WHO PHARMACEUTICALS NEWSLETTER

World Health Organization

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

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This is a double edition, that combines volumes No. 6, 2009 and No. 1, 2010. Some of the information might therefore be a bit outdated but we wish to present them anyhow, for those of you who do not have ready access to this information from other sources. Under 'Feature' we include an article on the WHO programme for the prequalification of quality control laboratories; and the recommendations from the thirty-second meeting of representatives participating in the WHO Programme for International Drug Monitoring.

We wish you all a very good year in 2010. And thank you for your interest in the newsletter

The aim of the 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:

Quality Assurance and Safety: Medicines, EMP-HSS, World Health Organization, 1211 Geneva 27, Switzerland, E-mail address: pals@who.int

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

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Safety of Medicines

Feature

Benfluorex

Withdrawal recommended

Europe. The European Medicines Agency (EMEA) has recommended the withdrawal of all medicines containing benfluorex in the European Union, because their risks, particularly the risk of heart valve disease, are greater than their benefits. Benfluorex is approved for use in overweight patients with diabetes, combined with an appropriate diet.

This recommendation follows a review by the EMEA's Committee for Medicinal Products for Human Use (CHMP) on the safety and efficacy of benfluorex. The CHMP considered that the data indicate a risk of heart valve diseases associated with the use of benfluorex, and that the efficacy of benfluorex in the treatment of diabetes is limited. Therefore, the Committee concluded that the benefits of benfluorex no longer outweigh its risks, and recommended the revocation of all marketing authorisations for medicines containing benfluorex in the European Union.

The EMEA advises that doctors should stop prescribing benfluorex and consider alternative treatments. For patients currently treated with benfluorex, the Agency recommends making an appointment with their doctor at a convenient time, to change their prescription. In addition, patients who have taken benfluorex in the past are advised to mention this to their doctor so that they can be checked for the signs and symptoms of heart valve disease, because heart valve disease can develop some years after treatment.

Reports in WHO Global ICSR database, Vigibase

Benfluorex

Reported reactions (number of events):
Aortic valve incompetence: 2
Heart valve disorders: 6
Mitral insufficiency: 8

Reference:
Press Release, Questions and Answers, EMEA
18 December 2009
(www.emea.europa.eu).

Ceftriaxone

Incompatibility with calcium-containing solutions

Canada (1). Health Canada has issued a Notice to Hospitals regarding updated prescribing information for ceftriaxone with the following new recommendations, which are based on the results of two recent in vitro studies that showed an increased risk of ceftriaxone-calcium precipitates in neonatal plasma.

- Contraindications: Ceftriaxone is contraindicated in neonates if they require (or are expected to require) treatment with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition, because of the risk of precipitation of ceftriaxone-calcium.

- Warnings: In patients other than neonates, ceftriaxone and calcium-containing solutions may be administered sequentially if the infusion lines are thoroughly flushed between infusions with a compatible fluid.

- Warnings: Diluents containing calcium, such as Ringer's solution or Hartmann's solution, are not to be used to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for intravenous administration because a precipitate can form. Ceftriaxone must not be administered simultaneously with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site, because precipitation of ceftriaxone-calcium can occur.

The Notice states that there have been no reports of interactions between ceftriaxone and oral calcium-containing products or interactions between intramuscular ceftriaxone and calcium-containing products (intravenous or oral).

Ceftriaxone is a long-acting broad spectrum cephalosporin antibiotic for parenteral use. It is indicated for the treatment of lower respiratory tract infections, urinary tract infections, bacterial septicaemia, skin and skin structure infections, bone and joint infections, intra-abdominal infections, and meningitis, when caused by susceptible organisms. Ceftriaxone is also indicated for uncomplicated gonorrhoea and for prophylaxis of patients undergoing certain surgical procedures.

UK (2). The Medicines and Healthcare products Regulatory Agency (MHRA) has emphasized that ceftriaxone should not be given simultaneously with calcium-containing solutions (other than total parenteral nutrition solutions) for intravenous administration because of a risk of calcium precipitation. Ceftriaxone is contraindicated in newborns up to age 28 days who need intravenous treatment with calcium-containing solution including total parenteral nutrition solutions as well as those who have jaundice or who are hypoalbuminaemic or acidotic, because these are conditions in which bilirubin

binding is likely to be impaired. Health-care professionals are also advised that calcium and ceftriaxone may be infused sequentially in patients aged 28 days or older provided that either a) the infusion line is rinsed or flushed between solutions, or b) the infusions are given via different infusion lines at different sites.

The MHRA explains that a review of the available data suggests that newborns (up to age 28 days) are at greater risk of calcium–ceftriaxone precipitation than older patients, particularly if they are premature or have impaired bilirubin binding. The risk of calcium–ceftriaxone precipitation in adults is likely to be low; however, as a precaution, ceftriaxone and calcium should not be administered simultaneously by the intravenous route. The Agency also warns that some total parenteral nutrition solutions contain similar levels of calcium to that in saline solutions such as Ringer's or Hartmann's, and may present a similar degree of risk.

