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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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.

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Azithromycin

Risk of potentially fatal cardiac arrhythmias

Canada. Pfizer Canada Inc., in collaboration with Health Canada, informed of revisions to the Product Monographs for azithromycin (Zithromax® and Zmax SR®) regarding the risk of potentially fatal cardiac arrhythmias.

A small absolute increase in the risk of cardiovascular deaths was observed in patients taking azithromycin as compared to those who took no antibiotics and those who took amoxicillin in a recent study. This risk mainly affected patients who were at a higher baseline risk for cardiovascular events.

Pfizer completed a review of all relevant available data, and has decided to update the Precautions section of the product monographs to include additional instructions.

- There have been rare reports of QT prolongation and torsades de pointes in patients receiving therapeutic doses of azithromycin.
- Caution is required when treating patients with congenital or documented QT prolongation; with electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesemia or with clinically relevant bradycardia, cardiac arrhythmia or cardiac insufficiency.
- Caution is also required when treating patients currently receiving treatment with other active substances known to prolong QT interval such as antiarrhythmics of classes IA and III, antipsychotic agents, antidepressants and fluoroquinolones.
- Elderly patients may be more susceptible to drug-associated effects on the QT interval.

Health care practitioners should consider the risk of fatal cardiac arrhythmias with azithromycin when prescribing antibacterial treatment for patients who are already at risk for cardiovascular events.

(See WHO Pharmaceuticals Newsletter No. 2, 2013 for risk of potentially fatal heart rhythms in the US).

Reference:
Advisories, Warnings and Recalls, Health Canada, 14 May 2013 (*www.hc-sc.gc.ca*).

Cilostazol-containing medicines

Restricted use in the treatment of intermittent claudication

Europe. The European Medicines Agency's Committee on Medicinal Products for Human Use (CHMP) recommended that the use of cilostazol-containing medicines (Pletal® and Ekistol®) in the treatment of intermittent claudication should be restricted with a range of new measures aimed at targeting a patient population in which there are clinical benefits, and at the same time minimising important risks.

The recommendations follow a review of current evidence which indicates that the modest benefits of these medicines, i.e. their ability to increase the distance patients are able to walk, are only greater than their risks, in particular the risks of side effects affecting the heart or serious bleeding, in a limited subgroup of patients.

The Committee recommended that cilostazol should only be used in patients whose symptoms have not improved despite prior lifestyle changes such as exercise, healthy diet and stopping smoking. In addition, cilostazol-containing medicines should not be used in patients who have suffered severe tachyarrhythmia (fast, abnormal heart rhythm), or recent unstable angina, heart attack or bypass surgery, or who take two or more antiplatelet or anticoagulant medicines such as aspirin and clopidogrel.

Doctors are advised to review their patients at their next routine appointment and assess the continued suitability of cilostazol treatment.

Cilostazol is a phosphodiesterase type 3 inhibitor indicated for the improvement of walking distances in patients with intermittent claudication, who do not have rest pain and who do not have evidence of peripheral tissue necrosis (Fontaine stage II). The effects of cilostazol include antiplatelet activity and vasodilation.

Reference:
Press release, EMA, 22 March 2013 (*www.ema.europa.eu*).

Denosumab

Severe hypocalcaemia

Australia. The Therapeutic Goods Administration (TGA) reminded health professionals to closely monitor patients being treated with denosumab (Prolia® and Xgeva®) for signs of severe hypocalcaemia, which in some cases can be fatal. Pre-existing hypocalcaemia must be corrected before initiating therapy with denosumab.

Denosumab is available in Australia as two brands which have different indications. Prolia (60 mg) is given once every 6 months for the treatment of osteoporosis in postmenopausal women, and for the treatment of men with osteopenia who are receiving

androgen deprivation therapy for nonmetastatic prostate cancer. Xgeva (120 mg) is given once every 4 weeks for the prevention of skeletal-related events in adults with bone metastases from solid tumours.

Denosumab is a fully human monoclonal.

Hypocalcaemia is a known risk with denosumab, especially in patients who:

- are predisposed to hypocalcaemia (for example, those with a history of hypoparathyroidism, thyroid surgery, parathyroid surgery, malabsorption syndromes and excision of small intestine)
- have severe renal impairment (creatinine clearance < 30 mL/min)
- are receiving dialysis.

