDA Public Health Advisory; the US FDA is investigating all circumstances surrounding the cases, and cannot confirm the causes of death. Four previous deaths from sepsis associated with off-label mifepristone (Mifeprex) and misoprostol use have been reported to the US FDA. The US FDA advises that all medical abortion providers and their patients should be aware of risks associated with mifepristone use, including sepsis, and that physicians should discuss early potential signs and symptoms warranting immediate medical evaluation. The FDA reiterates the approved mifepristone (Mifeprex) regimen for medical abortion, including misoprostol use; the US FDA says that these recommendations are consistent with warnings in the Prescribing Information and Medication Guide. The US FDA also emphasizes awareness of the following:

- When patients undergoing medical abortion present with vomiting, nausea, or diarrhoea and weakness without fever or other signs of infection > 24 hours after receiving misoprostol, the possibility of sepsis should be investigated and a complete blood count considered.
- Immediate antibacterial treatment including

coverage of *Clostridium sordellii* should be considered in patients with this presentation.

The US FDA says that it does not have enough information to recommend prophylactic antibacterial use, as this treatment carries its own risk of serious adverse effects, and fatal sepsis reports are very rare in women undergoing medical abortion.

(Reports in WHO database: Sepsis - 7).

Reference:

Public Health Advisory. United States Food and Drug Administration, 17 March 2006
(<http://www.fda.gov>).

Miracle Bion Risk of *E.coli* contamination

Canada. Health Canada is warning consumers not to use the health product Miracle Bion as it could be contaminated with bacteria such as *E.coli*. Miracle Bion is promoted and distributed as an immune system booster and as a treatment for serious diseases such as cancer, asthma, dementia, influenza, tuberculosis, epilepsy and arthritis. Health Canada warns that the product is not approved in Canada. Miracle Bion contains humic and fulvic acids, which come from humus. Humus is made of decomposed plant and animal residues, is found in soil and could be contaminated with bacteria such as *E.coli*. Health Canada advises that *E.coli* contamination could have serious health implications and consumers who have used these products and are concerned about their health should contact a health-care professional.

Reference:

Warning. Health Canada, 28 April 2006
(<http://www.hc-sc.gc.ca>).

Pimecrolimus and tacrolimus

Cautious use recommended

Europe. The benefits associated with pimecrolimus (Elidel) and tacrolimus (Protopic/Protopy) use outweigh their risks, but greater caution is advised to reduce potential skin cancer and lymphoma risks, the European Medicines Agency's (EMA's) Committee for Medicinal Products for Human Use (CHMP) concluded on completion of a safety review. The CHMP began the safety review after reports of skin cancer and lymphoma in patients using the medications, but, on the basis of available data, was unable to establish a causal relationship; the CHMP has asked for more long-term safety profile data. Patients using the products should not stop or alter their treatment without first consulting their physician, advises the CHMP. Product information changes recommended by the CHMP aim to raise patient and prescriber awareness of potential long-term risks associated with the products' use.

(Reports in WHO database: Pimecrolimus: skin neoplasm malignant - 4, lymphoma - 5; tacrolimus: skin neoplasm - 27, lymphoma - 27).

Reference:

Press Release. European Medicines Agency (EMA), 14 March 2006
(<http://www.emea.eu.int>).

Polygonum multiflorum Risk of liver effects

UK. The UK Medicines and Healthcare products Regulatory Agency (MHRA) has issued a warning about potential risks with *Polygonum multiflorum* use after the Agency received several suspected adverse drug

reaction reports of liver disorders, including jaundice and hepatitis. *Polygonum multiflorum* root tuber is traditionally used in Chinese medicines as a tonic and an anti-ageing remedy, particularly for hair loss and premature greying of hair. The Agency advises members of the public who experience liver-disorder symptoms while taking *Polygonum multiflorum*-containing products to see their doctor and to stop taking the product immediately if a liver disorder is diagnosed. *Polygonum multiflorum* is also known by the Chinese name He Shou Wu (Heshouwu), and may be an ingredient in other traditional health products including, Shou Wu Pian, Shou Wu Wan, and Shen Min. The MHRA says that the safety of this product will continue to be reviewed.

Reference:

Press Release. UK Medicines and Healthcare products Regulatory Agency, 28 April 2006
(<http://www.mhra.gov.uk>).

