# 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*

**No. 2, 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. It also includes a section on Signals from the Uppsala Monitoring Centre.

The feature article in this issue gives you a brief summary of WHO activities to support patient reporting of adverse drug reactions.

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**Printed by the WHO Document Production Services, Geneva, Switzerland**

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## Aliskiren containing medicines

### New contraindications and warnings for aliskiren containing medicines

**Europe.** The European Medicines Agency (EMA) finalized a review of aliskiren containing medicines, recommending that these medicines should be contraindicated in patients with diabetes or moderate to severe renal impairment who take angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). In addition, the Agency recommended the inclusion of a warning that the combination of aliskiren and ACE inhibitor or ARB is not recommended in all other patients because adverse outcomes cannot be excluded.

The EMA advised that doctors should stop prescribing aliskiren-containing medicines to patients with diabetes (type I or type II) or with moderate to severe kidney impairment who are also taking an ACE inhibitor or ARB, and should consider alternative antihypertensive treatment as necessary and that the balance of benefits and risks of continuing treatment should be considered carefully for all other patients receiving aliskiren-containing medicines in combination with an ACE inhibitor or an ARB.

The EMA also advised that patients should discuss their treatment with their doctor at their next scheduled (non-urgent) appointment. They should not stop any of their treatment before speaking to their doctor, because stopping anti-hypertensive medication without medical supervision can put them at risk. Patients in clinical trials with aliskiren should contact their study site for guidance on their medication.

(See WHO Pharmaceuticals Newsletter No.1, 2012 for contra-indication in patients with diabetes taking an ACE inhibitor or an ARB in Canada).

***Reference:***
Press release, EMA, 16 February 2012 (*www.ema.europa.eu*).

## Atomoxetine

### Risk of increased blood pressure and/or heart rate

**Australia.** The Therapeutic Goods Administration (TGA) advised health-care professionals of important safety information regarding the risk of clinically significant increases in blood pressure and/or heart rate with the use of atomoxetine (Strattera®).

Health-care professionals are advised that atomoxetine is contraindicated in patients with symptomatic cardiovascular diseases, moderate to severe hypertension or severe cardiovascular disorders whose condition would be expected to deteriorate if they experienced clinically important increases in blood pressure or heart rate.

It is also advised that atomoxetine should be used with caution in patients whose underlying medical conditions could be worsened by increases in blood pressure or heart rate, such as patients with hypertension, tachycardia or cardiovascular or cerebrovascular disease. The drug should be used with caution in patients with, or with a family history of, congenital or acquired QT prolongation.

Patients should be screened for pre-existing or underlying cardiovascular or cerebrovascular conditions before initiation of treatment with atomoxetine and monitored during the course of treatment.

Heart rate and blood pressure should be measured in all patients before treatment with atomoxetine is started, after the dose is increased, and periodically during treatment to detect possible clinically important increases, particularly during the first few months of therapy.

(See WHO Pharmaceuticals Newsletter No.2, 2006 for recommended new warnings in UK, No.6, 2011 for association with increased blood pressure and increased heart rate in Canada and No.1, 2012 for increases in blood pressure and heart rate in the UK).

***Reference:***
Medicines Safety Update Vol. 3, No. 1, February 2012 (www.tga.gov.au).

## Boceprevir

### Drug interactions with ritonavir-boosted Human Immunodeficiency Virus (HIV) protease inhibitor drugs

**USA (1).** The U.S. Food and Drug Administration (US FDA) notified health-care professionals and patients that drug interactions between the hepatitis C virus (HCV) protease inhibitor boceprevir (Victrelis®) and certain ritonavir-boosted human immunodeficiency virus (HIV) protease inhibitors (atazanavir, lopinavir, darunavir) can potentially reduce the effectiveness of these medicines when they are used together. The US FDA will be updating the boceprevir drug label to include information about these drug interactions.

Boceprevir is a HCV protease inhibitor used with the medicines peginterferon alfa and ribavirin to treat chronic (long-lasting) hepatitis C infection in adults. HIV protease inhibitors are a class

of anti-viral drugs used to treat HIV infection. Ritonavir is an HIV protease inhibitor used to "boost" other HIV protease inhibitors, increasing their levels in the blood and making them more effective.

A drug interaction study showed that taking boceprevir with ritonavir (Norvir®) in combination with atazanavir (Reyataz®) or darunavir (Prezista®), or with Kaletra® (lopinavir/ritonavir) reduced the blood levels of the HIV medicines and boceprevir in the body.

