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:

Quality Assurance and Safety: Medicines, EMP-HSS, World Health Organization, 1211 Geneva 27, Switzerland, E-mail address: pals@who.int

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, Box 1051 751 40 Uppsala
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The WHO Pharmaceuticals Newsletter provides you with the latest information on the safety of medicines and legal actions taken by regulatory authorities across the world. It also provides signals from the Uppsala Monitoring Centre's SIGNAL document.

The feature articles in this issue give you a brief summary of a course offered by the WHO Collaborating Centre for Drug Satistics Methodology; and a pilot project being launched by the Uganda National Drug Authority, to collect pharmacovigilance data in their HIV treatment programmes.

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Aliskiren-containing medicines

New warning and contraindication

**USA.** The U.S. Food and Drug Administration (US FDA) notified health-care professionals of possible risks when using blood pressure medicines containing aliskiren with other drugs called angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in patients with diabetes or renal impairment. These drug combinations are contraindicated in patients with diabetes. In addition, avoid use of aliskiren with ARBs or ACEIs in patients with moderate to severe renal impairment (i.e., where glomerular filtration rate [GFR] < 60 mL/min). The labels for the aliskiren drugs are being updated based on preliminary data from a clinical trial, "Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE).”

The US FDA recommended that concomitant use of aliskiren with ARBs or ACEIs in patients with diabetes is contraindicated because of the risk of renal impairment, hypotension, and hyperkalemia. Avoid use of aliskiren with ARBs or ACEIs in patients with renal impairment where GFR < 60 mL/min. Patients should not stop taking aliskiren without talking to a healthcare professional. Stopping aliskiren suddenly can cause problems if high blood pressure (hypertension) is not treated.

(See WHO Pharmaceuticals Newsletter No. 1, 2012 for contraindication in patients with diabetes taking an ACE inhibitor or an ARB in Canada and No.2, 2012 in Europe).

| Reference: |

**Belimumab**

**Association with Hypersensitivity and Infusion Reactions**

**Canada.** GlaxoSmithKline Inc., in consultation with Health Canada, informed health-care professionals of important new safety information related to hypersensitivity and infusion reactions associated with belimumab (BENLYSTA™) treatment.

At the time of authorization, the Product Monograph included information and warnings related to a reported higher incidence of hypersensitivity reactions in treated patients compared to placebo. After the review of post-marketing reports, the Product Monograph for belimumab has been updated with the following new safety information:

- administration of belimumab may result in infusion and hypersensitivity reactions, which can be severe, and can be fatal;
- patients with a history of multiple drug allergies or significant hypersensitivity may be at increased risk;
- health-care professionals should monitor patients during and for an appropriate amount of time after administration of belimumab, because a delay in the onset of acute hypersensitivity reactions has been observed. Patients should be informed of the potential risks.

Important information for health-care professionals is:

- in the event of a severe reaction, belimumab administration must be interrupted and appropriate medical therapy administered;
- patients treated with belimumab should be informed of the symptoms of hypersensitivity reactions, and the importance of immediately seeking medical attention.

Health-care professionals are reminded that:

- infusion reactions occurred more frequently with the first two infusions and tended to decrease with subsequent infusions;
- belimumab treatment should be initiated and supervised by a qualified physician experienced in the diagnosis and treatment of SLE;
- belimumab should be administered by qualified health-care providers trained to give infusion therapy and prepared to manage anaphylaxis;
- in clinical trials, severe and/or serious infusion or hypersensitivity reactions were reported in 1.2% and 0.6% of subjects receiving belimumab 10 mg/kg and placebo, respectively.

| Reference: |

**Boceprevir**

**Drug Interactions with ritonavir-boosted Human Immunodeficiency Virus (HIV) protease inhibitor drugs**

**USA.** The US FDA notified health-care professionals that the drug label has been revised to state that co-administration of boceprevir (Victrelis®) along with certain ritonavir-boosted HIV protease inhibitors is not recommended. The findings of a drug-drug interaction study and clinical trial showed that co-administration increased of the possibility of reducing the effectiveness of the medicines, permitting the amount of HCV or HIV virus in the blood to increase. Ritonavir-boosted
HIV protease inhibitors include ritonavir-boosted atazanavir (Reyataz®), ritonavir-boosted darunavir (Prezista®), and lopinavir/ritonavir (Kaletra®). (See WHO Pharmaceuticals Newsletters No. 2, 2012 for drug interactions with ritonavir-boosted HIV protease inhibitor drugs in the USA and in Europe).

**Reference:**
FDA Drug Safety Communication, US FDA, 26 April 2012 ([www.fda.gov](http://www.fda.gov)).

**Citalopram hydrobromide**

**Revised recommendations, potential risk of abnormal heart rhythms USA.** The US FDA is clarifying dosing and warning recommendations for citalopram hydrobromide (Celexa®; also available in generic form). In August 2011, the US FDA issued a Drug Safety Communication (DSC) stating that citalopram should no longer be used at doses greater than 40 mg per day because it could cause potentially dangerous abnormalities in the electrical activity of the heart.

Citalopram use at any dose is discouraged in patients with certain conditions because of the risk of QT prolongation. However, it may be important for some of those patients to use citalopram therefore the drug label has been changed to describe the particular caution that needs to be taken when citalopram is used in such patients. The revised drug label also describes lower doses that should be used in patients over 60 years of age.

Revised recommendations are:
- Citalopram is not recommended for use at doses greater than 40 mg per day because such doses cause too large an effect on the QT interval and confer no additional benefit;
- Citalopram is not recommended for use in patients with congenital long QT syndrome, bradycardia, hypokalemia, or hypomagnesemia, recent acute myocardial infarction, or uncompensated heart failure;
- Citalopram use is also not recommended in patients who are taking other drugs that prolong the QT interval;
- The maximum recommended dose of citalopram is 20 mg per day for patients with hepatic impairment, patients who are older than 60 years of age, patients who are CYP2C19 poor metabolizers, or patients who are taking concomitant cimetidine (Tagamet®) or another CYP2C19 inhibitor, because these factors lead to increased blood levels of citalopram, increasing the risk of QT interval prolongation and Torsade de Pointes.

(See WHO Pharmaceuticals Newsletters No. 5, 2011 for abnormal heart rhythms associated with high doses in the USA, No. 1, 2012 for QT interval prolongation in the UK and No.2, 2012 for association with dose-dependent QT Prolongation in Canada and Australia).

**Reference:**

**Dabigatran etexilate**

**Updated labelling regarding renal function assessment and use in patients with severe valvular disease or prosthetic heart valves**

Canada (1). Boehringer Ingelheim (Canada) Ltd., in consultation with Health Canada, informed health-care professionals of important new recommendations for dabigatran etexilate (Pradax®) regarding renal function assessment and use in patients with severe valvular disease or prosthetic heart valves.

Based on post-marketing reports of serious bleeding and the use of dabigatran etexilate in the elderly and patients at high risk of bleeding or patients with renal impairment, the Product Monograph has been updated to include new recommendations to assess renal function in patients being considered for, or already being treated with dabigatran etexilate and is as follows:

- prior to initiation of treatment with dabigatran etexilate, renal function should be assessed in all patients by calculating the creatinine clearance (CrCl) to exclude patients with severe renal impairment (i.e. CrCl < 30 mL/min);
- while on treatment with dabigatran etexilate, renal function should be assessed in clinical situations when it is suspected that renal function could decline or deteriorate rapidly, such as hypovolemia, dehydration, and with certain co-medications. These clinical situations may result in an increase of dabigatran exposure;
- in the elderly (> 75 years), or in patients with moderate renal impairment (CrCl 30-50 mL/min), renal function should be assessed routinely by calculating the creatinine clearance at least once a year.

