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/medicine

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

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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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 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).


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).


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:

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,
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, healthcare 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;

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

31 January 2012 (www.hc-sc.gc.ca).
### Abnormal Heart Rhythms

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](http://www.hc-sc.gc.ca)).

### 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](http://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](http://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 the known high rates of local reactions which occur more commonly after a repeat dose of Pneumovax® 23. The review concluded that the adverse events were not due to a problem with the vaccine manufacturing or handling.

This advice differs from that in the current Australian Immunisation Handbook, which recommends routine revaccination five years after the first dose. The Australian Technical Advisory Group on 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.


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 therapy in patients and as clinically indicated thereafter. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment, therapy should be interrupted. If an alternate etiology is not found, the statin should not be restarted.

Health-care professionals should follow the recommendations in the lovastatin label regarding drugs that may increase the risk of myopathy/rhabdomyolysis when used with lovastatin.


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 (Proteolos® 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 was identified in clinical trials and the risk of severe skin reactions had been reported post marketing. Information on these risks had been included in the product information as warnings or listed as reported side effects.

The CHMP has reviewed all available data on the safety of these medicines. The data show that the risk of VTE is higher in patients with a history of VTE, as well as in patients who are temporarily...
or permanently immobilised. The number of cases of VTE in elderly patients is also shown to be higher with the drug compared with placebo.

The data also show that the incidence rate of serious skin reactions such as drug rash with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) is low and no possible mechanism of action has been identified so far. Because the best results in managing these conditions come from early diagnosis and immediate discontinuation of any suspect drug, it is very important that doctors and patients are alert to the time-to-onset and signs and symptoms of these conditions.

The CHMP advised that:

- doctors should not prescribe strontium ranelate to patients with current VTE or a history of VTE, as well as patients who are temporarily or permanently immobilized;
- patients with current VTE or a history of VTE, and those who are temporarily or permanently immobilised are advised to discuss their treatment with their doctor at their next scheduled appointment;
- when treating patients over 80 years of age at risk of VTE, doctors should re-evaluate the need to continue treatment with strontium ranelate;
- prescribers should make patients aware of the time-to-onset and likely signs and symptoms of severe skin reaction such as DRESS, SJS or TEN. The highest risk for occurrence of SJS or TEN is within the first weeks of treatment and usually around three to six weeks for DRESS. Symptoms or signs of SJS or TEN include progressive skin rash, often with blisters or mucosal lesions; symptoms of DRESS include rash, fever, eosinophilia and systemic involvement (e.g. adenopathy, hepatitis, interstitial nephropathy, interstitial lung disease);
- patients should stop treatment immediately when symptoms of severe allergic reactions, including skin rash, occur. Treatment should not be re-started at any time in these patients.

(See WHO Pharmaceuticals Newsletter No. 1, 2008 for reports of severe allergic reactions associated with strontium ranelate in the UK and No. 3, 2008 for ADR update in Australia).

Reference:

Vandetanib

Serious risk of abnormal heart rhythm
Canada. AstraZeneca Canada Inc., in consultation with Health Canada, informed of important information regarding serious risks of QTc prolongation, Torsade de Pointes, and sudden death for vandetanib (CAPRELSA®). Cases of Torsade de Pointes and sudden deaths were reported in clinical trials. In addition to them, rash and other skin reactions, diarrhea, hypertension and vision abnormalities have also been reported in patients taking the drug. Vandetanib use should be carefully considered based on a risk-benefit assessment in patients with indolent, asymptomatic or slowly progressive disease because of the significant treatment-related risks.

Health Canada has recently approved the drug as a monotherapy for the treatment of symptomatic or progressive medullary thyroid cancer in adult patients with unresectable locally advanced or metastatic disease.

Vandetanib is only available through a Restricted Distribution Program. Only prescribers enrolled in the CAPRELSA Restricted Distribution Program can prescribe the drug. In order to prescribe CAPRELSA, physicians are required to complete mandatory online training which includes a full description of important safety issues, patient screening and selection criteria, dosage and administration guidelines, ECG and electrolyte monitoring requirements, drug interaction information, and an overview of the patient enrolment process.

Aprotinin

Lifting suspension of aprotinin recommended for Europe. The EMA recommended that the suspension of the marketing authorisations for aprotinin-containing medicines in the European Union (EU) be lifted. This follows a full review of the benefits and risks of all antifibrinolytic medicines, which found that the results of the BART study on which the suspension was based are unreliable.

The CHMP concluded that aprotinin’s benefits in preventing blood loss outweigh its risks in patients undergoing isolated heart bypass surgery who are at high risk of major blood loss. It should only be used in this narrower group of patients once the doctor has assessed the benefits and risks of treatment carefully and considered alternative treatments.

Aprotinin was suspended as a precautionary measure on the recommendation of the CHMP, following the preliminary results of the BART study, a randomised controlled trial in high-risk heart surgery patients. These results appeared to show an increased death rate in patients receiving aprotinin after 30 days compared to patients taking other medicines, and led to the early discontinuation of the study by its data safety monitoring board.

The current review was started after the publication of the final results of the BART study and looked at this study’s results, as well as the results of other clinical studies, data from the scientific literature, reports of side effects and information submitted by the companies that market antifibrinolytic medicines. The CHMP also took the views of its scientific advisory group into account.

The Committee found that there were a number of problems with the way the BART study was conducted, which cast doubt on the previous conclusions. These included the imbalances in the way blood-thinning medicines such as heparin were used, inappropriate monitoring of the use of these medicines and how problems with the way that data from some patients were excluded from the initial analysis. The Committee found that the BART study’s results were not replicated in other studies and that the overall data available showed that aprotinin’s benefits are greater than its risks in the restricted indication.

As a condition of the lifting of the suspension, the Committee also recommended that doctors be warned of the risk of giving patients too little heparin, as well as the establishment of a registry to record information on the use of aprotinin in the EU.

The review also included the antifibrinolytic medicines aminocaproic acid and tranexamic acid, which have been used since the 1960s in patients undergoing dental or surgical procedures or at risk of complications from bleeding. The Committee found no new safety concerns for these medicines. However, it noted that there is very limited information available on some of the conditions that these medicines are used to treat. Therefore, the Committee recommended a restricted list of conditions in which they should be used based on the currently available evidence.

The Committee also requested that a study be carried out to gather more information on how tranexamic acid should be optimally dosed in children.

(See WHO Pharmaceuticals Newsletter No. 6, 2007 and No. 1, 2008 for temporary market suspension of aprotinin worldwide, and No. 5, 2011 for the benefits outweigh the risks when it is used as authorized in Canada).


