WHO PHARMACEUTICALS NEWSLETTER

World Health Organization

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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Contents

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News & Issues

Three items in this issue have received much media attention: nelfinavir, nimesulide and rosiglitazone. Roche undertook a worldwide withdrawal of nelfinavir amidst concerns that some batches of the product were contaminated with a genotoxic substance. WHO issued a Statement for general information and an Information Exchange System Alert for the attention of global regulatory authorities.

Nimesulide on the other hand is an old issue revisited. In May 2007 the Irish Medicines Board withdrew the drug in the country on receiving six new reports of nimesulide-associated liver failure. It may be recalled that in 2003 the EMEA had adopted a positive opinion for nimesulide, that the drug had a favourable benefit-risk profile. This decision was based on a review of all available evidence at that time. Clearly a more critical reappraisal is needed now, given the current information. It is also of interest that the Irish reports were received from a liver transplant clinic. This is (arguably) the first time that adverse reaction reports have been received from this sector of health care.

A meta-analysis suggesting a significant risk of myocardial infarction with rosiglitazone has raised comments. Critics are discussing the reliability of meta-analysis in general and in particular, the absence of primary or time-to-event data in the current analysis. While the debate continues, rosiglitazone will have to be kept under close surveillance.

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TABLE OF CONTENTS

Regulatory Matters

Safety of Medicines

Feature

Antidepressant medications

Black box warning update about increased risks of suicidality

USA. The United States Food and Drug Administration (US FDA) is advising all manufacturers to update their labels for all of their antidepressant products. The black box warnings in the labels for these products will now include warnings about increased risks of suicidality (suicidal thinking and behaviour) in the early treatment period (first one to two months) in young adults aged 18 to 24 years. The labelling changes will also include language stating that scientific data did not show an increased risk of suicidality in adults older than 24 and that adults 65 years of age and above taking the antidepressants have a decreased risk of suicidality.

Results of individual placebo-controlled scientific studies are reasonably consistent in showing a slight increase in suicidality with most antidepressants in the early phase of treatment. Therefore the proposed labelling changes will apply to the entire category of antidepressants.

In 2004, the US FDA directed all manufacturers of all antidepressants to include a 'black box' warning about an increased risk of suicidality in children (see WHO Pharmaceuticals Newsletter No. 6, 2004). Later, in 2005, the Agency began a comprehensive review of 295 individual antidepressant trials that included over 77 000 adult patients with major depressive disorder (MDD) and other psychiatric disorders, to examine the risk of suicidality in adults receiving antidepressants.

The present updates to the boxed warning follows the US FDA's Psychopharmacologic Drug Advisory Committee's conclusions that the labels should indicate both the increased risk of suicidality in younger adults using antidepressants, and the apparent beneficial effect in older adults treated with the antidepressants. The current update is also intended to remind health-care professionals that the disorders themselves are the most important cause of suicidality.

Reference:
FDA News. U.S. Food and Drug Administration, 2 May 2007 (www.fda.gov).

Desmopressin nasal spray

Primary nocturnal enuresis (PNE) no longer an approved indication

UK. Primary nocturnal enuresis (PNE, bedwetting) is no longer an approved indication of desmopressin nasal spray products (Desmospray). This measure was requested by the UK Medicines and Healthcare products Regulatory Agency (MHRA) because, according to the Agency, the nasal formulations were associated with a majority of the adverse drug reactions occurring in PNE patients while the oral formulations had a more favourable risk-benefit profile. Rare, serious ADRs associated with nasal desmopressin included hyponatraemia, seizures and water intoxication. Nasal desmopressin is still approved in cranial diabetes insipidus and multiple sclerosis related nocturia.

Reference:
Letter to health-care providers from MHRA, 18 April 2007 (www.mhra.gov.uk).

Gadolinium-based contrast agents

Boxed warning about risk of nephrogenic systemic fibrosis

USA. The US FDA has asked manufacturers to include a boxed warning on the product labelling of all gadolinium-based contrast agents which are used to enhance the quality of magnetic resonance imaging (MRI). The warning will state that patients with severe kidney insufficiency who receive these agents are at risk for developing a debilitating and potentially fatal disease known as nephrogenic systemic fibrosis (NSF). In addition, the label will also state that patients just before or just after liver transplantation or those with chronic liver disease are also at risk for developing NSF with these agents if they are experiencing kidney insufficiency of any severity. Patients with NSF develop thickening of the skin and connective tissues that inhibits their ability to move and may result in broken bones. Other organs are at risk as well. The cause of NSF is not known and there is no consistently effective treatment of this condition. (See WHO Pharmaceuticals Newsletter No. 4, 2006 for reports of gadodamide-associated NSF in Canada).

Reference:
FDA News. U.S. Food and Drug Administration, 23 May 2007 (www.fda.gov).