Health-care professionals are also reminded that dabigatran etexilate is contraindicated in patients with severe renal impairment (i.e. CrCl < 30 mL/min), patients at high risk of bleeding should not be prescribed the drug, patients should be monitored clinically for signs of bleeding or anaemia and treatment with the drug should be discontinued if severe bleeding occurs, and the source of
bleeding should be investigated.

Safety and efficacy of dabigatran etexilate have not been studied in patients with hemodynamically significant rheumatic valvular heart disease, especially mitral stenosis, or patients with prosthetic heart valves. There are no data to support that dabigatran etexilate provides adequate anticoagulation in patients with prosthetic heart valves, with or without atrial fibrillation. Therefore, the use of dabigatran etexilate is not recommended in patients with hemodynamically significant rheumatic valvular heart disease or in patients with prosthetic heart valves.

Saudi Arabia (2). The Saudi Food and Drug Authority (SFDA) shared important safety information with healthcare professionals about an increased number of spontaneous reports of fatal cases resulting from bleeding episodes in patients treated with dabigatran etexilate. In Saudi Arabia, the drug is only approved for prevention of venous thromboembolism (VTE) in patients following hip or knee replacement surgery.

In October 2011, the Committee for Medicinal Products for Human Use (CHMP) at the European Medicine Agency (EMA) published a press-release notifying that clinicians should be aware of increasing number of spontaneous safety reports concerning death cases resulting from major bleeding events. CHMP urged the manufacturer to update the product labelling to ensure that patients receiving dabigatran are eligible for treatment.

The Advisory Committee for Pharmacovigilance at SFDA reviewed all available data on the concerned risk. In addition, it reviewed 260 fatal cases of bleeding attributed to dabigatran etexilate. It was concluded that there is a need to emphasize the risk of bleeding based on post-marketing reports of bleeding occurring with the use of dabigatran etexilate in the elderly and patients with high risk of bleeding or patients with severe renal impairment. The advisory committee recommended that the Patient Information Leaflet as well as the Summary of Product Characteristics should be updated to include new safety information. In addition, the committee required the marketing authorization holder to distribute a Dear Health Care Professional Letter to emphasize the risk of bleeding.

Based on that, the SFDA advised concerned physicians to consider the following recommendations when initiating dabigatran etexilate therapy:

1. Dabigatran etexilate is contraindicated in patients with severe renal impairment (CrCl<30 ml/min);
2. renal function should be assessed by calculating the creatinine clearance (CrCl) in all patients prior to initiating the therapy;
3. while on treatment, renal function should be assessed in clinical situations where a decline in renal function is suspected, such as hypoalbuminaemia, dehydration, and with certain co-medications, etc.;
4. in elderly patients (>75 years) or in patients with renal impairment the renal function should be assessed at least once a year.

(See WHO Pharmaceuticals Newsletters No. 1, 2012 for abnormal heart rhythms associated with high doses in the USA, No. 1, 2012 for QT interval prolongation in the UK and No. 2, 2012 for association with dose-dependent QT

Prolongation in Canada and Australia).

References:
(2) Communication from National Pharmacovigilance and Drug Safety Centre, SFDA, 23 May 2012.

Escitalopram

Updated information regarding the dose-related risk of QT interval prolongation

Canada. Health Canada informed that a warning on the dose-related risk of QT interval prolongation has been added to the drug label for escitalopram (Cipralex®), as well as revised prescribing and dosing recommendations.

It is recommended that escitalopram should not be used in patients with a heart condition known as congenital long QT syndrome, or in patients with QT interval prolongation. Use of escitalopram is discouraged in patients who are also taking drugs that prolong QT interval or that decrease electrolyte levels in the body. Examples of drugs that affect QT interval include: drugs used to treat heart rhythm problems, certain antipsychotics, certain antidepressants, opioid painkillers and certain drugs used to treat infections. Examples of drugs that may affect electrolyte levels include: diuretics and laxatives (including enemas). 10 mg per day is the maximum recommended dose for patients who are 65 years of age or older, or have liver problems, or are taking the heartburn drugs omeprazole or cimetidine which can increase the blood level of escitalopram. 20 mg per day is still the maximum recommended dose for most other patients.
Health Canada advised that before starting escitalopram, patients should tell a health-care professional if the patient has had any heart problems, what other medications the patient is taking (including natural health products), if the patient has a history of fainting, if the patient has a history of electrolyte disturbances (low levels of potassium, magnesium or calcium in the blood) or conditions that might lead to electrolyte disturbances such as vomiting, diarrhoea, dehydration, and if the patient is following a strict diet.

Patients are also advised to consult with a health-care professional when considering stopping or reducing the dose, as abruptly stopping or reducing the dose may cause side effects such as dizziness, unusual dreams, electric shock sensations, agitation, anxiety, difficulty concentrating, migraine, headache, shakiness, sweating, nausea, or vomiting. If patients experience any symptoms of abnormal heart rhythms such as heart palpitations, dizziness, fainting, or seizures while taking escitalopram, contact a health-care professional immediately. Patients with questions or concerns about their escitalopram treatment should speak to a health-care professional.

Reference:

**Finasteride and dutasteride**

**May increase the risk of high-grade prostate cancer**

Canada. Health Canada informed health-care professionals and the public that finasteride (Proscar®, Propecia® and their generic equivalents) and dutasteride (Avodart® and Jalyn® (a combination drug product containing dutasteride and tamsulosin)) may be associated with an increased risk of developing a serious form of prostate cancer known as high-grade prostate cancer. High-grade prostate cancer is an aggressive type of prostate cancer that grows and spreads more quickly than low-grade prostate cancer. This type of cancer is rare, and the increased risk seen with finasteride and dutasteride drugs is still considered very small.

Finasteride and dutasteride are for use in men only. Proscar®, Avodart®, and Jalyn® are used for the treatment of benign prostatic hyperplasia (BPH), which is an enlargement of the prostate that is not cancerous. BPH is a common condition in men over 40. Propecia® is used to treat male pattern hair loss.

The new safety information is based on Health Canada’s review of two large international clinical trials: the Prostate Cancer Prevention Trial (PCPT) and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial. The trials showed that the long-term daily use (over four years) of finasteride (5 mg) and dutasteride in men aged 50 years and older was associated with a small but statistically significant increased risk of high-grade prostate cancer. The 1 mg finasteride strength (Propecia®) was not included in these trials but a potential risk has not been ruled out.

The purpose of the clinical trials was to provide evidence in support of a new use for finasteride and dutasteride: to prevent prostate cancer. Both trials showed that the possible benefits of these drugs in preventing low-grade prostate cancer are small relative to the risk of developing high-grade prostate cancer. Finasteride and dutasteride are not approved for the prevention of prostate cancer in Canada.

The Canadian labels for the brand name drugs have been updated to inform about the increased risk of high-grade prostate cancer associated with these drugs and to emphasize that these drugs are not approved for the prevention of prostate cancer. Updates to the generics will follow.

As noted in the drug labels, before prescribing Proscar®, Avodart®, and Jalyn®, health-care practitioners should evaluate patients thoroughly to rule out other urological diseases, including prostate cancer as the symptoms of BPH and prostate cancer are similar.

Health Canada advised that patients with questions or concerns about their treatment with finasteride or dutasteride should talk to their health-care professional. Patients should not stop taking their medication unless they have been advised to do so by their health-care professional. Patients taking these drugs should see their doctor for periodic follow-up evaluations.

(See WHO Pharmaceuticals Newsletter No. 4, 2011 for Increased risk of prostate cancer in the USA).

