WHO PHARMACEUTICALS NEWSLETTER

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

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

Further information on adverse reactions may be obtained from the WHO Collaborationg Centre for International Drug Monitoring
Box 1051
751 40 Uppsala
Tel: +46-18-65.60.60
Fax: +46-18-65.60.80
E-mail: sten.olsson@who-umc.org
Internet: http://www.who-umc.org

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No. 4, 2010

The US FDA has recently uncovered fraudulent Tamiflu sold over the internet, which put many patients at risk for anaphylaxis. Read about this and other alerts in our regular sections, Safety of Medicines and Regulatory Matters.

This June, representatives from the pharmaceutical industry and regulatory authorities gathered in Beijing to discuss pharmaceutical development on paediatric formulations. This event was the fourth workshop organized by the Prequalification of Medicines Programme (PQP), which provided an open forum for information exchange on the development, formulation and manufacturing of paediatric medicines. The discussions covered technical, safety and ethical topics with an overall positive feedback from the participants.

Around the same time, Singapore's Health Sciences Authority (HAS) hosted the first pharmacovigilance training for ASEAN countries. The 5-day training course was a collaboration with WHO and UMC, and aimed to strengthen pharmacovigilance awareness and capabilities in ASEAN nations and to build future collaborations for medicines safety in the region.

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Dextropropoxyphene

Withdrawal

New Zealand. The New Zealand Medicines and Medical Devices Safety Authority (Medsafe) announced that the consents to distribute medicines containing dextropropoxyphene (Capadex and Paradex) in New Zealand will be revoked on 1 August 2010. Dextropropoxyphene is one of the opiates and used to treat chronic moderate pain. This decision follows a review by the Medicines Adverse Reactions Committee (MARC), which concluded that the risks of these medicines outweigh their benefits (See also *WHO Pharmaceuticals Newsletter* No. 2, 2010).

The Best Practice Advocacy Centre has issued the following advice for transferring patients from dextropropoxyphene:

- Most patients can be transferred to full doses of paracetamol alone. If pain relief is not sufficient, the next step is to add a weak opioid such as codeine (or use a combined paracetamol/codeine preparation). Alternatively, codeine alone could be trialed.
- Oxycodone should not be prescribed in place of dextropropoxyphene unless there has been an inadequate response to a weak opioid.

(See WHO Pharmaceuticals Newsletter No. 4, 2009 for recommendation to withdraw the marketing authorizations for dextropropoxyohene-containing medicines in Europe).

Reference:
Media Releases, Medsafe 26 March 2010
Prescriber Update Vol. 31 No. 2 June 2010.
(www.medsafe.govt.nz).

Gemtuzumab ozogamicin

Voluntary withdrawal

USA. The US Food and Drug Administration (US FDA) has announced that Pfizer Inc. will voluntarily withdraw gemtuzumab ozogamicin (Mylotarg) from the United States market. Gemtuzumab ozogamicin (Mylotarg) is indicated for treatment of acute myeloid leukemia (AML). This medicine was approved in May 2000 under the US FDA's accelerated approval program. In 2004, the company began a confirmatory, post approval clinical trial that was designed to determine whether adding gemtuzumab ozogamicin (Mylotarg) to standard chemotherapy demonstrated an improvement in clinical benefit (survival time) to AML patients. The US FDA says that the trial was stopped early when no improvement in clinical benefit was observed, and after a greater number of deaths occurred in the group of patients who received gemtuzumab ozogamicin (Mylotarg) compared with those receiving chemotherapy alone. The Agency also states that at initial approval, the medicine was associated with a serious liver condition called veno-occlusive disease, and this rate has increased in the post-market setting. The US FDA advises that patients who are currently receiving the medicine may complete their therapy following consultation with their health-care professional.

Reference:
News Release, US FDA, 21 June 2010 (www.fda.gov).

Leflunomide

New boxed warning for severe liver injury

USA. The US FDA announced that information on severe liver injury is being added to the Boxed Warning of leflunomide (Arava), following the Agency's review of adverse event reports. The medicine is used to treat rheumatoid arthritis. The warning includes the following.

- Patients with pre-existing liver disease should not receive leflunomide.
- Patients with elevated liver enzymes (ALT greater than two times the upper limit of normal) should not receive leflunomide.
- Caution should be used in patients who are taking other drugs that can cause liver injury.
- Liver enzymes should be monitored at least monthly for three months after starting leflunomide and at least quarterly thereafter.
- If the ALT rises to greater than two times the upper limit of normal while the patient is on leflunomide, leflunomide should be stopped; cholestryamine washout should be begun to speed the removal of leflunomide from the body; and follow-up liver function tests should be conducted at least weekly until the ALT value is within normal range.