Nelfinavir (Viracept)

Marketing authorization suspended due to possible contamination with genotoxic substance

Europe. The European Medicines Agency (EMEA) has recommended that the marketing authorization for nelfinavir (Viracept) should be suspended (1). Nelfinavir is an antiretroviral medicine used to treat HIV-1 infected adults, adolescents and children of three years of age and older. Viracept has also been suspended from the list of WHO prequalified products (2).

The current suspension follows an earlier Press Release from the EMEA (3) that nelfinavir was being recalled by the company Roche due to the presence of ethyl mesylate in some batches of the product. Ethyl mesylate is a genotoxic substance. As the contamination may have affected all strengths and presentations of Viracept, the company has undertaken a worldwide recall of this medicinal product. All packs of Viracept currently available on the market are being recalled. Packs of the product that patients may have at home are to be returned to the pharmacy.

Patients receiving Viracept have been directed to contact their doctor immediately for advice on appropriate treatment alternatives.

WHO has also issued various communications on the subject (4, 5).

The EMEA has now outlined a specific action plan to follow-up patients who were exposed to the contaminated product (1). The Agency:
1. has requested the company (Roche) to carry out studies in animals in order to establish precisely which doses of ethyl mesylate may be toxic to humans,
2. has asked Roche to identify the group of patients who have been exposed to batches of contaminated Viracept with a view to establishing appropriate follow-up and monitoring of these patients.

The EMEA's Committee for Medicinal Products for Human Use (CHMP) has also advised that the following groups should be followed up:
1. patients exposed to high levels of the contaminant in batches of Viracept released since March 2007,
2. all pregnant women who have ever been exposed to Viracept,
3. all children who have ever been exposed to Viracept, including those exposed in utero.

The EMEA will review the situation as data from these measures become available.

References:

1. Press Release. European Medicines Agency, EMEA/275367/2007, 21 June 2007. (www.emea.europa.eu).
2. Suspension of Viracept from the list of WHO prequalified products. WHO Prequalification Programme, 21 June 2007 (http://mednet3.who.int/prequal).
3. Press Release. European Medicines Agency, EMEA/251283/2007, 6 June 2007 (www.emea.europa.eu).
4. WHO Statement on Roche's Viracept recall. WHO Prequalification Programme, 14 June 2007. (http://mednet3.who.int/prequal).
5. WHO Information Exchange System Alert No. 114, 11 June 2007 (http://www.who.int/medicines/publications/drugalerts/en/index.html).

Nimesulide-containing products for oral use

Marketing suspended in Ireland due to reports of liver failure

Ireland. The Irish Medicines Board (IMB) has announced the suspension of the marketing and sale of nimesulide-containing medicinal products for oral use available in Ireland, with immediate effect (1). The suspended products include Aulin (100 mg tablets and granules), Mesulid (100 mg tablets and granules) and Mesine (100 mg tablets). The IMB decision was based on new information from a National Liver Transplant Unit that six patients required liver transplant following treatment with nimesulide.

Nimesulide is a non-steroidal anti-inflammatory medicine authorized in many countries for the treatment of acute pain, the symptomatic treatment of painful osteoarthritis and for primary dysmenorrhoea. Liver damage is a serious and rare damage known to occur with nimesulide and the IMB had previously issued advice to health-care professionals regarding this risk. The IMB has received 53 liver-related adverse reaction reports with nimesulide since the product was first approved for use in Ireland in 1995.

The IMB has notified the medicines regulatory authorities throughout Europe of the six new cases of nimesulide associated liver failure and has initiated a referral for a full safety review of nimesulide-containing products by the EMEA.

WHO has issued an Information Exchange System Alert for wider dissemination of the IMB decision to suspend oral

nimesulide-containing products from the Irish market (2).

In 2003 the Committee for Proprietary Medicinal Products (CPMP) made a referral to the EMEA that the benefit-risk profile of nimesulide-containing products for systemic topical use is favourable (see WHO Pharmaceuticals Newsletter No. 4, 2003).

In the WHO database there are a total number of 320 reports of liver and biliary system disorders in patients who received nimesulide. Of these, 18 cases have been shown to have a clear association with nimesulide use.

Reference:

1. Press Release from the Irish Medicines Board, 15 May 2007 (www.imb.ie).
2. WHO Information Exchange System Alert No. 113, (www.who.int/medicines/publications/drugalerts).