Reference:

**Fingolimod**

**New advice to better manage risk of adverse effects on the heart**

Europe (1). The European Medicines Agency recommended new advice to health-care professionals to reduce the risk of adverse effects on the heart associated...
with the use of fingolimod (Gilenya®). Following a review of the latest evidence of the safety of the medicine, the Agency’s Committee for Medicinal Products for Human Use (CHMP) recommended that doctors should not prescribe Gilenya to patients with a history of cardiovascular and cerebrovascular disease or who take heart-rate lowering medication. However, when treatment with fingolimod is considered necessary in these patients, their heart activity should be monitored at least overnight following the first dose of fingolimod and doctors should seek advice from a cardiologist on appropriate monitoring.

The CHMP also recommended that all patients starting treatment with fingolimod should have their heart activity monitored before receiving the first dose of the medicine and continuously for at least six hours after. Monitoring should be extended for at least two hours in patients whose heart rate is lowest six hours after receiving the first dose of fingolimod. In patients who develop clinically significant heart problems such as bradycardia or atrioventricular (AV) block monitoring should continue at least overnight and until the problems have been resolved.

USA (2). The US FDA announced that the agency completed its evaluation of a report of a patient who died after the first dose of fingolimod. The agency also evaluated additional clinical trial and post-market data for the drug, including reports of patients who died of cardiovascular events or unknown causes. The US FDA could not definitively conclude that the drug was related to any of the deaths. However, based on its re-evaluation of the data, the agency remains concerned about the cardiovascular effects of the drug after the first dose.

Data show that, although the maximum heart rate lowering effect of Gilenya usually occurs within six hours of the first dose, the maximum effect may occur as late as 20 hours after the first dose in some patients. For this reason, fingolimod is now contraindicated in patients with certain pre-existing or recent (within last six months) heart conditions or stroke, or who are taking certain antiarrhythmic medications. In addition, the US FDA is now also recommending that the time of cardiovascular monitoring be extended past six hours in patients who are at higher risk for or who may not tolerate bradycardia. Extended monitoring should include continuous ECG monitoring that continues overnight.

References:

Lenalidomide

Association with an increased risk of second primary malignancies

Canada (1). Celgene Inc., in consultation with Health Canada, informed that the following important new safety information was added to the Product Monograph for lenalidomide (REVLIMID®).

- An increase of second primary malignancies (SPM) has been observed in clinical trials in previously treated multiple myeloma patients receiving lenalidomide and dexamethasone (3.98 per 100 patient-years) compared to controls (1.38 per 100 patient-years).

- In clinical trials of newly diagnosed multiple myeloma (not an authorized indication in Canada), a 4-fold increased incidence of SPM has been observed in patients receiving the drug.

- The risk of occurrence of SPM must be taken into account before initiating treatment with the drug. Physicians should carefully evaluate patients before and during treatment to screen for the occurrence of new malignancies.

On-going safety review - Increased risk of developing new malignancies

USA (2). The US FDA notified the public of an increased risk of second primary malignancies in patients with newly-diagnosed multiple myeloma who received lenalidomide (Revlimid®). Clinical trials conducted after the drug was approved showed that newly-diagnosed patients treated with the drug had an increased risk of developing second primary malignancies compared to similar patients who received a placebo. Specifically, these trials showed there was an increased risk of developing acute myelogenous leukemia, myelodysplastic syndromes, and Hodgkin lymphoma.

This safety information has been added to the Warnings and Precautions section of the drug label. The patient Medication Guide is also being updated to inform patients about this risk. The US FDA recommended that health-care professionals should consider both the potential benefit of lenalidomide and the risk of second primary malignancies when deciding to treat patients with the drug, and monitor patients for this risk.
Proton pump inhibitors

Proton pump inhibitors in long-term use: reports of hypomagnesaemia

UK (1). The Medicines and Healthcare products Regulatory Agency (MHRA) reported that prolonged use of proton pump inhibitors (PPIs) has been associated with hypomagnesaemia. The MHRA advised that health-care professionals should consider measuring magnesium levels before starting PPI treatment and repeat measurements periodically during treatment for patients expected to be on prolonged treatment, and especially for those who take PPIs with digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics).

Severe hypomagnesaemia has been reported infrequently in patients treated with PPIs, although the exact incidence is unknown. A review of case reports described in the literature or reported to regulatory authorities in Europe suggests that PPIs may cause hypomagnesaemia. Some cases occurred after three months of PPI therapy, but most occurred after one year of treatment. Serious manifestations of hypomagnesaemia—fatigue, tetany, delirium, convulsions, dizziness, and ventricular arrhythmia—can occur, but they may begin insidiously and be overlooked. In most case reports, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.

The MHRA also advised that health-care professionals should take into account any use of PPIs obtained without prescription over-the-counter and those drugs should not be used for more than four weeks without consulting a doctor. If no symptom relief is obtained within two weeks of continuous treatment, the patient should consult a doctor. Provided that PPIs obtained over-the-counter are taken short-term and according to the recommended posology, their use is not expected to significantly increase the risk of hypomagnesaemia.

Patients who are currently taking non-prescription PPIs are advised not to use them for more than four weeks without consulting a doctor and to see a doctor if they are experiencing symptoms of hypomagnesaemia (e.g. muscle twitches, tremors, vomiting, tiredness, loss of appetite) while taking PPIs.

Proton pump inhibitors in long-term use: recent epidemiological evidence of increased risk of fracture

UK (2). The MHRA reported that there is recent epidemiological evidence of an increased risk of fracture with long-term use of PPIs. Patients at risk of osteoporosis should be treated according to current clinical guidelines to ensure they have an adequate intake of vitamin D and calcium.

Observational studies on a risk of fracture associated with PPIs suggest there may be a modest increase in the risk of hip, wrist, or spine fracture, especially if PPIs are used in high doses and for long durations (> one year). The increased risk was observed mainly in elderly patients, and it is possible that other risk factors contribute to the increase in risk.

The MHRA also advised that health-care professionals should take into account any use of PPIs obtained without prescription over-the-counter and those drugs should not be used for more than four weeks without consulting a doctor. If no symptom relief is obtained within two weeks of continuous treatment, the patient should consult a doctor. Provided that PPIs obtained over-the-counter are taken short-term and according to the recommended posology, their use is not expected to significantly increase the risk of fracture.

Patients who are currently taking non-prescription PPIs are advised not to use them for more than four weeks without consulting a doctor and to consult a doctor to make sure a patient taking enough vitamin D and calcium.

(See WHO Pharmaceuticals Newsletter No. 3 and No. 6, 2011 for investigation of risk of second primary malignancies in myeloma in the UK, and No. 5, 2011 for the risk of new cancers but benefit-risk balance remains positive in EU and reports in WHO global ICSR database).

Reference:

Terbutaline

Revoked “management of preterm labour” indication

Saudi Arabia. The SFDA advised health-care professionals that terbutaline MUST NOT be used in pregnant women for the management of preterm labor due to serious
maternal heart adverse events and deaths.

The SFDA has reviewed the available literature, to assess the benefit/risk balance of using terbutaline in preterm labour. These studies included a clinical trial, a systematic review and several case reports. Regarding the safety profile it was found that adverse events such as cardiopulmonary complications were reported in patients worldwide, in addition to the risk of serious adverse events for women and infants such as rapid or pounding heartbeat and nervousness, plus it may cause fetal tachycardia and hypoglycaemia.

These data showed that the terbutaline as tocolytic does not reduce the incidence of recurrent preterm labour or preterm delivery and does not improve perinatal outcome and some studies showed that terbutaline was equally effective with more adverse events compared with other tocolytic agents.

This issue was presented at the Pharmacovigilance Advisory Committee and it was concluded that the risks of using terbutaline for the aforementioned claims outweigh its potential benefits. The SFDA, therefore, advised health-care professionals that terbutaline is no longer approved for preterm labour.

