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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Three titles in this issue deserve special mention: nelfinavir, nimesulide and lumiracoxib. Nelfinavir was suspended in August 2007 in Europe when several batches of the active substance were contaminated with ethyl methanesulfonate, a known genotoxic substance. The European Medicines Agency (EMEA) has now reinstated the marketing authorization in Europe, having assured itself that the contamination has been eliminated and that future productions of nelfinavir would meet the required quality standards. In May 2007 the Irish Medicines Board (IMB) announced the suspension of the marketing and sale of oral nimesulide in Ireland. (The IMB also presented nimesulide as a drug of current interest at the Thirtieth Annual Meeting of National Pharmacovigilance Centres in Buenos Aires, Argentina, in October 2007; a report from this meeting will be included in the next issue of the newsletter.) The EMEA, on the other hand, has recently concluded that available data do not support a full suspension of nimesulide, thus only restricting its use. Reports of hepatotoxicity have provoked various regulatory measures for lumiracoxib: some countries have favoured its market withdrawal while others have retained the lower dose in the market.

Pharmacovigilance in resource limited settings faces several challenges, including the absence of qualified personnel. Recently, WHO organized a course for consultants in Ghana: the idea was to create a pool of pharmacovigilance experts who could provide cross-border consultancy services for pharmacovigilance in Africa. A report on the training is included.

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TABLE OF CONTENTS

Clobutinol-containing cough preparations

Withdrawn due to adverse cardiac effects

Europe, Worldwide. The European Medicines Agency (EMEA) has recommended withdrawing the marketing authorization for cough medicines containing clobutinol (1). This recommendation is based on the Agency's review of the safety of clobutinol and its conclusion that the benefits of medicines containing clobutinol no longer outweigh their risks. In 2007 the German medicines regulatory authority suspended the marketing authorization for medicines containing clobutinol based on information from the manufacturer (Boehringer Ingelheim) that clobutinol was linked to adverse cardiac effects. Boehringer Ingelheim had shared the preliminary results of a study that was being performed in healthy volunteers; these results showed that the use of clobutinol led to QT-prolongation. The Committee on Medicinal Products for Human Use (CHMP) has now reviewed all available information on the safety of clobutinol and has concluded that:

- the use of clobutinol is linked to a clear risk of QT prolongation
- this risk increases when patients take higher doses of the medicine

The EMEA advises that:

- patients who are currently taking clobutinol should consult their doctor or pharmacist to discuss alternative treatments;
- the risk linked to clobutinol therapy is temporary, so there is no risk in patients who have taken the medicine in the past; and
- prescription providers should not issue any new prescriptions for clobutinol.

In September 2007 Boehringer Ingelheim laboratories announced their decision to voluntarily withdraw the product (Silomat) from the global markets (2).

References:

1. Press Release. EMEA, 18 October 2007 (www.emea.europa.eu)
2. Letter to prescribers. AFSSAPS, 4 September 2007 (http://agmed.sante.gouv.fr).

Ephedrine and pseudoephedrine containing nasal decongestants

OTC products to have tighter controls

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) has announced today that pseudoephedrine and ephedrine contained in nasal decongestants in cold and flu remedies are to have tighter controls. This follows a public consultation initiated by the MHRA as there has been an increasing concern about the potential for pseudoephedrine and ephedrine to be extracted from over-the-counter (OTC) medicines and used in the illegal manufacture of methylamphetamine (crystal meth). The CHMP has recommended that large packs of pseudoephedrine and ephedrine should be replaced by smaller packs of 720 mg (the equivalent of 12 tablets or capsules of 60 mg or 24 tablets or capsules of 30 mg) and for there to be a limit of one pack per customer. The Commission also recommended that the sale should be carried out by a pharmacist. The legal status of products containing pseudoephedrine and ephedrine should be reclassified from 'pharmacy only' to 'prescription only' (POM) in 24 months time (2009) or earlier if necessary, unless the risk of the misuse of these OTC medicines in the illicit manufacture of methylamphetamine is contained by the measures outlined.

Reference:

Press Release. MHRA, 29 August 2007 (www.mhra.gov.uk).

