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:

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

Further information on adverse reactions may be obtained from the WHO Collaborating Centre for International Drug Monitoring
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The WHO Pharmaceuticals Newsletter provides you with the latest information on the safety of medicines and legal actions taken by regulatory authorities across the world. It also provides signals based on information derived from Individual Case Safety Reports (ICSRs) available in the WHO Global ICSR database, VigiBase®.

The Summary of Recommendations from the Twelfth Meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) is included as a feature item together with a small article from the Food and Drugs Authority in Ghana on patient reporting of adverse reactions.

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Abiraterone acetate

Risk of fulminant hepatitis and hepatic failure

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced the revision of the package insert for abiraterone acetate (Zytiga®) to include risk of fulminant hepatitis and hepatic failure.

Abiraterone acetate is indicated for castration-resistant prostate cancer.

The MHLW/PMDA stated that cases of fulminant hepatitis or hepatic failure have been reported in patients treated with abiraterone acetate in Japan.

Based on expert advice and available evidence, the MHLW/PMDA have recommended the addition of the description on the risk of fulminant hepatitis and hepatic failure to the information on hepatic function disorder in the section of "Important precaution" and to the subsection of the "Clinically significant adverse reactions" in the section of "Adverse reactions" in the package insert.

Reference:
Revision of Precautions, MHLW/PMDA, 7 July 2015 (www.pmda.go.jp/english/)

Adefovir pivoxil

Risk of fracture

Japan. The MHLW and the PMDA have announced the revision of the package insert for adefovir pivoxil (Hepsera®) to include risk of fracture.

Adefovir pivoxil is indicated for the inhibition of hepatitis B virus replication in type B chronic liver disease in which abnormality of liver function with replication of hepatitis B virus is confirmed.

The MHLW/PMDA stated that cases of fractures have been reported in patients treated with adefovir pivoxil in Japan.

Based on expert advice and available evidence, the MHLW/PMDA have recommended adding risk of fracture to the section of "Important precautions" and to the subsection of the "Clinically significant adverse reactions" in the section of "Adverse reactions" in the package insert.

Reference:
Revision of Precautions, MHLW/PMDA, 7 July 2015 (www.pmda.go.jp/english/)

Anagliptin

Risk of intestinal obstruction

Japan. The MHLW and the PMDA have announced the revision of the package insert for anagliptin (Suiny®) to include risk of intestinal obstruction.

Anagliptin is indicated for type 2 diabetes mellitus.

The MHLW/PMDA stated that cases associated with intestinal obstruction have been reported in patients treated with anagliptin in Japan.

Based on expert advice and available evidence, the MHLW/PMDA have recommended the addition of "Patients who have a history of abdominal surgery or intestinal obstruction" to the section of "Careful administration" in the package insert and the addition of the following texts to the subsection of the "Clinically significant adverse reactions" under "Adverse reactions" in the package insert.

Reference:
Revision of Precautions, MHLW/PMDA, 7 July 2015 (www.pmda.go.jp/english/)

Intestinal obstruction:
Intestinal obstruction may occur. Patients should be carefully monitored. If any abnormalities such as severe constipation, abdominal distension, sustained abdominal pain, or vomiting are observed, administration of this drug should be discontinued, and appropriate measures should be adopted.

Asunaprevir and daclatasvir hydrochloride

Risk of hepatic failure

Japan. The MHLW and the PMDA have announced the revision of the package insert for asunaprevir (Sunvepra®) and daclatasvir hydrochloride (Daklinza®) to include risk of hepatic failure.

Asunaprevir and daclatasvir hydrochloride are used for improvement of viraemia in patients with serogroup 1 (genotype I) chronic hepatitis C or compensated cirrhosis type C.

The MHLW/PMDA stated that cases of decreased hepatic residual function such as decreased albumin level, prolonged prothrombin time, ascites, hepatic encephalopathy, and those resulting in hepatic failure have been reported in patients treated with asunaprevir and daclatasvir hydrochloride in Japan.

Based on expert advice and available evidence, the MHLW/PMDA have recommended the addition of an alert on decreased hepatic residual function to the
subsection relevant to "the assessment of hepatic function" in the section of "Important precautions" and the addition of hepatic failure to the subsection of the "hepatic function disorder" in the section of "Clinically significant adverse reactions section" in the package insert.

Reference:
Revision of Precautions, MHLW/PMDA, 7 July 2015 (www.pmda.go.jp/english/)

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Crizotinib

**Risk of cardiac failure**

**Japan.** The MHLW and the PMDA have announced the revision of the package insert for crizotinib (Xalkori®) to include risk of cardiac failure.