(See WHO Pharmaceuticals Newsletter No. 1, 2011 for new warnings against use of terbutaline due to treat preterm labour in the US and reports in WHO global ICSR database).

**Reference:**
Communication from National Pharmacovigilance and Drug Safety Centre, SFDA, 23 May 2012.

**Tolvaptan**

**Over-rapid increase in serum sodium and risk of serious neurological events**

**UK.** The MHRA reported that treatment with tolvaptan (Samsca®) can result in over-rapid correction of hyponatraemia, which can lead to serious neurological events. Careful monitoring of serum sodium is therefore important and co-administration of other drugs that may increase serum sodium is not recommended. Tolvaptan may also reduce the effect of vasopressin analogues used to control or prevent bleeding.

Tolvaptan achieves its therapeutic effect by increasing free water clearance without affecting sodium excretion, thereby raising serum sodium. However, there have been reports of serious neurological events in patients treated with tolvaptan where the correction of serum sodium has exceeded the suggested rate. Increases in serum sodium which are too rapid can be harmful and cause osmotic demyelination, resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriaparesis, seizures, coma, or death. Close monitoring of serum sodium during tolvaptan treatment is recommended, especially in patients with very low serum sodium (< 120 mmol/L) at baseline or in those at high risk of demyelination syndromes—for example, those with hypoxia, alcoholism, or malnutrition.

Sodium correction that exceeds 6 mmol/L during the first 6 hours of administration or 8 mmol/L during the first six to 12 hours may be too rapid; in such patients close monitoring of serum sodium and administration of hypotonic fluid is recommended. If the increase in serum sodium exceeds 12 mmol/L in 24 hours, or 18 mmol/L in 48 hours tolvaptan treatment should be interrupted or discontinued and followed by administration of hypotonic fluid.

There is also a risk of a rapid rise in serum sodium when tolvaptan is given concomitantly with medicines with a high sodium content or with other treatments for hyponatraemia (for example normal or hypertonic saline). Treatment with such combinations is therefore not recommended.

In addition to its effect on the renal tubule, tolvaptan can block vasopressin V2-receptors involved in the release of coagulation factors (e.g. von Willebrand factor). Therefore, tolvaptan may interact with vasopressin analogues such as desmopressin used to prevent or control bleeding, reducing their effect.

**Reference:**

**Topiramate**

**Change in the pregnancy category**

**Australia.** The Therapeutic Goods Administration (TGA) advised health-care professionals of the change in the pregnancy category for topiramate-containing products from B3 to D. The Australian Product Information (PI) already contains warnings regarding the potential effects on the fetus, and recommends that women considering using topiramate receive pregnancy counselling to ensure they are aware of the potential risks to the fetus.

Topiramate is indicated for the treatment of epilepsy in adults and children aged two years and over, and for the prophylaxis of migraine headache in adults. There are also reports of off-label use of
topiramate to assist with weight loss.

In May 2011, the US FDA advised that there were new data from the North American Antiepileptic Drug Pregnancy Registry that showed an increased risk for the development of cleft lip and/or palate in infants exposed to topiramate during the first trimester of pregnancy. Following a review of these data, the TGA has changed the pregnancy category for topiramate products from Australian Pregnancy Category B3 to Category D. Category D medicines are defined as 'Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage.

The TGA also advised that health-care professionals should advise women of childbearing age of the increased risk for oral clefts when topiramate is used during pregnancy. Topiramate should be used in pregnancy only if the potential benefits outweigh the potential risks to the fetus. Consideration should be given to prescribing other medicines that have a lower risk of adverse birth outcomes in women of childbearing age. If a decision is made to prescribe topiramate, health-care professionals should recommend an appropriate method of contraception for women. In doing so, it should be kept in mind that there is the potential for decreased contraception efficacy when using topiramate with estrogen-containing contraceptives.

(See WHO Pharmaceuticals Newsletter No. 2, 2011 for Label change due to the risk for development of cleft lip and cleft palate in newborn in the US and reports in WHO global ICSR database).

**Reference:**

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**Pioglitazone hydrochloride**

**Potential association with bladder cancer**

**Canada.** Takeda Canada Inc., in collaboration with Health Canada, informed health-care professionals of important safety information regarding a potential risk of bladder cancer in patients treated with pioglitazone hydrochloride (Actos®). Health Canada has recently completed a safety assessment of the available data and the Product Monograph was updated to include the followings:

- findings from new studies reveal that there is a potential increased risk of bladder cancer in patients treated with pioglitazone-containing products;
- Pioglitazone hydrochloride is now contraindicated in patients with active bladder cancer, a history of bladder cancer or uninvestigated macroscopic haematuria;
- any macroscopic haematuria should be investigated before starting pioglitazone therapy;
- risk factors for bladder cancer should be assessed before initiating treatment with pioglitazone (risks include age, smoking, family history of bladder cancer, exposure to chemicals in the workplace, certain cancer treatments and radiation therapy).

Patients prescribed pioglitazone should be advised to seek medical attention if macroscopic haematuria or other symptoms such as dysuria or urinary urgency develop during treatment, as these may be symptoms of bladder cancer.

(See WHO Pharmaceuticals Newsletter No. 5, 2010 for ongoing safety review on potential increased risk of bladder cancer in the USA, No. 4, 2011 for the suspension in France and risk-characterization study in EU and reports in WHO global ICSR database and No. 6, 2011 for an increased risk of bladder cancer for Australia).

**Reference:**
Advisories, Warnings and Recalls, Health Canada, 16 April 2012 (www.hc-sc.gc.ca).
Dasatinib

Pulmonary arterial hypertension

Australia. The TGA urged physicians and general practitioners with patients taking dasatinib to be vigilant for pulmonary arterial hypertension and report any suspected cases of the adverse effect associated with the use of the medicine to the TGA.

Pulmonary arterial hypertension (PAH) is a rare subtype of pulmonary hypertension, characterised by smooth muscle cell hyperplasia and vascular remodelling of the pulmonary arteries. This results in elevated mean pulmonary arterial pressure (>25 mmHg at rest or >30 mmHg during physical activity) as measured by right heart catheterisation.

In the five years from June 2006, 60 serious cases of pulmonary hypertension were reported worldwide in association with dasatinib use to the sponsor’s global pharmacovigilance database. Of these 60 cases, 36 cases were reported as pulmonary hypertension, and 24 cases were reported as PAH, including a subset of 12 cases of PAH confirmed by right heart catheterisation. In these 12 cases, PAH was reported after initiation of therapy with dasatinib, including after more than one year of therapy. Patients diagnosed with PAH during dasatinib therapy were often taking concomitant medications and had comorbidities in addition to the underlying malignancy. To date, the TGA has received one report of reversible PAH secondary to dasatinib treatment for CML.

According to the TGA, the potential for a class-effect involving other tyrosine kinase inhibitors has not yet been investigated. The related drugs, imatinib and nilotinib have not been implicated in reports of PAH to date. Compared with these, dasatinib appears to have a broader range of activity, affecting multiple kinase and non-kinase targets. This provides a possible explanation for dasatinib-associated PAH and the observed differences in toxicities of drugs within this therapeutic class.

The TGA informed that before commencing dasatinib therapy, patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease. Patients taking dasatinib who develop symptoms of PAH, such as dyspnoea and fatigue, should be evaluated for more common aetologies, including pleural effusion, pulmonary oedema, anaemia, or lung infiltration. Treatment should be withheld in these patients during evaluation. If no alternative diagnosis is found, the diagnosis of PAH should be considered. If PAH is confirmed, dasatinib should be permanently discontinued.

(See WHO Pharmaceuticals Newsletter No. 5, 2011 for safety information regarding pulmonary arterial hypertension in Canada and No. 6, 2011 for risk of pulmonary arterial hypertension in the USA).