Exenatide

Reports of acute pancreatitis; label to be updated

USA. The United States Food and Drug Administration (US FDA) is advising that some postmarketing reports suggest an association between acute pancreatitis and exenatide (Byetta) use. Exenatide is the first of a new class of medications (incretin mimics) approved in the treatment of type 2 diabetes. It is used as an injection (s.c), with either sulfonylureas, metformin or with thiazolodinediones and increases insulin synthesis and secretion in the presence of glucose. The US FDA has reviewed 30 postmarketing reports of acute pancreatitis in patients treated with exenatide (Byetta), 27 of the 30 patients had at least one other risk factor for acute pancreatitis such as gallstones, severe hypertriglyceridaemia, and alcohol use. In six patients the symptoms of pancreatitis began or worsened soon after the dose of exenatide was increased from 5 micrograms twice daily to 10 micrograms twice daily. Twenty-one patients were hospitalized. There were no reports of hemorrhagic or necrotizing pancreatitis. However, five patients developed serious complications including dehydration and renal failure; suspected ileus; phlegmon; and ascites. Twenty-two of the 30 reports indicated that the patients improved after discontinuing exenatide (Byetta).

Details in three reports indicated that the symptoms of acute pancreatitis returned when exenatide was restarted. Nausea and vomiting returned in two patients when exenatide was restarted. In a third patient, abdominal pain returned when exenatide was restarted and abated after exenatide was permanently discontinued.

The Agency advises health-care professionals to instruct patients taking exenatide to seek prompt medical care if they experience unexplained persistent severe abdominal pain which may or may not be accompanied by vomiting. If pancreatitis is suspected, exenatide should be discontinued. If pancreatitis is confirmed, exenatide should not be restarted unless an alternative etiology is identified.

The US FDA has asked the manufacturer (Amylin Pharmaceuticals, Inc) to include information about acute pancreatitis in the Precautions section of the product label.

Reference:
Information for health-care professionals. US FDA, 16 October 2007 (www.fda.gov).

Haloperidol

Labelling updated with risk of *torsade de pointes*

USA. The US FDA has advised that the labelling for haloperidol, (Haldol, Haldol Decanoate, and Haldol Lactate) has been revised with regard to the risk of *torsades de pointe* and QT prolongation in patients treated with the drug. The Agency explains that the labelling changes have been prompted by a number of case reports of sudden death, *torsades de pointe* and QT prolongation in patients who have received treatment with haloperidol, especially when administered intravenously or at higher than recommended doses. The updated Warnings section states that higher doses and intravenous administration of haloperidol appear to be linked with a higher risk of *torsades de pointe* and QT prolongation. Particular caution is recommended in patients who have other QT-prolonging conditions (such as electrolyte imbalance), underlying cardiac abnormalities, hypothyroidism or familial long QT syndrome, or who are receiving drugs known to prolong QT interval. ECG monitoring is recommended if haloperidol is administered IV. The Warnings section also states that haloperidol is not approved for intravenous administration.

Reports in WHO database:
Haloperidol
QT prolonged - 57
Torsades de pointe - 62
Haloperidol decanoate
QT prolonged - 3
Torsades de pointe - 1
Haloperidol lactate
QT prolonged - 1

Reference:
Information for health-care professionals. US FDA, September 2007 (www.fda.gov).

Lumiracoxib

Risk of serious hepatotoxicity

Lumiracoxib (Prexige), is a COX-2 selective non-steroidal anti-inflammatory drug (NSAID) used to treat painful symptoms of osteoarthritis of the knee and hip at a dose of 100 mg once daily. It is approved in more than 50 countries worldwide and was first launched in Brazil in 2005. Concern was raised worldwide after rare reports of serious liver reactions, mostly relating to daily doses that were higher than licensed for use in osteoarthritis. Some post-marketing reports of severe hepatic adverse effects have been reported in some countries around the world. Some countries have reacted with specific regulatory measures:

Australia (1). In August 2007 Australia's Therapeutic Goods Administration (TGA) cancelled the registration of lumiracoxib due to reports of serious liver adverse effects associated with the use of the drug.
As of 10 August this year, the TGA had received eight reports of serious liver adverse reactions related to lumiracoxib, including two deaths and two liver transplants. These reports were "urgently investigated" by the TGA and its expert advisory committee, the Adverse Drug Reactions Advisory Committee (ADRAC). ADRAC subsequently recommended the cancellation of registration for lumiracoxib, "due to the severity of the reported side effects associated with this drug". The TGA is advising patients to discontinue lumiracoxib use immediately, and to discuss alternative treatments with their physician.