(See WHO Pharmaceuticals Newsletters No. 3, 2009 and No. 4, 2008 for related information in USA and Canada respectively).

***References**:*
(1) Advisories, Warnings and Recalls, Health Canada, 15 October 2009 (www.hc-sc.gc.ca).
(2) Drug Safety Update, MHRA, Volume 3, Issue 3, October 2009 (www.mhra.gov.uk).

Clopidogrel

Drug interaction with omeprazole

USA. The United States Food and Drug Administration (US FDA) has warned health-care professionals and the public about an interaction between clopidogrel (Plavix), an anti-clotting medicine, and omeprazole (Prilosec and Prilosec OTC), a proton pump inhibitor (PPI). New data show that when clopidogrel and omeprazole are taken together, the effectiveness of clopidogrel is reduced. Separating the administration of clopidogrel and omeprazole in time will not reduce this drug interaction.

The US FDA explains that omeprazole inhibits the drug metabolizing enzyme (CYP2C19) which is responsible for the conversion of clopidogrel into its active metabolite. The new studies compared the amount of clopidogrel's active metabolite in the blood and its effect on platelets (anti-clotting effect) in people who took clopidogrel plus omeprazole versus those who took clopidogrel alone. A reduction in active metabolite levels of about 45% was found in people who received clopidogrel with omeprazole compared to those taking clopidogrel alone. The effect of clopidogrel on platelets was reduced by as much as 47% in people receiving clopidogrel and omeprazole together. These reductions were seen whether the drugs were given at the same time or 12 hours apart.

With regard to other medicines that are expected to have a similar effect, the US FDA recommends avoiding the concomitant use of the following medicines and clopidogrel: cimetidine, fluconazole, ketoconazole, voriconazole, etravirine, felbamate, fluoxetine, fluvoxamine, and ticlopidine. In addition, esomeprazole, which is a component of omeprazole, inhibits CYP2C19 and should be avoided in combination with clopidogrel. The Agency states that at this time, it does not have sufficient information about drug interactions between clopidogrel and PPIs other than omeprazole and esomeprazole to make specific recommendations about their co-administration. Health-care professionals and patients are advised to consider all treatment options carefully before beginning therapy.

Health-care professionals are also advised that there is no evidence that other drugs that reduce stomach acid, such as most H2 blockers ranitidine, famotidine, nizatidine, except cimetidine (a CYP2C19 inhibitor) or antacids interfere with the anti-clotting activity of clopidogrel. The clopidogrel label has been updated with new warnings on omeprazole and other medicines that inhibit the CYP2C19 enzyme that could interact with clopidogrel in the same way.

(See WHO Pharmaceuticals Newsletters No. 2, 3, 4 and 5, 2009 for previous information from USA, Canada and New Zealand, Europe, and Ireland respectively).

***Reference**:*
Safety Information, US FDA, 17 November 2009 (www.fda.gov).

Cough and cold medicines

Contraindication recommended

New Zealand. New Zealand Medicines and Medical Devices Safety Authority (Medsafe) has announced that the Cough and Cold Review Group (CCRG) concluded the risk-benefit balance of cough and cold medicines to be unfavourable in children under six years of age. The CCRG has therefore recommended that cough and cold medicines containing the following substances be

contraindicated for use in children under six years of age; brompheniramine, chlorphenamine, dextromethorphan, diphenhydramine, doxylamine, guaifenesin, ipecacuanha, phenylephrine, pholcodine, promethazine, pseudoephedrine, and triprolidine. The CCRG considered that cough and cold medicines containing bromhexine alone, or intra-nasal decongestants (such as oxymetazoline and xylometazoline) should remain available to adults and children over two years of age. Medsafe states that it will work closely with the pharmaceutical industry to implement the recommendations as soon as possible.

(See WHO Pharmaceuticals Newsletters No. 2 and 3, 2009 for new advice on the use of cough and cold medicines in children in Kenya and the UK, Canada and New Zealand, respectively).

***Reference**:*
Prescriber Update Vol. 30, No.4, November 2009 (www.medsafe.govt.nz).

Cyproterone acetate

Risk of meningiomas

UK. The MHRA has advised health-care professionals that patients with existing meningioma or a history of meningioma must not be prescribed cyproterone acetate at doses of 25 mg per day or higher (Cyprostat-50, Cyprostat-100, or Androcur-50). The Agency states that this advice does not apply to medicines that contain low-dose cyproterone acetate such as co-cyprindiol (Dianette). Product information for all products that contain high-dose cyproterone acetate will be updated accordingly.

High-dose cyproterone acetate is indicated for use in the treatment of prostate cancer (dose 50–300 mg per day) and for the control of libido in men with severe hypersexuality or sexual deviation. Lower-dose cyproterone acetate (2 mg) is available for use in women as co-cyprindiol (Dianette) in combination with 35 micrograms ethinylestradiol for the treatment of severe acne that is refractory to prolonged antibiotic therapy, and for moderately severe hirsutism.