Reference:

Topical phenylephrine

Pulmonary oedema

Australia. The TGA reminded health-care professionals of the potential for serious systemic adverse effects, including pulmonary oedema, when topical phenylephrine is used concomitantly with a beta blocker.

Phenylephrine, an alpha agonist, is used as a topical vasoconstrictor in ear, nose and throat surgery and as a pupil dilator in eye surgery. There are published case reports of patients who developed pulmonary oedema associated with topical phenylephrine used in the perioperative setting. In the majority of cases, this occurred after a beta blocker was given in an attempt to correct hypertension likely due to systemic absorption of the topical phenylephrine.

The New York State Department of Health developed guidelines following the intraoperative death of a four-year-old attributed to topical phenylephrine and the guidelines advise that:

• the lowest effective dose of topical phenylephrine should be given to minimise the potential for systemic adverse effects;
• beta blockers and calcium channel blockers should not be used to treat alpha agonist-induced hypertension (as a result of systemic absorption);
• anaesthetists should be consulted prior to administration of phenylephrine (or any other medication) to the surgical site.

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 22). For information on the UMC Measures of Disproportionate Reporting please refer to WHO Pharmaceuticals Newsletter Issue No. 1 2012.

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. To leave a comment regarding the signals in this Newsletter, please contact: the Uppsala Monitoring Centre, Box 1051, SE-751 40 Uppsala, Sweden. E-mail: info@who-umc.org.

**Everolimus and serious gastrointestinal disorders**

**Summary**

Everolimus is a macrolide immunosuppressant and antineoplastic drug used in organ transplantation and oncology. As of November 2011, VigiBase contained 47 individual case safety reports (ICSRs) of selected serious gastrointestinal (GI) reactions (GI haemorrhages, ulcers, haematemesis and melena) associated with the use of everolimus. The majority of the cases were added to the database in 2010-2011, which could partly be explained by the extended indications of everolimus in the last two years. Co-reported drugs included sorafenib, bevacizumab and anticoagulant drugs, all of which may cause GI haemorrhages, but information on other possible confounders was often missing. GI toxicities, such as hemorrhages and ulcers, are not mentioned as adverse drug reactions (ADRs) in the product labelling. However, VigiBase reports suggest a possible connection between everolimus and the development or worsening of GI toxicity which has previously been unidentified.

**Introduction**

Everolimus is a macrolide immunosuppressant and anti-neoplastic drug.\(^1\)\(^2\) It inhibits the protein called mammalian Target Of Rapamycin (mTOR), a key regulatory kinase, as well as the antigenic and interleukin stimulated activation and proliferation of T and B lymphocytes.\(^3\)\(^4\) Everolimus has been authorized in the European Union for the prevention of organ transplant rejection since 2003, for advanced renal cell carcinoma and pancreatic neuroendocrine tumours since 2009 and for patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex, not amenable for surgery since 2011.\(^5\) Some differences regarding the date of authorization in the specific indications have been observed between EU and the United States. Everolimus has been marketed in the US for the treatment of advanced renal cell carcinoma since 2009, for kidney and heart transplant rejection and SEGA since 2010 and for neuroendocrine tumours since 2011.\(^6\)\(^7\) A large number of published and ongoing clinical studies have recently shown promising antitumor activity of everolimus against different tumour types such as breast cancer, advanced gastrointestinal cancer, hepatocellular carcinoma, and lymphoma, when used as monotherapy or in combination with vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) inhibitors.\(^8\)\(^9\)

The recommended initial dose for the prophylaxis of organ rejection in adult patients is 0.75 mg orally twice a day in combination with other immunosuppressant drugs, whereas in oncology the recommended dose is 10 mg once a day.\(^1\)\(^2\)
Literature and Labelling

In the everolimus EU product labelling the most frequent grade 3-4 adverse reactions (incidence >2% in at least one pivotal study) were anaemia, fatigue, diarrhoea, infections, stomatitis, hyperglycaemia, thrombocytopenia, lymphopenia, neutropenia, hypophosphataemia, hypercholesterolaemia, diabetes mellitus, and pneumonitis.\(^{10}\)

Apart from the official labelling, many of the known adverse reactions of everolimus come from its extensive use in transplantation patients and solid organ malignancy, notably renal cell carcinoma. Oral treatment with everolimus 10 mg daily or 50 mg once weekly resulted in adverse effects including stomatitis, rash, fatigue, headache, anorexia, diarrhoea, neutropenia, hyperglycaemia, hypercholesterolemia, hypertriglyceridaemia, mild leukocytopenia, and thrombocytopenia. Other toxicities include infectious and non-infectious pneumonitis.\(^{11}\)

Regarding gastrointestinal (GI) toxicity, post-marketing studies confirmed the already known and labelled adverse drug reactions (ADRs), with no new findings regarding GI haemorrhage or GI ulcers. A recent review on the management of adverse events related to targeted therapies in renal cell carcinoma pointed out the problem of everolimus-related infectious and non-infectious pneumonitis and other disorders associated with metabolism and nutrition (hypercholesterolemia and hyperglycaemia). Upper GI complications associated with everolimus included stomatitis and mucositis whereas gastrointestinal perforation, a complication associated with bevacizumab and other therapies in renal cell carcinoma, has not been reported with everolimus.\(^{12}\)

Two case reports of GI bleeding (grade 5 and 2 respectively) regarding patients with hepatocellular carcinoma recurrence after liver transplantation, treated with sorafenib and everolimus have recently been published.\(^{13,14}\) The authors did not exclude a possible additive effect of everolimus on the already known increase in risk of GI and non GI bleeding for sorafenib and other vascular endothelial growth factor receptor (VEGFR) tyrosine-kinase inhibitors.\(^{15}\)

Reports in VigiBase

The WHO Global Individual Case Safety Report (ICSR) database, VigiBase\(^{TM}\), contains 636 reports of GI system disorders associated with everolimus as of November 2011. The first report dates back to 2002, however the majority of the reports were added to the database in 2010-2011. This could be explained by the extended indications of everolimus in the last two years and the related increase in the number of patients using the drug for different indications.

This assessment focused on three categories of serious GI adverse reactions: GI haemorrhages, GI ulcers and the two related symptoms haematemeses and melaena. After exclusion of duplicate reports, everolimus was associated with GI haemorrhages in 27 reports, duodenal ulcers in eight, gastric ulcers in four, peptic ulcers in five, haematemeses in nine and melaena in 9 reports.

In the reports which presented multiple simultaneous reactions, the cases were classified following this priority: GI haemorrhage, ulcer, melaena and haematemeses. That is, if both GI haemorrhage and melaena were present in the same report, the report was considered belonging to the group of GI haemorrhage. After this adjustment, the cases of serious GI disorders associated with everolimus present in VigiBase and considered for the assessment were 47 in total. The reports originated from eight different countries: 27 from the United States, 11 from Germany, two each from United Kingdom, Canada and Italy and one each from Austria, Czech Republic and Sweden. The characteristics of the case reports are shown in Table 1.

In the majority of cases, other GI symptoms reported were vomiting, diarrhoea and abdominal pain. In some cases disorders in other organs or tissues were also referred to, such as haematologic reactions, metabolic alterations, cardiovascular disorders and infections. However, in nearly half of the cases the adverse reactions appeared to be related to GI haemorrhage or ulcer and no other pathologies were described.