Signs and symptoms of hypocalcaemia include altered mental status, tetany, seizures and QTc prolongation.

The precaution in the Xgeva Product Information (PI) regarding hypocalcaemia has been updated to advise health professionals that severe symptomatic hypocalcaemia has been reported in the postmarketing setting. Similar text has also been added to the adverse effects section.

The adverse effects section of the Prolia PI has been updated to advise health professionals that rare events of severe symptomatic hypocalcaemia have been reported in patients at increased risk of hypocalcaemia. The PI was also updated to specify that atypical femoral fractures have been reported in patients being treated with Prolia.

(See WHO Pharmaceuticals Newsletter No. 6, 2012 for fatal cases of severe symptomatic hypocalcaemia and No.2, 2013 for Rare cases of atypical femoral fracture with long-term use in the UK).

Reference:
Medicines Safety Update Vol 4, No. 2, April 2013 (www.tga.gov.au).

Lapatinib ditosylate

Updated Information on Efficacy

Canada. GlaxoSmithKline Inc., in consultation with Health Canada, informed that there have been results reported from two comparative studies of lapatinib ditosylate (Tykerb®) in combination with chemotherapy versus trastuzumab (Herceptin®) in combination with chemotherapy in HER2+ metastatic breast cancer patients:

- EGF111438/CEREBEL, lapatinib/capecitabine versus trastuzumab/capecitabine in HER2+ metastatic breast cancer patients who have progressed on anthracyclines or taxanes
- EGF108919/COMPLETE, lapatinib/taxanes (paclitaxel or docetaxel) versus trastuzumab/taxane in 1st Line HER2+ metastatic breast cancer.

Based on the results of pre-planned interim analyses of these two studies, GlaxoSmithKline advised the following:

- In patients with HER2+ metastatic breast cancer who have not received prior trastuzumab, comparative data have shown that lapatinib-based regimens are less effective than trastuzumab based treatment regimens.
- Prescribers are reminded that lapatinib ditosylate should not be prescribed in combination with capecitabine unless patients have progressed on prior trastuzumab therapy in the metastatic setting.
- Product Monograph was updated to include a statement that lapatinib-based regimens are less effective than trastuzumab-based regimens in certain settings.

Although no new safety information or changes in the established safety profile of lapatinib for the market authorized indications has been reported as a result of these analyses, the Canadian Product Monograph was recently revised to provide more comprehensive guidance on the successful management of lapatinib associated diarrhea, and to highlight the association between lapatinib-induced ALT elevation and severe liver injury with the highly correlated HLA alleles DQA*02:01 and DRB1*07:01.

Reference:
Advisories, Warnings and Recalls, Health Canada, 20 March 2013 (*www.hc-sc.gc.ca*).

Proton pump inhibitors

Risk of bone fractures

Canada. Health Canada informed of the potential risk of bone fractures associated with the use of drugs known as proton pump inhibitors (PPIs). Health-care professionals are advised to closely monitor patients with risk factors for osteoporosis who use PPIs, and to report any adverse reactions to Health Canada. Health professionals are also reminded that PPIs should be prescribed at the lowest dose and shortest duration of therapy appropriate to the condition being treated.

According to Health Canada, several scientific studies suggest that PPI therapy may be associated with a small increased risk for fractures of the hip, wrist, or spine related to osteoporosis, a disease resulting in the weakening of bones. The risk of fracture was higher in patients who received multiple daily doses of PPIs

and therapy for a year or longer. Additional risk factors for osteoporosis, such as age, gender and the presence of other health conditions, may also contribute to the increased risk of fractures.

At Health Canada's request, manufacturers of all PPIs marketed in Canada have updated the drug labels for their products to include information on this risk.

PPIs are drugs used to reduce stomach acid and are widely used to treat conditions such as acid reflux and stomach ulcers.
(See WHO Pharmaceuticals Newsletter No. 2, 2009 for possible risk of fracture in Australia and No.4, 2011 for class labelling change due to possible increased risk of fractures of the hip, wrist, and spine in the USA).