Benzyl alcohol-containing parenteral products

Risk of gasping syndrome

Saudi Arabia The Saudi Food and Drug Authority (SFDA) advised health-care professionals about the potential risk of developing Gasping Syndrome in neonates and infant after administering parenteral products that contain benzyl alcohol (BA) as a preservative.

In the US, 16 cases of fatalities of pre-term neonates weighing 2.5 Kg where flush solutions contained 0.9% BA used periodically. The fatal reaction was gasping syndrome, the symptoms may include metabolic acidosis, seizure, bradycardia, gasping respiration and cardiovascular collapse.

A report estimated the fatal intake of BA was 130 mg/kg/day. However, another study reported that the average intake of BA in children who experienced gasping syndrome was 99 to 234 mg/kg, while a control group of infants received 27 to 99 mg/kg. However, it should be noted that there is a limitation in determining the volume of flush solution used in these reports. It could be argued that quantity of BA delivered by medications is lower than that available in saline and sterile water. However, the minimum toxic level has not been established, and therefore, the safety of
use of medicines containing BA in neonates has not been established.

The World Health Organization appealed for a mandatory declaration of all excipients involved in pharmaceutical manufacturing especially in developing countries. Similar recommendation was raised by the Advisory Committee for Pharmacovigilance at SFDA, especially for BA content.

Therefore, the SFDA issued a circular to all health-care professionals to include the following considerations:

- the use of benzyl alcohol containing diluents in preparing injectable medicines for paediatric patients is not recommended;
- when applicable, use acceptable alternative medicines that do not contain benzyl alcohol;
- health-care professionals should be aware about the potential risk of Gasping syndrome and to weight the benefits compared to potential risk when using benzyl alcohol-containing parenteral products.

Reference:
Personal communication from SFDA, 25 February 2012 (www.tga.gov.au).

Blue dyes

Risk of serious allergic reactions

UK. The UK Pharmacovigilance Expert Advisory Group of the Commission on Human Medicines advised health-care professionals that emergency measures should be available to treat patients that may experience allergic reactions or anaphylaxis.

Blue dyes (e.g. Patent Blue V®, isosulfan blue) used for imaging purposes during surgery are associated with the occurrence of serious allergic reactions, including anaphylaxis. Surgeons are reminded to have competent personnel and emergency facilities available for at least 1 hour after administration of the blue dye. Blue dyes such as Patent Blue V imported from the EU are used in lymphatic mapping for sentinel lymph node biopsy (SLNB) in breast surgery. Patent Blue V does not carry a UK marketing authorization.

On the basis of a clinical study (the ALMANAC trial) and follow-up program (the NEW START program) serious allergic reactions were estimated at an incidence rate of 0.1%. Since 1975 a total of 70 case reports of allergic reactions with Patent Blue V were reported to the Medicines and Healthcare products Regulatory Agency (MHRA). 58 of these reports have been received since 2007, 26 of which were serious reactions. With currently increasing usage of Patent Blue V in the UK, the number of serious allergic reactions reported to us is also expected to rise.

Reference:

Doripenem

Higher mortality rate and a lower clinical cure rate observed during a comparative clinical trial

Canada. Janssen Inc., in consultation with Health Canada, informed of new safety information regarding the use of doripenem (DORIBAX®) in the treatment of ventilator-associated pneumonia (VAP). A prospective, randomized, double-blind, double-dummy, multicentre Phase III study of an investigational use of the drug in VAP was prematurely terminated when interim analyses of data from 274 of the planned 524 subjects showed a higher mortality rate and a lower clinical cure rate among subjects treated with a fixed seven-day course of the drug 1g q8h compared to those treated with a fixed ten-day course of imipenem-clavulanic.

Doripenem is approved in Canada for the treatment of adults with Nosocomial Pneumonia, including VAP, complicated Intra-Abdominal Infections (cIAI) and complicated Urinary Tract Infections (cUTI), including Pyelonephritis. The approved dosage of the drug for patients with nosocomial pneumonia including VAP is 500 mg administered as a one or four hour intravenous infusion every eight hours for seven to 14 days.

The use of doripenem 1 g every eight hours in a fixed seven-day course has been associated with a higher mortality rate and a lower clinical cure rate compared to a fixed ten-day course of imipenem-clavulanic. Treatment duration should be guided by the severity of illness, infecting pathogen and the patient’s clinical response.

The Canadian Product Monograph contains information on the recommended dose and duration of treatment in the Dosage and Administration section. However, based on the new information from this investigational VAP study, the Product Monograph will be updated regarding the treatment of VAP.

Reference:
Fingolimod

Under review in light of serious adverse events in Canada. Health Canada informed of an on-going safety review of fingolimod (Gilenya®). The review was initiated following reports of serious adverse events, including 11 deaths reported internationally. No deaths have been reported in Canada.

According to Health Canada, currently, it is not clear whether the deaths were caused by fingolimod or whether other factors may have played a role. Four of the 11 reports involved serious heart-related events (three involved heart attacks and one involved a disturbance of the heart rhythm), while the other seven are unexplained. Among these seven is a report involving a patient in the United States who died within 24 hours of taking the first dose.

At the time of authorization, it was known that fingolimod can be associated with certain types of heart rhythm disturbances. The Canadian labelling contains several important warnings with respect to these risks. At this time, when the drug is used as recommended in the authorized Canadian drug label, the benefits of fingolimod are considered to outweigh the risks.

Health Canada advised health-care professionals to continue to follow the labelling instructions closely, particularly with respect to patient monitoring. Specifically, the label recommends that physicians:

- obtain an ECG before the first dose if one is not available in the last six months;
- observe patients for signs and symptoms of bradycardia, including periodic assessment of heart rate, for at least six hours after the first dose (or if more than two weeks have passed since the previous dose);
- initiate appropriate treatment if clinically important heart-related symptoms occur. Symptoms include bradycardia or atrioventricular block. Continue to manage and monitor patients until symptoms have resolved;
- measure blood pressure regularly as fingolimod is known to increase blood pressure.

Health Canada advised that patients taking fingolimod who experience symptoms of heart problems should report them immediately. Symptoms include chest pain, slow or irregular heartbeat, or feeling dizzy. Patients should not stop taking fingolimod without first consulting a health-care professional. Patients who have any questions or concerns about their fingolimod therapy should speak to their healthcare professional.

Before starting fingolimod, patients should tell their doctor if they are taking other medications such as drugs used to treat abnormal heart rhythms, beta blockers or calcium channel blockers, or if they have a history of heart-related problems such as low heart rate, heart rhythm disorders, congestive heart failure, or fainting.