Canada (2). Health Canada has reviewed all safety and efficacy data for lumiracoxib from Novartis and has concluded that the risk of serious hepatotoxicity associated with the use of lumiracoxib cannot be safely and effectively managed. Health Canada has thus requested that Novartis stop the sale of lumiracoxib in Canada. Consistent with this decision to cease sales and marketing of lumiracoxib, Novartis is asking Canadian pharmacists and distributors to return the product to the company. Patients taking lumiracoxib have been advised to discontinue its intake and contact their physician for advice about alternative therapies.

Prescribers are advised:
not to initiate treatment of new patients;
to advise patients to discontinue lumiracoxib;

to review treatment options for patients currently taking lumiracoxib.

Pharmacists are advised:
not to dispense further prescriptions for lumiracoxib;
to tell patients to discontinue lumiracoxib and contact their physician if they have any concerns.

Consumers are advised to return the product to their pharmacy.

New Zealand (3). The regulatory agency has withdrawn the market authorization for 200 mg and 400 mg lumiracoxib tablets for acute use, but kept the licenses of 100 mg once daily for osteoarthritis.

Turkey (3). Turkey has suspended the marketing authorization for 100 mg lumiracoxib tablets pending further review.

United Kingdom (3). Concern was raised worldwide after rare reports of serious liver reactions mostly relating to daily doses of lumiracoxib that are higher than licensed in the EU. Following consultation with the MHRA and other European regulators, the manufacturer of the osteoarthritis drug, lumiracoxib (Prexige), has written to health professionals to inform them of new restrictions on the prescribing of lumiracoxib.

A summary of the latest advice from MHRA includes the following:
Lumiracoxib should not be used in patients with current or past liver disease, those taking other medicines that may cause liver problems, or who have had previous drug-induced liver reactions.
Blood tests to check liver function are needed before treatment, at monthly intervals during treatment, and at any stage if patients are unwell with possible liver problems. Patients already taking lumiracoxib should have their treatment reviewed at the next convenient opportunity.
Blood tests should be taken if continued treatment is considered appropriate.
Do not exceed 100 mg once daily and use only for the shortest duration necessary to control symptoms.

Reports in WHO database:
Hepatic function abnormal - 3

Reference:
1. Media Statement. Therapeutics Goods Administration, 11 August 2007 (www.tga.gov.au)
2. 'Dear Health-care Professional' letter from Novartis Pharmaceuticals Canada Inc. 3 October 2007 (www.hc-sc.gc.ca)
3. Lumiracoxib and liver adverse reactions: MHRA, updated 24 October 2007 (www.mhra.gov.uk)

Nelfinavir

Guidance on process impurity in North America; licence re-established in Europe

Canada (1). Pfizer in consultation with Health Canada has notified health professionals about the presence of low levels of ethyl methanesulfonate (EMS), a process-related impurity in nelfinavir (Viracept) and has provided guidance on the use of nelfinavir (Viracept) in patients, including pregnant women and paediatric patients. Nelfinavir was removed by Roche Limited from the European market in June 2007 (see WHO Pharmaceuticals Newsletter No. 3, 2007), due to detection of high levels of EMS in some products there. In the Canadian product (manufacturing source is different from that of the European formulations), the level of exposure is over 200 times less than that found in Europe.

EMS is a potential human carcinogen. Data from animal studies indicate that EMS is teratogenic, mutagenic and carcinogenic. However, no data from humans exist. Animal studies do not necessarily predict human risk. Pfizer advises that at this time, physicians should consider the risks and benefits of prescribing nelfinavir to their HIV-infected adult patients.