Reference:
Advisories, Warnings and Recalls, Health Canada, 4 April 2013 (*www.hc-sc.gc.ca*).

Strontium ranelate

Risk of serious cardiac disorders—restricted indications, new contraindications, and warnings

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) announced that strontium ranelate (Protelos®) is restricted to second-line treatment of severe osteoporosis in postmenopausal women at high risk of fracture and in men at increased risk of fracture.

A review of available safety data for strontium ranelate has raised concern about its cardiovascular safety beyond the already recognised risk of venous thromboembolism. An analysis of randomised controlled trial data has identified an increased risk of serious cardiac disorders, including myocardial infarction (relative risk compared with placebo was 1.6 [95% CI 1.07–2.38]).

The European Medicines Agency will fully evaluate the benefits and risks of strontium ranelate in the coming months. In the meantime, in order to help minimise these risks, it is advised:

- Treatment should only be initiated by a physician with experience in the treatment of osteoporosis, and the decision to prescribe strontium ranelate should be based on an assessment of the individual patient's overall risks
- Strontium ranelate should not be used in patients with: ischaemic heart disease, peripheral arterial disease; cerebrovascular disease; a history of these conditions; or in patients with uncontrolled hypertension
- Prescribers are advised to assess the patient's risk of developing cardiovascular disease before starting treatment and thereafter at regular intervals
- Patients with significant risk factors for cardiovascular events (eg, hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with strontium ranelate after careful consideration
- Treatment should be stopped if the patient develops ischaemic heart disease, peripheral arterial disease, cerebrovascular disease, or if hypertension is uncontrolled
- Health-care professionals should review patients at a routine appointment and consider whether or not to continue treatment

Reference:
Drug Safety Update, March 2013, Volume 6, issue 9, S1 MHRA, (*www.mhra.gov.uk*).

Tetrazepam-containing medicines

Recommendation to suspend tetrazepam-containing medicines endorsed by CMDh

Europe. Following the recent recommendation by the Pharmacovigilance Risk Assessment Committee (PRAC), the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) has endorsed by majority the PRAC recommendation to suspend the marketing authorisations of tetrazepam-containing medicines across the European Union (EU). The CMDh, a body representing EU Member States, is responsible for ensuring harmonised safety standards for medicines authorised via national marketing authorisation procedures across the EU.

Tetrazepam, a medicine of the benzodiazepine class, is used in several EU Member States to treat painful contractures (such as in low back pain and neck pain) and spasticity (excessive stiffness of muscles).

The review of tetrazepam was triggered by the French National Agency for the Safety of Medicine and Health Products (ANSM), following reports of serious skin reactions with this medicine in France. Having assessed all available data on the risk of skin reactions, including post-marketing data in the EU and the published literature, the PRAC concluded that, compared with other benzodiazepines, tetrazepam is associated with an increased risk of serious skin reactions (including Stevens-Johnson syndrome, toxic epidermal necrolysis and drug-rash-with-eosinophilia-and-systemic-symptoms [DRESS] syndrome). The Committee

also noted that, in the light of the risks identified, the available data on the effectiveness of tetrazepam were not sufficiently robust to support its use in the authorised indications.

The CMDh agreed with the PRAC conclusion that the benefits of these medicines do not outweigh their risks, and adopted a final position that the marketing authorisations should be suspended throughout the EU.

It is recommended that, in light of the unfavourable benefit-risk balance, doctors should review their patients' treatment at their next appointment, and may consider an appropriate alternative treatment.Pharmacists should refer patients on a new or repeat prescription for tetrazepam to their treating physician.

(See WHO Pharmaceuticals Newsletter No. 2, 2013 for review started because of concerns over serious skin reactions in Europe).

Reference:
Press release, EMA, 29 April 2013 (*www.ema.europa.eu*).

Thalidomide

Risk of arterial thromboembolic events

Canada (1). Celgene Inc., in consultation with Health Canada, informed that new safety information regarding arterial thromboembolic events have been added to the Product Monograph for thalidomide capsules (Thalomid®).

Thalidomide is an immunomodulatory agent indicated for the treatment of patients who are 65 years of age or older with previously untreated multiple myeloma, in combination with melphalan and prednisone.