The US FDA recommended that patients should not stop taking any of their medicines without talking to their health-care professional. Patients should contact their health-care professional if they have any questions or concerns. The agency also recommended health-care professionals who have started patients infected with both chronic HCV and HIV on boceprevir and antiretroviral therapy containing a ritonavir-boosted protease inhibitor to closely monitor patients for HCV treatment response and for potential HCV and HIV virologic rebound.

**Europe (2).** The European Medicines Agency(EMA) recommended updating the prescribing information for boceprevir (Victrelis®) with information about drug interactions between this hepatitis C medicine and the ritonavir-boosted HIV protease inhibitors atazanavir, darunavir and lopinavir.

The EMA's Committee for Medicinal Products for Human Use (CHMP) concluded that the lower blood levels seen in the drug interaction study could mean that the medicines are less effective when given together to patients who are co-infected with hepatitis C and HIV. However, the Committee acknowledged that data from ongoing clinical studies in co-infected patients are needed to assess the clinical impact of these drug-interaction findings on these patients.

Studies on the efficacy and safety of boceprevir when used in patients co-infected with HIV and hepatitis C are ongoing. While data from these studies are awaited, the CHMP has recommended updating the product information to inform prescribers and patients of the findings as a precautionary measure.

The CHMP recommended that doctors treating patients co-infected with hepatitis C and HIV should be aware of the findings of the drug interaction study. They should not co-administer boceprevir with ritonavir-boosted darunavir or lopinavir in HIV and hepatitis C co-infected patients. Co-administration of boceprevir with ritonavir-boosted atazanavir may be considered on a case-by-case basis if deemed necessary in patients with suppressed HIV viral loads and with an HIV strain without any suspected resistance to the HIV regimen. Increased clinical and laboratory monitoring is warranted.

The CHMP recommended that patients should not stop taking any of their medicines without talking to their health-care professional. Patients should contact their health-care professional if they have any questions or concerns.

***References:***

(1) FDA Drug Safety Communication, US FDA, 9 February 2012 (*www.fda.gov*).
(2) Press release, EMA, 16 February 2012 (*www.ema.europa.eu*).

## Bortezomib

### Fatal if given intrathecally

**Canada.** Janssen Inc., in consultation with Health Canada, alerted the risk of fatal outcome associated with the inadvertent intrathecal administration of bortezomib (VELCADE®).

Since the first global approval of the drug in May 2003, three cases of inadvertent intrathecal administration with fatal outcome have been reported worldwide; these occurred in France and Italy. Each case occurred when intrathecal oncology chemotherapy was scheduled at the same time as the bortezomib intravenous administration.

It is advised that:

- bortezomib should only be administered via the approved intravenous (IV) route;
- health-care professionals are encouraged to administer chemotherapy intended via the intrathecal route at a different time than other parenteral chemotherapy. Different connectors should be used for medicinal products to be administered via the intrathecal or intravenous route;
- health-care professionals are encouraged to clearly label syringes with the name of the medicinal product and route of administration to be used and ensure procedures are in place to enforce a double check of syringe labelling before administration;
- train and inform health-care professionals involved in administration and/or management of oncology chemotherapy on dangers of intrathecal administration of bortezomib and the above risk minimization measures.

***Reference:***

Advisories, Warnings and Recalls, Health Canada,

31 January 2012 (www.hc-sc.gc.ca).

## Citalopram hydrobromide

### Association with dose-dependent QT Prolongation

**Canada (1).** Lundbeck Canada, in collaboration with Health Canada, informed that citalopram hydrobromide (Celexa®), should no longer be used at doses greater than 40 mg per day due to study results indicating a dose-dependent potential for QT prolongation. 20 mg per day is the maximum recommended dose for patients with hepatic impairment, patients who are 65 years of age or older, patients who are CYP2C19 poor metabolizers, or patients who are taking concomitant cimetidine or another CYP2C19 inhibitor. Citalopram hydrobromide is contraindicated in patients with congenital long QT syndrome or known QT interval prolongation.

ECG monitoring is recommended in patients with risk factors for Torsade de Pointes such as congestive heart failure, recent myocardial infarction, bradyarrhythmias or in patients taking concomitant medications that prolong the QT interval as well as in patients with altered citalopram metabolism (e.g. liver impairment).

Patients at particular risk for developing prolongation of the QT interval include those with underlying heart conditions and those who are predisposed to low blood levels of potassium and magnesium. Hypokalaemia and hypomagnesaemia should be corrected before administering citalopram hydrobromide.

