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

Further information on adverse reactions may be obtained from the WHO Collaborating Centre for International Drug Monitoring

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No. 1, 2012

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.

Drug safety problems not identified in clinical trials, known as signals are published in the Uppsala Monitoring Centre's SIGNAL document and shared with drug regulatory authorities. The WHO Advisory Committee on the Safety of Medicinal Products (ACSoMP) recommended that SIGNAL articles should be made public and shared with a wider audience. We have therefore started a new section in the newsletter, to bring you these articles. We must however caution that a 'signal' is to be seen as a hypothesis together with data and arguments; it is not only uncertain but also preliminary in nature.

The feature article in this issue gives you the conclusions from the working groups at the thirty-fourth annual meeting of representatives of the national centres participating in the WHO Programme for International Drug Monitoring.

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Aliskiren containing drugs

Contra-indication in patients with diabetes taking an ACE inhibitor or an ARB

Canada. Novartis Pharmaceuticals Canada Inc. ("Novartis"), in collaboration with Health Canada, informed health-care professionals about important new safety information for aliskiren-containing products following interim results review from the Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE). Interim results indicated a higher incidence of non-fatal strokes, renal complications (end stage renal disease and renal death), hyperkalemia and hypotension in aliskiren-treated patients. Analyses of the ALTITUDE interim results from the ALTITUDE study are ongoing. However, pending further analyses, a contra-indication in patients with diabetes taking an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) is now advised.

Aliskiren (RASILEZ®) is currently indicated for the treatment of mild to moderate essential hypertension. It may be used alone or concomitantly with thiazide diuretics, angiotensin converting enzyme inhibitors, angiotensin II AT1 receptor blockers or dihydropyridine calcium channel blockers. Aliskiren and hydrochlorothiazide (RASILEZ HCT®) are indicated for the treatment of mild to moderate essential hypertension in patients for whom combination therapy is appropriate.

It is advised that the treatment of diabetic patients taking aliskiren-containing products should therefore be reviewed as early as possible, taking the following advice into consideration:

- Aliskiren or aliskiren-containing fixed combination products should not be used in combination with ACE inhibitors or ARB in patients with diabetes, therefore:
  - health-care professionals should stop aliskiren-containing treatment in patients who are diabetic and also taking an ACE inhibitor or an ARB. Alternative antihypertensive treatment should be considered if necessary;
  - treatment with aliskiren-containing products should not be initiated in diabetic patients who are also taking either an ACE inhibitor or ARB;
  - patients should NOT stop any of these treatments before discussing with a healthcare professional.

Reference:
Advisories, Warnings and Recalls, Health Canada, 23 January 2012 (*www.hc-sc.gc.ca*).

Atomoxetine

Increases in blood pressure and heart rate: new contraindications, warnings, and advice for monitoring

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) advised health-care professionals that atomoxetine (Strattera®) should not be used in patients with severe cardiovascular or cerebrovascular disorders. Thorough pretreatment screening and regular monitoring of cardiovascular status is recommended. Specialist cardiac evaluation and advice should be sought if pretreatment findings suggest cardiac disease or history, or if symptoms suggesting cardiac disease are found during treatment. It is also recommended that patients who take atomoxetine for extended periods (i.e. one year) should have their treatment reviewed at least once a year by a specialist to determine whether continuation is needed.

Atomoxetine is a selective noradrenaline reuptake inhibitor for treatment of attention-deficit/hyperactivity disorder (ADHD) diagnosed according to DSM-IV criteria or ICD-10 guidelines, as part of a comprehensive treatment regimen. Treatment must be initiated by a specialist in the treatment of ADHD.

According to the MHRA, a recent review of clinical trial data in children and adults with ADHD showed mean increases in blood pressure and heart rate with atomoxetine to be as previously estimated (blood pressure: <5 mm Hg; pulse: <10 beats per minute). However, approximately 6–12% of children and adults experienced clinically important changes in blood pressure (≥15–20 mm Hg) or heart rate (≥20 beats per minute), or both. Of these, 15–32% had sustained or progressive increases. Although there is no strong evidence from other data sources for an increased risk of adverse clinical cardiovascular or cerebrovascular outcomes, these increases in heart rate or blood pressure could have serious clinical implications for a small proportion of patients who take atomoxetine—especially when increases are sustained or progressive.

(See WHO Pharmaceuticals Newsletter No.2, 2006 for recommended new warnings in UK and No.6, 2011 for association with increased blood pressure and increased heart rate in Canada).

