WHO PHARMACEUTICALS NEWSLETTER

World Health Organization

prepared in collaboration with the
WHO Collaborating Centre for
International Drug Monitoring,
Uppsala, Sweden

The aim of the Newsletter is to disseminate information on the safety and efficacy of pharmaceutical products, based on communications received from our network of "drug information officers" and other sources such as specialized bulletins and journals, as well as partners in WHO. The information is produced in the form of résumés in English, full texts of which may be obtained on request from:

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This Newsletter is also available on our Internet website: http://www.who.int/medicines

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No. 1, 2012

The WHO Pharmaceuticals Newsletter provides you with the latest information on the safety of medicines and legal actions taken by regulatory authorities across the world.

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

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

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Aliskiren containing drugs

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

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

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

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

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

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

Atomoxetine

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

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

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

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

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

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

Bevacizumab

Suspended approval for use in metastatic breast cancer

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

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

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

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

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

Bisphosphonate drugs

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

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

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

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

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

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

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

Brentuximab vedotin

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

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

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

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

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

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

Citalopram and escitalopram

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

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

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

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

The MHRA also advised health-care professionals that:

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

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

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

Dronedarone

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

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

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

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

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

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

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

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

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

Meprobamate-containing medicines

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

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

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

The review of meprobamate-containing medicines was started because the French authorities announced in July 2011 their intention to suspend the marketing authorisations for oral meprobamate-containing medicines because of serious side effects seen with these medicines.

The Agency's Committee for Medicinal Products for Human Use (CHMP) reviewed all available data on the safety and efficacy of these medicines, including data from studies, post-marketing surveillance and the published literature, as well as from poison control centres on cases of poisoning with meprobamate.

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

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

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

Natalizumab

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

USA. The US FDA notified health-care professionals that testing positive for anti-JC virus (JCV) antibodies has been identified as a risk factor for PML. PML is a rare but serious brain infection associated with use of natalizumab (Tysabri®) for the treatment of multiple sclerosis (MS) or Crohn's disease.

A patient's anti-JCV antibody status may be determined using an anti-JCV antibody detection test that has been analytically and clinically validated, and has been ordered by a healthcare professional. The Stratify JCV Antibody ELISA test2 was cleared by FDA on 20 January 2012. Testing positive for anti-JCV antibodies means that a person has been exposed to JCV in the past.

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

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

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

Simvastatin

Label change - new restrictions, contraindications, and dose limitations

USA. The US FDA notified the public that the dose limitation for simvastatin is revised from 10 mg to 20 mg when it is co-administered with the cardiac drug amiodarone. The simvastatin drug labels (Zocor® and generics,

Vytorin®) have been updated to reflect this correction.

(See WHO Pharmaceuticals Newsletter No. 4, 2011 for new restrictions, contraindications, and dose limitations in the USA).

Reference:
FDA Drug Safety Communication, US FDA, 15 December 2011 (*www.fda.gov*).

Ursodiol

Association of high-dose with serious liver side effects

Canada. The manufacturers of ursodiol (Aptalis Pharma Canada Inc., Dominion Pharmacal, Pharmascience Inc., Pharmel Inc., Teva Canada Ltd.), in consultation with Health Canada, informed health-care professionals to be aware that the Canadian Product Monographs (PMs) for ursodiol (ursodeoxycholic acid, UDCA) products have been updated in October 2011 to reflect data from a long-term clinical trial in primary sclerosing cholangitis (PSC) finding an increase in serious liver adverse events in patients taking an unapproved ursodiol dose (twice the recommended dose).

It is notified that:

- the recommended ursodiol dose is 13-15 mg/kg/d for adults with cholestatic disease;
- in a clinical trial in patients with PSC, long-term use of twice the recommended dose of ursodiol (i.e., of 28-30 mg/kg/d) was associated with improvement in serum liver tests but did not improve survival, and was associated with higher rates of serious adverse events (including death or liver transplantation) compared to placebo;
- improved serum liver tests do not always correlate with improved liver disease status.

The PMs for the drug have been revised to describe the clinical trial, and advise that improved serum liver tests (e.g. AST, ALP) do not always correlate with an improved liver disease status. The PMs continue to recommend monitoring of GGT, alkaline phosphatase, AST, ALT and bilirubin every month for three months after start of therapy, and every six months thereafter. Treatment should be discontinued if the levels of these parameters increase.

Reference:
Advisories, Warnings and Recalls, Health Canada, 5 December 2011 (*www.hc-sc.gc.ca*).

Varenicline tartrate

Updated safety information for the smoking-cessation drug

Canada. Health Canada informed that the review of varenicline tartrate (Champix®) completed and the label was updated to include a more detailed description of the study and findings, along with precautions for patients with respect to cardiovascular safety.

Health Canada evaluated data from a quit-smoking clinical trial involving 700 smokers with cardiovascular disease (approximately 350 who received the drug and 350 who received a placebo or "sugar pills"). Although a slightly increased number of patients experienced serious heart-related events in the group treated with varenicline tartrate compared to the group treated with placebo, the study was not adequately designed to be able to test the cardiovascular safety of the drug. The small study size combined with other study design weaknesses make it impossible to draw conclusions based on these data. The possibility of an increased risk of heart attack or stroke in patients with cardiovascular disease can neither be confirmed nor ruled out at this time.

Patients are advised to seek immediate medical attention if they think they might be experiencing a heart attack or stroke. Symptoms of a heart attack include chest pain; pain in the arms, back, neck, jaw or stomach; shortness of breath; sweating; and nausea. Symptoms of stroke include suddenly feeling weak or numb in the face, arms or legs; trouble speaking; vision problems; sudden severe headache; and dizziness.

It is important to note that smoking by itself is a major known risk factor for cardiovascular disease and that patients with cardiovascular disease can benefit greatly from quitting smoking. Patients with questions or concerns about varenicline tartrate should talk to their health-care professional.

(See WHO Pharmaceuticals Newsletter No. 4, 2011 for risk of certain cardiovascular adverse events in the USA and reports in WHO Global ICSR database).

Reference:
Advisories, Warnings and Recalls, Health Canada, 19 January 2012 (*www.hc-sc.gc.ca*).

Aliskiren-containing medicines

Review of aliskiren-containing medicines following termination of ALTITUDE study started

Europe. The EMA announced that the Agency is reviewing aliskiren-containing medicines, to assess the impact of data coming from the ALTITUDE study on the balance of benefits and risks of these medicines in their approved indication.

While the review is ongoing, the CHMP recommended, as a precautionary measure, that doctors should not prescribe aliskiren-containing medicines to diabetic patients in combination with ACE inhibitors or ARBs. Doctors should therefore review the treatment of patients taking aliskiren at a routine (non-urgent) appointment, and if patients are diabetic and are also taking ACE inhibitors or ARBs, aliskiren should be stopped and alternative treatments considered. Patients 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. They are advised to discuss their treatment with their doctor at their next scheduled (non-urgent) appointment. The CHMP also advised that patients in clinical trials with aliskiren should contact their study site for guidance on their medication.

The CHMP started the review after it was informed on 19 December 2011 by the marketing authorisation holder of the decision to terminate the ALTITUDE study early. This clinical trial included patients with type 2 diabetes and renal impairment and/or cardiovascular disease. In most patients arterial blood pressure was adequately controlled. The patients included in the trial received aliskiren in addition to either an angiotensin converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB).