Health Canada continues to assess all available information, including information from the company (Novartis), and information from other regulators. Health Canada will take appropriate action based on the results of its review.

Reference:

Orlistat-containing medicines

Positive benefit-risk balance of orlistat-containing medicines confirmed in Europe. Finalizing its review on orlistat-containing medicines and the possible risk of severe liver injuries, the CHMP concluded that the benefit of these medicines continue to outweigh their risks in the treatment of obese or overweight patients with a body mass index of 28 kg/m² or above.

The Committee recommended that the product information for these products should be harmonized to ensure that the information on possible very rare liver-related side effects is the same for all orlistat-containing medicines. This review included the centrally authorized medicines Xenical® which is available as capsules (120 mg) and Alli® which is available as capsules (60 mg) and chewable tablets (27 mg) which can be obtained without a prescription (‘over-the-counter’) as well as nationally authorized orlistat-containing generics.

The risk of very rare liver-related side effects in association with orlistat has been under close review by the CHMP since 2001 for Xenical®, when the product information was updated to reflect post-marketing reports of liver reactions in association with orlistat. The current product information for orlistat-containing medicines lists hepatitis, cholelithiasis and a change in liver enzyme levels as potential liver-related side effects.

The CHMP reviewed all available data on the risk of liver injury and other side effects with orlistat, including post-marketing surveillance, data from the studies supporting the marketing
authorization and population-based studies in the published literature, and results of an ‘expected versus observed’ analysis of reports of severe liver injuries conducted by the marketing authorization holders at the request of the Committee.

The CHMP considered that there was no strong evidence that orlistat increased the risk of severe liver injury, and there was no known mechanism by which orlistat was expected to cause liver disorders. The Committee concluded that the number of reported severe liver reactions in orlistat users was low and below the background rate expected in these people, given the large number of users. A pattern was not seen in the type of liver problems reported, and in most cases there were other factors which were likely to increase the risk of liver injury, such as existing health problems or the use of other medicines. The Committee considered that while there may be very rare cases of serious liver injury for which causality with orlistat cannot be excluded, the cases do not provide good evidence of a causal association. The CHMP also noted that published population-based studies suggest that obesity may be associated with a higher risk of liver disease.

(See WHO Pharmaceuticals Newsletter No. 5, 2009 for early communication about an on-going safety review and No. 4, 2010 for labelling change due to reports of severe liver injury in the USA and the reports in WHO Global ICSR database).

Reference:

Proton Pump Inhibitors (PPIs)

Possible risk of Clostridium Difficile-Associated Diarrhoea (CDAD)

USA. The US FDA notified the public that the use of PPIs which include rabeprazole sodium, dexlansoprazole, esomeprazole magnesium, omeprazole, lansoprazole, omeprazole and pantoprazole sodium, may be associated with an increased risk of Clostridium difficile-associated diarrhoea (CDAD). A diagnosis of CDAD should be considered for patients taking PPIs who develop diarrhoea that does not improve. The US FDA is working with manufacturers to include information about the increased risk of CDAD with use of PPIs in the drug labels.

The US FDA is also reviewing the risk of CDAD in users of histamine H2 receptor blockers. H2 receptor blockers are used to treat conditions such as gastroesophageal reflux disease (GERD), stomach and small intestine ulcers, and heartburn.

Clostridium difficile (C. difficile) is a bacterium that can cause diarrhoea that does not improve. Symptoms include watery stool, abdominal pain, and fever, and patients may go on to develop more serious intestinal conditions. The disease can also be spread in hospitals.

The US FDA recommended that patients should immediately contact their health-care professional and seek care if they take PPIs and develop diarrhoea that does not improve. The agency informed health-care professionals that:

• a diagnosis of CDAD should be considered for PPI users with diarrhoea that does not improve;
• advise patients to seek immediate care from a healthcare professional if they experience watery stool that does not go away, abdominal pain, and fever while taking PPIs;
• patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Canada (2). Health Canada informed of a possible association between the use of PPIs and an increased risk of CDAD and announced that Health Canada is assessing this data on an on-going basis.

The studies acknowledge important limitations with regards to study design and the impossibility of establishing a definite cause-and-effect relationship between PPIs and an increased risk of CDAD, as there are a number of other factors that may play a role. While a definite association between PPI use and CDAD has not been confirmed, the possibility has not been ruled out at this time. The potential for an increased risk of C. difficile infection is identified in the Canadian labelling for PPI drugs. Health Canada will continue to monitor this issue, evaluate the scientific evidence as it emerges and take appropriate action as necessary.

Health Canada advised that patients taking a PPI who develop a diarrhoea that does not improve should speak to a health-care professional immediately as this may be CDAD. Symptoms include severe watery or bloody diarrhoea (at least three bowel movements per day for two or more days); fever; loss of appetite; nausea; and abdominal pain or tenderness. Patients taking a PPI should talk with their doctor or pharmacist if they have questions or concerns about their antacid treatment.

Health-care professionals are reminded that PPIs should be prescribed at the lowest dose...
and shortest duration of therapy appropriate to the condition being treated. A diagnosis of CDAD should be considered for any patient who has risk factors for CDAD and who has persistent or severe diarrhoea.

References:
(2) Advisories, Warnings and Recalls, Health Canada, 16 February 2012 (www.hc-sc.gc.ca).

Statins and HIV or Hepatitis C Protease inhibitors

Interaction increases risk of muscle injury

USA. The US FDA notified health-care professionals of updates to the prescribing information concerning interactions between HIV or HCV protease inhibitors and certain statin drugs. Protease inhibitors and statins taken together may raise the blood levels of statins and increase the risk for myopathy. The most serious form of myopathy, called rhabdomyolysis, can damage the kidneys and lead to kidney failure, which can be fatal.

The US FDA recommended that health-care professionals should follow the recommendations in the prescribing information when prescribing HIV or HCV protease inhibitors with statins.

Reference:
A signal is defined by WHO as reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information. A signal is a hypothesis together with data and arguments and it is important to note that a signal is not only uncertain but also preliminary in nature.

The signals in this Newsletter are based on information derived from Individual Case Safety Reports (ICSRs) available in the WHO Global ICSR database, VigiBase™. The database contains over 7 million reports of suspected adverse drug reactions, submitted by National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring. VigiBase is, on behalf of the WHO, maintained by the Uppsala Monitoring Centre (UMC) and periodic analysis of VigiBase data is performed in accordance with UMC’s current routine signal detection process.

More information regarding the ICSRs, their limitations and proper use, is provided in the UMC Caveat document available at the end of SIGNAL (page 25).