Crizotinib is indicated for Anaplastic lymphoma kinase (ALK)-positive, unresectable, advanced or relapsed non-small-cell lung cancer.

The MHLW/PMDA stated that cases of cardiac failure have been reported in patients treated with crizotinib in Japan.

Based on expert advice and available evidence, the MHLW/PMDA have recommended the addition of the following texts to the subsection of the "Clinically significant adverse reactions" in the section of "Adverse reactions" in the package insert

Cardiac failure:
Cardiac failure may occur. Patients should be carefully monitored. If the fluid retention (pulmonary oedema, pleural effusion, pericardial effusion, etc.), rapid increased weight, cardiac failure symptoms (shortness of breath, dyspnoea, oedema, etc.) are observed, appropriate measures such as drug suspension, dose reduction, or discontinuation of administration, should be adopted.

Reference:
Revision of Precautions, MHLW/PMDA, 2 June 2015 (www.pmda.go.jp/english/)

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Denosumab

**Further measures to minimise risk of osteonecrosis of the jaw**

**UK.** The Medicines and Healthcare Products Regulatory Agency (MHRA) has reminded health-care professionals to advise patients to take precautionary measures to minimise the risk of osteonecrosis of the jaw (ONJ) in patients taking denosumab and intravenous bisphosphonates.

Denosumab and bisphosphonates are used to treat osteoporosis, Paget's disease, and as part of some cancer regimens, particularly for metastatic bone cancer and multiple myeloma. Individual bisphosphonates and denosumab-containing medicines have different indications (information available in the summary of product characteristics (SmPC) of the medicine in question).

The advice follows a review conducted by MHRA and other EU medicines regulators. Patients should be advised to: maintain good oral hygiene, attend routine dental check-ups and immediately report any oral symptoms such as dental mobility, pain, or swelling to a doctor and dentist before being prescribed oral bisphosphonates. Further recommendations include: introducing patient reminder cards for denosumab and intravenous bisphosphonates, to inform patients of the risk of ONJ and precautions to take before and during treatment; denosumab 120 mg should be contraindicated in patients with

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Dimethyl fumarate

**Risk of serious allergic reactions including skin reactions and anaphylaxis**

**Canada.** Canadian prescribing information for dimethyl fumarate has been updated to inform prescribers and patients of hypersensitivity reactions, including angioedema and anaphylaxis. However, following a safety review, Health Canada has concluded that the overall benefits of dimethyl fumarate (Tecfidera®) continue to outweigh the risks if used as recommended.

The Canadian prescribing information was also updated to mention that the possibility of hypersensitivity or anaphylactic reactions should be considered in patients experiencing severe flushing reactions (e.g. flushing, hot flushes, warmth, redness, itching, and/or burning sensations). These symptoms may present similarities with hypersensitivity reactions.

Dimethyl fumarate is used to reduce the number of flare-ups (relapses) and slow the progression of physical disability in multiple sclerosis.

At the time of this review, Health Canada considered the evidence provided in both domestic (nine reports) and international reports (five reports), including those
Ethinylestradiol/etonogestrel vaginal ring

**Thromboembolic risk**

**Australia.** The Therapeutic Goods Administration (TGA) has advised health-care professionals that the Product Information for ethinylestradiol/etonogestrel vaginal ring (NuvaRing®) has been updated to provide further information about thromboembolic risks.

Ethinylestradiol/etonogestrel vaginal ring is a contraceptive ring for vaginal use, which releases ethinylestradiol and etonogestrel over a period of three weeks.

While ethinylestradiol/etonogestrel vaginal ring is delivered vaginally, the active ingredients are the same as combined hormonal oral contraceptives, and the risks of arterial and venous thromboembolism (ATE and VTE) are similar for all of these products. It is possible that the risk of VTE may also increase with the presence of superficial thrombophlebitis and varicose veins.

Ethinylestradiol/etonogestrel vaginal ring should not be used in the presence of any of the following conditions:

- Presence or history of ATEs or VTEs, such as deep venous thrombosis, pulmonary embolism or myocardial infarction, or of a cerebrovascular accident.
- Known predisposition for ATE or VTE.
- Presence or history of prodromi of a thrombosis, for example transient ischaemic attack or angina pectoris.
- History of migraine with focal neurological symptoms.
- Diabetes mellitus with vascular involvement.

Presence of severe or multiple risk factor(s) for ATE or VTE may also constitute a contraindication.