The information available at present is limited. The Committee has asked the company to provide additional analyses to allow the CHMP to assess the impact of the results of the ALTITUDE trial on the overall benefit-risk profile of aliskiren-containing medicines and to determine the need for regulatory action.

Reference:
Press release, EMA, 22 December 2011 (www.ema.europa.eu).

Bevacizumab

Reports of cases of severe eye inflammation leading to blindness following use in the Eye

Canada. Hoffmann-La Roche Limited (Roche), in consultation with Health Canada informed health-care professionals of following important new safety information regarding unauthorized intravitreal use of bevacizumab (AVASTIN®).

- Bevacizumab is not formulated for intravitreal use.
- Three clusters of serious ocular complications, including acute ocular inflammation, endophthalmitis, and infectious endophthalmitis resulting in blindness, have been recently reported in Florida, Tennessee, and California, all associated with intravitreal injection of bevacizumab.
- Although these clusters continue to be investigated, it is possible that the events of blindness from streptococcal endophthalmitis in Florida were due to repackaging of bevacizumab without proper aseptic technique.
- The production methods, formulation and dosages for bevacizumab were specifically developed for intravenous use in the oncology setting. Use of bevacizumab in the ophthalmology setting is not authorized in Canada.

(See WHO Pharmaceuticals Newsletter No. 5, 2010 for association with hypersensitivity and infusion reactions in Canada).

Reference:
Advisories, Warnings and Recalls, Health Canada, 7 December 2011 (www.hc-sc.gc.ca).

Dabigatran etexilate mesylate

Safety review of post-market reports of serious bleeding events in the USA, Australia and New Zealand; Risk of serious haemorrhage– need for renal function testing in UK

USA (1). The US FDA announced that it is evaluating post-marketing reports of serious bleeding events in patients taking dabigatran etexilate mesylate (Pradaxa®). Bleeding that may lead to serious or even fatal outcomes is a well-recognized complication of all anticoagulant therapies.

The US FDA is working to determine whether the reports of bleeding in patients taking dabigatran etexilate mesylate

are occurring more commonly than would be expected, based on observations in the large clinical trial that supported the approval of dabigatran etexilate mesylate.

At this time, the US FDA continues to believe that dabigatran etexilate mesylate is a blood thinning (anticoagulant) medication used to reduce the risk of stroke in patients with non-valvular atrial fibrillation (AF), the most common type of heart rhythm abnormality, provides an important health benefit when used as directed and recommends that health-care professionals who prescribe dabigatran etexilate mesylate follow the recommendations in the approved drug label. The US FDA also recommended that patients with AF should not stop taking dabigatran etexilate mesylate without talking to their health-care professional. Stopping use of blood thinning medications can increase their risk of stroke. Strokes can lead to permanent disability and death.

Australia (2). The Therapeutic Goods Administration (TGA) urged clinicians to give careful consideration to the suitability of their patients for dabigatran particularly with regard to recognized risks of bleeding.

The TGA has received an increase in the number of bleeding-related adverse events reports for dabigatran since its approval. The analysis of these reports shows that some of the bleeding adverse events occurred during the transition from warfarin to dabigatran; many of the adverse events are occurring in patients on the reduced dosage regimen; and the most common site of serious bleeding for dabigatran is the gastrointestinal tract, whereas for warfarin it is intracranial.

New Zealand (3). Medsafe (New Zealand Medicines and Medical Devices Safety Authority) reported summary of 295 reports detailing suspected adverse reactions to dabigatran to the Centre for Adverse Reactions Monitoring (CARM) up to 7 November 2011.

UK (4). The Medicines and Healthcare products Regulatory Agency (MHRA) advised health-care professionals that renal function should be assessed in all patients before starting dabigatran and at least once a year in patients older than 75 years or those with a suspected decline in renal function. Dabigatran is contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/min). The MHRA also advised health-care professionals to check for signs of bleeding or anaemia and stop treatment if severe bleeding occurs

Dabigatran is a reversible inhibitor of free thrombin, fibrin-bound thrombin, and thrombin-induced platelet aggregation. Dabigatran has a rapid onset of action and does not require therapeutic monitoring. It is eliminated unchanged in urine. Exposure to dabigatran is substantially increased in patients with renal insufficiency.

According to the MHRA, the receipt of a number of case reports of fatal haemorrhage in patients who received dabigatran for SSE in Japan has resulted in a strengthening of the advice for prescribers. All patients were reported to be older than 75 years, with renal impairment and additional risk factors for bleeding, including concomitant medication. All cases reportedly received the lower recommended dose of dabigatran (i.e., 220 mg/day). Half the patients were also reported to have severe renal impairment, which is a contraindication for dabigatran therapy.

Reference:

(1) FDA Drug Safety Communication, US FDA, 7 December 2011 (*www.fda.gov*).
(2) Medicines Safety Update Vol 2, No. 6, December 2011 (www.tga.gov.au).
(3) Prescriber Update Vol. 32 No. 4, December 2011 (*www.medsafe.govt.nz/*).
(4) Drug Safety Update, December 2011, Volume 5, issue 5, A2, MHRA, (*www.mhra.gov.uk*).

Fingolimod

Safety review of a reported death after the first dose in the USA; Review of fingolimod and advise to intensify cardiovascular monitoring after first dose in Europe

USA (1). The US FDA has received a report of a patient with multiple sclerosis (MS) who died within 24 hours of taking the first dose of fingolimod (Gilenya®). At this time, FDA cannot conclude whether the drug resulted in the patient's death. The Agency is continuing to evaluate the case and will communicate any new information that results from this investigation. Fingolimod is an oral medication for the treatment of relapsing forms of MS in adults and used to reduce the frequency of flare-ups (clinical exacerbations) and delay physical disability.

At this time, the US FDA continues to believe that fingolimod provides an important health benefit when used as directed and recommended that health-care professionals who prescribe

fingolimod follow the recommendations in the approved drug label. Patients with MS should not stop taking fingolimod without talking to their healthcare professional.

Europe (2). The EMA announced that the agency began a review of the benefits and risks of filgolimod. This follows concerns over the effects of the medicine on the heart after the first dose. While the review is ongoing, the CHMP is advising doctors to increase their level of monitoring of patients after the first dose of the medicine. This includes electrocardiogram (ECG) monitoring before treatment and then continuously for the first six hours after the first dose, and measurement of blood pressure and heart rate every hour. After six hours, any patients with clinically important heart-related effects, such as bradycardia or atrioventricular block, should continue to be managed and monitored until their condition has improved.

Fingolimod has been authorized in the European Union since March 2011 for the treatment of relapsing-remitting multiple sclerosis in patients whose disease has failed to respond to a beta-interferon or is severe and getting worse rapidly. More than 30,000 patients have received the drug worldwide.

The review was started following reports of heart problems in patients taking filgolimod, as well as the death of one patient in the US less than 24 hours after the first dose. The exact cause of this patient's death is still unexplained. The Committee expects to finalize its review by the time of its plenary meeting in March 2012.

