WHO PHARMACEUTICALS NEWSLETTER

World Health Organization

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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The WHO Pharmaceuticals Newsletter provides you with the latest information on the safety of medicines and legal actions taken by regulatory authorities across the world. It also provides signals from the Uppsala Monitoring Centre's SIGNAL document.

The feature articles in this issue give you information of new dosage recommendations for morphine and other opioid analgesics in children. And you will also find a summary of discussions and recommendations from the ninth meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP).

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Calcitonin-containing medicines

Intranasal formulation for osteoporosis treatment to be withdrawn; new restriction to indication for injectable use in Paget's disease

Europe. The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended that calcitonin-containing medicines should only be used for short-term treatment, because of evidence that long-term use of these medicines is associated with an increased risk of cancer. Doctors should no longer prescribe calcitonin-containing medicines as nasal spray for the treatment of osteoporosis.

Taking into account the limited efficacy of calcitonin when used to treat post-menopausal osteoporosis to reduce the risk of vertebral fractures, the CHMP concluded that the benefits of calcitonin-containing medicines did not outweigh their risks in this indication. As the nasal spray is only used in osteoporosis, the CHMP recommended that this formulation be withdrawn.

For all other approved indications the CHMP considered that the benefit-risk balance remains positive, but recommended that calcitonin treatment should be given for the shortest possible time. For the treatment of patients with Paget's disease, the CHMP also recommended limiting the use of calcitonin to a second-line indication in patients who do not respond to alternative treatments or for whom such treatments are not suitable. Treatment in this condition should normally be limited to 3 months; however, it may be extended to 6 months in exceptional circumstances, and intermittently repeated if it is considered that the potential benefits outweigh the risks.

Calcitonin will only be available as a solution for injection and infusion, and should only be used for:

- prevention of acute bone loss due to sudden immobilisation, with treatment recommended for two weeks with a maximum duration of four weeks;
- Paget's disease in patients who do not respond to alternative treatments or for whom such treatments are not suitable, with treatment normally limited to three months;
- hypercalcaemia caused by cancer.

Treatment with calcitonin should be limited to the shortest possible time and using the minimum effective dose.

Reference:
Press release, EMA, 20 July 2012 (*www.ema.europa.eu*).

Candesartan

Fetal malformations

Australia. The Therapeutic Goods Administration (TGA) reminded health-care professionals that candesartan and other angiotensin II receptor antagonists, as well as Angiotensin Converting Enzyme (ACE) inhibitors, are contraindicated in pregnancy. Exposure to these drugs in pregnancy can cause fetotoxicity. Patients who are pregnant or planning a pregnancy should be switched to an alternative antihypertensive agent.

The TGA advised that health-care professionals should review the use of angiotensin II receptor antagonists and ACE inhibitors in women of child-bearing age. These women should be advised of the risks to the fetus and counseled on the use of appropriate contraception to avoid inadvertent fetal exposure. Patients taking an angiotensin II receptor antagonist or ACE inhibitor should be advised to speak to their doctor if they may be pregnant, or planning a pregnancy. Women who are pregnant or planning a pregnancy should be switched to an alternative antihypertensive agent.

The TGA has received four reports of fetal abnormalities following candesartan use in pregnancy, including three reports in 2011. The TGA has also received reports of fetal abnormalities following the use of irbesartan, enalapril, lisinopril, perindopril and captopril during pregnancy.

Angiotensin II receptor antagonists and ACE inhibitors are classified as Australian pregnancy category D. Their use is contraindicated in pregnancy. Antihypertensives acting on the renin-angiotensin system have been associated with decreased renal function, oligohydramnios and retardation of skull ossification in the fetus. Their use in pregnancy has been associated with neonatal problems such as renal failure, hypotension and hypokalaemia. The risk of fetal abnormalities is considered greatest with second and third trimester exposure.

Reference:
Medicines Safety Update Vol 3, No. 3, June 2012 (www.tga.gov.au).

Dabigatran etexilate

Positive benefit-risk balance confirmed. Modifications to product information for clearer guidance

Europe. The European Medicines Agency (EMA) recommended updating the product information for dabigatran etexilate (Pradax®), to give clearer guidance to doctors and patients on how to reduce and manage the risk of bleeding associated with the anticoagulant medicine.