In 20 cases, everolimus was indicated as the only suspected drug and in eight of them no other concomitant drug was listed. However, considering the type of patients treated, this is more likely due to incomplete reporting than to a real monotherapy. Sorafenib was suspected together with everolimus in association with serious GI disorders in five patients and bevacizumab in three patients. Among concomitant drugs the most frequent was ciclosporin (five patients), which was also reported as suspected in one case. As everolimus, ciclosporin and sorafenib are all substrates of CYP3A4 a potential interaction could be speculated, however the reports do not allow to further assess the role or relevance in these cases. Eight of the GI haemorrhage cases also reported use of other drugs interfering with blood coagulation, such as acetylsalicylic acid, warfarin and heparins.

In total there were 13 fatal cases, regardless of death cause, among the 47 reports. In five of them (three GI haemorrhages, two GI ulcers) sorafenib or bevacizumab was co-reported with everolimus.

For cases where complete treatment dates were provided, twelve of the patients were treated with everolimus for a duration of one to six months, in
a few cases for less than one month or more than one year. Although incomplete treatment dates, six additional patients had used everolimus for at least two months.

Table 1. Characteristics of reports of serious gastrointestinal (GI) system disorders associated with everolimus in VigiBase™.

<table>
<thead>
<tr>
<th>Reactions</th>
<th>N° of reports</th>
<th>Gender (M/F)</th>
<th>Mean age</th>
<th>Everolimus sole suspect</th>
<th>Fatal cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI haemorrhage</td>
<td>27</td>
<td>15/10</td>
<td>49yrs (N=10)(25-69)</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>GI ulcers</td>
<td>11</td>
<td>5/5</td>
<td>73yrs (N=4) (65-79)</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Haematemia or Melaena</td>
<td>9</td>
<td>4/4</td>
<td>42yrs (N=1)</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>TOTAL</td>
<td>47</td>
<td>24/19</td>
<td>55yrs (N=15)</td>
<td>20</td>
<td>13</td>
</tr>
</tbody>
</table>

Table 2 shows the indication for use of everolimus in the 47 patients experiencing the selected serious GI disorders.

Table 2. Indication of use in everolimus reports associated with serious gastrointestinal (GI) system disorders in VigiBase™.

<table>
<thead>
<tr>
<th>Everolimus indication</th>
<th>N° of reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transplant (kidney and liver)</td>
<td>10</td>
</tr>
<tr>
<td>Renal Cancer</td>
<td>10</td>
</tr>
<tr>
<td>Neuroendocrine Cancer</td>
<td>3</td>
</tr>
<tr>
<td>Other tumours*</td>
<td>18</td>
</tr>
<tr>
<td>No indication</td>
<td>6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>47</strong></td>
</tr>
</tbody>
</table>

*Among the 18 other tumours, breast, stomach, liver cancer and melanoma involved more than one patient.

**Discussion and Conclusion**

VigiBase reports of selected serious GI adverse reactions (GI haemorrhages and ulcers) associated with everolimus allow us to suspect a possible connection between the drug and the development or worsening of GI toxicity.

We would like to stress that patients' typology is various and ranges from transplantation to oncology. Many of the patients are taking other drugs and potential and individual risk factors for the development of GI toxicity cannot be gathered from the reports. However, the proportion of fatal outcomes is high in patients who experienced the selected GI disorders in association with everolimus treatment. The prospective of an increase in use of everolimus in different clinical settings, also in combination with other drugs such as bevacizumab and sorafenib, makes the issue of the risk profile crucial for defining the clinical utility of this drug. Vigilance is therefore necessary for identifying any emerging toxicity which has not been reported yet.

**References**


Ondansetron and serotonin syndrome

Summary

Ondansetron is a potent, highly selective serotonin (5-HT3) receptor antagonist. Ondansetron is sometimes mentioned in association with serotonin syndrome in the literature, and there are some published case reports. Nothing, however, is mentioned about serotonin toxicity neither in the UK Summary of Product Characteristics (SPC) nor in the US FDA product labelling. There are nine individual case safety reports (ICSRs) in VigiBase, out of which four have been published in literature. In addition to the ondansetron cases, there are five cases of other 5-HT3 antagonists associated with serotonin syndrome in VigiBase; three cases with granisetron and two cases with dolasetron. VigiBase case reports, together with published case reports, indicate that ondansetron may contribute to the development of the serotonin syndrome in susceptible patients concomitantly receiving other drugs affecting the serotonin system.

Introduction

Ondansetron is a potent, highly selective serotonin receptor subtype 5-HT3 antagonist. Therapeutic indications include the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy (for patients aged 6 months and older), and the prevention and treatment of post-operative nausea and vomiting (for patients aged one month and older). The recommended adult dose ranges from a single dose of 4 mg to 32 mg a day.1

Serotonin syndrome is a drug-induced condition resulting from use of medications that increase the level of intrasynaptic serotonin, primarily acting at
serotonin receptor subtype 5-HT₂A and possibly 5-HT₁A. Several drugs have, either alone or in combination, been associated with the syndrome, including monoamine oxidase inhibitors (MAOIs), selective serotonin re-uptake inhibitors (SSRIs), serotonin-norepinephrine re-uptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and opioids. The diagnosis is clinical and symptoms include mental status alterations (agitation and confusion), autonomic signs (fever, diaphoresis, tachypnoea and tachycardia) and neuromuscular changes (tremor, clonus, myoclonus, hyperreflexia and rigidity). The onset of symptoms is usually rapid.

Mason et al. found that patients with serotonin syndrome most often presented within 24 hours of medication initiation, an overdose or a change in dosing. Symptoms usually resolve within 24 hours after discontinuation of serotonergic drugs and the initiation of supportive therapy, but symptoms may last longer after use of drugs with long elimination half-life or active metabolites.

**Literature and Labelling**

Ondansetron is sometimes mentioned in association with the serotonin syndrome in the literature, and there are some published case reports. Nothing, however, is mentioned about serotonin toxicity neither in the UK Summary of Product Characteristics (SPC) nor in the US FDA product labelling. This is also the case for other 5-HT3 antagonists, including dolasetron, granisetron, tropisetron and palonosetron.

The following nervous system disorders are listed as adverse drug reactions (ADRs) in the ondansetron UK SPC: headache, seizures, movement disorders including extrapyramidal reactions (such as dystonic reactions, oculogyric crisis and dyskinesia), and dizziness during intravenous administration. Other ADRs listed as common for ondansetron (frequency >1/100 and <1/10) are sensation of warmth or flushing, constipation and local injection site reactions. Concomitant use with apomorphine is contra-indicated, based on reports of profound hypotension and loss of consciousness.

Five case reports on serotonin syndrome associated with the use of ondansetron were found published in the literature. Four of the cases were identified in VigiBase and are further described in the next section. The fifth case involves a 12 year old male patient seriously ill with disseminated Ewing's Sarcoma, receiving mirtazapine and morphine in addition to chemotherapy. The following day after starting ondansetron he was confused and tremulous with myoclonus. Ondansetron and mirtazapine were both discontinued, and the reaction resolved with a single dose of droperidol the following day. Mirtazapine was reintroduced several days later without problem.

**Reports in VigiBase**

After exclusion of duplicate reports, there are nine unique individual case safety reports (ICSRs) of ondansetron associated with the serotonin syndrome in the WHO Global ICSR database, VigiBase™, as of January 2012. The cases originate from seven different countries; United States, Canada, Spain, New Zealand, Germany, United Kingdom and Australia. Six of the patients are females and three are males. Patient age ranges from 12 months to 69 years. Five of the cases have a time to onset reported; the reaction then started on the day of the first ondansetron administration or on the following day. In the adult cases, ondansetron dose ranges from a single dose of 4 mg up to 16 mg daily. The characteristics of the individual cases are listed in Table 1 (unpublished cases) and Table 2 (published cases). In addition to the information available on the cases in VigiBase, further information has been retrieved from original reports received from the national pharmacovigilance centres from which the reports originated, or from the published case reports.
Table 1. Reports of serotonin syndrome associated with ondansetron in VigiBase™ (excluding published case reports).