Reference:

(1) FDA Drug Safety Communication, US FDA, 20 December 2011 (www.fda.gov).
(2) Press release, EMA, 20 January 2011 (www.ema.europa.eu).

Modafinil

Review completed

New Zealand. Medsafe completed a safety review of modafinil and concluded that the benefits of treatment outweigh the potential risks when used:

- to improve wakefulness in patients with excessive daytime sleepiness (EDS) associated with narcolepsy;
- to treat EDS associated with moderate to severe chronic shift work sleep disorder (SWSD) where non-pharmacological interventions are unsuccessful or inappropriate;
- as an adjunct to continuous positive airways pressure (CPAP) to treat excessive daytime sleepiness in patients with obstructive sleep apnoea hypopnoea syndrome (OSAHS).

The drug's datasheet is being updated to include more information about the risk of multi-organ hypersensitivity reactions, serious skin reactions, psychiatric disorders, cardiovascular disease, and the potential for dependence.

Medsafe advised health-care professionals that:

- Modafinil treatment should be initiated and supervised by physicians with experience in sleep disorders such as neurologists or respiratory specialists;
- Modafinil is contraindicated for use in pregnancy and is not approved for use in children or adolescents for any indication;
- the development of skin and hypersensitivity reactions, central nervous system, psychiatric and cardiovascular system adverse reactions appears to be related to higher doses of modafinil. Therefore, modafinil should always be started and maintained at the lowest possible dose;
- the effectiveness of oral contraceptives may be impaired in patients receiving modafinil due to the induction of the CYP 3A4 enzyme system;
- PHARMAC currently subsidises modafinil (under special authority criteria) for the treatment of EDS associated with narcolepsy only.

(See WHO Pharmaceuticals Newsletter No. 5, 2010 for a review of the benefits and risks of modafinil in Europe, No. 1, 2011 for restriction of the use to narcolepsy in the UK and No. 6, 2011 for product information update in Australia).

Reference:

Prescriber Update Vol. 32 No. 4, December 2011 (www.medsafe.govt.nz).

Quetiapine

Cardiomyopathy – an emerging safety signal

New Zealand. Medsafe advised that health-care professionals should consider quetiapine as a possible cause in patients presenting with unexplained cardiomyopathy and that Specialist advice should be sought and consideration given to discontinuing quetiapine treatment if cardiomyopathy occurs. The New Zealand quetiapine data sheets are in the process of being updated to indicate that cardiomyopathy has been reported in patients taking quetiapine.

Quetiapine is approved for use in New Zealand for the treatment of acute and chronic psychoses (including schizophrenia), and bipolar affective disorder. Quetiapine is structurally related to clozapine and olanzapine; clozapine has previously been associated with cases of myocarditis and cardiomyopathy.

CARM has received seven reports of cardiomyopathy associated with the use of quetiapine. These reports describe quetiapine being used for depression (3), bipolar disorder (2), and schizophrenia (2). The age range of patients was 20-52 years, and duration of quetiapine use was six months to five years. A total of two reports were confounded (one by clozapine use and one by excessive alcohol consumption) and one patient's symptoms improved despite continuing quetiapine.

According to Medsafe, a biologically plausible mechanism for this association is yet to be confirmed; however some authors have suggested that, as with clozapine, a hypersensitivity myocarditis is the likely mechanism. Quetiapine may also have an indirect effect on the development of cardiomyopathy by causing obesity and diabetes.

Reference:
Prescriber Update Vol. 32 No. 4, December 2011 (www.medsafe.govt.nz).

Selective Serotonin Reuptake Inhibitors

Use during pregnancy and potential risk of persistent pulmonary hypertension of the newborn in the USA; Cases of bleeding in New Zealand

USA (1). The US FDA notified health-care professionals and the public on the use of selective serotonin reuptake inhibitor (SSRI) antidepressants including citalopram (Celexa®), escitalopram (Lexapro®), fluoxetine (Prozac®, Sarafem®, Symbyax®), fluvoxamine (Luvox®, Luvox® CR), paroxetine (Paxil®, Paxil® CR, Pexeva®), sertraline (Zoloft®) and vilazodone (Viibryd®) by women during pregnancy and the potential risk of a rare heart and lung condition known as Persistent Pulmonary Hypertension of the Newborn (PPHN).

PPHN occurs when a newborn baby does not adapt to breathing outside the womb. Newborns with PPHN may require intensive care support including a mechanical ventilator to increase their oxygen level. If severe, PPHN can result in multiple organ damage, including brain damage, and even death.

According to the US FDA, the initial Public Health Advisory in July 2006 on this potential risk was based on a single published study. Since then, there have been conflicting findings from new studies evaluating this potential risk, making it unclear whether use of SSRIs during pregnancy can cause PPHN. The US FDA reviewed the additional new study results and concluded that, given the conflicting results from different studies, it is premature to reach any conclusion about a possible link between SSRI use in pregnancy and PPHN. The US FDA will update the SSRI drug labels to reflect the new data and the conflicting results.

The US FDA advised health-care professionals not to alter their current clinical practice of treating depression during pregnancy.

New Zealand (2). Medsafe reminded health-care professionals that selective serotonin reuptake inhibitors (SSRIs) increase the risk of bleeding, possibly due to altering platelet function. Haemorrhages reported in association with the use of SSRIs include bruising, purpura, epistaxis, and peri-operative, vaginal, and gastrointestinal bleeding. It is also noted that the bleeding risk also applies to Venlafaxine, a Selective Serotonin Noradrenaline Reuptake Inhibitor (SNRI) with similar properties to the SSRIs.

According to Medsafe, the CARM continues to receive reports of bleeds in which SSRIs have been identified as being a co-suspect medicine or may have contributed to the bleed. One such report describes a patient who experienced a subdural haematoma with severe consequences while taking warfarin and an SSRI. Importantly, the patient's INR was found to be within the normal range.

The risk of bleeding appears to be higher when SSRIs are used with other medicines that are known to increase the risk of bleeding, such as anticoagulants and NSAIDs. Combining any SSRI and NSAIDs is thought to result in one in 250 patients experiencing an upper GI bleed if no acid suppressant agent is used.

Health-care professionals are advised to use caution when considering co-prescribing an SSRI with an anticoagulant or NSAIDs. Should an SSRI need to be prescribed with a NSAID, a proton pump inhibitor should also be considered. Medsafe also recommended prescribers to inform patients to closely monitor for signs of bleeding

and to seek urgent advice should this occur.

Reference:
(1) FDA Drug Safety Communication, US FDA, 14 December 2011 (*www.fda.gov*).
(2) Prescriber Update Vol. 32 No. 4, December 2011 (*www.medsafe.govt.nz*).

Somatropin-containing medicines

Positive benefit-risk balance confirmed

Europe. Finalizing its review of somatropin-containing medicines, the CHMP confirmed that the benefit-risk balance of these medicines remains positive. However, the CHMP wished to remind prescribers to strictly follow the approved indications and doses and to carefully consider the warnings and precautions for somatropin-containing medicines.

This review was initiated in December 2010 further to initial results from a long-term epidemiological study in patients treated with somatropin-containing medicines during childhood for idiopathic lack of growth hormone and idiopathic or gestational short stature.