Patients should be advised to contact a health-care professional immediately if they experience signs and symptoms of an abnormal heart rate or rhythm while taking citalopram hydrobromide. These include dizziness, palpitations, syncope or seizures. Patients should be cautioned not to stop taking citalopram hydrobromide or to change the dose without first consulting their health-care professional. Withdrawal symptoms such as dizziness, feelings of agitation or anxiety, difficulty concentrating, abnormal dreams, nausea or vomiting may occur when SSRI treatment is discontinued, particularly if this is abrupt.

In the event that citalopram hydrobromide is discontinued or the dose is reduced, health-care professionals should monitor patients closely for the re-emergence or worsening of any symptoms of depression.

The manufacturer is working closely with Health Canada to determine if there is a need to include further information regarding QT prolongation in addition to that already present in the labelling for escitalopram oxalate (Cipralex®), a drug related to citalopram hydrobromide.

**Australia (2).** The TGA announced that a study of citalopram's effect on cardiac conduction, which showed dose-dependent QT prolongation with the medicine, has led to the recommended maximum daily dose of citalopram being reduced to 40 mg, along with other important changes to dosing recommendations for citalopram.

Given the above study results, the following changes to dose recommendations have been made:

- the recommended maximum daily dose of citalopram is 40 mg;
- in people over 65 years of age, those with hepatic dysfunction, those taking medicines such as cimetidine or omeprazole which are known to inhibit the metabolism of citalopram, or those known to metabolise poorly via CYP2C19, the recommended maximum daily dose is 20 mg;
- the recommended starting dose in the elderly is 10 mg daily.

In addition, citalopram is contraindicated in patients with congenital long QT syndrome.

Citalopram should be used with caution in patients at higher risk of developing prolongation of the QT interval, including those with congestive heart failure, bradyarrhythmias, a predisposition to hypokalaemia or hypomagnesaemia and concomitant medicines that prolong the QT interval.

There are also new monitoring recommendations for patients on citalopram:

- hypokalaemia and hypomagnesaemia should be corrected prior to initiation of treatment and potassium and magnesium levels should be periodically monitored;
- more frequent ECG monitoring should be considered for patients at higher risk of QT prolongation.

It is also reminded health-care professionals that suddenly stopping citalopram may cause withdrawal symptoms. If citalopram is discontinued or the dose reduced, the patient should be monitored closely for the re-emergence or worsening of any symptoms of depression.

A similar study of escitalopram found much more limited dose-dependent QT prolongation. No changes to dosing recommendations for escitalopram have been made.

(See WHO Pharmaceuticals Newsletters No. 5, 2011 for

abnormal heart rhythms associated with high doses in the USA and No. 1, 2012 for QT interval prolongation in the UK).

***References:***
(1) Advisories, Warnings and Recalls, Health Canada, 30 January 2012 (*www.hc-sc.gc.ca*).
(2) Medicines Safety Update Vol 3, No. 1, February 2012 (www.tga.gov.au).

## Domperidone

### Association with serious ventricular arrhythmias and sudden cardiac death

**Canada.** The manufacturers of domperidone, in collaboration with Health Canada, informed health-care professionals that the domperidone should be initiated at the lowest possible dose in adults, including in patients with Parkinson's disease. Recent epidemiological studies have shown that the use of domperidone may be associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death, particularly in patients taking daily doses greater than 30 mg, and in patients older than 60 years of age.

Caution should be exercised when using domperidone concomitantly with drugs that prolong the QT interval, in patients who have existing prolongation of cardiac conduction intervals, particularly QTc, and in patients with significant electrolyte disturbances or underlying cardiac disease such as congestive heart failure.

Domperidone should be initiated at the lowest possible dose, which may be adjusted upward with caution to achieve the desired effect as needed. In addition, the expected benefit of an increased dose should outweigh the potential risks. Co-administration of domperidone with ketoconazole is contraindicated. Caution should be exercised when using domperidone concomitantly with other CYP3A4 inhibitors, which may increase plasma levels of domperidone.

Patients should be advised to stop taking domperidone and seek immediate medical attention if they experience signs or symptoms of an abnormal heart rate or rhythm while taking domperidone. These include dizziness, palpitations, syncope or seizures.

The manufacturers of all domperidone products are working with Health Canada to include this new drug dosage and usage recommendations, as well as information about the risk of serious ventricular arrhythmias and sudden cardiac death in all Canadian Product Monographs for the drug.

(See WHO Pharmaceuticals Newsletters No. 2, 2007 for heart rate and rhythm disorders in Canada).