If any of the above conditions appear for the first time during the use of ethinylestradiol/etonogestrel vaginal ring, it should be removed immediately.

**Reference:**

**Ferumoxytol**

**Risk of serious allergic reactions**

**Canada.** Health Canada has announced that the Canadian prescribing information for ferumoxytol (Feraheme®) has been updated with advice to avoid giving ferumoxytol in patients with a history of drug allergies, and on how it should be given to reduce the risk of serious hypersensitivity reactions.

Health Canada issued both a health-care professional and a public communication stating limitations for ferumoxytol use. Ferumoxytol should not be used in patients with allergies to injectable iron products or with multiple drug allergies. Another communication for health-care professionals was issued with advice on how to minimise the risk of serious hypersensitivity reactions during ferumoxytol administration.

Ferumoxytol is an injectable iron product used to treat low levels of iron in the blood (iron deficiency anaemia) in adults with chronic kidney disease.

This advice follows a safety review conducted to determine if current strategies to minimize the risk were sufficient.

As of February 28, 2014, there were more than 20 Canadian reports of serious hypersensitivity reactions, including 2 deaths, received through the Canada Vigilance Program. Over half were reported in a 6 month period.

Many of the international cases of serious or fatal hypersensitivity reactions reported with ferumoxytol, also documented patients as having allergies to other medicines.

**Reference:**

**Fusidic acid and HMG-CoA reductase inhibitors**

**Risk of rhabdomyolysis by drug-drug interaction**

**Ireland.** The Health Products Regulatory Authority (HPRA) has stated that cases of
rhabdomyolysis (including some with a fatal outcome) suspected to be due to an interaction between fusidic acid and a HMG-CoA reductase inhibitor (collectively known as “statins”) have been reported to the HPRA and other European medicines agencies. The exact mechanism for this interaction is unknown and therefore may occur with some, or all, statins. The product information for systemic fusidic acid indicates that concomitant treatment with statins is contraindicated, while the product information for the individual statins highlights the need to temporarily discontinue statin therapy when treatment with fusidic acid is considered essential.

Statins are a class of medicines used as an adjunct to diet for the treatment of hypercholesterolaemia, when the response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate. They are also authorised as an adjunct to treatment in the secondary prevention of major cardiac events in patients with cardiovascular disease.

Fusidic acid and its salts (including sodium fusidate) are antistaphylococcal agents used for the treatment of serious or deep-seated infections requiring good tissue or bone penetration, such as osteomyelitis. Systemic formulations of fusidic acid include tablets, suspensions and intravenous infusions. There is no evidence that topical formulations (creams and eye drops) interact with statins.

**Reference:**
Drug Safety Newsletter, HPRA, July 2015
(See WHO Pharmaceuticals Newsletter No.5, 2012 for Updated advice on drug interactions - updated contraindications in the UK)

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### Ibuprofen

**Small increased cardiovascular risk with daily doses at or above 2,400mg**

**Ireland.** The HPRA has announced that the product information for all systemic ibuprofen containing products will be updated as soon as possible to reflect small increased cardiovascular risk with daily doses at or above 2,400mg.

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) commonly used for the reduction of pain, inflammation and fever. The most recent EU review completed by the Pharmacovigilance Risk Assessment Committee (PRAC) has confirmed a small increase in the risk of arterial thrombotic events (e.g. myocardial infarction or stroke) in patients taking high doses of ibuprofen (at or above 2,400mg/day).

The HPRA has advised healthcare professionals that:

- Ibuprofen should be prescribed at the lowest dose for the shortest duration possible.
- Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration and high doses (2400 mg/day) should be avoided.
- Careful consideration should also be exercised before initiating long-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, and smoking), particularly if high doses of ibuprofen (2400 mg/day) are required.

**Reference:**
Drug Safety Newsletter, HPRA, June 2015
(See WHO Pharmaceuticals Newsletter No.3, 2015 for Risk of serious heart and stroke adverse events at high doses in Canada)

### Indapamide

**Risk of Toxic epidermal necrolysis (TEN)**

**Japan.** The MHLW and the PMDA have announced the revision of the package insert for indapamide (Natrix® and Tenaxil®) to include risk of toxic epidermal necrolysis (TEN).

Indapamide is indicated for Essential hypertension.

The MHLW/PMDA stated that cases of TEN have been reported in patients treated with indapamide in Japan.

Based on expert advice and available evidence, the MHLW/PMDA have recommended the addition of the description on risk of TEN to the subsection of the “Clinically significant adverse reactions” in the section of “Adverse reactions” in package insert.