The study results suggested a possibly increased risk of mortality with somatropin therapy compared with the general population. In particular, an increased risk of mortality due to bone tumours and subarachnoid or intracerebral haemorrhage was observed. In addition to the epidemiological study, the CHMP considered all available data on the safety of somatropin-containing medicines in its review, including data from clinical trials, registries, cohorts and from spontaneous reports of side effects, to assess the impact on the overall benefit-risk balance of these medicines.

The CHMP concluded that the study had significant methodological limitations and that the other safety data examined did not corroborate a potentially higher risk of mortality associated with somatropin-containing medicines. Taking into account all available data, the Committee considered that the benefit-risk balance of somatropin-containing medicines remains positive in the approved indications and doses.

The CHMP took the opportunity of this review to harmonize the existing contraindications, warnings and precautions for these medicines throughout the EU. The harmonized wording emphasizes that somatropin must not be used if there is any evidence of a tumour activity, and that the recommended maximum daily dose should not be exceeded. The Committee will review any new important data on the safety of somatropin-containing medicines that may emerge and will communicate the outcome as appropriate.

(See WHO Pharmaceuticals Newsletter No. 1, 2011 for on-going review of somatropin and possible increased risk of death in EU and the USA).

Reference:
Press release, EMA, 15 December 2011 (*www.ema.europa.eu*).

Zolpidem tartrate

Association with complex sleep behaviours

Canada. MEDA VALEANT PHARMA CANADA INC., in consultation with Health Canada, informed health-care professionals of important safety information concerning the association of zolpidem tartrate (Sublinox™) with complex sleep behaviours. The drug is a sublingual formulation of zolpidem that was recently authorized for use in adults in Canada. Zolpidem tartrate is indicated for the short-term treatment and symptomatic relief of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakenings.

On the international market, zolpidem has been reported in association with cases of complex sleep behaviours, where people rise from bed while not fully awake and engage unknowingly in activities which they do not remember doing the following morning, such as driving a car, leaving the house, eating food and making phone calls. Complex sleep behaviours are rare but potentially dangerous.

It is recommended that prescribers should consider the following to ensure appropriate use of this medication:

- Zolpidem tartrate is contraindicated in patients with a personal or family history of somnambulism;
- Zolpidem tartrate is not to be taken with alcohol;
- complex sleep behaviours have been reported in patients using CNS-active drugs in combination with zolpidem;
- treatment with zolpidem tartrate should be immediately discontinued in patients who report complex sleep behaviours.

According to the letter, complex sleep behaviours may be more likely to occur in patients with a personal or family history of sleep-walking, or when zolpidem tartrate is

taken with alcohol or CNS-active drugs or at doses higher than recommended. Some cases of complex sleep behaviours have occurred when zolpidem was taken as directed.

It is also recommended that patients, their families, and caregivers should be counselled on the benefits, risks and appropriate use of zolpidem tartrate. The failure of insomnia to remit after seven to ten days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated. Patient selection is therefore important before prescribing this medication. The drug must be taken no earlier than bedtime and only if patients are expected to remain in bed for a full night's sleep prior to resuming activity and should not be taken in the middle of the night or at any other time than bed time.

Patients should be advised not to exceed the maximum dose of 10 mg for adults. The 10 mg tablet of zolpidem tartrate cannot be split in half and there is no lower strength available for use in the elderly. Zolpidem is not recommended for use in the paediatric population below the age of 18 years.

(See WHO Pharmaceuticals Newsletter No. 2, 2008 for boxed warning added about sleep disorders in Australia).

Reference:

Advisories, Warnings and Recalls, Health Canada, 5 December 2011 (*www.hc-sc.gc.ca*).

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 24).

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.

Saxagliptin and Pancreatitis

Introduction

Saxagliptin is a selective, reversible, competitive, dipeptidyl peptidase 4 (DPP-4) inhibitor.[1] In patients with type 2 diabetes mellitus, administration of saxagliptin leads to inhibition of DPP-4 enzyme activity for a 24 hour period.[1] The drug improves glycaemic control by reducing fasting and postprandial glucose concentrations in patients with type 2 diabetes.[1] DPP-4 inhibitors are recent additions to the list of oral drugs used to treat type 2 diabetes. Sitagliptin and vildagliptin were authorised in the European Union in 2007, saxagliptin in 2009 and linagliptin in 2011. Saxagliptin is indicated as monotherapy, initial combination therapy with metformin or add-on therapy with metformin, sulphonylurea or a glitazone depending on the approving regulatory authority. Common adverse effects (AEs) include infections and infestations such as upper respiratory infection, urinary tract infection, gastroenteritis and sinusitis, gastrointestinal effects such as vomiting, nervous system disorders such as headache, and general disorders such as fatigue.[2] Many AEs reported in clinical trials may have been due to the other component in combination therapy.

Pancreatitis is inflammation of the pancreas, which can be either acute or chronic. Diagnostic criteria include abdominal pain together with increased levels of serum amylase and lipase, and the absence of other causes explaining the symptoms. Acute pancreatitis is most commonly caused by alcoholism and alcohol abuse (30%–60% of cases, 70% in the United States).[3,4] Gallstones is another major cause of this condition accounting for about 15%–30% of cases.[3] Other common causes include hypertriglyceridaemia, hyperparathyroidism, endoscopic retrograde cholangiopancreatography (ERCP), trauma, pancreatic tumours, and surgery (post-abdominal and non-abdominal procedures).[3] Drug-induced pancreatitis is less common, with an incidence of 2%–5% of reported cases of acute pancreatitis in the general population.[3] The estimated time of onset varies highly between and within different groups of drugs, from occurring on the first day of use up to several years later.[5]

Reports in VigiBase™

As of 15 November 2011 there are 55 individual case safety reports (ICSRs) of pancreatitis in association with saxagliptin in the WHO Global ICSR database: VigiBase™. The majority of the cases (49) were added to the database during 2011. The association has a relatively high IC value of 3.63 with an IC_{025} of 3.23 (for further explanation of the IC value and disproportionate reporting see the document available on page 23 at the end of SIGNAL). Two duplicate reports and one cluster of five reports that seems to concern the same patient existed among the reports. The cases were excluded from further analysis, ending up with 49 cases to assess. There are suspicions of a few more duplicates but it is not possible to be certain due to lack of information on the reports. Most of the reports were submitted by the US except for two cases from Germany and one each from the UK, Greece and Austria. The patients ranged in age from 4 to 87 years with a median of 60 years in the 36 cases in which this information was provided. In the 43 cases which provided the information, the gender distribution was relatively even with 24 males and 19 females.

Saxagliptin was the only drug suspected in 30 cases but 14 of these included one or more concomitant drugs. The remaining cases had one or more co-suspected drugs together with concomitant drugs. Co-reported drugs included many of the drugs which might be anticipated in a population being treated for diabetes. These included other antidiabetics such as insulin, metformin or sulfonylureas (in 23 cases), antihypertensives such as ACE inhibitors, beta receptor blockers, angiotensin receptor blockers or calcium channel blockers (21), hypolipidaemics (17), proton pump inhibitors (9), and acetylsalicylic acid (7).