The following points summarize the updated Product Monograph safety information:

- Cases of arterial thromboembolic events (ATEE), sometimes fatal, have been reported in patients treated with thalidomide. Events reported included myocardial infarction, cerebrovascular accident and transient ischemic attack, among others. The risk of thromboembolism (including ATEE) appears to be greatest during the first 5 months of therapy.
- Risk factors associated with ATEE (in addition to the underlying malignant disease, age ≥ 65 years, and being male) include hyperlipidemia, hypertension, diabetes, obesity, renal disease and tobacco use.
- Health-care professionals are advised to be observant for the signs and symptoms of ATEE. Patients should be instructed to seek medical care if they develop symptoms related to stroke or heart attack. Thromboprophylaxis should be recommended especially in patients with additional thrombotic risk factors. The decision to take antithrombotic prophylactic measures should be made after careful assessment of an individual patient's underlying risk factors.

This new information is in addition to information regarding the established risk of venous thromboembolic events, which was already reflected in the THALOMID® Product Monograph.

An increased risk of second primary malignancies

Canada (2). Celgene Inc., in consultation with Health Canada, informed of important new safety information which has been added to the Product Monograph for thalidomide capsules (Thalomid®).

The following points summarize the updated Product Monograph safety information:

- Second primary malignancies, in particular acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), have been observed in an on-going clinical trial in patients with previously untreated multiple myeloma receiving the combination melphalan, prednisone and thalidomide (MPT). AML and MDS have been rarely reported in the post-market setting.
- The risk of AML and MDS must be taken into account before initiating treatment with MPT. Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of second primary malignancies.

Reference:
(1) Advisories, Warnings and Recalls, Health Canada, 26 April 2013 (*www.hc-sc.gc.ca*).
(2) Advisories, Warnings and Recalls, Health Canada, 16 May 2013 (*www.hc-sc.gc.ca*).

Tolvaptan

Restrictions due to possible liver injury leading to organ transplant or death

USA. The U.S. Food and Drug Administration (FDA) determined that tolvaptan (Samsca®) should not be used for longer than 30 days and should not be used in patients with underlying liver disease because it can cause liver injury, potentially leading to liver transplant or death. The US FDA has worked with the manufacturer to revise the drug label to include new limitations.

Tolvaptan is a selective vasopression V_2-receptor antagonist indicated for the treatment of clinically significant hypervolemic and euvolemic hyponatremia, including patients with heart failure and Syndrome of Inappropriate Antidiuretic Hormone (SIADH).

The US FDA recommended that tolvaptan treatment should be stopped if the patient develops signs of liver disease. Treatment duration should be limited to 30 days or less, and use should be avoided in patients with underlying liver disease, including cirrhosis. Patients should be made aware that tolvaptan may cause liver problems, including life-threatening liver failure, and should contact their health-care professional to discuss any questions or concerns about the drug.

(See WHO Pharmaceuticals Newsletter No. 2, 2013 for new warning regarding a potential risk of liver damage in Canada and No. 1, 2013 for potential risk of liver injury in the USA).

References:
FDA Drug Safety Communication, US FDA 30 April 2013 (*www.fda.gov*).

Valproate sodium, divalproex sodium, valproic acid

Contraindicated in

(Depacon®), divalproex sodium (Depakote®, Depakote® CP, and Depakote® ER), valproic acid (Depakene® and Stavzor®), and their generics. Valproate products are approved for the treatment of certain types of epilepsy, the treatment of manic episodes associated with bipolar disorder, and the prevention of migraine headaches. They are also used off-label for other conditions, particularly other psychiatric conditions.

This alert is based on the final results of the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study showing that children exposed to valproate products while their mothers were pregnant had decreased IQs at age 6 compared to children exposed to other anti-epileptic drugs.

Stronger warnings about use during pregnancy will be added to the drug labels, and valproate's pregnancy category for migraine use will be changed from "D" (the potential benefit of the drug in pregnant women may be acceptable despite its potential risks) to "X" (the risk of use in pregnant women clearly outweighs any possible benefit of the drug). Valproate products will remain in pregnancy category D for treating epilepsy and manic episodes associated with bipolar disorder.

(See WHO Pharmaceuticals