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:

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

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In this edition of the WHO Pharmaceuticals Newsletter our readers will find reference to decisions around the world on some old medicines such as dextropropoxyphene, acetaminophene, bisphosphonates and quinine, as well as newer ones such as dolasetron, dronedarone, saquinavir and sitaxentan. Sitaxentan has been withdrawn worldwide by the manufacturer because of unpredictable serious liver injury. Read the background information from Australia, Canada and EMA.

In a feature article of this edition of the Newsletter we continue to give information about WHO's Prequalification of Medicines Programme; this time about inspection of manufacturing sites for Active Pharmaceutical Ingredients (APIs).

A report of the latest meeting (8 – 9 December 2010) of the WHO Global Committee of Vaccine Safety is found as the second feature article of the Newsletter.

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Acetaminophen (Paracetamol INN) prescription products

The maximum amount will be limited to 325 mg per dosage unit; A Boxed Warning will highlight the potential for severe liver failure.

USA. The U.S. Food and Drug Administration (The US FDA) decided to limit the strength of acetaminophen in prescription drug products, which are predominantly combinations of acetaminophen and opioids, to 325 mg per tablet, capsule, or other dosage unit. In addition, a Boxed Warning highlighting the potential for severe liver injury and a Warning highlighting the potential for allergic reactions (swelling of the face, mouth, and throat, difficulty breathing, itching or rash) will be added to the label of all prescription products that contain acetaminophen. The Agency says that these actions will help to reduce the risk of severe liver injury and allergic reactions associated with acetaminophen. Examples of prescription products that contain acetaminophen include hydrocodone with acetaminophen (Vicodin, Lortab), and oxycodone with acetaminophen (Tylox, Percocet). Over-the-counter (OTC) products containing acetaminophen (e.g. Tylenol) are not affected by these actions.

The US FDA advised health-care professionals that severe liver injury, including cases of acute liver failure resulting in liver transplant and death, has been reported with the use of acetaminophen. Rare cases of anaphylaxis and other hypersensitivity reactions have occurred with the use of acetaminophen. Health-care professionals are also reminded to advice patients not to exceed the acetaminophen maximum total daily dose (four grams/day), and not to drink alcohol while taking acetaminophen-containing medications.

Reference:
MedWatch Safety Information, US FDA, 13 January 2011 (www.fda.gov)

Benzonatate

Accidental ingestion by children

USA. The US FDA has warned the public that accidental ingestion of benzonatate (Tessalon®) by children under the age of 10 years can result in death from overdose. Benzonatate is approved for relief of cough in patients over 10 years of age. The safety and effectiveness of benzonatate in children under 10 years of age have not been established. Therefore, prescribing benzonatate to that age group is not recommended.

The US FDA states that all accidental ingestions reported to the Agency until 19 May 2010 (seven cases) occurred in children less than 10 years of age. Five of the seven accidental ingestions resulted in death in children less than two years of age. Two pediatric patients (ages 12 months and four years) were hospitalized due to accidental benzonatate ingestion and survived the event. Overdose with benzonatate in children less than two years of age has been reported following accidental ingestion of as few as one or two capsules. Individuals who experience overdose of benzonatate may exhibit restlessness, tremors, convulsions, coma, and cardiac arrest.

Signs and symptoms of benzonatate overdose have been reported within 15 to 20 minutes and death has been reported within hours of ingestion.

The US FDA advises patients to keep benzonatate in a child-resistant container and to store it out of reach of children. The Agency also advises parents and caretakers to seek medical attention immediately if a child accidentally ingests benzonatate. The US FDA is revising the benzonatate drug label to warn about accidental ingestion resulting in overdose and death in children below the age of 10 years.

Reference:
FDA Drug Safety Communication, US FDA, 14 December 2010 (www.fda.gov)

Bevacizumab

Withdrawal of authorization of combination with docetaxel for breast cancer treatment in Europe; removal of breast cancer indication in the USA

Europe (1). The European Medicines Agency (EMA) has confirmed that the benefits of bevacizumab (Avastin®) in combination with paclitaxel outweigh its risks and that this combination remains a valuable treatment option for patients suffering from metastatic breast cancer. The Agency's Committee for Medicinal Products for Human Use (CHMP) also concluded that the balance of benefits and risks of bevacizumab in combination with docetaxel is negative and that this combination should no longer be used in the treatment of breast cancer. Bevacizumab is used in combination with other anticancer medicines to treat cancers of the colon, rectum, lung, kidney or breast that are either advanced or metastatic.