**Reference:**
Revision of Precautions, MHLW/PMDA, 7 July 2015 (www.pmda.go.jp/english/)

### Influenza HA vaccine

**Risk of optic neuritis**

**Japan.** The MHLW and the PMDA have announced the revision of the package insert for influenza HA vaccine to include risk of optic neuritis.

Influenza HA vaccine is used in the prophylaxis of influenza.

The MHLW/PMDA stated that cases of optic neuritis have
been reported in persons injected with influenza HA vaccine in Japan.

Based on expert advice and available evidence, the MHLW/PMDA have recommended the addition of the description on the risk of optic neuritis to the subsection of the "Encephalitis/encephalopathy and myelitis" in the section of "Clinically significant adverse reactions" in the package insert.

Reference: Revision of Precautions, MHLW/PMDA, July 2015 (www.pmda.go.jp/english/)

Interferon beta-1a

Risk of fulminant hepatitis

Japan. The MHLW and the PMDA have announced the revision of the package insert for interferon beta-1a (Avonex®) to include risk of fulminant hepatitis.

Interferon beta-1a is used for prophylaxis of relapse of multiple sclerosis.

The MHLW/PMDA stated that a case of fulminant hepatitis has been reported in a patient treated with interferon beta-1a in Japan.

Based on expert advice and available evidence, the MHLW/PMDA have recommended the addition of the advice for health-care professionals: "Patients should be instructed to contact a doctor if they experience the symptoms of liver disorder" to the "Important precautions" section in package insert.

The MHLW/PMDA also recommended to revise the title of subsection "Serious liver disorder" in the section of "Clinically significant adverse reactions" to "Hepatitis and hepatic function disorder" and to add the description on the risk of fulminant hepatitis to the subsection in package insert.

Reference: Revision of Precautions, MHLW/PMDA, 7 July 2015 (www.pmda.go.jp/english/)

Ivabradine

Risk of cardiovascular events in patients with angina

Australia. The TGA has announced that the Product Information for ivabradine has been updated to reduce the risk of cardiovascular events in patients who take the medicine for angina.

Ivabradine is a heart rate lowering agent, used for symptoms of chronic stable angina or treatment of symptomatic chronic heart failure. It works on the cardiac pacemaker current which effects the sinus node and regulates heart rate.

The approved indications in the Product Information for ivabradine was updated to include:

- Symptomatic treatment of chronic stable angina due to atherosclerotic coronary artery disease in patients with normal sinus rhythm and heart rate at or above 70 beats per minute (bpm), who are unable to tolerate or have a contraindication to the use of beta-blockers, OR in combination with atenolol 50 mg once daily when angina is inadequately controlled.
- Treatment of symptomatic chronic heart failure of New York Heart Association Classes II or III and with documented left ventricular ejection fraction ≤ 35% in adult patients in sinus rhythm and with heart rate at or above 77 bpm, in combination with optimal standard chronic heart failure treatment.

The contraindications have been amended to change resting heart rate prior to treatment from '60 bpm' to '70 bpm', as well as to add examples of potent cytochrome P450 3A4 (CYP3A4) inhibitors. A new contraindication for 'combination with verapamil or diltiazem which are moderate CYP3A4 inhibitors with heart rate reducing properties' has also been added.

The Precautions, Interactions with Other Medicines, Adverse Events and Dosage and Administration sections of the Product Information have also been updated to include new information to help reduce the risk of cardiovascular events for patients with angina.

These changes follow preliminary results of a pre-specified subgroup of patients with symptomatic angina in the SIGNIFY phase III study ("Study assessInG the morbiDity-mortalitY benEfits of the IF inhibitor ivabradine in patients with coronary artery disease").

The SIGNIFY study findings indicated that some patients with angina have a small but statistically significant increase in the combined risk of death and non-fatal heart attack with ivabradine compared to placebo. Analysis of the data indicates that cardiovascular adverse events may be associated with the patient's heart rate being less than 60 beats per minute. The incidence of bradycardia was high for ivabradine compared to placebo (17.9% vs 2.1%), with more than 30% of the patients in the ivabradine group having a resting heart rate below 50 beats per minute on at least one occasion.

The TGA is continuing to monitor all adverse events reports involving ivabradine.
Reference:

(See WHO Pharmaceuticals Newsletters No.1, 2015 for Risk of cardiovascular events in Europe, No.4, 2014 and No.3, 2014 for related information)

**Methotrexate**

**Risk of hepatitis B reactivation**

**Australia.** The TGA has informed health-care professionals of the update of the Product Information for methotrexate to include a precaution regarding reactivation of hepatitis B virus. The TGA also recommends that health professionals closely monitor such patients who are already taking methotrexate.