The MHRA says that meningiomas are the most common intracranial tumours, with an annual incidence of 6 per 100 000 in the general population. Multiple meningiomas account for approximately 1 to 10% of all cases. Though histologically benign, they can have serious consequences. The occurrence of (multiple) meningiomas has been reported in association with longer-term use (years) of cyproterone acetate at doses of 25 mg/day or higher. According to the Agency, until September 2009, 36 cases of meningioma, of which 19 described multiple meningioma, have been reported worldwide in association with high-dose cyproterone acetate. Of the 36 cases, 32 occurred in women and four in men. Duration of treatment with cyproterone acetate ranged from 4 years to 27 years, and in all but one case it was prescribed at doses higher than 25 mg per day. None of the reported cases had a fatal outcome.

***Reference**:*
Drug Safety Update, MHRA, Volume 3, Issue 3, October 2009 (www.mhra.gov.uk).

Desipramine hydrochloride

Update to prescribing information

USA. Health-care professionals were notified of changes to the Warnings and Overdosage sections of the prescribing information for desipramine hydrochloride (Norpramin). The medicine is indicated for the treatment of depression. The new safety information warn that extreme caution should be used when this medicine is given to patients who have a family history of sudden death, cardiac dysrhythmias or cardiac conduction disturbances; and that seizures precede cardiac dysrhythmias and death in some patients.

Reference:
Safety Information, US FDA 2 December 2009 (www.fda.gov).

Diclofenac sodium

Revisions to the prescribing information to warn of hepatic reactions

USA. Health-care professionals were notified of revisions to the prescribing information to add new warnings and precautions about the potential for adverse liver effects with all products containing diclofenac sodium.

According to Dear Healthcare Professional Letter for diclofenac sodium topical gel (Voltaren® Gel) 1% (non-steroidal anti-inflammatory medicine), in post-marketing reports, cases of drug-induced hepatotoxicity have been reported in the first month but can occur at any time during treatment with diclofenac. Post-marketing surveillance has reported cases of severe hepatic reactions, including liver necrosis, jaundice, fulminant hepatitis with and without jaundice, and liver failure. Some of these reported cases resulted

in fatalities or liver transplantation.

Physicians are advised to measure transaminases periodically in patients receiving long-term therapy with diclofenac, because severe hepatotoxicity may develop without a prodrome of distinguishing symptoms. It is also stated that transaminases should be monitored within 4 to 8 weeks after initiating treatment with diclofenac; however, severe hepatic reactions can occur at any time during treatment with diclofenac.

Reports in WHO Global ICSR database, Vigibase:

Diclofenac sodium

Number of reports with liver and biliary system disorders: 1855

Most reported reactions (number of events):
Hepatic enzymes increased: 159
SGOT increased: 269
SGPT increased: 280
Gamma-GT increased: 133
Hepatic function abnormal: 580
Hepatitis: 507
Hepatitis cholestatic: 167
Bilirubinaemia: 214
Jaundice: 279

Diclofenac

Number of reports with liver and biliary system disorders: 2235

Most reported reactions (number of events):

(www.fda.gov).

Etravirine

Risk of severe skin and hypersensitivity reactions

Canada. Health-care professionals have been informed that severe, potentially life-threatening, and fatal skin reactions have been reported in patients receiving combination therapy that included etravirine (INTELENCE) tablets. These include cases of Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme. Hypersensitivity reactions have also been reported and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure. The advise emphasizes the importance of immediate discontinuation of etravirine (INTELENCE) in cases where signs or symptoms of severe skin reactions or hypersensitivity reactions develop, including severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, eosinophilia. Health-care professionals are also advised that clinical status including liver transaminases should be monitored and appropriate therapy should be initiated. This safety information will be incorporated in the

due to rash. Rash occurred most commonly during the first six weeks of therapy. The most frequently reported adverse drug reaction (ADR) of at least Grade 2 in severity in the Phase 3 studies was rash (9.0%). Stevens-Johnson syndrome, severe hypersensitivity reaction, and erythema multiforme were reported in < 0.1% of subjects during clinical development with etravirine (INTELENCE). In general, rash was mild to moderate, occurred primarily in the second week of therapy and was infrequent after Week 4. Rash generally resolved within one to two weeks on continued therapy.

(See WHO Pharmaceuticals Newsletter No. 5, 2009 for revisions to the prescribing information for etravirine in USA and the number of reports in the WHO Global Individual Case Safety Reports (ICSR) database, Vigibase).

***Reference**:*
Advisories, Warnings and Recalls, Health Canada
15 October 2009
(www.hc-sc.gc.ca).

Exenatide

Reports of renal failure

USA. The US FDA has notified health-care professionals of revisions to the prescribing information for exenatide (Byetta) to include information