The EMA explains that the CHMP started a review of the use of bevacizumab in the treatment of metastatic breast cancer because new data from a study suggested that bevacizumab in combination with docetaxel may have a negative impact on the overall survival. The study was submitted to the Agency to support an application to extend the breast cancer indication to include combination therapy with capecitabine. The Agency says that the new data add uncertainty about the effect on overall survival and that a detrimental effect on overall survival cannot be excluded.

The new data also question the size of the effect on progression-free survival, which appears to be smaller than previously observed. Because the increase of progression-free survival remains very small, the CHMP concluded that the benefits of bevacizumab) in combination with docetaxel no longer outweigh its risks, and that the authorisation for this combination treatment should be withdrawn.

For bevacizumab in combination with capecitabine, the CHMP adopted a negative opinion on the proposed new indication for metastatic breast cancer, because the relatively modest benefits were considered not to outweigh the high toxicity of this combination, given that the proposed new indication was aimed at patients for whom a relatively mild treatment would be appropriate.

For bevacizumab in combination with paclitaxel, the CHMP concluded that the benefits continue to outweigh the risks, because the available data have been shown to prolong progression-free survival of breast cancer patients without a negative effect on the overall survival.

Therefore, the CHMP recommended that for the treatment of breast cancer, bevacizumab should only be used in combination with paclitaxel. This recommendation does not affect the other indications than breast cancer.

USA (2). The US FDA has recommended removing the breast cancer indication for bevacizumab (Avastin®) because the medicine has not been shown to be safe and effective for that use. This recommendation will not affect the approvals for colon, kidney, brain, and lung cancers.

The decision has been made after the Agency reviewed the results of four clinical studies of bevacizumab in women with breast cancer and determined that the data indicate that the medicine does not prolong overall survival in breast cancer patients or provide a sufficient benefit in slowing disease progression to outweigh the significant risk to patients. The US FDA states that none of the studies demonstrated that patients receiving bevacizumab lived longer, and that patients receiving bevacizumab experienced a significant increase in serious side effects. These risks include severe high blood pressure; bleeding and haemorrhage; the development of perforations in the body, including in the nose, stomach, and intestines; and heart attack or heart failure.

The US FDA advises that oncologists currently treating patients with bevacizumab for metastatic breast cancer should use their medical judgment when deciding whether a patient should continue treatment with the medicine or consider other therapeutic options.

Bevacizumab was approved in combination with chemotherapy (paclitaxel) in February 2008 under the FDA's accelerated approval program. The US FDA explains that the data submitted after the accelerated approval showed only a small effect on "progression-free survival" without evidence of an improvement in overall survival or a clinical benefit to patients sufficient to outweigh the risks. The small increase in "progression-free survival" reflects a small, temporary effect in slowing tumour growth. The Agency says that bevacizumab has also been associated with several other serious and potentially life-threatening side effects

including the risk of stroke, wound healing complications, organ damage or failure; and the development of a neurological condition called reversible posterior leuko-encephalopathy syndrome. On the basis of all available data relating to the use of bevacizumab (Avastin) to treat metastatic breast cancer, the Agency has determined that the risks of the medicine outweigh the benefits for this use.

Reports in WHO Global ICSR database, Vigibase:

Bevacizumab

Total number of reports: 10,047

Number of reactions similar to those mentioned in communication from US FDA:

Nasal septum perforation	*37*
Intestinal perforation	*413*
Circulatory failure	*34*
Cardiac failure	*219*
Hypertension pulmonary	*39*
Hypertension	*512*
Hypotension	*261*
Myocardial infarction	*172*
Haemorrhage NOS	*106*
Prothrombin decreased	*90*
Embolism pulmonary	*410*
Thrombocytopenia	*338*
Thrombosis	*117*

References:

(1) Press release, Questions and answers, EMA, 16 December 2010 (www.ema.europa.eu).

(2) MedWatch Safety Information, US FDA, 16 December 2010 (www.fda.gov)

Bisphosphonate

Safety measures against osteonecrosis and osteomyelitis of jaw

Japan (1). The Ministry of Health, Labour and Welfare (MHLW), Japan decided to alert health-care professionals to the risk of osteonecrosis of jaw associated with oral formulations of bisphos-phonates (BPs) (alendronate, etidronate, risedronate), in addition to BP injections, for which the MHLW had issued an alert in October 2006. Bisphosphonates are used as oral medications for treatment of osteoporosis and as injections for treatment of hypercalcaemia of malignancy, bone lesion of multiple myeloma, bone lesion from bone metastasis of solid carcinoma, and osteolytic bone metastasis of breast cancer.