On the basis of the available evidence, the CHMP concluded that the benefits of dabigatran etexilate continue to outweigh its risks and that it remains an important alternative to other blood-thinning agents. However, the advice to doctors and patients should be updated and strengthened to give clearer guidance on the best use of the medicine. This includes more specific guidance on when the drug must not be used as well as advice on managing patients and reversing the anticoagulant effect of the drug if bleeding occurs.

The EMA advised patients who are taking dabigatran etexilate or any other blood thinner to be aware that they are at an increased risk of bleeding. If they fall or injure themselves during treatment, especially if they hit their head, they should seek urgent medical attention.

(See WHO Pharmaceuticals Newsletters No. 1, 2012 for safety review of post-market reports of serious bleeding events in the USA, Australia and New Zealand; Risk of serious haemorrhage, need for renal function testing in UK and No.3, 2012 for updated labelling regarding renal function assessment and use in patients with severe valvular disease or prosthetic heart valves in Canada and Saudi Arabia.)

Reference:
Press release, EMA, 25 May 2012 (*www.ema.europa.eu*).

Dalfampridine

Seizure risk for multiple sclerosis patients

USA. The U.S. Food and Drug Administration (US FDA) updated health-care professionals and the public about the risk of seizures in patients with multiple sclerosis (MS) who are starting dalfampridine (Ampyra®).

Dalfampridine was approved to improve walking in patients with MS. Seizures are a known side effect of the drug, and seizure risk increases with higher blood levels of the drug. Dalfampridine is eliminated from the body through the kidneys, and patients with kidney impairment may develop higher blood levels of the drug, thereby increasing their seizure risk.

The US FDA reminded health-care professionals that there are age-related decreases in renal function, and mild renal impairment is common after age 50, even when serum creatinine is normal. Renal function should be assessed by estimating creatinine clearance. Dalfampridine should not be used in patients with a history of seizures or who have moderate to severe renal impairment. A patient's creatinine clearance (CrCl) should be known before initiating the treatment and monitored at least annually while the treatment continues, even when serum creatinine levels appear to be normal.

It is also advised to tell patients they should not take double or extra doses of dalfampridine if a dose is missed. Adverse effects, including seizures, are more frequent at higher doses. Dalfampridine should be discontinued permanently if a seizure occurs.

Reference:
FDA Drug Safety Communication, US FDA 23 July 2012 (*www.fda.gov*).

Denosumab

Risk of severe symptomatic hypocalcemia, including fatal cases

Canada. Amgen Canada Inc., in collaboration with Health Canada, informed of new important safety information on severe symptomatic hypocalcemia associated with denosumab (XGEVA®) treatment.

Denosumab is indicated in patients with bone metastases from breast cancer, prostate cancer, non-small cell lung cancer, and other solid tumours for reducing the risk of developing skeletal-related events (SREs). The drug is not indicated in patients with multiple myeloma.

Post-marketing cases of severe symptomatic hypocalcemia have occurred at an estimated rate of 1 - 2%, including some cases which were fatal. Signs and symptoms of these cases included altered mental status, tetany, seizures and QTc prolongation, which were temporally associated with denosumab use, when serum calcium levels were decreased. Patients treated with denosumab should be informed of these symptoms and the need to seek immediate medical attention if they occur.

It is informed that the risk of severe symptomatic hypocalcemia among patients receiving denosumab may be minimized by the following:

- Correcting pre-existing hypocalcemia prior to initiating denosumab therapy

- Supplementing patients with calcium and vitamin D, unless hypercalcemia is present
- Monitoring calcium levels as necessary while patients are receiving denosumab
- Identifying risk factors for hypocalcemia in patients receiving denosumab. Patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis are at a greater risk of developing hypocalcemia in the absence of calcium supplementation.
- If hypocalcemia occurs while receiving denosumab, additional short-term calcium supplementation may be necessary

If severe symptomatic hypocalcemia occurs, the benefit of continuing the treatment in these patients should be reassessed.

Reference:
Advisories, Warnings and Recalls, Health Canada, 28 May 2012 (*www.hc-sc.gc.ca*).

Doripenem

Higher dosing may be needed in nosocomial pneumonia

Europe. The EMA gave new advice for the treatment of patients with nosocomial pneumonia with doripenem (Doribax®). A review of available data raises concerns that the currently approved dose of the drug of 500mg every 8 hours may not be sufficient to treat all patients with nosocomial pneumonia, including ventilator-associated pneumonia. Nosocomial pneumonia is caused by bacterial infection, and doripenem is one of a limited number of medicines available to treat this life-threatening disease.