Yohimbine- containing products Dangerous in high-risk groups

Canada. Health Canada has issued an Advisory, warning consumers not to use unapproved yohimbine- or yohimbine-containing bark products, including Strauss Energy SIX* capsules manufactured by Strauss Herb Company, because yohimbine may pose serious health risks for people with underlying risk factors such as hypertension or heart, liver or kidney disorders. Health Canada says that the most consistently reported yohimbine-associated adverse effects (AEs) are anxiety and increased urinary frequency; other AEs include dizziness, GI disorders, diaphoresis, insomnia, headache,

palpitations, severe hypertension and tremors. Health Canada advises consumers who have used the products, and have health concerns, to contact their physician, and that yohimbine should not be used in pregnant or nursing women, or children.

(* Not authorized for sale in Canada but promoted to increase energy levels, build body mass and restore or enhance sexual performance).

Reference:

*Advisory. Health Canada,
10 April 2006
(<http://www.hc-sc.gc.ca>).*

Pharmacists reporting ADRs in the UK

Pharmacists are responsible for almost one in five adverse drug reaction (ADR) reports sent to the UK Medicines and Healthcare products Regulatory Agency (MHRA), according to the Agency's annual report for 2004–2005. According to the report, hospital pharmacists submitted 13% of yellow card ADR reports and community pharmacists submitted 5%; general practitioners and hospital doctors submitted 28% and 25% of ADR reports, respectively. The Agency also noted that there was a 4% increase in yellow card reporting from health professionals compared with the previous year, which it attributes mainly to an increased number of electronic reports received via their new website.

(Reference: <http://www.mhra.gov.uk>).

New Challenges in Safety of Medicines: highlights from the Twelfth International Conference of Drug Regulatory Authorities

The International Conference of Drug Regulatory Authorities (ICDRA) provides a forum for drug regulatory authorities of WHO Member States to meet and discuss ways to strengthen collaboration. The Conferences have been held since 1980 and are important for WHO and drug regulatory authorities in their efforts to harmonize regulation and improve the safety, efficacy and quality of medicines.

The Twelfth meeting of the ICDRA was held 3-6 April 2006 in Seoul, Republic of Korea. 'New Challenges in Safety of Medicines' was a plenary of particular interest and relevance. Several old issues and many new developments provided the perfect reason and background to this session.

High-profile drug safety issues, like those of cisapride and rofecoxib have presented numerous challenges for drug regulators. New ways to improve knowledge about benefit/risk assessment, methods of signal detection, and communications to health professionals and the public are continually being sought. Spontaneous adverse drug reaction reporting has long been the cornerstone of pharmacovigilance and continues to serve a vital function, but changes in public expectations and drug development are encouraging regulators to think about pharmacovigilance as early as possible in the product "life cycle".

The International Conference on Harmonization (ICH) guideline on Pharmacovigilance Planning, which was presented at the session emphasizes that although a great deal is known about a medicine when it is approved for marketing, not everything is known yet. New information about a medicine, including safety information, continues to evolve as experience with the drug grows after the time of its initial marketing. A case in point is the development in Ghana where regulators have been facing a challenging situation since the policy for treatment of malaria was changed. The new malaria treatment policy was implemented from the beginning of 2005 to phase out the use of chloroquine because of high levels of resistance and to recommend combination therapy with artesunate-amodiaquine tablets in Ghana. In November 2005, over 50 reports of serious adverse reactions to certain of these products were reported to the national pharmacovigilance centre. The media became involved and a press conference by the Ministry of Health led to the withdrawal of the suspected products from the market, the establishment of a ministerial task force to review the policy implementation and the initiation of pharmacovigilance studies in the country. The cause of these adverse reactions is still being carefully investigated.

The aim of Pharmacovigilance Planning is to provide regulators with a proactive approach to filling in knowledge gaps, while also improving the probability of detecting important safety signals as early as possible. Ultimately this will result in better treatment choices for patients as they and their caregivers will have better information with which to make those choices. Pharmacovigilance Planning is an exciting opportunity in which to implement current best practices for pharmacovigilance as new ones continue to be developed.

Specific areas of change within the United States Food and Drug Administration (US FDA) were also presented at the ICDRA. These are the involvement of more outside expert consultations, the improvement of drug safety management practices by the publication of various risk management guidances, the improvement of scientific methods of adverse event signal detection and better and earlier communication to health professionals and the public of drug safety concerns. A web-based solution for reporting adverse events following immunization in the Republic of Korea was presented. This has been an important development addressing the huge problem of collecting and reporting adverse events for vaccines. The web-based approach has resulted in a major increase in the number of reports in Korea. It is clear that, in addition to pharmacovigilance planning, challenges in obtaining quality adverse event reports, cooperation between regulatory agencies, and communicating effectively with the public are to the fore.