In general, Health Canada recommends that HIV-infected patients should be switched from nelfinavir to an alternative therapy if this can be done safely. Health-care professionals are requested to facilitate access for these patients. However, patients should NOT stop taking nelfinavir without first consulting with their physician. Pregnant women and children may be more susceptible to harm from EMS and should be switched to alternative therapy as soon as medically feasible. Nelfinavir should NOT be prescribed for adults and children needing to initiate therapy. Pharmacists should notify the treating HIV physician when patients request for renewal of nelfinavir prescriptions. Patients taking nelfinavir should contact their physician for discussion of whether they should continue or be switched to other treatments. For patients without other reasonable treatment options, Health Canada and Pfizer agree that there remains a positive benefit/risk for continued use of nelfinavir.

The levels currently deemed acceptable for long-term exposure to EMS suggest a theoretical lifetime increased cancer risk in adults of less than one case per 100 000 patients exposed. While no data on the impact of high EMS levels in humans exist, estimates from in-vitro and animal data suggest that currently observed EMS levels in Canadian formulations may result in cancer risk in adults between 1 and 17 cases per 100 000 patients exposed for a lifetime. Current estimates of

the background incidence of cancer in the HIV population are about 20 to 30 cases per 1000 patient-years. Pfizer is working with Health Canada to prospectively limit EMS levels in nelfinavir while still considering the immediate needs of patients on therapy. Further relevant information will be provided as it becomes available.

USA (2). Pfizer has issued a 'Dear Health-care Professional' letter regarding the presence of process-related EMS in nelfinavir (Viracept) 250 mg and 625 mg tablets and in nelfinavir powder for oral suspension in the USA. The letter was prompted by detection of excess levels of EMS in Roche-manufactured nelfinavir in June 2007; the US FDA and Pfizer have agreed new limits for EMS in Pfizer-manufactured nelfinavir marketed in the US. Testing showed that the levels of EMS were substantially lower than those that led to the Roche recall. At this point, Pfizer advises that paediatric patients and pregnant women starting HIV therapy should not receive regimens containing nelfinavir. The US FDA and Pfizer determined that the benefit-risk ratio remains favourable for paediatric patients who are stable on nelfinavir-based regimens and that they should continue to receive nelfinavir. Pregnant women should be switched from nelfinavir to an alternative antiretroviral therapy while progress is made towards the long-term EMS specification. However, for those the manufacturer of nelfinavir in Europe. The CHMP is reassured that the cause of the contamination has been eliminated and that future productions of nelfinavir would meet the required quality standards. The CHMP has therefore recommended lifting of the suspension of the marketing authorization for nelfinavir in Europe. Roche intends to re-supply nelfinavir as soon as possible. Roche has advised that the timing of the re-introduction will vary from country to country and it is likely to be a few months before it is fully available to prescibers and patients.

Reference:

1. 'Dear Health-care Professional' letter from Pfizer Canada Inc. 10 September 2007 (www.hc-sc.gc.ca)
2. 'Dear Health-care Professional' letter from Pfizer Inc. 10 September 2007 (www.fda.gov)
3. Press Release. EMEA, 20 September 2007 (www.emea.europa.eu)

Nimesulide

Restricted use recommended

Europe. The EMEA has completed a review of liver safety data for nimesulide-containing medicinal products. The Agency advises that the benefits of these medicines still

(In May 2007, the Irish Medicines Board announced the suspension of the marketing and sale of oral nimesulide in Ireland. WHO issued an Information Exchange System Alert with this information; see WHO Pharmaceuticals Newsletter No. 3, 2007).

Reference:

Questions and answers on the CHMP recommendation on nimesulide-containing medicines. EMEA, 21 September 2007 (www.emea.europa.eu)

PDE5 Inhibitors

Reports of sudden decreases in or loss of hearing

USA. The US FDA informed health-care professionals of reports of sudden decrease in, or loss of hearing following the use of phosphodiesterase type 5 enzyme (PDE5) inhibitors sildenafil (Viagra), vardenafil (Levitra), tadalafil (Cialis) for the treatment of erectile dysfunction, and sildenafil citrate (Revatio) for the treatment of pulmonary arterial hypertension. In some cases, the sudden hearing loss was accompanied by tinnitus and dizziness. Medical follow-up on these reports was often limited, which makes it difficult to determine if the loss of hearing was related to the use of one of the drugs, an underlying medical condition or other risk