Methotrexate is an immunosuppressive agent with the indication for the treatment of rheumatoid arthritis, severe psoriasis and certain types of cancers, including breast cancer, gestational choriocarcinoma and lymphosarcoma. Its principal mechanism of action is the competitive inhibition of the enzyme folic acid reductase.

Up until 21 February 2015, the TGA has received two reports of possible hepatitis B reactivation associated with methotrexate treatment, which include one published case. Analysis of these two cases found that they were confounded by other drug therapy. However, a causal role for methotrexate could not be excluded.

Considering the seriousness of complications associated with hepatitis B reactivation and the fact that methotrexate is now the most commonly used first-line drug therapy for rheumatoid arthritis in Australia, the TGA concluded that health professionals should be provided further information about this potential adverse event.

Reference:

**Methylphenidate transdermal system**

**Permanent skin colour changes**

**USA.** The US Food and Drug Administration (FDA) has warned that permanent loss of skin colour may occur with use of the methylphenidate transdermal system (Daytrana patch®) for Attention Deficit Hyperactivity Disorder (ADHD). The FDA has added a new warning to the drug label to describe this skin condition, which is known as chemical leukoderma.

The methylphenidate transdermal system treats ADHD symptoms in children and adolescents who are overactive, cannot concentrate for very long, or are easily distracted and impulsive.

Chemical leukoderma is a skin condition that causes the skin to lose colour due to repeated exposure to specific chemical compounds. The condition is not physically harmful, but it is disfiguring. The areas of skin colour loss described with the methylphenidate transdermal system ranged up to 8 inches in diameter. This condition is not thought to be reversible, which may cause emotional distress.

The FDA reviewed cases of chemical leukoderma associated with the methylphenidate transdermal system reported to the FDA Adverse Event Reporting System (FAERS) database and described in the medical literature. FDA identified 51 FAERS cases from April 2006 to December 2014 and one published case that was not recorded in FAERS. The time to onset of leukoderma after starting methylphenidate transdermal system ranged from 2 months to 4 years. All of the patients described a decrease in or loss of skin colour. In most cases, the loss of skin colour was limited to the areas around where the patch was rotated. However, a small number of patients also reported skin colour changes on parts of the body where the patch was never applied. In all cases, the decreased skin colour was permanent.

The FDA is recommending that health-care professionals consider alternative treatments for patients who experience these skin colour changes.

Reference:

**Methylprednisolone (intravenous injection)**

**Risk of liver injury**

**Canada.** Health Canada has announced that evidence of an association between intravenous methylprednisolone and the occurrence of liver injury with a variable time to onset. The prescribing information for Solu-medrol® and Solu-medrolact-o-vials® have been updated to reflect the available evidence regarding the risk of liver injury. Manufacturers of generic versions of this drug will also be asked to update their product information.

Methylprednisolone is a corticosteroid drug typically used for its anti-inflammatory effects. Administration into a vein (intravenous) is generally only used for short periods in...
Severe inflammatory conditions.

A safety review was initiated following the identification of 28 published international cases of liver injury associated with intravenous methylprednisolone, four of which had a fatal outcome.

Up until December 31, 2013, three Canadian reports were received and only one case of liver injury was possibly associated with intravenous methylprednisolone.

Among the 28 cases identified in the literature, the time to onset of the liver injury varied from several days to several months. Of these cases, 27 were considered severe, and death was reported in four cases. Patients’ signs and symptoms of liver injury improved when the treatment was stopped in 22 of these 28 cases. When intravenous methylprednisolone was restarted, liver injury reappeared in almost half of the cases.

Reference:

Non-aspirin Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Increased chance of heart attack or stroke

USA. The US FDA has announced the strengthening of the existing label warnings of non-aspirin NSAIDs for increased risk of heart attack or stroke. Based on the FDA’s comprehensive review of new safety information, the FDA has requested updates to the drug labels of all prescription NSAIDs. The FDA will also request updates to the over-the-counter (OTC) non-aspirin NSAID Drug Facts labels.