The US FDA says that 49 cases of severe liver injury were reported between August 2002

and May 2009. Of the 49 cases, there were 14 deaths.
An additional five patients required a liver transplant and nine patients experienced a life-threatening event. Twenty-three reports described jaundice at the time of diagnosis, 11 reported coagulopathy, and five reported encephalopathy. Other presenting symptoms in these cases included vomiting, rash and/or itching, abdominal pain and fever. Seventeen cases reported normal liver enzymes prior to starting leflunomide. Of the 49 patients, 46 patients were also taking other medications that have been associated with liver injury, including methotrexate, TNF-α blockers, hydroxychloroquine, acetaminophen, non-steroidal anti-inflammatory drugs and statins. In addition, 14 patients had pre-existing liver disease such as active or chronic hepatitis, and/or a history of alcohol abuse. Although many patients who developed severe liver injury were also taking other drugs that can damage the liver, or had pre-existing liver disease, the US FDA concluded that use of leflunomide was associated with the development of severe liver injury in these patients.

Reports in WHO Global ICSR database, Vigibase:

Leflunomide

Number of reports (SOC liver and biliary system disorders, and additional terms containing liver or hepatic): 960

Most reported reactions (number of events):

Hepatic enzymes increased	*186*
SGOT increased	*163*
SGPT increased	*196*
Gamma-GT increased	*62*
Hepatic failure	*61*
Hepatic function abnormal	*331*
Hepatitis	*111*
Hepatocellular damage	*74*
Bilirubinaemia	*68*
Jaundice	*56*

Reference:
FDA Drug Safety Communication, US FDA 13 July 2010 (www.fda.gov).

Long-Acting Beta-Agonists

New recommendations included in labelling

USA. The US FDA announced that Long-Acting Beta-Agonists (LABAs), which are used for the treatment of asthma and chronic obstructive pulmonary disease (COPD), now contain new recommendations on their appropriate use in their drug labels. The new recommendations apply only to the treatment of asthma and do not apply to the use of LABAs for the treatment of COPD. This follows the Agency's decision (in February 2010) to revise the drug labels of LABAs because of an increased risk of severe exacerbation of asthma symptoms in paediatric and adult patients, as well as death in some patients using LABAs for the treatment of asthma. (See *WHO Pharmaceuticals Newsletter* No.2 2010*).*

The new recommendations in the updated labels include the following.

- Use of a LABA alone without use of a long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated in the treatment of asthma.
- LABAs should not be used in patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.
- LABAs should only be used as additional therapy for patients with asthma who are currently taking but are not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid.
- Once asthma control is achieved and maintained, patients should be assessed at regular intervals and step down therapy should begin (e.g., discontinue LABA), if possible without loss of asthma control, and the patient should continue to be treated with a long-term asthma control medication, such as an inhaled corticosteroid.
- Paediatric and adolescent patients who require the addition of a LABA to an inhaled corticosteroid should use a combination product containing both an inhaled corticosteroid and a LABA, to ensure adherence with both medications.

Health-care professionals are also advised that LABAs should not be started in patients with acutely deteriorating asthma, and that a rescue inhaler, such as an albuterol inhaler, should be prescribed to treat sudden asthma symptoms.

The US FDA states that when LABAs are used according to those new recommendations and the approved drug labels, the benefits of LABAs in improving asthma symptoms outweigh their risks of increasing severe asthma exacerbations and deaths from asthma.

Reference*:*
Safety Information, US FDA 3 June 2010 (www.fda.gov).

Omeprazole

Risk of hypomagnesaemia

New Zealand. Medsafe advised health-care professionals that an association between omeprazole treatment and hypomagnesaemia has been identified, and that they should be alert to the possibility of hypomagnesaemia in patients taking omeprazole and displaying symptoms such as muscle cramps, weakness, irritability or confusion. The data sheets for medicines containing omeprazole will be updated to include information about this association.

Medsafe says that most case reports of hypomagnesaemia have been associated with long-term use of omeprazole at normal doses (20 to 40 mg per day) and magnesium levels normalised after stopping treatment. Reports of hypomagnesaemia were usually also associated with hypocalcaemia, with some patients displaying symptoms of severe hypocalcaemia and hypomagnesaemia (seizures, cardiac arrhythmia, tetany, severe vomiting leading to other electrolyte disturbances and psychiatric symptoms).

***Reference**:*
Prescriber Update Vol.31 No. 2 June 2010 (www.medsafe.govt.nz).

Orlistat

Labelling change due to reports of severe liver injury

USA. The US FDA has announced that it has approved a revised label for orlistat (Xenical) to include new safety information about cases of severe liver injury that have been reported rarely with the use of this medication. Orlistat is used for weight-loss. Xenical (orlistat 120 mg) is available by prescription and Alli (orlistat 60 mg) is sold over-the-counter (OTC) without a prescription. The Agency is also adding a new warning about rare reports of severe liver injury to the OTC label for Alli. This follows the completed safety review by the Agency of reports of severe liver injury in patients taking orlistat. The review identified 13 total reports of severe liver injury with orlistat; 12 foreign reports with Xenical and one US report with Alli. At this time, a cause and effect relationship of severe liver injury with orlistat use has not been established.