Time to onset was reported in 17 of the reports and ranged from three days to two years with a median of eight weeks. In one of those cases saxagliptin use was discontinued three weeks before reaction onset. One case which provided dates was not included as the therapy stop date preceded the therapy start date. Where mentioned, the indication for saxagliptin use was diabetes mellitus in 25 cases, of which diabetes mellitus was specified as type 2 in nine and type 1 in one. Of the 28 reports in which the outcome was stated, it was recovered or recovering in 23 cases, recovered with sequelae in one case, not recovered in three cases and the outcome was fatal in one case. In the cases where the patient recovered or was recovering (with or without sequelae), saxagliptin was withdrawn in 17 cases.

Literature and Labelling

The product literature does not refer to pancreatitis. In the Australian Public Assessment Report (AusPAR) for saxagliptin, however, it is noted that the Risk Management Plan (RMP) "currently does not include fractures and pancreatitis, as these have only recently been identified as AEs of interest. However, the sponsor committed to updating the RMP before launch of the product to include these two additional AEs".[6] There has been some debate in the literature whether incretin mimetics like GLP-1 analogs (such as exenatide and liraglutide) and DPP-4 inhibitors (such as saxagliptin, sitagliptin and vildagliptin) can cause pancreatitis. Olansky argued against the proposition noting that the incidence of acute pancreatitis is higher in patients with type 2 diabetes.[7] Ward noted that reports of pancreatitis had been received in association with exenatide by both the US Food and Drug Administration (FDA) and the Therapeutic Goods Administration (TGA).[8,9] Sternthal noted that the FDA had received post marketing reports of pancreatitis in association with sitagliptin and the US product information for sitagliptin makes reference to the possibility of this association.[10,11] Pathak and Bridgeman noted that "although there are no data to suggest that pancreatitis is a class effect of these agents at this time, it would be prudent to discontinue saxagliptin as well if pancreatitis is suspected.[12]

Discussion and Conclusion

Case reports in VigiBase™ suggest that there is a signal for the association of saxagliptin and pancreatitis. Many of the cases have saxagliptin as the sole suspected drug, a positive dechallenge and a reasonable time to onset, supporting a signal. Confounders such as the underlying diabetes and concomitantly used medicines may however have a role in the development of pancreatitis as well.

There have been a significant number of reports to the UMC during the last year (2011) and the statistical significance (IC) is high. However, the total number of 49 cases is relatively low when the total numbers of reports of pancreatitis forwarded to the UMC is considered. For example, there have been over 1000 reports in association with four drugs (quetiapine; 3331, exenatide; 1620, olanzapine; 1401, valproate; 1276) and there are many other drugs with many hundreds of reports. Included in these are sitagliptin (498) and liraglutide (262). Compared to these drugs, saxagliptin has been marketed for only a short time and it is likely that pancreatitis is a class effect of DPP-4 inhibitors.

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Response from MAH regarding a signal between Saxagliptin therapy and Pancreatitis

Introduction

This document is being prepared in response to the WHO signal based on the review of case reports of pancreatitis in VigiBase as of November 15 2011. The signal describes a patient safety concern for an association between saxagliptin and pancreatitis and is expected to be published in the next issue of the WHO signal document.
This response addresses the labelling aspects and will focus on providing information with regard to RMP strategy on pancreatitis. In addition, the Marketing Authorization Holder (MAH) acknowledges the data described in the WHO draft signal document.

Response

The MAH has continued to monitor all the adverse events of pancreatitis as part of its safety surveillance process for saxagliptin. All post-marketing cases of pancreatitis have been submitted as expedited 15 day reports regardless of whether these reports are classified as serious, unexpected or related. Pancreatitis has been categorized as an important potential risk in the global RMP version 6 dated 29 June 2010 and was initially added to the RMP based on the post marketing experience from other DPP4 inhibitors. Pancreatitis is being further evaluated as secondary safety objective in the SAVOR cardiovascular (CV) outcomes trial. In addition, enhanced safety surveillance is in place based on targeted questionnaires for spontaneous reports and supplemental case report forms in the CV outcomes trial. As part of signal detection and evaluation, periodic Multi-item Gamma Poisson Shrinker (MGPS) analysis of post marketing surveillance database including Adverse Event Reporting System (AERS) and Vigibase are also conducted on an ongoing basis.

Current status on EU and US labeling for Onglyza and Kombiglyze XR/Komboglyze

USPI

In August 2011, the FDA's Office of Surveillance and Epidemiology (OSE) noted a pancreatitis safety signal during an AERS Database review. Based on this information, the FDA requested a change to the United States Package Inserts (PI) for Onglyza (saxagliptin) and Kombiglyze XR (saxagliptin/metformin) regarding pancreatitis and the Company received acceptance of the proposed PI changes on November 15, 2011. The Warnings and Precautions section for both products were updated to include the following text: There have been post-marketing reports of acute pancreatitis in patients taking ONGLYZA. After initiation of ONGLYZA, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, ONGLYZA should promptly be discontinued and appropriate management should be initiated. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using ONGLYZA.

EU SmPC

The Marketing Authorization for Komboglyze (saxagliptin/metformin) was granted on 24 November 2011 and the SmPC includes information regarding pancreatitis in sections 4.4 Special warnings and precautions for use, and 4.8 Undesirable effects. The Onglyza SmPC is being updated regarding pancreatitis for sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects. The CHMP opinion was on 17 November 2011 and the European Commission Decision is pending.
Based on the recent review of post-marketing reports of pancreatitis with saxagliptin of spontaneous origin, the MAH is in the process of updating the Company's Core Data Sheet (CCDS) with inclusion of pancreatitis, which will result in subsequent updates to labelling in all markets worldwide. Accordingly, the global RMP will be updated to reflect pancreatitis as an important identified risk

Venlafaxine, pre-eclampsia, eclampsia and related disorders of pregnancy

Introduction

Venlafaxine is an antidepressant agent that inhibits re-uptake of serotonin and noradrenaline (SNRI). It is indicated for the treatment of major depression, generalized anxiety disorder, social anxiety disorder and panic disorder.

Pre-eclampsia is defined as the new onset of hypertension (blood pressure >140/90 mmHg) and proteinuria (>300 mg/24 h) after 20 weeks of gestation. The pathophysiology is not well understood but endothelial and renal glomerular functions are disrupted resulting in oedema, hypertension and proteinuria. Pre-eclampsia is associated with abnormalities of cerebral circulatory auto regulation which increase the risk of stroke at near-normal blood pressures. Severe pre-eclampsia is the presence of new-onset hypertension and proteinuria accompanied by end organ damage.[1] Eclampsia refers to the development of grand mal seizures in a woman with gestational hypertension or pre-eclampsia.[2] The HELLP syndrome of haemolysis, elevated liver enzymes and low platelets is a special subgroup of severe pre-eclampsia and is a major cause of morbidity and mortality in this disease.

Approximately 5-7% of all pregnant women develop pre-eclampsia. Risk factors for its development include nulliparity, diabetes mellitus, a history of renal disease or chronic hypertension, a prior history of pre-eclampsia, extremes of maternal age (>35 years or <15 years), obesity, antiphospholipid syndrome and multiple gestation.[1]

Reports in VigiBase™

Since the combination of venlafaxine and eclampsia in the WHO Global Individual Case Safety Report (ICSR) database, VigiBase™, has recently become statistically prominent and the venlafaxine/pre-eclampsia combination is also prominent, the reports for eclampsia and pre-eclampsia were clinically assessed to establish if there was evidence for a causal association with venlafaxine. Reports for gestational hypertension and two reports of HELLP syndrome associated with venlafaxine in pregnant patients were also examined.