UMC, a WHO Collaborating Centre, is an independent foundation and a centre for international service and scientific research within the field of pharmacovigilance. UMC’s vision is to improve worldwide patient safety and welfare by reducing the risk of medicines. For more information visit www.who-umc.org

Donepezil – SSRI and SNRI – interaction and Serotonin syndrome

Summary
Donepezil is a specific and reversible inhibitor of acetylcholinesterase used to treat Alzheimer’s disease. A number of combinations of donepezil and the adverse reaction serotonin syndrome appeared in VigiBase. This is not listed for donepezil. The reports showed that different antidepressants like serotonin reuptake inhibitors SSRIs, selective serotonin-norepinephrine reuptake inhibitors (SNRIs) and a serotonin antagonist and reuptake inhibitor (SARI) were co-reported with donepezil suspected to cause this effect. An extended search was made to investigate a possible interacting effect between donepezil and antidepressants. After removing suspected duplicates 13 reports from six countries remained. In four cases donepezil was added to pre-existing SSRI/SNRI/SARI treatment and in five cases SSRI/SNRI/SARI was added to pre-existing donepezil treatment. In three of the four cases where donepezil was added to pre-existing treatment the reporters suspected an interaction between donepezil and the other drug/drugs. Studies in the brain of mice and rats have shown that donepezil seem to affect serotonin levels and serotonin receptors, however there is limited information in literature about donepezil’s serotonergic effects in human brain. These spontaneous reports from several countries indicate that donepezil might have an effect on serotonin levels in human brain and that there might be an interacting effect of this drug and SSRIs/SNRIs/SARIs.

Introduction
Donepezil is a specific and reversible inhibitor of acetylcholinesterase, the dominating cholinesterase in the brain. The pathogenesis of Alzheimer’s disease has been linked to the deficiency of the neurotransmitter acetylcholine and the acetylcholinesterase inhibitors were subsequently introduced as treatment for Alzheimer’s. Its efficacy is believed to be attained through the augmentation of acetylcholine-mediated synaptic transmission. It is also shown that this type of drug protects cells from the toxicity of free radicals and β-amyloid-induced injury. Studies in rats and mice show effects on serotonin or serotonin receptors in brain but the effect in humans remains unclear. Serotonin syndrome is not listed for donepezil.

Serotonin syndrome is a potentially life-threatening reaction that may occur in patients using drugs that elevate the serotonin levels. The most common drugs causing this reaction are monoamine oxidase inhibitors (MAO-inhibitors), tri-cyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs), SNRIs and SARIs. The excess serotonin activity in receptors in the central nervous system and peripheral serotonin receptors results in myoclonus, hyperreflexia, diaphoresis, mental changes, autonomic symptoms, shivering, tremor and in severe cases neuromuscular rigidity, delirium and life-threatening hyperthermia. Complications are common and include dehydration, infection, respiratory and renal failure and disseminated intravascular coagulation. The primary treatment consists of discontinuation of suspected
drugs and sometimes administration of serotonin receptor antagonists. The symptoms of the syndrome usually resolve within 24 hours if discontinuing the causative drugs, but confusion may last for days and complications may result in death.

**Reports in VigiBase**

A total of eleven reports of donepezil and serotonin syndrome exist in VigiBase (20 October 2011). The reports showed that different selective serotonin reuptake inhibitors (SSRIs), selective serotonin-norepinephrine reuptake inhibitors (SNRIs) as well as a serotonin antagonist and reuptake inhibitor (SARI) were co-reported with donepezil suspected to cause this effect. The majority of the reports contained SSRIs and SNRIs. In order to investigate a possible interacting effect a new search was performed where all other reports containing SSRIs and SNRIs, donepezil and serotonin syndrome were extracted from VigiBase. Table 1 lists the drugs found co-reported as suspected with donepezil to cause serotonin syndrome. In total 27 reports were found, out of which 13 were left when suspected duplicates were removed. These thirteen reports came from six different countries: Australia, France, Germany, Switzerland, United Kingdom and USA. Two of the reports from USA have been published.7,8

In four cases donepezil was added to an existing treatment with SSRI/SNRI/SARI and in five cases it was instead an SSRI/SNRI/SARI that was added to pre-existing donepezil treatment. There was also one case where the drugs were started on the same day and three cases where there was no information on the administration order of the drugs. In the four cases where donepezil was added to pre-existing treatment the reporter suspected an interaction between donepezil and other drugs in three of the reports. In one of those reports the reporter also hypothesized that an interaction between donepezil, mirtazapine and venlafaxine could be both pharmacokinetic and pharmacodynamic.

Time to onset of serotonin syndrome (counted from the start date of the latest added suspected drug until the onset of signs of serotonin syndrome) was listed in four reports and was: the same day, three days, four days and 15 days. There was also one report that listed serotonin syndrome to have occurred within a month (no specific start date was listed for the drug, only the month), one report listed the syndrome to have started two days after the patient started taking donepezil (although no dates were listed for the other drugs taken concomitantly) and one report listed the adverse reaction to start one day before donepezil was added (but since it was unclear if the tremor the patient experienced the day before starting treatment with donepezil was a sign of serotonin syndrome, this case will be kept in the evaluation). The time to onset of the reaction seem to be plausible when comparing to a post-marketing surveillance study aiming to identify serotonin syndrome cases in United Kingdom in the late nineties. Out of 19 patients identified with serotonin syndrome the time to onset was less than 14 days for all.9

Most of the patients were, as expected for Alzheimer’s disease, quite old. In eight of the nine reports where age was listed the age varied between 72-85 years and there was one patient that was 40 years old. Dechallenge was listed in all but one report. In all of the thirteen reports the SSRIs/SNRIs/the SARI were withdrawn when serotonin syndrome was suspected. Totally eleven patients recovered and two patients died. In two cases donepezil was withdrawn at the same time as the SSRIs/SNRIs/the SARI. In one of these the SARI trazodone was withdrawn but myoclonus persisted for over 24 hours which lead to withdrawal of donepezil as well, two days later. No more information exists on the event but the reporter listed the patient as recovering.
Table 1. Overview of individual case reports for donepezil and serotonin syndrome