Reference:
Drug Safety Update, January 2012, Volume 5, issue 6, A1, MHRA, (www.mhra.gov.uk).

Bevacizumab

Suspended approval for use in metastatic breast cancer

Canada. Health Canada made a final decision to suspend the Notice of Compliance with conditions (NOC/c) for bevacizumab (AVASTIN®) in combination with paclitaxel for treatment of patients with metastatic breast cancer (mBC) on 25 November 2011.

This action is specific to bevacizumab's breast cancer indication and does not impact the drug's approved uses for other cancer types in Canada. As such, the current Product Monograph was updated to reflect the suspension of the metastatic breast cancer indication, including the removal of any reference to clinical trials in mBC.

An NOC/c is authorization to market a drug (i.e. a Notice of Compliance (NOC)), with the condition that the sponsor undertake additional studies to verify the clinical benefit.

(See WHO Pharmaceuticals Newsletter No.2, 2011 for withdrawal of authorization of combination with docetaxel for breast cancer treatment in EU and removal of breast cancer indication in the USA, and reports in WHO Global ICSR database.)

Reference:
Advisories, Warnings and Recalls, Health Canada, 29 November 2011 (www.hc-sc.gc.ca).

Bisphosphonate drugs

Updated with new warnings and precautions regarding small but increased risk of unusual thigh bone fractures

Canada. Health Canada updated with respect to its review of bisphosphonate drugs and the risk of an atypical femur fracture. Health Canada's review of the evidence has shown a slightly increased risk of this type of fracture with bisphosphonate use. Although the risk is higher with bisphosphonate use, it is still extremely small. The benefits of using bisphosphonate drugs in preventing fractures associated with osteoporosis outweigh the risk of an atypical femur fracture. The product information for bisphosphonate drugs has been updated with new warnings and precautions regarding this risk, including signs of a possible atypical femur fracture that patients and health-care professionals should watch for. Updates to the labels for generic drugs will follow.

An atypical femur fracture can occur with minimal or no impact to the thigh area, and can occur in both legs in the same person. Signs of a potential fracture are dull, aching pain in the thigh, hip or groin area. A partial fracture could take weeks or months to become a complete fracture.

Health Canada advised that patients who are currently taking or who have taken a bisphosphonate drug in the past, and who notice new or unusual pain in the hip, groin or thigh should talk to their health-care professional as this may be a sign of an atypical femur fracture. Patients should not stop taking their bisphosphonate drug unless on the advice of their health-care professional. Health Canada recommended that consumers should consult with their health-care practitioner with any questions or concerns regarding the use of these products.

Health-care professionals should be aware of the possible risk of atypical femur fractures in patients taking bisphosphonates. As noted in the updated product information, health-care professionals should evaluate patients who report new hip, thigh or groin pain to rule out a partial femur fracture. Patients with an atypical femur fracture should also be assessed for possible signs of fracture in the other leg. Discontinuation of bisphosphonate therapy should be considered pending an assessment of the patient or the risk/benefit of using it. Health-care professionals are reminded that the need for continued bisphosphonate therapy should be periodically re-evaluated.

(See WHO Pharmaceuticals Newsletters No. 3, 2011 for rare atypical fractures of the femur: a class effect of bisphosphonates in EU).

Reference:
Advisories, Warnings and Recalls, Health Canada, 19 December 2011 (www.hc-sc.gc.ca).

Brentuximab vedotin

New boxed warning highlighting progressive multifocal leukoencephalopathy and new contraindication warning against use with bleomycin due to increased risk of pulmonary toxicity

USA. The U.S. Food and Drug Administration (US FDA) notified health-care professionals that two additional cases of progressive multifocal leukoencephalopathy (PML), a rare but serious brain infection that can result in death, have been reported with the lymphoma drug brentuximab vedotin (Adcetris®). Due to the serious nature of PML, a new Boxed Warning highlighting this risk has been added to the drug label. In addition, a new Contraindication warning was added against use of brentuximab vedotin with the cancer drug bleomycin due to increased risk of pulmonary toxicity.

The signs and symptoms of PML may develop over the course of several weeks or months. They may include changes in mood or usual behaviour, confusion, thinking problems, loss of memory, changes in vision, speech, or walking, and decreased strength or weakness on one side of the body.

Brentuximab vedotin is used to treat Hodgkin lymphoma and a rare lymphoma known as systemic anaplastic large cell lymphoma. At the time of its approval in August 2011, one case of PML was described in the Warnings and Precautions section of the label.