Thirty-one reports of pregnancy-related hypertensive disorders were identified as shown in Table 1.

Table 2 shows the reports in more detail. Mean ages were consistent with the fact that older age is a risk factor although three patients aged between 20 and 28 years were affected. The 20 year old also had type 2 diabetes mellitus which is a risk factor for pre-eclampsia. Daily doses, documented for 25 patients ranged from a very low dose of 9.375 mg daily to 300 mg (mean 154 mg) at the time of onset of the pregnancy-related hypertensive disorders. Seven of the 25 patients had reduced venlafaxine dose during pregnancy. The patient taking 9.375 mg daily remained on this dose because of withdrawal symptoms.

The duration of use (recorded in 16 patients) ranged from 19 days to several years. These patients could be grouped into those who took venlafaxine throughout pregnancy and had taken it for more than one year (11 patients), and those who started it just prior to or early in pregnancy and took it until or beyond the onset of the hypertensive event. The stage of pregnancy at which exposure occurred could not be established for the other patients.

In only five reports were other medicines also regarded as suspects. These are listed in Table 2. However, methyldopa is unlikely to be suspect as it has been used to treat hypertension in pregnancy for many years. It is not possible to exclude the other suspect medicines as potential causes of the hypertensive disorders. Other medicines also taken during pregnancy, but not considered suspect by the reporters, included another SSRI (sertraline), buspirone, olanzapine, amitriptyline, cyclobenzaprine, alimemazine, cetirizine, bupropion, lorazepam and a drug for acid-related disorders. These were taken by six patients. Several patients also took vitamin and mineral supplements and/or short courses of antibiotics.

Three patients were taking antihypertensive agents (one for preeclampsia, one for essential hypertension and one had no indication). No data was provided to identify if these women were already hypertensive. Other relevant adverse drug reactions (ADRs) reported included premature labour and births which are known consequences of pre-eclampsia. Since pre-eclampsia and eclampsia can be life-threatening or fatal and patients usually recover on delivery the number of caesarian sections is not unexpected. Serious consequences of pre-eclampsia with end-organ damage are illustrated in the reports of pulmonary oedema and hepatic failure. The patient with gestational hypertension and leg oedema had experienced these events towards the end of a previous pregnancy when she was not taking venlafaxine but the events occurred much earlier in the subsequent pregnancy reported here.

In the majority of patients the indications for venlafaxine were depressive or anxiety disorders

or both. Outcome was recorded for 17 patients and all of these recovered. No dechallenge data was provided.

Literature and Labelling

A retrospective cohort study of 5731 women with non-malformed infants who participated in the Slone Epidemiology Center Birth Defects study found a significantly increased risk of gestational hypertension in patients who used selective serotonin re-uptake inhibitors (SSRIs) during pregnancy compared with those who did not (adjusted relative risk 1.90; 95% CI 1.35-2.67). The increased risk was greatest for those who went on to develop pre-eclampsia, especially if they continued SSRIs beyond the first trimester. However, the number of cases was small in these subgroup analyses.[3]

In a prospective study of 3494 women by Magnussen et al 3.8% developed pre-eclampsia and the odds ratio (OR) was increased for women with a systolic blood pressure >130 mmHg compared with a systolic blood pressure <111 mmHg (OR 7.3; 95% CI 3.1-17.2) and a similar difference was found between diastolic blood pressures of >78 mmHg and <64 mmHg.[4] In pre-marketing trials of venlafaxine in the treatment of depression 0.7% of patients discontinued treatment because of increased blood pressure and in most of these the increase was in the order of 12-16 mmHg. In generalized anxiety disorder trials the increases were in the range 12-25 mmHg in the 0.7-1.3% of patients who discontinued the treatment.[5]

Discussion

There is a limited possibility to assess causality of pregnancy-related disorders. There was no record of venlafaxine being discontinued during pregnancy without delivery. There is therefore no data on dechallenge outcome since patients usually recover from pregnancy-related hypertensive disorders on delivery. There is however some evidence of biological plausibility and some supporting data concerning SSRIs and gestational hypertension from the Slone Epidemiology Center Birth Defects study by Toh et al which lend weight to a causal role for venlafaxine.[3] In this study 2.4% of the women (135 patients) not exposed to SSRIs developed pre-eclampsia compared with 9% (18 patients) who were exposed. Using Cox proportional hazards model the adjusted relative risk was greatest for the 14 women who took venlafaxine throughout pregnancy (4.86; 95% CI 2.70-8.76) and not significantly increased if venlafaxine was discontinued by the end of the first trimester. The information in the Vigibase reports is consistent with this finding as most of the patients for whom dates were documented took venlafaxine throughout pregnancy.

Toh et al discussed other studies that showed an increased risk of pre-eclampsia in women who had depressive and anxiety disorders which is another explanation for these findings. However these studies did not distinguish between medication and illness effects. Toh et al therefore looked at the relative risk for patients taking non-SSRI antidepressants and found that the percentage of women developing pre-eclampsia was greater than baseline but not significantly so. This could indicate the contribution of depression and anxiety to the pre-eclampsia. This non-SSRI antidepressant user group did include women taking SNRIs but the numbers were too small to draw conclusions. It is not clear how SSRIs or SNRIs might induce or exacerbate pregnancy-related hypertensive disorders but Toh et al suggested that an effect on maternal haemodynamics is most likely if there is an association since in their study there was no increase in risk in patients who only took SSRIs in early pregnancy when placentation occurs.[3] Chronic hypertension is a risk factor but documentation of pre-existing hypertension was absent in the VigiBase™ reports although three women received antihypertensive treatment. However venlafaxine has been found to induce a dose-dependent increase in blood pressure with some patients developing sustained hypertension.[5]

In pre-marketing trials of venlafaxine in the treatment of depression 0.7% of patients discontinued treatment because of increased blood pressure and in most of these the increase was in the order of 12-16 mmHg. In generalized anxiety disorder trials the increases were in the range 12-25 mmHg in the 0.7-1.3% of patients who discontinued treatment.[5] Elevations of this order may not necessarily lead to treatment and may have been masked in the second trimester by maternal vasodilatation. However, they may be important in contributing to pre-eclampsia when Magnussen's study is considered.[4]

Some features of the reports do not support a causal role for venlafaxine. As expected with pregnancy-related hypertensive disorders most of the women were older, there was no unexpected effect on younger women. Also these disorders still occurred even when there were significant dose reductions in venlafaxine. The youngest patient had type 2 diabetes mellitus at a surprisingly young age and this is likely to have been the main determinant in the development of pre-eclampsia for her. The patient who had developed some features of pre-eclampsia towards the end of her first pregnancy was therefore at increased risk of pre-eclampsia in the second.

Conclusion

It appears that there is a need to conduct more formal studies of venlafaxine and other SNRIs in pregnancy so that there is better information on which to base consideration of the risks and expected benefits. In the interim, if a decision is made to continue venlafaxine throughout pregnancy, the evidence from this case series together with the documented potential of venlafaxine to cause hypertension and the possible association between SSRIs and pre-eclampsia, suggest that consideration should be given to the role of venlafaxine if gestational hypertension with or without pre-eclampsia develops.