<table>
<thead>
<tr>
<th>Gender /Age</th>
<th>Other reported ADRs</th>
<th>Suspected drugs</th>
<th>Other possible confounder s</th>
<th>Time to onset from the latest added drug</th>
<th>Interaction with Donepezil suspected by reporter</th>
</tr>
</thead>
<tbody>
<tr>
<td>F/85</td>
<td>Tremor, hyperreflexia</td>
<td>donepezil, citalopram, flecainide</td>
<td>age</td>
<td>-1 day*</td>
<td>No</td>
</tr>
<tr>
<td>M/78</td>
<td>Rhabdomyolysis, fever, dyskinesia</td>
<td>sertraline, serotonin</td>
<td>age</td>
<td>≤ 1 month**</td>
<td>No</td>
</tr>
<tr>
<td>F/72</td>
<td>Agitation, tremor, confusion, seizure anoxic</td>
<td>mirtazapine, venlafaxine, donepezil</td>
<td>age</td>
<td>4 days</td>
<td>Yes, between venlafaxine, mirtazapine and donepezil</td>
</tr>
<tr>
<td>F/-</td>
<td>-</td>
<td>paroxetine</td>
<td>-</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>F/76</td>
<td>-</td>
<td>donepezil, cyamemazine (antipsychotic with serotonin antagonistic properties)</td>
<td>age, fluoxetine, diltiazem (CYP2D6 metabolized)</td>
<td>15 days</td>
<td>Yes, between donepezil and fluoxetine</td>
</tr>
<tr>
<td>M/81</td>
<td>Fatigue, myoclonus</td>
<td>donepezil, trazodone</td>
<td>age</td>
<td>Same day as trazodone was added to preexisting donepezil treatment.</td>
<td>No</td>
</tr>
<tr>
<td>F/79</td>
<td>Extrapyramidal syndrome w/ urinary retention, dysphagia, rigor, disorientation, repeated finger movement, hallucinations</td>
<td>duloxetine</td>
<td>age, mirtazapine,</td>
<td>3 days</td>
<td>No (“the reporter sees a causal relationship between duloxetine &amp; the events but can't evaluate if there was an interaction”)</td>
</tr>
<tr>
<td>M/40</td>
<td>Convulsions NOS, hypertension NOS, confusion, short term memory loss, muscle rigidity, tensing, cramping, hyperthermia etc.</td>
<td>venlafaxine</td>
<td>-</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>F/81</td>
<td>Fever, urinary tract infection, decreased alertness, dehydration, failure to thrive</td>
<td>escitalopram</td>
<td>age, urinary tract infection</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>M/-</td>
<td>Urinary incontinence, confusional state, delirium, decreased appetite</td>
<td>citalopram</td>
<td>-</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>F/79</td>
<td>Altered mental status, acute onset of chills, reduced appetite, urinary incontinence, elevation of body temp</td>
<td>mirtazapine</td>
<td>age, paroxetine,</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>F/74</td>
<td>Diarrhoea, tremulousness, myoclonus, hyperreflexia, gait instability, fever</td>
<td>risperidone, citalopram</td>
<td>age</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>M/-</td>
<td>Sweating increased, confusion, hypertension</td>
<td>paroxetine, donepezil</td>
<td>-</td>
<td>-</td>
<td>Yes, between donepezil and paroxetine</td>
</tr>
</tbody>
</table>
Literature and labelling

In vitro studies have shown that the cytochrome P450 isoenzymes CYP3A4 and to some extent CYP2D6 are involved in the metabolism of donepezil. Interaction studies in vitro have also shown that drugs like ketokonazol and kinidin (inhibitors of CYP3A4 and CYP2D6 respectively) inhibits the metabolism of donepezil. This means that these drugs and other inhibitors of these enzymes could inhibit the metabolism of donepezil and thus lead to higher concentrations of the drug.

There are no human studies on serotonin or serotonin receptors with donepezil. An in vitro study on rats showed changes in serotonin levels by acute doses of donepezil and another study on mice showed that twice daily treatment of donepezil for two weeks significantly increased striatal 5HT2A mRNA levels.

Alzheimer’s disease has itself shown to affect serotonin receptors. It has also been shown that serotonergic transmission is impaired in Alzheimer’s disease.

Discussion/Conclusion

The reports in VigiBase indicate an interaction between donepezil and SSRIs and SNRIs, causing serotonin syndrome. It is known that drugs that inhibit CYP2D6, could inhibit the metabolism of donepezil, leading to higher concentrations of the drug. There are studies that show an effect of donepezil on serotonin levels and serotonin receptors in mice and rats and so it is possible that donepezil is in itself affecting this substance but it is still unclear exactly what effect the drug has on these systems and on serotonin levels in humans.

In nine of the cases the age might have been a contributory factor (varying from 72-85 in all but one case where age was listed), since the metabolism slows down with age. This was also listed as the probable cause of the syndrome in one of the reports from the USA; "poor drug excretion and half-life prolongation probably caused the syndrome". With age more drugs are often used together and the possible interaction mechanisms might be more complex. This as well as the fact that Alzheimer’s disease in itself is affecting serotonin levels are factors that might be confounders in these cases.

The reports in VigiBase could in some cases be the result of a SSRI/SNRI acting alone. It is not possible to say to what extent donepezil was involved in the possible interaction when the patients were already treated with donepezil and a SSRI/SNRI was added followed by the syndrome. However when the patient was already treated with a SSRI/SNRI and donepezil was added followed by the syndrome the same day as in one case or within four or 15 days as in two other cases this is indicative for an interaction. In one of these cases donepezil was added last but SSRIs were added only two and five days before donepezil followed by symptoms of serotonin syndrome four days after donepezil was added. In another case were donepezil was added to a pre-existing SSRI treatment donepezil was added six weeks after the SSRI which makes the confounding less. However, in this case we do not have the information on the exact time of the onset of the syndrome. But even if these two cases might have confounding factors there is one report where a 76 year-old female had been treated with the drug fluoxetine (SSRI) for two years and when donepezil was added the serotonin syndrome occurred within 15 days. In this case it is not very likely that the SSRI is causing the syndrome on its own. This is by itself a strong enough case to suspect an interaction. It is also important to notice that in three of the four cases where donepezil was added to pre-existing treatment with SSRIs/SNRIs the reporter suspected an interaction to have occurred and in one report the reporter hypothesized that an interaction could be both pharmacokinetic and pharmacodynamic. We suggest awareness of this possible interaction for all prescribers that are using these drugs together.