Prescription NSAID labels will be revised to reflect the following information:

- The risk of heart attack or stroke can occur as early as the first weeks of using an NSAID. The risk may increase with longer use of the NSAID.
- The risk appears greater at higher doses.
- It was previously thought that all NSAIDs may have a similar risk. Newer information makes it less clear that the risk for heart attack or stroke is similar for all NSAIDs; however, this newer information is not sufficient for us to determine that the risk of any particular NSAID is definitely higher or lower than that of any other particular NSAID.
- NSAIDs can increase the risk of heart attack or stroke in patients with or without heart disease or risk factors for heart disease. A large number of studies support this finding, with varying estimates of how much the risk is increased, depending on the drugs and the doses studied.
- In general, patients with heart disease or risk factors for it have a greater likelihood of heart attack or stroke following NSAID use than patients without these risk factors because they have a higher risk at baseline.
- Patients treated with NSAIDs following a first heart attack were more likely to die in the first year after the heart attack compared to patients who were not treated with NSAIDs after their first heart attack.

There is an increased risk of heart failure with NSAID use.

Reference:


Pregabalin

Risk of abuse

Saudi Arabia. The Saudi Food and Drug Authority (SFDA) has announced that dispensing of pregabalin is now restricted to hospitals and government primary care centres only. The drug should no longer be dispensed in community pharmacies due to increased local reports of abuse.

Pregabalin is a gamma-aminobutyric acid (GABA) analogue indicated for the treatment of peripheral and central neuropathic pain in adults, as an adjunctive therapy in adults with partial seizures with or without secondary generalisation, for the treatment of Generalised Anxiety Disorder (GAD) in adults and for the management of fibromyalgia.

In 2013, the SFDA had received several enquiries regarding the risk of pregabalin abuse. Although pregabalin is not recognised as a drug with high potential abuse, literature data showed that there is an association between pregabalin and risk of abuse and dependence. Moreover, there was a marked increase in the utilization of pregabalin products in Saudi Arabia, which raised some concerns. As a result, the SFDA requested all marketing authorisation holders to update the SmPC, patient information leaflet and to distribute direct health-care professional communication (DHPC) to advise about the potential risk of abuse. In addition, the SFDA published a safety update on...
the use of sorafenib. Hyperthyroidism is a type of thyroid gland dysfunction where excessive amounts of thyroid hormones are released into the blood that may cause fast heartbeat, tiredness, weight loss, nervousness and/or trembling.

There were many case reports of thyroid gland dysfunction associated with the use of sorafenib in the scientific literature, manufacturer's database and the World Health Organization's database at the time of this safety review. Up until January 31, 2015, there were no Canadian reports of thyroid gland dysfunction received through the Canada Vigilance Program.

The analysis of the cases showed evidence that thyroid gland dysfunction may occur with sorafenib use, including, very rarely, thyroid storm.


### Tramadol hydrochloride

**Risk of respiratory depression**

**Japan.** The MHLW and the PMDA have announced the revision of the package insert for tramadol hydrochloride (Tramal®) to include risk of respiratory depression.

Tramadol is used for relief of pain.

The MHLW/PMDA stated that cases associated with respiratory depression have been reported in patients treated with tramadol hydrochloride or tramadol hydrochloride/acetaminophen in Japan.

Based on expert advice and available evidence, the MHLW/PMDA have recommended the addition of

### Technetium (99mTc) hydroxymethylenediphosphonate injection

**Risk of shock and anaphylaxis**

**Japan.** The MHLW and the PMDA have announced the revision of the package insert for technetium (99mTc) hydroxymethylenediphosphonate (Clearbone®) to include risk of shock and anaphylaxis as a contraindication.

Technetium (99mTc) hydroxymethylenediphosphonate is used as a diagnostic agent for bone diseases with scintigraphic imaging of the bone.

The MHLW/PMDA stated that cases of shock and anaphylaxis have been reported in patients

### Sorafenib

**Risk of thyroid gland dysfunction**

**Canada.** Health Canada has updated the Canadian prescribing information for sorafenib (Nexavar®) to inform health-care professionals, caregivers, and patients about the risks of thyroid dysfunction. Thyroid function monitoring should be considered before and during sorafenib use.

Sorafenib is an anti-cancer drug from the multikinase inhibitor family of drugs used to treat specific types of liver, kidney, and thyroid cancers in adults.

A safety review was conducted following a published report of severe hyperthyroidism, known as thyroid storm associated

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the following texts in the section of “Adverse reactions” in the package insert.

Respiratory depression: Respiratory depression may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be adopted.

Reference:
Revision of Precautions, MHLW/PMDA, 7 July 2015 (www.pmda.go.jp/english/)

### Ustekinumab

**Risk of rare but serious skin reactions**

**Singapore.** The Health Science Authority (HSA) has announced that the package inserts of ustekinumab-containing products have been strengthened to include warnings on severe and life-threatening rare but serious skin reactions, which could lead to hospitalisation.