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Table 1. Number of reports, statistical prominence and number of countries reporting eclampsia, pre-eclampsia and related disorders in association with venlafaxine use in VigiBase™.

ADRs reported (MedDRA Preferred terms)	No. of reports	Total reports of venlafaxine	Total reports of ADR	No. of countries	IC	IC_{025}
Eclampsia	4	31,187	139	3	1.96	0.22
Pre-eclampsia	21 (one duplicate)	31,187	683	9	2.53	1.84
Gestational hypertension	6 (1 pt also had pre-eclampsia)	31,187	155	2	2.40	1.02
HELLP syndrome (pregnancy-related)	2	31,187	125 (not all pregnancy-related)	2	1.69	-0.36

Table 2. Details of reports of eclampsia, pre-eclampsia and related disorders in association with venlafaxine use in VigiBase™.

	Age	Venlafaxine sole suspect	Dose (mg)	Duration of use	Other suspect medicines	Other relevant ADRs reported (MedDRA Preferred Terms)	Outcome
Eclampsia (4)	2 pts 34, 36 yrs	3 pts	2 pts 37.5 – 150 mg Dose reduction during pregnancy (2 pts)	1 pt 5 yrs	1 pt Methyldopa	Antepartum haemorrhage (1 pt), Caesarean section (2 pts)	Recovered (4 pt)
Pre-eclampsia (20)	17 pts 20-38 yrs Mean 31 yrs	18 pts	16 pts 18.75 – 300 mg Mean 170 mg; Dose reduction during pregnancy (2 pts)	12 pts >1yr (8 pts); 7-10 m (3 pts); 19 days during pregnancy (1 pt);	2 pts Bupropion (1pt), Lamotrigine (1pt)	Caesarian section (4 pts) Premature baby (4 pts) (with low birth weight (1 pt)) Premature labour (twins) (1 pt) Premature separation of placenta (1 pt) Uterine rupture (1 pt) Hepatic failure (1 pt) Gestational hypertension (1 pt) Headache (1 pt) Drug ineffective (1 pt) Anxiety (1 pt) Convulsion neonatal (1 pt)	Recovered (11 pts), Not stated or Unknown (9 pts)
Gestational hypertension (5) (one other in pre-eclampsia section, with hepatic failure)	3 pts 28-37 yrs Mean 32 yrs	3 pts	5 pts 9.375 – 300 mg Mean 144,5 mg Dose reduction during pregnancy (2 pts)	2 pts 7 mths, 15 mths	2 pts Topiramate+ quetiapine+ citalopram (1 pt), Ethanol (1 pt)	Oligohydramnios (1 pt), Induced labour (1 pt), Drug withdrawal syndrome (2 pts), Pulmonary oedema (1 pt), Caesarian section (2 pts), Premature labour (1 pt), Uterine hypotonus (1 pt), Oedema peripheral (lower limb) (1 pt), Premature rupture of membranes (1 pt)	Recovered (1 pt) Not stated or Unknown (4 pts)
HELLP syndrome (2)	2 pts 25, 28 yrs	2 pts	2 pts 75 mg – 150 mg Dose reduction during pregnancy (1 pt)	1 pt 4 - 5 yrs	None	Glucose tolerance impaired in pregnancy (1 pt), Premature labour (1 pt), Cervical incompetence (1 pt), Caesarian section (2 pts)	Recovered (1 pt), Unknown (1 pt)

Pt/pts = patient/patients Yr/yrs = years Mth/s = month/months

The UMC Measures of Disproportionate Reporting
A brief guide to their interpretation

The Information Component (IC)

The Information Component (IC), originally *introduced through the BCPNN (Bayesian Confidence Propagation Neural Network), is a measure of the disproportionally between the observed and the expected reporting of a drug-*ADR pair. A positive IC value indicates that a particular drug-ADR pair is reported more often than expected, based on all the reports in the database. Similarly, a negative IC value means that the drug-ADR pair is reported less frequently than expected. The higher the value of the IC, the more the combination stands out from the background. The IC value is solely calculated from:

- the total number of reports in the database (N_{tot})
- the total number of reports on the ADR term (N_{adr})
- the number of reports on the drug (N_{drug}), and
- the total number of reports on the specific drug-ADR pair (N_{comb}).

New reports may cause the IC to either increase or decrease. When the IC is calculated from large numbers, a new report is less likely to cause a major fluctuation in the IC value. The IC025 value is the lower limit of a 95% credibility interval for the IC. The credibility interval provides information about the stability of a particular IC value: the narrower the interval, the higher the stability. The IC does not imply causality of a potential adverse reaction caused by a drug. The IC shows the quantitative dependency between the ADR and the drug, based on the reporting to the WHO Global ICSR database. If the IC value increases over time and the IC025 value is positive, this is suggestive of a connection between the drug and the adverse reaction. However as alternative explanations for the positive IC need to be considered, clinical assessment remains essential in the identification of a signal.

Omega (Ω)

Omega (Ω) is, just as the IC, a measure of disproportionate reporting, however not for a drug-ADR pair but for a drug-drug-ADR triplet. The purpose of Ω is to detect potential signals of drug-drug interactions. For Ω, the expected reporting on a drug-drug-ADR triplet is based on a model where both drugs add to the baseline risk of the ADR, independently of each other. A positive Ω indicates that the two drugs, when used together, increase the risk of the ADR more than the sum of the risks attributable to each drug separately.

Ω is calculated based on the following information:

- the relative reporting rate of the ADR for reports listing neither of the drugs (f_{00})
- the relative reporting rate of the ADR for reports listing drug 1 but not drug 2 (f_{10})
- the relative reporting rate of the ADR for reports listing drug 2 but not drug 1 (f_{01}), and
- the relative reporting rate of the ADR for reports listing both drugs (f_{11}).

As the IC, Ω may fluctuate over time as new reports enter the database. Also like the IC, each Ω comes with a 95% credibility interval, whose lower limit is denoted Ω_{025}. Ω does not imply causality of a potential drug-drug interaction. It is a quantitative measure of the deviation in reporting on the drug-drug-ADR triplet relative to a baseline model where the drugs are assumed to independently add to the baseline risk of the ADR. If Ω increases over time and Ω_{025} is positive, this is suggestive of a drug-drug interaction, based on the reporting to the WHO Global ICSR database. However, as alternative explanations for the positive Ω need to be considered, clinical assessment of the case series is essential in the identification of an interaction signal.

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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.

Thirty-fourth annual meeting of representatives of national centres participating in the WHO Programme for International Drug Monitoring

30 October - 2 November 2011

The thirty-fourth annual meeting of representatives of national pharmacovigilance centres participating in the WHO Programme for International Drug Monitoring was held 31 October - 2 November 2011, at Dubrovnik, Croatia. The meeting included eight working groups that discussed various issues in pharmacovigilance. The summary of discussions and / or recommendations from each working group are presented here.