<table>
<thead>
<tr>
<th>Gender/Age</th>
<th>Drugs*</th>
<th>Time to onset</th>
<th>Action taken with drug(s) and outcome</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/30</td>
<td>Ondansetron (S) Mirtazapine (S) Hydromorphone (C) Clonzaepam (C) Docusate (C)</td>
<td>0 days (after third injection within 12-hour period)</td>
<td>Ondansetron discontinued. Patient recovered following treatment with hydroxyzine.</td>
<td>3 mg three times per day</td>
<td>Serotonin reaction possibly attributed to venlafaxine and ondansetron mentioned by reporter, but subsequently the patient's physician reported that the events probably were related to another medication (unspecified).</td>
</tr>
<tr>
<td>F/56</td>
<td>Ondansetron (S) Fentanyl (S) Oxycodone (S) Tramadol (S) Haloperidol (C)</td>
<td>All suspect drugs discontinued. Patient recovered.</td>
<td></td>
<td>As necessary</td>
<td></td>
</tr>
<tr>
<td>F/35</td>
<td>Ondansetron (S) Venlafaxine (S) Morphine (C)</td>
<td>0 days (after third injection within 12-hour period)</td>
<td>Ondansetron discontinued. Patient recovered following treatment with hydroxyzine.</td>
<td>3 mg three times per day</td>
<td></td>
</tr>
<tr>
<td>F/69</td>
<td>Ondansetron (S) Oxycodone (S) Phenelzine (C) Diazepam (C)</td>
<td>1 day</td>
<td>Ondansetron and oxycodone discontinued. Patient slowly recovered within 3-4 days.</td>
<td>4 mg twice daily</td>
<td></td>
</tr>
<tr>
<td>F/63</td>
<td>Ondansetron (S) Metoclopramide (S) Sertraline (S) Nifedipine (C) Metoprolol (C) Hydrochlorothiazide/ Irbesartan (C)</td>
<td>0 days</td>
<td>All suspect drugs discontinued. Patient recovered.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*S=drug is reported as suspected, C=drug is reported as concomitant.
Table 2. Published case reports of serotonin syndrome associated with ondansetron, present in VigiBase™.

<table>
<thead>
<tr>
<th>Gender/Age</th>
<th>Suspected drugs*</th>
<th>Time to onset</th>
<th>Action taken with drug(s) and outcome</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>F/49</td>
<td>Ondansetron (S)</td>
<td>Hours</td>
<td>Single dose of ondansetron. Patient recovered within 2 days.</td>
<td>Single dose of 4 mg</td>
<td>Serotonin toxicity suggested being due to interaction between methylthioninium and paroxetine. The authors did not exclude that interaction between ondansetron and residual paroxetine could increase the vulnerability to serotonin toxicity (paroxetine withdrawn two days before reaction onset).</td>
</tr>
<tr>
<td></td>
<td>Methylthioninium (S)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paroxetine (S)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>For concomitants, see articles.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F/44</td>
<td>Ondansetron (I)</td>
<td>1 hour</td>
<td>Single dose of ondansetron. Patient recovered within 5-6 days.</td>
<td>Single dose of 4 mg</td>
<td>Medical history included major depression, polysubstance abuse and overdose. Paracetamol/Hydrocodorate first administered second day after reaction onset.</td>
</tr>
<tr>
<td></td>
<td>Duloxetine (I)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fentanyl (I)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Lithium (I)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Quetiapine (I)</td>
<td></td>
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<tr>
<td></td>
<td>Propofol (S)</td>
<td></td>
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<tr>
<td></td>
<td>Rocuronium (S)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Desflurane (S)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Hydromorphone (S)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paracetamol/Hydrocodorate (S)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>For concomitants, see article.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M/5</td>
<td>Ondansetron (S)</td>
<td>3 hours</td>
<td>Single dose. Patient died.</td>
<td>Single dose of 2 mg</td>
<td>Medical history included malignant hyperthermia (MH). Authors suggested that a putative episode of MH, not serotonin syndrome, was triggered by ondansetron.</td>
</tr>
<tr>
<td>M/1</td>
<td>Ondansetron (S)</td>
<td>20 minutes</td>
<td>Single dose. Patient was recovering 20 hours post-ingestion.</td>
<td>Single dose of 56-64 mg</td>
<td>Accidental intake by healthy infant, overdose.</td>
</tr>
</tbody>
</table>

*S—drug is reported as suspected, I—drug is reported as interacting.

In addition to the ondansetron case reports, there are five cases of other 5-HT₃ antagonists associated with serotonin syndrome in VigiBase (one duplicate excluded). Three cases include granisetron and two cases dolasetron. One case was found published in literature and reports an 11 year-old female with acute lymphoblastic leukemia. The patient developed symptoms of serotonin syndrome when a worsening medical condition led to compromised endothelial function, coinciding with the use of granisetron and fentanyl. The second case reports a 69 year-old female. Suspected drugs include granisetron, venlafaxine, sufentanil and methylthioninium and the reporter mentions the suspicion of interaction between venlafaxine and methylthioninium, with...
contributions from the other drugs. Venlafaxine had been used for almost one year when adding the other three drugs and serotonin syndrome started with a latency of hours after start of the new drugs. The third case reports a 12 year-old male with acute lymphatic leukaemia. Granisetron and olanzapine were reported as suspected drugs, but many concomitant drugs were also mentioned, including fentanyl and other anaesthetics. Neuroleptic malignant syndrome was reported as an additional ADR. The two cases involving dolasetron report sertraline as a co-suspected drug. These reports are very poorly documented.

**Discussion**

VigiBase contains nine ICSRs of serotonin syndrome in association with ondansetron use, many of them quite complex and with alternative explanations. Seven of the cases describe a plausible time to onset, as the reaction occurred on the same day or the day after ondansetron was first administered to the patient. Several cases report a positive dechallenge but it is impossible to fully evaluate this information since not only ondansetron but also other suspect drugs were withdrawn.

Seven of the cases report other drugs that, alone or in combination with other drugs, are known to have the ability to cause serotonin syndrome. Co-administration of different drugs affecting the serotonergic system is a known risk of developing the syndrome. It is not possible to completely assess the involvement of ondansetron in the cases including several other suspect drugs, but it is also impossible to rule out that ondansetron had a contributory role. Interestingly, some of the cases have no or only one other suspect drug in addition to ondansetron.

A mechanism for a suggested increased vulnerability to serotonin syndrome when concomitantly using 5-HT\(_3\) antagonists and other serotonergic drugs might be that blocking of the 5-HT\(_3\) receptor subtype, and at the same time increasing the levels of serotonin, results in excessive serotonin to other serotonin receptor subtypes (including 5-HT\(_{1A}\) and 5-HT\(_{2A}\)). A pharmacokinetic interaction might also be considered, as ondansetron is metabolized by cytochrome P-450 enzymes; CYP3A4, CYP2D6 and CYP1A2. Two of the cases concern children and in both cases ondansetron is the only drug administered. Although there are certain circumstances complicating the assessment of these cases, i.e. history of malignant hyperthermia and overdose, it should be considered whether ondansetron may cause the serotonin syndrome without co-administration of other drugs affecting the serotonin system and whether children might be at higher risk of serotonin toxicity from ondansetron only.

Ondansetron is a widely used drug, however, the number of reports of ondansetron associated with serotonin syndrome in VigiBase is quite low. This might indicate that an association between the drug and the ADR is rare, but it should also be considered that serotonin syndrome is not always recognized as a diagnosis and hence not reported as such. Mackay et al. found that awareness of the serotonin syndrome among prescribing doctors was poor; 85% of general practitioners in the United Kingdom were unaware of the syndrome as a diagnosis.\(^{13}\)

**Conclusion**

VigiBase case reports, together with published case reports, indicate that ondansetron may contribute to the development of the serotonin syndrome in susceptible patients concomitantly receiving other drugs affecting the serotonin system. Additional cases on other 5-HT\(_3\) antagonists in VigiBase might indicate a possible class effect.