Tizanidine

Concomitant use with fluvoxamine or ciprofloxacin contraindicated

USA. Tizanidine is a centrally acting α-2 adrenergic agonist. It is used to treat the spasms, cramping, and tightness of muscles caused by medical problems such as multiple sclerosis, spastic diplegia, back pain, or certain other injuries to the spine or central nervous system. Acorda Therapeutics, in consultation with the US FDA has issued a 'Dear health-care professional' letter warning that tizanidine should not be used concomitantly with the potent CYP1A2 inhibitor drugs flouvoxamine and ciprofloxacin. This contraindication is based on the fact that both fluvoxamine and ciprofloxacin are potent inhibitors of the enzyme CYP1A2, an enzyme needed for the metabolism of tizanidine. Acorda warns that the interaction between tizanidine and either flovoxamine or ciprofloxacin is characterized by dangerously high serum levels of tizanidine and is most likely due to the inhibition of CYP1A2 by fluvoxamine or ciprofloxacin. Although there are no clinical studies evaluating the effect of other CYP1A2 inhibitors on tizanidine, other CYP1A2 inhibitors may lead to substantial increases in tizanidine blood concentrations. Therefore, concomitant use of tizanidine with other CYP1A2 inhibtors such as zileuton, other fluoroquinolones, antiarrhythmics (amiodarone, mexiletine, propafenone and verapamil), cimetidine, famotidine, oral contraceptives, acyclovir and ticlopidine should ordinarily be avoided. The product label for tizanidine has been updated with this contraindication.

References:

'Dear health-care professional' letter from Acorda Therapeutics, 5 March 2007 (www.fda.gov).

Trimetho-benzamide

Suppository drug products not approved

USA. The US FDA has announced that suppository products of trimethobenzamide are not approved to treat nausea and vomiting in adults or children. The Agency has asked the responsible companies to stop manufacturing and distributing these products which are marketed under various names (Tigan, Tebamide, T-Gen, Trimazide and Trimethobenz). The US FDA warns that there is no evidence of effectiveness of suppository trimethobenzamide in nausea and vomiting. Consumers are urged to contact their health provider regarding alternative products approved to effectively treat nausea and vomiting: these are available in a variety of dosage forms, including tablets, capsules, solutions, injectables and suppositories.

The Agency adds that several oral capsules and injectable products containing trimethobenzamide have been approved by FDA and are not affected by the current action. Any company wishing to market a product containing trimethobenzamide in suppository form must now obtain an approved new drug application prior to marketing.

Reference:

FDA News. U.S. Food and Drug Administration, 6 April 2007 (www.fda.gov).

Bevacizumab

Tracheo-esophageal fistulas if given with concurrent chemotherapy and radiation in SCLC patients

USA, UK. Genentech (in the USA) and Roche (in the UK) have written to health-care professionals that tracheo-esophageal (TE) fistula occurred in patients with limited stage small cell lung cancer (SCLC) in a study combining concurrent chemotherapy and radiation plus bevacizumab (Avastin) in these patients. Bevacizumab is not indicated in SCLC.

The patients in the study received four cycles of concurrent irinotecan, carboplatin, radiation therapy, and bevacizumab followed by maintenance bavacizumab for up to six months. The letters note that there were two confirmed serious adverse events of TE fistula (one fatal) reported amongst the first 29 patients enrolled in the study. A third fatal event was also reported in which TE was suspected but not confirmed. All three events occurred during the bevacizumab maintenance phase.

The letters advise that health-care providers should

2. 'Dear Health-care provider' letter from Roche, 8 May 2007 (www.mhra.gov.uk).

Citrus auranthium (bitter orange)

Reports of adverse cardiovascular effects

Canada. Between 1 March 2004 and 31 October 2006, Health Canada received 21 domestic reports of adverse reactions suspected of being associated with *Citrus auranthium* (bitter orange). Of these, 15 reports were of cardiovascular adverse reactions, 10 of which were serious and included one report of myocardial infarction. According to Health Canada, synephrine, an alpha-adrenoceptor agonist found in bitter orange, can have serious adverse effects on heart rate and blood pressure; these effects are significantly potentiated by caffeine. Synephrine is found in various natural health products that are promoted for weight loss. Health Canada cautions that the following people may be particularly at risk of adverse reactions from synephrine-containing products:

- those with heart conditions, Central Nervous System (CNS) disorders, diabetes mellitus, enlarged prostate, glaucoma, hypertension, phaeochromocytoma,

Clozapine

Reports of myocarditis

Australia. Clozapine, an antipsychotic drug, was approved in Australia in 1993. 116 cases of suspected myocarditis associated with the use of clozapine had been reported to the Australian Adverse Drug Reactions Advisory Committee (ADRAC) during 1993-2003. A boxed warning in the product label for clozapine alerts prescribers to the risk of myocarditis and cardiomyopathy with the product. ADRAC warns that potentially fatal myocarditis may develop early after the commencement of clozapine treatment, often within the first 28 days. Initial symptoms may be non-specific such as tachycardia, fever and flu-like symptoms. According to ADRAC, if myocarditis is confirmed, clozapine should be discontinued.

Reports in the WHO database: Myocarditis - 436

Reference:
Australian Adverse Drug Reactions Bulletin, Vol. 26(3): 10, June 2007 (www.tga.gov.au).

Metformin

Risk factors for lactic acidosis

Sweden. The Medical Products Agency (MPA) in Sweden is