Assessing the preventability of medicines-related problems

The 'P method' was developed in the context of the Monitoring Medicines (MM) project (www.monitoringmedicines.org), to identify preventable adverse drug reactions (ADRs) in pharmacovigilance (PV) databases and to assist health care providers in taking necessary measures to minimize medication errors (ME). The method consists of 20 criteria, which are specific questions that help classify whether an ADR is a "preventable", "non preventable" or a "not assessable" case.

Within this working group, discussions were held on the use of the P method in assessing the preventability of ADRs. Discussions centred on the applicability and efficacy of the P method in preventing MEs, and recommendations for using the method more effectively, including the harmonization of various terms and the development of a guideline on the use of the method.

Optimizing communications between national PV centres (e.g., through VigiMed)

National PV centres communicate with each other to effectively share and discuss safety data on particular medicines, and on regulatory decisions. Many national centres use VigiMed (the information exchange forum managed by the Uppsala Monitoring Centre, the UMC), along with other forms of communication. National centres share PV information also through formal agreements and contracts, through informal interaction, e.g. through links from training programs, and through their websites. VigiMed appears to be the most commonly used and preferred form of informal communication among the participants. Problems and challenges in regard to the new version of VigiMed include: the time taken to familiarize with the current (new) version, the need to login with a password, the lack of criteria, e.g. priority of posts, repetition of issues over time. The group recommended an easier access to the official VigiMed website; information on unregistered and withdrawn drugs; establishing a search-friendly index of issues or topics with links to other documents; and using medical translator for documents. The UMC was requested to provide quick tips on the use of VigiMed and to include the function to "flag" topics of high priority, provide a linked access to PV bulletins and reports, continue monitoring experiences with VigiMed (data on use and users).

Involving traditional medicine (TM) practitioners in pharmacovigilance

In many countries across the world, particularly in Asia, Americas and Africa, a significant portion of the population has relied on traditional medicines to meet their health needs, especially in the context of primary health care. Traditional medicines, such as herbal medicines, are highly lucrative in the international marketplace, but are subject to adulteration and counterfeiting, posing serious threat to patient safety. There is a strong need to expand the scope of PV, to include traditional medicines, while strengthening effective national regulatory and quality assurance measures, so that health risks due to such medicines can be prevented.

This working group discussed various issues surrounding traditional medicines, identified the major challenges, proposed solutions, and recommended an approach to incorporate these medicines into PV practices, including the creation of a task force for traditional medicines in national pharmacovigilance centres, necessary education and training for TM practitioners, enhanced communication between physicians and TM practitioners, such as herbalists, and training TM practitioners to report ADRs and other information

How to demonstrate impact of pharmacovigilance activities

Pharmacovigilance systems collect reports, ensure quality of reports, detect and evaluate signals and implement measures based on findings from analyses (e.g. label changes). Measuring the impact of PV systems on public health is necessary for increasing awareness of drug safety and stakeholders involvement, and making critical decisions on resource use and allocation. This working group held discussions on how the impact of PV activities on health can be measured. Discussions centred on potential indicators, their relevance and ease of use. The group identified possible indicators (from the least relevant / easiest to measure, to the most relevant / difficult to measure) as: number of ADR reports of adverse drug reactions, quality of reports, number and percentage of signals that lead to action, assessment of knowledge, change in prescription volume, change in prescription patterns and actual patient outcome.

Improving safety information to patients and their carers (parents, partners, etc.)

Effective communication of drug safety information to patients and their care takers is crucial for making informed decisions about medicines and managing risks involved with use of medicines. This working group discussed the tools and options that are available, and ways to improve the use of these to improve communication between health care practitioners and patients. The group recommended that education related to drug safety should start at an early age, e.g. in schools; relevant information should be provided to the public through radio programme, short films etc; there needs to be face to face communication, between health care practitioners and patients on medicines safety; information sheets, pictograms and various visual tools that target different sub-populations of the public should be developed; and such materials should be adjusted to country, culture, life-style, accessibility to media and specific patient characteristics.

Experiences in using documentation grading statistics to improve data quality

Documentation grading is a system, developed at UMC over the last year, for measuring the amount of information provided on Individual Case Safety Reports (ICSRs) as they appear in VigiBase (the WHO ICSR database). Secondary, the more information a report contains, the more useful it usually is for e.g. signal analysis. Documentation grading is also used to identify any problems in the data of the reports received at UMC. This working group held discussions on the effective use of documentation grading statistics in enhancing the quality of reports, enhancing feedback from UMC to NCs on the quality and improving drug safety. When a report is received, the data will be assessed for "completeness" A 'completeness score' from 0 to 1 is generated for each report using an algorithm of the following criteria: age and gender, time of onset, age at onset, primary source and drug start date. A 'completeness' score is a quantitative measure and is calculated as a mean of the scores for each drug-ADR combination. "Relevance," a new parameter that is still under development by the UMC, is a qualitative measure that aims to identify information that may strengthen causal associations between a drug and an ADR in ICSRs.

The following suggestions were made in regard to improving documentation grading statistics: include more criteria in reports, such as information on the reporter and sender, causality, medical history, action taken, concomitant drugs, medical confirmation, follow up and senders' comments; establish different criteria for vaccines and include information on batch number, dose number; implement a policy so that results are received twice a year; incorporate documentation grading statistics into VigiLyze.

The group recommended that, in order to enhance ICSR quality, it was important to decide what information is unnecessary, make appropriate improvements to reporting forms; identify technical problems in extraction of data; improve educational materials and define target groups for training; assess impact of activities by comparing grading results from different periods and by evaluating the impact of the quality of reports in producing signals.

Future role of Periodic Safety Update Reports (PSURs): requirements for generic manufacturers

This working group discussed the European (EU) and other legislations on PSURs and their consequences, PSUR obligations in low- and middle-income countries, who is responsible for PSURs, and problems and challenges concerning PSURs for generic medicines. Of the 23 countries represented in the group, 14 have established requirements for PSURs for generic products, with the majority harmonized with EU legislations; three countries are in the process of developing requirements; and no requirements exist in four countries. In two countries, older requirements for other types of periodic reports that are not PSURs exist. The quality of generic pharmaceutical manufacturing and the regulatory and inspection resources vary widely among countries, some countries need generic PSURs as a "safety net"; but reviewing PSURs is time consuming and the volume of work can be a real challenge when agencies do not have enough staff and other resources. With regard to work load, the group considered the European model of collective (reciprocal) reviews and work-sharing; reviewing the entire PSUR for new products but only the executive summary and table of contents for generic products. But in general the group agreed that generics manufacturers should not be exempt from submitting PSURs.

Integrating national pharmacovigilance and public health programmes

Efforts have been made, especially in resource-limited countries, to integrate national PV and public health programmes (PHPs). Closing the gap between PV and PHPs can yield benefits for both sides and the country. PV capacity may be improved and a monitoring system may be established through PHPs, if this is lacking in the country. PHPs can benefit by regularly receiving information on ADRs of drugs used in the programmes, which can lead to improvements in patient safety. National PV centres and PHPs, thus, need each other. The members of the working group discussed how to integrate pharmacovigilance and public health programmes. The shared their experience and proposed a model for integration. It was stressed that each country has specific needs, so one model wouldn't fit all. It is important to establish a legal framework and clarify the roles and responsibilities of the various stakeholders, across PV centres and PHPs, for information sharing, training and capacity building, technical support and communication and feedback.