The US FDA recommended that patients who develop any signs and symptoms of PML should notify their health-care professional immediately. Health-care professionals should hold brentuximab vedotin dosing if PML is suspected and discontinue the drug if a diagnosis of PML is confirmed.

Reference:
FDA Drug Safety Communication, US FDA, 13 January 2012 (*www.fda.gov*).

Citalopram and escitalopram

QT interval prolongation: new maximum daily dose restrictions (including in elderly patients), contraindications, and warnings

UK. The MHRA advised that citalopram and escitalopram are associated with dose-dependent QT interval prolongation and should not be used in those with: congenital long QT syndrome; known pre-existing QT interval prolongation; or in combination with other medicines that prolong the QT interval and that ECG measurements should be considered for patients with cardiac disease, and electrolyte disturbances should be corrected before starting treatment. The agency also announced that new restrictions on the maximum daily doses applied for citalopram: 40 mg for adults; 20 mg for patients older than 65 years; and 20 mg for those with hepatic impairment and for escitalopram, the maximum daily dose for patients older than 65 years is reduced to 10 mg/day; other doses remain unchanged

Citalopram, a racemic mixture of R and S citalopram, is a selective serotonin reuptake inhibitor (SSRI) indicated for the treatment of major depressive disorder, panic disorder, and obsessive compulsive disorder. Escitalopram is the S enantiomer of citalopram indicated for major depressive episodes, panic disorder with or without agoraphobia, social anxiety disorder (social phobia), generalized anxiety disorder, and obsessive compulsive disorder.

According to the MHRA, the potential for citalopram and escitalopram to cause QT interval prolongation is reflected in the product information. However, recent data have further defined this risk and have clarified that their effects on the QT interval are dose dependent. For both citalopram and escitalopram, elderly patients have a higher exposure due to age-related decline in metabolism and elimination. The maximum dose of both medicines has therefore been restricted in patients older than 65 years.

The MHRA also advised health-care professionals that:

- patients who currently take doses higher than the new recommended daily maximum should have their treatment reviewed;
- the balance of benefits and risks of citalopram and escitalopram should be considered carefully, particularly at higher doses, in patients with pre-existing risk factors for QT interval prolongation—including patients with significant bradycardia; recent acute myocardial infarction; or decompensated heart failure;
- if cardiovascular symptoms, such as palpitations, vertigo, syncope, or seizures develop during treatment, cardiac evaluation including an ECG should be undertaken to exclude a possible malignant cardiac arrhythmia
  - o if QTc interval is >500 milliseconds, treatment should be withdrawn gradually
  - o if QTc interval duration is between 480 milliseconds and 500 milliseconds, the balance of benefits and risks of continued treatment should be carefully considered, alongside options for dose reduction or gradual withdrawal.

(See WHO Pharmaceuticals Newsletters No. 5, 2011 for abnormal heart rhythms associated with high doses in the USA).

Reference:
Drug Safety Update, December 2011, Volume 5, issue 5, A1, MHRA, (www.mhra.gov.uk).

Dronedarone

Revised indication, new contraindications, new warnings and precautions and new monitoring recommendations in Canada; Increased risk of death or serious cardiovascular events in the USA

Canada (1). Sanofi-aventis Canada Inc., in collaboration with Health Canada, informed health-care professionals that the Product Monograph (PM) of dronedarone (Multaq®) has been revised. The revisions reflect updated cardiovascular safety information from the analysis of the PALLAS study, and updated pulmonary safety information following post-market reports of pulmonary injury.

The PM has been modified to include a revised indication, new contraindications, new warnings and precautions and new monitoring recommendations:

- Dronedarone is now indicated for the treatment of patients with paroxysmal or persistent atrial fibrillation who are in sinus rhythm or who are intended to be cardioverted, to reduce the risk of cardiovascular hospitalization due to atrial fibrillation;
- Dronedarone should only be prescribed after alternative treatment options have been considered;
- the use of dronedarone has been further restricted to exclude patients with permanentatrial fibrillation of any duration, patients with a history of, or current heart failure, regardless of New York Heart Association (NYHA) functional class, patients with left ventricular systolic dysfunction (LVSD), patients with certain conduction abnormalities and patients with liver or lung toxicity related to previous use of amiodarone;
- updated information has been added to the "Warnings and Precautions" section of the Product Monograph regarding anticoagulation therapy as well as the use of dronedarone in the elderly, in patients with coronary artery disease and in patients who develop congestive heart failure or LVSD during treatment with dronedarone. New cardiovascular and renal monitoring recommendations as well as the need for pulmonary clinical evaluation have also been added to the Product Monograph.