Health-care professionals are advised of the following.

- Post-marketing cases of severe liver injury with hepatocellular necrosis or acute hepatic failure have been reported rarely in people using orlistat (Xenical and Alli). Some of these cases resulted in liver transplant or death.
- Weigh the benefits of weight-loss with orlistat (Xenical and Alli) against the potential risks when determining if these medications are appropriate for patients.
- Instruct patients to report any symptoms of hepatic dysfunction (anorexia, pruritus, jaundice, dark urine, light colored stools, or right upper quadrant pain) when using these medications.
- If liver injury is suspected, orlistat and other suspect medications should be discontinued immediately and liver function tests and ALT and AST levels should be obtained.

Reports in WHO Global ICSR database, Vigibase:

Orlistat

Number of reports (SOC liver and biliary system disorders, and additional terms containing liver or hepatic): 598

Most reported reactions (number of events):

Hepatic enzymes increase	*100*
Cholecystitis	*66*
Cholelithiasis	*161*
Gallbladder disorder	*79*
Hepatic function abnormal	*84*

(See WHO Pharmaceuticals Newsletters No.5 2009 for early communication about an ongoing safety review in the USA).

***Reference**:*
Safety Information, US FDA 26 May 2010 (www.fda.gov).

Proton pump inhibitors

Class labelling change due to possible increased risk of fractures of the hip, wrist, and spine

USA. The US FDA announced that it is revising the prescription and over-the-counter (OTC) labels for proton pump inhibitors to include new safety information about a possible increased risk of fractures of the hip, wrist and spine with the use of these medications. Proton pump inhibitors are used to treat conditions such as gastroesophageal reflux disease, stomach and small intestine ulcers, and inflammation of the esophagus. Health-care professionals are advised to consider whether a lower dose or shorter duration of therapy would adequately treat the patient's condition when

prescribing proton pump inhibitors.

The decision on class labelling change is based on the US FDA's review of seven published epidemiological studies, six of which reported an increased risk of fractures of the hip, wrist and spine with proton pump inhibitor use. Some studies found that those at greatest risk for these fractures received high doses of proton pump inhibitors or used them for one year or more. The majority of the studies evaluated individuals 50 years of age or older and the increased risk of fracture primarily was observed in this age group. According to the Agency, it is not clear at this time if the use of proton pump inhibitors is the cause of the increased risk of fractures seen in those studies.

The US FDA states that while the greatest increased risk for fractures in these studies involved people who had been taking prescription proton pump inhibitors for at least one year or who had been taking high doses of the prescription medications, as a precaution, the labelling for the OTC proton pump inhibitors (indicated for 14 days of continuous use) also is being revised to include information about this risk.

Reports in WHO Global ICSR database, Vigibase:

Lansoprazole

Fracture	*11*
Fracture pathological	*3*

Omeprazole

Fracture	*27*
Fracture pathological	*5*

Pantoprazole

Fracture	*7*
Fracture healing impaired	*1*
Fracture pathological	*2*
Fracture spontaneous	*1*

Proton pump inhibitors

Fracture	*1*

Rabeprazole

Fracture	*10*
Fracture healing impaired	*1*
Fracture spontaneous	*1*

(See WHO Pharmaceuticals Newsletter No. 2, 2009 for possible risk of fracture in Australia).

Reference:
Safety Information, US FDA 21 April 2010 (www.fda.gov).

Quinine

Warning against the routine use for nocturnal leg cramps in the UK; New risk management plan in the USA

UK (1). The Medicines and Healthcare products Regulatory Agency (MHRA) has warned that have not worked (e.g., passive stretching exercises). After an initial trial of four weeks, treatment should be stopped if there is no benefit. Treatment should be interrupted approximately every three months to reassess the benefit. In patients taking quinine long term, a trial discontinuation may be considered.

In the *Drug Safety Update*, MHRA states that overall efficacy of quinine is modest, based on a meta-analysis of eight randomised placebo controlled trials, which indicated that patients had around 20% fewer cramps in a four-week period (around one episode a week difference) when taking quinine compared with placebo.

With regard to safety of quinine, adverse events may include tinnitus, impaired hearing, headache, nausea, disturbed vision, confusion, flushing and abdominal pain. MHRA advises that treatment should be stopped if these occur. Moreover, thrombocytopenia is a rare but potentially life-threatening adverse reaction associated with quinine. The Agency says that a small number of deaths linked to thrombocytopenia have been reported in patients taking quinine for the treatment of leg cramps, including two cases in the UK Yellow Card database. Health-care professionals are