Based on the epidemiological studies on oral BP and reports of adverse events in Japan, the MHLW concluded that safety measures equivalent to those for BP injections should be taken for oral BPs to prevent osteonecrosis and osteomyelitis of jaw. In June 2010, the MHLW required manufacturers to revise the package inserts of BP products to include the following descriptions.

- Administration of BPs may increase possible risks of osteonecrosis and osteomyelitis of jaw regardless of the route of administration. The risk may be higher in patients treated with BP injections.
- Physicians need to advise patients of the following: to receive appropriate dental examinations before using BPs and, if necessary, to have planned invasive dental procedures such as tooth extraction done before treatment, as well as to receive periodic dental checkups and to avoid invasive dental procedures in the jaw bone, such as tooth extraction, during treatment.

According the MHLW, approximately 80 to 100 cases of osteonecrosis and osteomyelitis of jaw have been reported as adverse drug reactions (ADRs) of oral BPs annually. A detailed review of reports showed that some patients had received dental procedures such as tooth extraction by dentists who had been unaware of the treatment.

There were also patients who had failed to maintain oral hygiene while taking BP. From 2007 to 2009, osteonecrosis and osteomyelitis of jaw were reported as ADRs as follows (numbers of ADR cases (numbers of ADRs)).

Alendronate sodium hydrate (oral dosage form): 197 (238)

Etidronate disodium (oral dosage form): seven (eight)

Sodium risedronate hydrate (oral dosage form): 61 (64)

In addition, the manufacturers were required to prepare and distribute patient cards for BP users to help health-care professionals inform patients of precautions concerning BP use, as well as for their use of BP to be known at dental or oral surgery services.

(See WHO Pharmaceuticals Newsletters No. 1, 2010, No. 1, 2008, No.5, 2006 and No.6, 2004 for a review on the risk of osteonecrosis of the jaw in Europe, for alert on musculoskeletal pain in USA, reports of osteonecrosis of the jaw in Australia, and reports of osteonecrosis of the jaw in USA, respectively.)

UK (2). The Medicines and Healthcare products Regulatory Agency (MHRA) advised that treatment with bevacizumab or sunitinib, which are used to treat certain cancers, may be a risk factor for the development of osteonecrosis of the jaw (ONJ), particularly if a patient has previously received, or is treated concurrently with, bisphosphonates. Health-care professionals are advised that dental examination and appropriate preventive dentistry should be considered before treatment with bevacizumab or sunitinib. Invasive dental procedures should be avoided, if possible, in patients treated with bevacizumab or sunitinib who have previously received, or who are receiving, intravenous bisphosphonates.

According to the Drug Safety Update, cases of ONJ have been reported in patients with cancer in association with treatment with bevacizumab or sunitinib, most of whom had received previous or concomitant treatment with intravenous bisphosphonates. The MHRA states that there is sufficient evidence to suspect that bevacizumab and sunitinib may independently increase the risk of ONJ.

References:

(1) Pharmaceuticals and

Dextropropoxyphene

Recall and withdrawal due to risk of abnormal heart rhythms

Canada. Health Canada and Paladin Labs Inc announced that the company has decided to voluntarily recall and withdraw dextropropoxyphene (Darvon-N) on the Canadian market and discontinue the sale of the product. Dextropropoxyphene is an opioid pain reliever used to treat mild to moderate pain.

The company states that results of a new study show that, even at therapeutic doses, dextropropoxyphene can significantly prolong the PR interval, widen the QRS complex, prolong the QT interval and therefore increase the risk of serious abnormal heart rhythms. Elderly patients and those with renal insufficiency may be especially susceptible to the proarrhythmic effects of dextropropoxyphene. Health-care professionals are advised to stop prescribing and dispensing dextropropoxyphene (Darvon-N) to patients, and to be aware of the possible risk of cardiac conduction abnormalities in patients taking this medicine and assess patients for these events if they present with any signs or symptoms of arrhythmia.

Dolasetron mesylate

Reports of abnormal heart rhythms

USA. The US FDA notified health-care professionals that the injection form of dolasetron mesylate (Anzemet®) should no longer be used to prevent chemotherapy induced nausea and vomiting (CINV) in paediatric and adult patients. A contraindication against this use is being added to the product label for dolasetron mesylate injection. The Agency warns that new data demonstrate that dolasetron mesylate injection can increase the risk of developing torsade de pointes, which can be fatal. Patients at particular risk are those with underlying heart conditions or those who have existing heart rate or rhythm problems.

The US FDA advises the following:

- Dolasetron mesylate should not be used in patients with congenital long-QT syndrome.
- Hypokalemia and hypomagnesemia should be corrected before administering dolasetron mesylate. These electrolytes should be monitored after administration as clinically indicated.