References

Response from Marketing Authorization Holders (MAH) regarding a signal of Donepezil and Serotonin Syndrome

**Background**
Alzheimer disease (AD) is the most common form of dementia, affecting more than 35 million people worldwide. Age is the primary risk factor for AD. The incidence of the disease doubles every five years after 65 years of age with the chance of receiving a diagnosis of AD approximately one in three by the age of 85.\(^1\)

Serotonin syndrome is a potentially life-threatening condition that occurs due to excess serotonergic agonism of central nervous system receptors and peripheral serotonergic receptors. Signs of excess serotonin range from mild cases of tremor and diarrhea to life-threatening cases of delirium, neuromuscular rigidity and hyperthermia. The true incidence of serotonin syndrome is unknown. However, it has been noted that the apparent increase in incidence is consistent with the increase in use of proserotonergic agents, including selective serotonin-reuptake inhibitors (SSRIs) and selective serotonin-norepinephrine reuptake inhibitors (SNRIs) and other antidepressant agents.\(^2\)

Serotonin syndrome is more likely to occur after chronic ingestion of a serotonergic agent, and is most often seen in patients who are on multiple serotonergic agents. However, serotonin syndrome has been reported in patients on a single serotonergic agent at a therapeutic dose.\(^3\)

Individuals with AD are known to have a high rate of depression. One study examined the use of 4 drug classes in patients with AD and found that greater than 30% of AD patients were receiving antidepressants.\(^4\)

**Pharmacology**
Donepezil is a potent, selective, reversible, central inhibitor of acetylcholinesterase. A study of donepezil’s effect on the rat cortex found that donepezil elevated extracellular acetylcholinesterase without any effect on the level of serotonin (S-HT).\(^5\)

Donepezil has demonstrable effects on cognitive and global function parameters in patients with Alzheimer’s disease. Steady state is achieved within three weeks and there is little diurnal variability. Elimination is mainly renal and there is no evidence of enterohepatic re-circulation.\(^6\)

Donepezil is primarily metabolized by the cytochrome P450 (CYP) isoenzymes 2D6 and 3A4\(^7\), and has minimal inhibitory activity against these isoenzymes\(^8\), and a low potential to interact with drugs that inhibit CYP 2D6 and CYP 3A4, e.g. cimetidine and ketoconazole\(^8,9\). In addition a study in healthy volunteers indicated that there were no significant differences in either the PK or tolerability of donepezil HCl or sertraline HCl (a SSRI metabolized by CYP3A4 and CYP 2D pathways) during multiple-dose co-administration at steady-state.\(^10\)

**Clinical Trial Experience**
In the donepezil clinical studies analyzed to date, which have included over 6 million patient days of exposure there have been no reports of a serious adverse event of serotonin syndrome. The majority of these patient days of exposure were in studies that allowed the concomitant use of SSRIs and SNRIs as well as other medications with serotonergic activity.\(^11\) In a recent study of donepezil 23 mg in patients with severe AD, over 27% of the subjects were receiving concomitant antidepressants at baseline.\(^12\)

**Post-marketing Experience**
Aricept (donepezil hydrochloride) was first marketed in the US in 1997 and is now available in over 90 countries with over 6.5 billion patient days of exposure. A review of the post marketing spontaneous and literature reports of serotonin syndrome\(^13\) where donepezil was considered as a suspect product indicates that:
- the incidence of such reports was very rare with less than one report received for every three years of marketing (reporting rate of
approximately two per ten million years of patient exposure);

- all of the patients had other risk factors for serotonin syndrome including the use of one or more known serotonergic agents, and age;
- there were no reports of a positive rechallenge and one report of a negative rechallenge;
- the reports generally had only minimal information concerning the event, the drug exposure, and/or the patient’s past medical history.

Therefore while there are cases where a relationship to the donepezil therapy cannot be excluded, there is no single case that suggests donepezil therapy is the precipitating factor in the development of serotonin syndrome.

Conclusion
The very rare reports of serotonin syndrome in patients who were receiving both a pro-serotonergic agent and donepezil contain multiple confounders. The rate of reporting is consistent with these events being due solely to the SSRI/SNRI given the high concomitant use of such agents in the population receiving donepezil therapy. The currently available data, including the lack of evidence suggesting that donepezil increases serotonin, either directly or through a pharmacokinetic interaction, does not suggest donepezil therapy is associated with an increased risk of serotonin syndrome. Reports of serotonin syndrome will continue to be monitored closely.

I. Surick, MD, MPH
Eisai Inc.
Woodcliff Lake, NJ
United States, December 2011.

References
11. Data available in-house.
12. Data available in-house.
13. Manufacturer’s International Adverse Event database.
Ranolazine and Hallucination

Summary
There are 13 reports of ranolazine and hallucination in VigiBase. Two of these reports had diltiazem co-reported and might be explained by an interaction between the drugs. Only two cases had the time to onset reported which was the same day as drug administration was started. The outcome was recovered in five cases and was unknown in the remaining eight cases. In the five cases in which recovery was documented, ranolazine was withdrawn in three cases, reduced in dose in another case and there was no information on withdrawal in the last case. In six of the eight cases where the outcome was reported as unknown, the reaction was reported to have abated with ranolazine withdrawal. Although information is lacking in most of the reports, the common factor for all is the use of ranolazine. The reports describing recovery after withdrawal or reduction of dose of the drug further strengthen a strong support for the existence of a causal association.

Introduction
Ranolazine is a recently marketed drug for the treatment of chronic angina pectoris. The mechanism of action is largely unknown but ranolazine may have some antianginal effects through inhibition of the late sodium current in cardiac cells. This reduces intracellular sodium accumulation and consequently decreases intracellular calcium overload. Via its action to decrease the late sodium current, ranolazine is considered to reduce these intracellular ionic imbalances during ischaemia. The approved indication is as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or intolerant to first-line antianginal therapies (such as beta-blockers and/or calcium antagonists). Common adverse reactions observed in clinical trials with ranolazine include dizziness, headache, constipation, nausea, vomiting and asthenia. Psychiatric reactions are listed as rare and include anxiety, insomnia and disorientation.

Hallucination is a perception of visual, auditory, tactile, olfactory or gustatory experiences without an external stimulus and with a compelling sense of the reality, usually resulting from a mental disorder or as a response to a drug. The medical meaning of hallucination is generally consistent with the ordinary use of the word. In WHOART, the preferred term “hallucination” describes all types of hallucinations while MedDRA contains a preferred term on each of auditory, gustatory, olfactory, synaesthetic, tactile, visual and mixed as well as the general term. In reporting hallucinations in general, many reporters simply write “hallucinations” even though they often mean visual hallucinations. This general situation is reflected in the 13 reports in association with ranolazine in which "hallucination" was reported in nine cases without further presentation, visual hallucination was reported in 3 cases and both visual and auditory hallucinations were reported in the remaining case.