Ustekinumab (Stelara®) is a fully human IgG1k monoclonal antibody, used for the treatment of moderate to severe plaque psoriasis in adult patients who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including cyclosporine, methotrexate, and psoralen combined with ultraviolet A (PUVA). It is also used to treat adult patients with active psoriatic arthritis when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate.

The HSA has not received any local reports of exfoliative dermatitis and erythrodermic psoriasis associated with the uses of ustekinumab.

In other country, cases of exfoliative dermatitis and erythrodermic psoriasis have been reported rarely (≥1/10,000 to <1/1,000) in psoriasis patients receiving ustekinumab, some of which occurred days after receiving dose. It is acknowledged that there could be a potential for confounding by indication in these cases.

The HSA decision follows both a PRAC and a Health Canada review. The PRAC concluded that the package insert for ustekinumab should be updated to include the risk of exfoliative dermatitis and skin exfoliation. In Canada, a communication letter was issued to inform health-care professionals about this safety concern and changes made to the Canadian prescribing information.

The HSA has advised health-care professionals to take into consideration the above safety information and signs and symptoms of erythrodermic psoriasis or exfoliative dermatitis, when prescribing ustekinumab.

Reference:
(See WHO Pharmaceuticals Newsletters No.2, 2015 for Risk of exfoliative dermatitis in the UK and No.1, 2015 for Serious skin disorders (Exfoliative dermatitis and erythrodermic psoriasis) in Canada)

### Ziprasidone

**Risk of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)**

**Singapore.** The HSA has announced that the package insert for ziprasidone (Zeldox®) has been strengthened to include warnings on the risk of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).

Ziprasidone is an antipsychotic indicated for the treatment of schizophrenia, related psychoses, prevention of relapse and for the maintenance of clinical improvement during continuation therapy. It is also indicated for the treatment of manic or mixed episodes associated with bipolar disorder, with or without psychotic features.

DRESS is a serious adverse drug-induced reaction that is potentially life-threatening with a mortality rate of up to 10%. It has a delayed onset, usually appearing two to six weeks after initiation of the causative drug. Manifestations of DRESS may include cutaneous reactions such as rash or exfoliative dermatitis, fever, lymphadenopathy, eosinophilia and other systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, pericarditis and pancreatitis.

The HSA has not received any adverse drug reaction reports of DRESS associated with ziprasidone-use in Singapore.

The US FDA reviewed six worldwide cases of DRESS associated with the use of ziprasidone that were reported to the FDA Adverse Event Reporting System (FAERS). In all six cases, the signs and symptoms of DRESS appeared between 11 and 30 days after ziprasidone treatment was initiated. Of these, a recurrence of symptoms following the discontinuation and re-initiation of ziprasidone was reported for three cases, where a faster time to onset of the symptoms was observed following the re-initiation. Three cases were reported to have concomitant therapy with drugs associated with the occurrence of DRESS. While none of the cases reported death, serious outcomes including hospitalisation had
been reported. Based on an assessment of these reports, the FDA concluded that an association between ziprasidone use and the occurrence of DRESS was supported, and issued a drug safety communication in December 2014.

The FDA requested the package insert of ziprasidone-containing products to be updated to include warnings on the risk of DRESS in US.

Health-care professionals in Singapore have been advised to be vigilant to possible signs and symptoms of DRESS, such as skin rash, fever, lymphadenopathy and eosinophilia, in patients prescribed ziprasidone.

**Reference:**
Product Safety Alerts, HSA, 29 May 2015
(http://www.hsa.gov.sg/)

(See WHO Pharmaceuticals Newsletter No.1, 2015 for Rare but potentially fatal skin reactions in the US)
Codeine Cough-and-Cold Medicines in Children

Potential risk of serious side effects

USA. The US FDA has announced the investigation of the safety of codeine-containing medicines used to treat coughs and colds in children under 18 years because of the potential for serious side effects, including slowed or difficult breathing. FDA has recommended that parents and caregivers should stop giving their child codeine and seek medical attention immediately if they notice any signs of slow or shallow breathing, difficult or noisy breathing, confusion, or unusual sleepiness in their child.

Codeine is a specific type of narcotic medicine called an opioid that is used to treat mild to moderate pain and also to reduce coughing. It is usually combined with other medications in prescription and OTC cough-and-cold medicines.