***Reference:***
Advisories, Warnings and Recalls, Health Canada, 7 March 2012 (*www.hc-sc.gc.ca*).

## Fluoroquinolone

### Association with worsening of symptoms of myasthenia gravis in patients with myasthenia gravis

**Canada.** The manufacturers of the fluoroquinolone innovator products (Bayer Inc. and Janssen Inc.) in consultation with Health Canada informed of important updates reflecting the potential for the exacerbation of myasthenia gravis symptoms in patients with myasthenia gravis to the labelling for fluoroquinolone antibiotics (AVELOX®, CIPRO®, CIPRO® XL, and LEVAQUIN®).

Fluoroquinolones have neuromuscular blocking activity and may exacerbate muscle weakness in patients with myasthenia gravis. Exacerbation of myasthenia gravis symptoms in patients with myasthenia gravis can lead to a requirement for respiratory support in some patients. It is advised that fluoroquinolone antibiotics should be avoided in patients with a known history of myasthenia gravis.

The association between the exacerbation of myasthenia gravis and fluoroquinolone use has been established based on the review of post-marketing reports. Cases of serious adverse events, including deaths and requirement for ventilatory support have been associated with fluoroquinolone use in patients with myasthenia gravis.

Exacerbation of symptoms of myasthenia gravis was already included as an undesirable effect in earlier versions of the Product Monographs of these medicines. To reinforce the warning, the Product Monographs for the innovator fluoroquinolone antibiotics have been revised under the Warnings and Precautions section to include information that they may exacerbate muscle weakness in patients with myasthenia gravis.

(See WHO Pharmaceuticals Newsletters No. 6, 2011 for risk of worsening of symptoms of myasthenia gravis in Canada).

***Reference:***
Advisories, Warnings and Recalls, Health Canada, 9 March 2012 (*www.hc-sc.gc.ca*).

## Pneumovax® 23 (pneumococcal vaccine polyvalent)

### Updated revaccination recommendations

**Australia.** The TGA advised health-care professionals not to routinely revaccinate immunocompetent individuals with Pneumovax® 23. Revaccination should be considered for patients at a high risk of serious pneumococcal disease, provided that at least five years have passed since the previous dose of Pneumovax 23.

In April 2011 the TGA advised health-care professionals not to administer a second or subsequent dose of Pneumovax® 23 vaccine pending the outcome of a review of an apparent increased rate of injection site reactions following administration of the second dose. This review has been completed and the TGA advised health-care professionals not to routinely revaccinate immunocompetent individuals. Revaccination of patients at high risk of serious pneumococcal disease should be in accordance with the Product Information.

Pneumovax® 23 is used to prevent life-threatening infections by pneumococcal bacteria. The TGA review noted that the adverse events observed were consistent with

Immunisation has reviewed the place of Pneumovax 23 in the National Immunisation Program and their updated recommendations have been published at www.immunise.health.gov.au.

It is noted that this advice does not apply to Prevenar®, Prevenar® 13 and Synflorix® pneumococcal conjugate vaccines.

***Reference:***
Medicines Safety Update Vol. 3, No. 1, February 2012 (www.tga.gov.au).

## Statins

### Class labelling change

**USA.** The US FDA approved important safety label changes for statins. The changes include removal of routine monitoring of liver enzymes from drug labels. Information about the potential for generally non-serious and reversible cognitive side effects and reports of increased blood sugar and glycosylated hemoglobin (HbA1c) levels has been added to the statin labels. The lovastatin label has been extensively updated with new contraindications and dose limitations when it is taken with certain medicines that can increase the risk for muscle injury.

The US FDA recommended that health-care professionals should perform liver enzyme tests before initiating statin

risk of myopathy/rhabdomyolysis when used with lovastatin.

***Reference:***
FDA Drug Safety Communication, US FDA, 28 February 2012 (*www.fda.gov*).

## Strontium ranelate

### No longer recommended for use in immobilised patients or patients with venous thromboembolism (VTE); update of warnings regarding serious skin reactions.

**Europe.** The CHMP has finalised a review of strontium ranelate (Protelos® and Osseor®). The Committee concluded that these medicines remain an important treatment for women with osteoporosis, but that changes to the prescribing advice are necessary to better manage associated risks.

The review of these medicines was started following the publication of a study in France identifying 199 severe adverse reactions reported with these medicines from January 2006 to March 2009. Around half of these were VTE events, and about a quarter related to skin reactions. VTE and severe skin reactions are known risks of these medicines and have been kept under close review by the CHMP. The risk of VTE