VigiBase Reports
At the time of assessment (4 May 2011), VigiBase had received 13 cases of hallucination in association with ranolazine (see Table 1). The association had an IC value of 1.47 with an ICo25 of 0.58 (for further explanation of the IC value and disproportionate reporting see The UMC Measures of Disproportionate Reporting - a brief guide to their interpretation, in the Signal section of WHO Pharmaceuticals Newsletter No.1, 2012). The 13 cases were submitted by two national centres: the US (12 cases) and the UK (one case). The patients ranged in age from 52 to 93 years with a median of 77 years and there were two males and six females in the eight reports which provided information on age and gender. Ranolazine was the only drug suspected in all but one of the 13 cases. In the remaining case, an interaction between ranolazine and diltiazem was suspected. Ranolazine is a substrate of cytochrome CYP3A4 and inhibitors of CYP3A4 increase plasma concentrations of ranolazine. Potent inhibitors of CYP3A4 are contraindicated and moderately potent inhibitors such as diltiazem should be used with caution. Another case has diltiazem as a concomitant drug and it is possible that an interaction may have occurred in this case also. Eight of the cases have several concomitant drugs (see Table 1) which are generally typical of the drugs which might be expected to be used concomitantly in this patient population. In the two cases where the time to onset was reported, it was reported as the same day as drug administration was started. The outcome was recovered in five cases and was unknown in the remaining eight cases. In the five cases in which recovery was documented, ranolazine was withdrawn in three cases, reduced in dose in another case and there was no information on withdrawal in the last case. In six of the eight cases where the outcome was reported as unknown, the reaction was also reported to have abated with ranolazine withdrawal.

In the 12 cases where the indication was reported, it was angina pectoris in ten cases, chest pain in one case and coronary artery disease in the other case, consistent with the approved use of the drug. Additional psychiatric adverse reactions were reported in nine of the 13 cases. There did not appear to be any particular pattern to these additional reactions with reports of confusion.
disorientation, amnesia and delirium reported more than once.

Table 1. VigiBase case reports of hallucination with ranolazine

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender/Age</th>
<th>Other reactions (WHO-ART terms)</th>
<th>Concomitant drugs</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F/86</td>
<td>Delusion</td>
<td>Quetiapine, memantine, mirtazapine, duloxetine</td>
<td>Unknown*</td>
</tr>
<tr>
<td>2</td>
<td>M/93</td>
<td>Disorientation, confusional state</td>
<td>Isosorbide, metoprolol, atorvastatin, furosemide, acetylsalicylic acid, warfarin, temazepam, clopidogrel</td>
<td>Unknown*</td>
</tr>
<tr>
<td>3</td>
<td>F/52</td>
<td>Syncope, renal function abnormal, mental status changes, fall, drug level increased, delirium, confusional state, asthenia</td>
<td>None</td>
<td>Unknown*</td>
</tr>
<tr>
<td>4</td>
<td>F/52</td>
<td>Delirium, aggressive reaction</td>
<td>None</td>
<td>Unknown*</td>
</tr>
<tr>
<td>5</td>
<td>M/75</td>
<td>Dizziness, ataxia, dreaming abnormal</td>
<td>Doxazosin, nicotinic acid, glyceryl trinitrate, diltiazem</td>
<td>Unknown</td>
</tr>
<tr>
<td>6</td>
<td>F/81</td>
<td>Urinary tract infection, muscle contractions involuntary, amnesia, hypokinesia, apathy, dysphonia, chest pain, asthenia, medication error</td>
<td>Acetylsalicylic acid, amlodipine, atenolol, clopidogrel, colchicine, furosemide, glyceryl trinitrate, insulin, isosorbide, lisinopril, metoclopramide, multivitamins, pantoprazole, simvastatin, warfarin</td>
<td>Unknown*</td>
</tr>
<tr>
<td>7</td>
<td>-/-</td>
<td>None</td>
<td>Acetylsalicylic acid, cetirizine, clopidogrel, escitalopram, esomeprazole, glyceryl trinitrate, hydralazine, isosorbide, metoprolol, multivitamins, paracetamol, simvastatin</td>
<td>Recovered</td>
</tr>
<tr>
<td>8</td>
<td>-/-</td>
<td>Amnesia, coma, incoherence, stupor, speech disorder, drug prescribing error, drug interaction, dizziness, coordination abnormal, coma, medication error</td>
<td>Acetylsalicylic acid, carvedilol, metformin, Diltiazem(interacting)</td>
<td>Recovered</td>
</tr>
<tr>
<td>9</td>
<td>-/-</td>
<td>None</td>
<td>None</td>
<td>Unknown</td>
</tr>
<tr>
<td>10</td>
<td>F/68</td>
<td>Pruritus, confusion, disorientation, nausea</td>
<td>Acetylsalicylic acid, atorvastatin, bisoprolol, candesartan, fluticasone propionate/salmeterol xinafoate, furosemide, isosorbide, lansoprazole, spironolactone, theophylline, tiotropium</td>
<td>Recovered</td>
</tr>
<tr>
<td>11</td>
<td>F/79</td>
<td>None</td>
<td>None</td>
<td>Unknown*</td>
</tr>
</tbody>
</table>
Response from MAH regarding a signal of Ranolazine and Hallucination

The WHO identified "hallucination" as a potential safety signal for ranolazine on 29 August 2011 and invited the Marketing Authorization Holders (MAH) for ranolazine (Gilead Sciences, Inc. in North America and Menarini International Operations Luxembourg S.A., MIOL in European countries) to comment on the signal.

A licensing agreement is in place between Gilead and Menarini. Gilead is the holder of the global safety database and is responsible for production of aggregate reports (including PSURs) and the identification, investigation, monitoring and management of any safety issues specific to ranolazine in collaboration with Menarini. Menarini is responsible for the maintenance of the European Union Risk Management Plan (EU-RMP).

Prior to identification of "hallucination" as a potential safety signal by WHO, the MAH for ranolazine had already identified, analysed and managed the above mentioned signal.

Through routine signal detection activities, "hallucination" was identified as a potential signal for ranolazine. To further evaluate and characterize the signal, the MAH initiated a cumulative review of Individual Case Safety Reports (ICSRs) describing Adverse Drug Reactions (ADRs) included in the System Organ Class (SOC) "Psychiatric disorders".

This review was presented within the Periodic Safety Update Report covering the period 27 January 2010 to 26 July 2010. The cumulative review identified 13 ICSRs related to the medical concept of hallucination. Based on this review,
there was some evidence of a causal relationship between ranolazine and "hallucination." Thus, "hallucination" was added to the Undesirable Effects - Postmarketing Experience section of the ranolazine Company Core Data Sheet (CCDS) on 5 October 2010.