For the treatment of patients with augmented renal clearance or with infections with non-fermenting gram-negative pathogens, the CHMP recommended that doctors double the dose to 1g every 8 hours. The Committee advised doctors that a longer treatment period (10-14 days) is required in patients with nosocomial pneumonia, including ventilator-associated pneumonia.

The Committee also advised doctors to exercise particular caution in patients for whom non-fermenting gram-negative pathogens such as *Pseudomonas aeruginosa* and *Acinetobacter* are suspected or confirmed as the cause of infection. In some of these patients, doctors should consider initiating concomitant treatment with an aminoglycoside antibiotic.

It is noted that, in addition to nosocomial pneumonia, doripenem is also used to treat complicated infections in the abdomen and the urinary tract. These indications were not affected by this review.

(See WHO Pharmaceuticals Newsletters No. 2, 2012 for higher mortality rate and a lower clinical cure rate observed during a comparative clinical trial in Canada.)

Reference:
Press release, EMA, 22 June 2012 (*www.ema.europa.eu*).

Febuxostat

Stop treatment if signs or symptoms of serious hypersensitivity occur

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) advised health-care professionals that febuxostat (Adenuric®) treatment should be stopped immediately if signs or symptoms of serious hypersensitivity reactions occur and must not be re-started in patients who have ever developed a hypersensitivity reaction to febuxostat, including Stevens-Johnson syndrome.

Febuxostat (Adenuric®) is a non-purine, xanthine oxidase inhibitor licensed for the treatment of chronic hyperuricaemia in adults, in whom urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis).

Since its launch in 2009 there have been rare but serious reports of hypersensitivity reactions to febuxostat, some associated with systemic symptoms. These have included rare reports of Stevens-Johnson syndrome and acute anaphylactic shock. In most cases, the reactions occurred during the first month of treatment. Some, but not all, of the patients experiencing hypersensitivity reactions to febuxostat were reported to have a prior history of hypersensitivity to allopurinol and/or renal disease.

It is also advised that patients should be informed of signs and symptoms of severe hypersensitivity or Stevens-Johnson syndrome. These include: infiltrated maculopapular eruption; generalised or exfoliative rashes; skin lesions; facial oedema, fever, haematologic abnormalities such as thrombocytopenia, a single or multiple organ involvement (liver and kidney including tubulointerstitial nephritis), progressive skin rashes associated with blisters or mucosal lesions and eye irritation

Reference:
Drug Safety Update, June 2012, Volume 5, issue 11, A3 MHRA, (*www.mhra.gov.uk*).

Tolperisone

Benefit-risk profile for oral tolperisone considered positive only for adults with post-

stroke spasticity and negative for injectable tolperisone

Europe. The EMA recommended restricting the use of tolperisone, a muscle relaxant authorised to treat a variety of different conditions, including spasticity due to neurological disorders and muscle spasms associated with diseases of the spine and large joints in several European Union countries since the 1960s.

The EMA recommended that doctors should stop prescribing tolperisone for any indication other than post-stroke spasticity in adults. They should also no longer use injectable tolperisone.

It is advised that patients currently using tolperisone for any other indication or using injectable tolperisone should speak to their doctor at their next routine appointment so they can switch to an appropriate alternative treatment. Patients should be made aware of the possibility of developing hypersensitivity reactions during treatment with tolperisone. They should stop treatment with tolperisone and speak to their doctor if they experience symptoms such as flushing, rash, severe itching of the skin (with raised lumps), wheezing, difficulty breathing, difficulty in swallowing, fast heartbeat, low blood pressure or a fast decrease in blood pressure.

The above advice follow the review by the CHMP that was initiated by Germany following concerns over several hypersensitivity reactions reported post-marketing and insufficiently demonstrated efficacy in some indications.

Reference:
Press release, EMA, 22 June 2012 (*www.ema.europa.eu*).

Trimetazidine-containing medicines

Restricted use in patients with stable angina pectoris and deletion of existing indications for treatment of vertigo, tinnitus and vision disturbance

Europe. The EMA recommended restricting the use of trimetazidine-containing medicines in the treatment of patients with angina pectoris to second-line, add-on therapy. For all other indications, the CHMP concluded that the benefits of these medicines were not sufficiently demonstrated and did not outweigh the risks. The CHMP therefore recommended their deletion from the marketing authorisation. It is advised that there is no need for an urgent change in treatment, but doctors should review their patients' treatment at their next routine appointment.