USA (2). The US FDA completed a safety review of dronedarone (Multaq®). This review showed that dronedarone increased the risk of serious cardiovascular events, including death, when used by patients in permanent atrial fibrillation (AF). The review was based on data from two clinical trials, PALLAS and ATHENA. The US FDA is providing new information and recommendations for the use of dronedarone to manage the potential serious cardiovascular risks with the drug.

The dronedarone drug label has been revised with the following changes and recommendations:

- health-care professionals should not prescribe dronedarone to patients with AF who cannot or will not be converted into normal sinus rhythm (permanent AF), because dronedarone doubles the rate of cardiovascular death, stroke, and heart failure in such patients;
- health-care professionals should monitor heart (cardiac) rhythm by electrocardiogram (ECG) at least once every three months. If the patient is in AF, dronedarone should be stopped or, if clinically indicated, the patient should be cardioverted;
- Dronedarone is indicated to reduce hospitalization for AF in patients in sinus rhythm with a history of non-permanent AF (known as paroxysmal or persistent AF);
- patients prescribed dronedarone should receive appropriate antithrombotic therapy.

(See WHO Pharmaceuticals Newsletter No. 4, 2011 for increased risk of death or serious cardiovascular events in Canada and the USA and No. 5 for information on increase in cardiovascular events in patients with permanent atrial fibrillation in Canada and EU).

Reference:
(1) Advisories, Warnings and Recalls, Health Canada, 8 December 2011 (www.hc-sc.gc.ca).
(2) FDA Drug Safety Communication, US FDA, 19 December 2011 (www.fda.gov).

Meprobamate-containing medicines

Suspension of marketing authorisations for meprobamate-containing medicines in the EU recommended

Europe. The European Medicines Agency (EMA) has recommended the suspension of all marketing authorisations for meprobamate-containing medicines for oral use in the European Union (EU), because their risks, particularly the risk of serious side effects affecting the nervous system, are greater than their benefits. To ensure prescribers have enough time to determine the most appropriate treatments for individual patients, the Committee has recommended that the withdrawal of the medicines from the market be carried out gradually, within 15 months of the European Commission decision.

Meprobamate is a sedative medicine used to treat the symptoms of anxiety and related conditions, including anxiety states, alcohol withdrawal, migraine attacks, digestive disorders, muscle tension or cramps, and insomnia.

The review of meprobamate-containing medicines was started because the French authorities announced in July well as from poison control centres on cases of poisoning with meprobamate.

The CHMP noted that there was a risk of serious and potentially fatal side effects, such as coma, in patients taking meprobamate-containing medicines under normal conditions of use. The CHMP considered that these risks were increased due to the danger of unintentional overdose because of the small difference between the treating dose and the dose that can harm patients, including elderly people. The CHMP also noted that some patients can become addicted to the medicine, leading to serious and sometimes fatal side effects if they stop treatment abruptly after using it for a long time.

(See WHO Pharmaceuticals Newsletter No. 2, 2008 for Benefit/risk profile no longer favourable in UK).

Reference:
Press release, EMA, 20 January 2011 (*www.ema.europa.eu*).

Natalizumab

Anti-JC virus antibodies: new risk factor for progressive multifocal leukoencephalopathy

analytically and clinically validated, and has been ordered by a healthcare professional. The Stratify JCV Antibody ELISA test2 was cleared by FDA on 20 January 2012. Testing positive for anti-JCV antibodies means that a person has been exposed to JCV in the past.

The US FDA recommended that the risks and benefits of continuing treatment with natalizumab should be carefully considered in patients who are found to be anti-JCV antibody positive and have one or more of the other known risk factors for PML. Patients with all three known risk factors have an estimated risk of PML of 11/1,000 users.

(See WHO Pharmaceuticals Newsletters No. 2, 2010 for updates on the risk of PML and IRIS in the UK and the USA, No. 1, 2010 for recommendations of new measures to minimize the risk of PML in Europe and No. 3, 2010 for updates on the risk of PML in Canada as well as No. 3, 2011 for update of information about the risk of PML in the USA).

Reference:
FDA Drug Safety Communication, US FDA, 20 January 2012 (*www.fda.gov*).

Simvastatin