In the US, a labelling supplement to add "hallucination" as a postmarketing adverse reaction in the United States Prescribing Information (US PI) was submitted to the US Food and Drug Administration (FDA) on 1 October 2010 and was approved by the US FDA and implemented in the US PI on 11 July 2011.

In the EU, a variation to incorporate "hallucination" as an uncommon ADR in the Psychiatric disorders SOC within Section 4.8 (Undesirable effects) of the EU-Summary of Product Characteristics (EU-SmPC) was submitted and was validated by the European Medicines Agency (EMA) on 18 February 2011. The Committee for Medicinal Products for Human Use (CHMP) gave a positive opinion on the variation on 14 April 2011 and the European Commission approved the CHMP opinion on 17 June 2011.

On 7 July 2011 another variation to introduce into Section 4.7 of the EU-SmPC the PT "hallucination" as an ADR potentially capable of interfering with the ability to drive and use machines was submitted to the EMA. This variation is still ongoing.

Within the EU, ranolazine has a Risk Management Plan. A revision of the EU-RMP to introduce "hallucination" as a newly identified risk is ongoing, and the revised EU-RMP will be submitted to the EMA no later than 26 March 2012.

Local labelling updates in other applicable territories based upon the updated CCDS are either ongoing or planned.

All adverse events received by the MAH are carefully reviewed for new safety signals. As a new safety signal is identified, the MAH takes appropriate actions to manage the risk associated with the signal, which could include but is not limited to updating the product labelling information or more urgent safety restrictions. Upon recognition of the signal for "hallucination", which occurred prior to its identification by WHO, the MAH managed, and communicated the signal to applicable regulatory authorities and prescribers.
CAVEAT DOCUMENT

Accompanying statement to data released from the Uppsala Monitoring Centre,
WHO Collaborating Centre for International Drug Monitoring

Uppsala Monitoring Centre (UMQ in its role as the WHO Collaborating Centre for International Drug Monitoring receives reports of suspected adverse reactions to medicinal products from National Centres in countries participating in the WHO pharmacovigilance network, the WHO Programme for International Drug Monitoring. Limited details about each suspected adverse reaction are received by the UMC. The information is stored in the WHO Global Individual Case Safety Report database, VigiBase. It is important to understand the limitations and qualifications that apply to this information and its use.

The reports submitted to UMC generally describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a specific medicinal product (rather than, for example, underlying illness or other concomitant medication) is the cause of an event.

Reports submitted to National Centres come from both regulated and voluntary sources. Some National Centres accept reports only from medical practitioners; other National Centres accept reports from a broader range of reporters, including patients. Some National Centres include reports from pharmaceutical companies in the information submitted to UMC; other National Centres do not.

The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the reactions and other factors. No information is provided on the number of patients exposed to the product.

Some National Centres that contribute information to VigiBase make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not.

Time from receipt of a report by a National Centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from those obtained directly from National Centres.

For the above reasons interpretations of adverse reaction data, and particularly those based on comparisons between medicinal products, may be misleading. The supplied data come from a variety of sources. The likelihood of a causal relationship is not the same in all reports. Any use of this information must take these factors into account.

Some National Centres strongly recommend that anyone who intends to use their information should contact them for interpretation.

Any publication, in whole or in part, of information obtained from UMC must include a statement:

(i) regarding the source of the information,
(ii) that the information comes from a variety of sources, and the likelihood that the suspected adverse reaction is drug-related is not the same in all cases,
(iii) that the information does not represent the opinion of the World Health Organization.

Omission of this statement may exclude the responsible person or organization from receiving further information from VigiBase.
Empowering patients in pharmacovigilance: current developments in WHO

The Monitoring Medicines (MM) project was developed by the World Health Organization (WHO). It is a major international project, with the full title 'Optimizing drug safety monitoring to enhance patient safety and achieve better health outcomes'. It started in September 2009 and is coordinated by the Uppsala Monitoring Centre (UMC), Sweden, with funds from the European Commission. 11 partners make the project consortium (see below) and represent a wide range of organizations dedicated to improving public health through the safe use of medicines.

The project aims to improve patient safety both within the European Union and in other regions. One of the project objectives is to support and strengthen consumer reporting of suspected adverse drug reactions (ADRs). The project partners represent a wide range of organizations dedicated to improving public health through the safe use of medicines:

- The Uppsala Monitoring Centre (UMC), Sweden;
- WHO;
- Copenhagen HIV Programme, Denmark;
- University of Ghana Medical School, Ghana;
- Pharmacy and Poisons Board, Kenya;
- Centre Anti Poison et de Pharmacovigilance du Maroc, Morocco;
- Lareb, Netherlands Pharmacovigilance Centre;
- Zuellig Family Foundation, the Philippines;
- Medical Products Agency, Sweden;
- Elliot Brown Consulting Ltd, UK;
- National Patient Safety Agency, UK.

In an increasing number of countries consumers are being encouraged to report adverse reactions to medicines. Organizations such as WHO and the European Commission acknowledge the role of the consumer in spontaneous reporting. Representatives of national pharmacovigilance centres requested WHO in 2008 to develop a handbook on how to establish a reporting system for medicine-related problems for the general public. The implementation of the task became feasible under the objectives of the Monitoring Medicines project. A WHO guidance document 'Safety Monitoring of Medicinal Products – Reporting system for the general public' is now available as a direct project deliverable. Anne Kiuru, Medical Products Agency, Sweden and Linda Härmark, Netherlands Pharmacovigilance Centre, Lareb, kindly assisted WHO in writing the original manuscript. It was later reviewed by members of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) and selected national experts, and is an important step forward in strengthening patients around the world.

In tandem to the document development, the UMC has been working on a tool to support the consumer reporting of ADRs. Several patient organizations have provided their inputs in developing this tool.
The WHO guidance document and the tool were introduced to pharmacovigilance centres and consumer / patient organizations at a recent workshop in s-Hertogenbosch, the Netherlands, from 7 to 9 March 2012. The Netherlands Pharmacovigilance Centre, Lareb hosted this workshop and was a lead project partner for this activity. Participants came from Belgium, Croatia, Denmark, Moldova, Netherlands, Portugal, Philippines, Spain, Sweden, Switzerland and the United Kingdom and included a good mix of representatives from pharmacovigilance centres and patient / consumer organizations. Invited presentations, interactive sessions and hands-on exercises allowed workshop participants to share their experiences and common concerns related to patient reporting of ADRs. The elements of the new European Union (EU) pharmacovigilance legislation were presented and the expected impact in and outside the EU were also discussed at length.

Piloting the UMC patient reporting tool in selected countries and any subsequent adaptation of the tool will form the next steps in this journey towards patient empowerment in pharmacovigilance.