It is advised that;

- Doctors should no longer prescribe trimetazidine for the treatment of patients with tinnitus, vertigo or disturbances in vision. Patients who are taking trimetazidine in these indications should discuss alternatives with their doctor.
- Doctors can continue to prescribe trimetazidine for the treatment of angina pectoris, but only as an add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled by or intolerant to first-line anti-anginal therapies.

The review was initiated by France, mainly because of concerns that the efficacy of trimetazidine was not sufficiently demonstrated. It also looked at reports regarding the occurrence of movement disorders such as Parkinsonian symptoms, restless leg syndrome, tremors and gait instability associated with the medicine. Although patients usually recovered fully within four months after treatment with trimetazidine was discontinued, the Committee recommended new contraindications and warnings to reduce and manage the possible risk of movement disorders associated with the use of this medicine.

Doctors are advised not to prescribe the medicine to patients with Parkinson's disease, Parkinsonian symptoms, tremors, restless-leg syndrome or other related movement disorders, nor to patients with severe renal impairment. Doctors should exercise caution when prescribing trimetazidine to patients with moderate renal impairment and to elderly patients, and consider dose reduction in these patients.

It is also advised that trimetazidine should be discontinued permanently in patients who develop movement disorders such as Parkinsonian symptoms. If Parkinsonian symptoms persist for more than four months after discontinuation, a neurologist's opinion should be sought.

Reference:
Press release, EMA, 22 June 2012 (*www.ema.europa.eu*).

Hepatitis B Immune Globulin (Human) Injection

Theoretical risk of thrombotic events with intravenous administration

Canada. Cangene Corporation, in cooperation with Health Canada, informed of planned changes to the Canadian Product Monograph for Hepatitis B Immune Globulin (Human) (HepaGam B®), including pertinent precautions regarding thrombotic events.

There is a theoretical risk for the arterial and venous thrombosis at the intravenous doses of HepaGam B® for the liver transplantation indication. Such a risk may exist because an in-house analysis detected measurable levels of procoagulant (factor XIa) activity in HepaGam B®. The significance of these levels is being evaluated. Changes to the manufacturing process for HepaGam B® are planned to minimize the occurrence of procoagulant activity.

It is advised that patients should be informed of signs and symptoms of thrombotic events and that caution should be used when administering immune globulins, including HepaGam B®, to patients with risk factors for thrombotic events.

Patients at risk include those with a history of thrombotic and embolic events. Patients should also be informed what to do if these symptoms occur.

Reference:
Advisories, Warnings and Recalls, Health Canada, 11 June 2012 (*www.hc-sc.gc.ca*).

Immune Globulin Intravenous (Human)

Association of haemolysis following administration and related labelling update

Canada. CSL Behring Canada, Inc., in collaboration with Health Canada informed of a recent labelling update regarding the risk of haemolysis following Immune Globulin Intravenous (Human) (Privigen®) administration.

Delayed haemolytic anaemia and acute haemolysis have been reported following therapy with Immune Globulin Intravenous (Human). Isolated cases of haemolysis-related renal dysfunction/failure or disseminated intravascular coagulation have occurred. Increased vigilance is recommended in patients with the following risk factors for developing a haemolytic reaction:

o High doses (whether given as a single administration or divided doses over several days),

after receiving IGIV, cross-matching should be performed.

(See WHO Pharmaceuticals Newsletter No. 6, 2009 and No.1, 2010 for risk of haemolytic reactions with intravenous immune globulin in Canada)

Reference:
Advisories, Warnings and Recalls, Health Canada, 29 May 2012 (*www.hc-sc.gc.ca*).

Oral tacrolimus

Prescribe and dispense by brand name only

UK. The MHRA recommended that oral tacrolimus products should be prescribed and dispensed by brand name only to ensure maintenance of therapeutic response when a patient is stabilised on a particular brand, and to minimise the risk of inadvertent switching between products from different suppliers. If a prescriber considers that switching a patient to a different brand of oral tacrolimus would be of benefit, the change requires careful supervision and therapeutic monitoring by an appropriate specialist

Since 2008, the MHRA has been aware of reports of unintended switching between different pharmaceutical forms of oral tacrolimus products in patients who have been treated with tacrolimus for the prevention of organ transplant