Ondansetron is sometimes mentioned in association with the serotonin syndrome in the literature and there are some published case reports, however nothing is mentioned about serotonin toxicity in the product labelling for ondansetron. Serotonin syndrome is not an idiosyncratic drug reaction, but it is predictable and preventable\(^4\), and therefore patient safety would be served if it was considered to also be mentioned in the product labelling.

**References**


7. Turkel SB, Nadala JG, Wincor MZ. Possible serotonin syndrome in association with 5-


CAVEAT DOCUMENT

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

Uppsala Monitoring Centre (UMC) 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.
Drug utilisation methodology - International ATC/DDD course in Oslo

H Strom, Director, WHO Collaborating Centre for Drug Statistics Methodology

The international course on the Anatomical Therapeutic Chemical (ATC) classification system for medicines and their Defined Daily Dose (DDD) took place 7-8 June 2012. This was the 19th annual course organized by the WHO Collaborating Centre for Drug Statistics Methodology in Oslo. These courses provide a detailed introduction to the ATC classification system and the DDD unit of measurement. The purpose of the ATC/DDD and how to use the methodology are also covered in the course, which consists of lectures, discussions and working groups. The aim is to train present and future users in the ATC/DDD methodology, and get input from the users of the system. The users' opinions are very important for the development of the system, and the courses are one way of getting feedback and discussing challenges faced by users in different countries and organisations.

This year 26 participants from 13 different countries attended the course (e.g. Kyrgyzstan, Scandinavia and a number of other European countries, UK, Ukraine and the USA). They were either professionals from the pharmaceutical industry, health authorities, university/academia, pharmacovigilance, or pharmacy associations.

The staff of the Centre were responsible for the lectures and working groups. Professor Morten Andersen, member of the International Working Group for Drug Statistics Methodology, was the invited speaker.

During the two days there were several interactive sessions. The course participants challenged the lecturers with questions which initiated interesting discussions. The Centre received high rated evaluations for this course.

The Centre may also arrange courses on request in other countries that plan to start using the ATC/DDD methodology. Regional courses have been arranged in the past, for example, in Ecuador, Japan and Morocco. The latest regional ATC/DDD course was held in Johannesburg in January 2012. 52 participants had attended, representing health authorities, pharmaceutical industry, research organizations and hospitals.

The next annual course in ATC/DDD will be held in Oslo in June 2013. The course is open to all interested parties.
Targeted spontaneous reporting in antiretroviral treatment programmes: pilot efforts in Uganda

H Byomire-Ndagije, National Drug Authority, Uganda

All medicines are authorized to be marketed based on safety and efficacy data from clinical trials. However it is important to continuously collect and analyse as much information as possible about medicines in a post marketing phase, to understand and evaluate the actual benefit-risk balance with these medicines in clinical practice.

The Ugandan Ministry of Health in collaboration with partners has successfully scaled-up Antiretroviral Therapy (ART) to people infected with HIV, providing access to treatment right up to the health sub-district level. By March 2011, 274,208 people were accessing ART from 432 health facilities while 496,623 (41%) of the 1.2 million people living with HIV were accessing chronic HIV care services, 96% of whom received co-trimoxazole prophylaxis. In addition, prevention of mother-to-child transmission (PMTCT) services have been rolled out to over 1,300 sites in the country and provide antiretroviral (ARV) prophylaxis to 60% of the 25,000 HIV-infected women who get pregnant, annually. This widespread access to HIV treatment and PMTCT services, while being an important achievement, has also greatly increased the number of people who are at risk of potential adverse drug reactions (ADRs).

Despite increased awareness and advocacy for monitoring and reporting of ADRs in Uganda over the last five years, there is still limited data on the actual burden of ADRs in terms of prevalence and their cost implications. The National Pharmacovigilance Centre (NPC) receives reports of suspected ADRs from the 12 regional pharmacovigilance centres and their catchment health facilities. To-date, about 700 ADR reports have been received by the NPC, of which 200 reports are due to ARV drugs. Unfortunately, only known or suspected ADRs are reported and most reports are incomplete, while many of the reports are received long after the ADR occurrence. The presence of ADRs may be underestimated in part because of failure to recognize them or due to reporting bias. In addition, the poor quality of reports makes assessment of the causal relationship difficult. These factors, together with the under-reporting make it difficult to quantify the ADRs and the risks.

In order to improve reporting of ADRs with ART in the country, the National Pharmacovigilance Centre in conjunction with the STD/AIDS Control Programme has adopted Targeted Spontaneous Reporting (TSR) of ADRs\(^1\), which focuses on a few drugs and on particular ADRs of interest.

In Uganda, tenofovir (TDF) was recommended as part of the alternative first-line ART regimen in the 2009 national ART guidelines and has of recent been made the preferred first-line regimen. However, little is known about its toxicity profile in the Ugandan population. Use of TDF by patients with mild renal dysfunction and/or use for longer durations might be associated with renal toxicity, as suggested by animal studies.

In view of the above, the TSR approach will be piloted in two of the Regional Pharmacovigilance Centres, namely the Masaka and Mbale regional referral hospitals, to monitor renal ADRs to the tenofovir-based ART regimen

Following the release of the revised PMTCT guidelines by the World Health Organization in 2010, Uganda adopted and is currently rolling out the new PMTCT guidelines aimed at elimination of new paediatric HIV infections resulting from mother-to-child transmission (MTCT). ‘Option B’ has been chosen as the preferred PMTCT regimen, where Option B recommends giving ART to all HIV-positive pregnant women from 14 weeks of pregnancy until one week after breastfeeding has stopped. The recommended first-line ART regimen for pregnant women is tenofovir, lamivudine and efavirenz or nevirapine. The present project will also closely monitor mothers on the tenofovir-based regimen (for renal toxicity) as well as those who have been on zidovudine (for all ADRs).

Information obtained from this project will inform Ministry of Health policy, and the future rollout of TSR for HIV medicines. The project is also intended to enhance collaboration between the national pharmacovigilance centre and the public health programmes.

**Project Goals**

1. To improve care and safety of patients on antiretroviral therapy in Uganda.
2. To provide data for future reference on the safety of tenofovir and zidovudine.
3. To enhance pharmacovigilance in public health programmes and among health professionals in Uganda.

**Specific objectives**

1. To monitor renal toxicities related to the use of tenofovir-based regimens in adults.
2. To monitor adverse drug reactions related to the use of zidovudine (AZT) for PMTCT.
3. To establish a quality assessment system for ADR reporting for all drugs in Uganda.
4. To enhance pharmacovigilance in the STD/AIDS Control Program.
5. To establish timely dissemination of information to stakeholders and health care providers on adverse events due to ARVs and other drugs.

The Minister responsible for Health launched the TSR project in a formal ceremony on 11 May 2012, at the Golf Course Hotel in Kampala. The function was attended by representatives from WHO, regional pharmacovigilance centres, district health officers, directors of regional hospitals, and officers from the AIDS Control Programme and the National Drug Authority.

**Project funding**

The project has been funded by the Monitoring Medicines Project, a major international project, with the full title 'Optimizing drug safety monitoring to enhance patient safety and achieve better health outcomes'. 'Monitoring Medicines' was developed by WHO and is coordinated by the Uppsala Monitoring Centre, with funds from the European Commission (Seventh Framework Programme (FP-7) of the Research Directorate). The project aims to improve patient safety both within the European Union and in other regions.