In April 2015, the European Medicines Agency (EMA) announced that codeine must not be used to treat cough and cold in children under 12 years, and that codeine is not recommended in children and adolescents between 12 and 18 years who have breathing problems, including those with asthma and other chronic breathing problems. FDA will continue to evaluate this safety issue and will consider the EMA recommendations. Final conclusions and recommendations will be communicated when the FDA review is complete.

Reference:
(See WHO Pharmaceuticals Newsletters No.3, 2015 for more information)

Combined hormonal birth control products

Evaluating effectiveness in women who are obese

Canada. Health Canada has requested that labels for newly marketed combined hormonal birth control products in Canada should contain information regarding the weight and Body Mass Index (BMI) of the people studied in clinical trials. This information is not required for older combined hormonal birth control products as it may not be available (for example, BMI may not have been collected during the clinical trials). This information is being added for specificity to provide further context on the parameters of the studies even though, at this time, the current safety review did not find a higher risk of pregnancy in obese women.

Combined hormonal birth control products containing forms of estrogen and progestin are used to prevent pregnancy. These products are available as pills, skin patches and vaginal rings. The pill is the most common form.

A safety review evaluated information about the risk of decreased effectiveness of combined hormonal birth control products when used by women who are obese. Obesity was calculated using a BMI, a measure of fat based on a person's height and weight. Women in the safety review were considered obese if they had a BMI of 30 kg/m² or greater.

The safety review did not find a higher risk of pregnancy in obese women compared to non-obese women when using combined hormonal birth control products. Health Canada will continue to monitor this issue.

Reference:

Denosumab

No evidence of increased risk of cardiovascular events

Canada. After conducting a safety review, Health Canada announced that the available evidence does not support an association between denosumab (Prolia®) and the risk of cardiovascular adverse events at this time. The risk of low blood calcium and its effects on heart rhythm (e.g. QT interval prolongation) is already described in the prescribing information for denosumab.

Denosumab is a unique immune system protein (monoclonal antibody), which works by binding to, and inhibiting, specific cells that remove bone mass, to slow bone loss and increase bone strength. It is used to treat weak and brittle bones (osteoporosis) and to increase bone mass.

As of June 30, 2014, Health Canada identified three cases of heart rhythm problems (QT interval prolongation) as possibly related to low blood calcium (hypocalcaemia) due to use of denosumab. Cases of cardiovascular events in those taking denosumab reported internationally, occurred in patients who had other pre-existing risk factors or information about the patients were incomplete. It was therefore difficult to determine whether the cardiovascular adverse events were caused by...
the use of denosumab or were due to other reasons. In addition, four research articles were identified in the literature. The frequency of cardiovascular adverse events associated with the use of denosumab was comparable to placebo (sugar pill). Overall, the link between the use of denosumab and cardiovascular adverse events could not be concluded.

Reference:

### Diazoxide

**Reports of pulmonary hypertension in infants and newborns**

**USA.** The US FDA has issued a warning of potential pulmonary hypertension, (high pressure in the blood vessels leading to the lungs), in infants and newborns treated with diazoxide (Proglycem®) for low blood sugar.

The FDA identified 11 cases of pulmonary hypertension in infants and newborns treated with diazoxide, since the drug was approved in 1973. In all cases, the pulmonary hypertension resolved or improved after diazoxide was stopped. The FDA is continuing to investigate this safety issue and will determine whether changes are needed in diazoxide prescribing information.

Diazoxide is usually given in the hospital, and health-care professionals should closely monitor babies receiving it, especially those with risk factors for pulmonary hypertension such as meconium aspiration syndrome, respiratory distress syndrome, transient tachypnea of the newborn, pneumonia, sepsis, congenital diaphragmatic hernia, and congenital heart disease. Diazoxide treatment should be stopped if pulmonary hypertension is identified.

**Reference:**

### Febuxostat

**Risk of agranulocytosis (severe reduction in the number of white blood cells)**

**Canada.** Health Canada has requested the manufacturer of febuxostat (Uloric®) to submit information updates on the safety of febuxostat. Health Canada will monitor and assess this information.

Febuxostat is an oral medication used to lower uric acid levels in patients with gout (a painful form of arthritis).

A safety review was initiated following the identification of international cases of febuxostat-associated agranulocytosis.

Agranulocytosis is a condition involving a severe reduction in the number of white blood cells, increasing the risk of infections.

At the time of this review, there were no reported cases of agranulocytosis suspected of being associated with the use of febuxostat in Canada, however, the World Health Organization (WHO) Global Individual Case Safety Reports database (VigiBase®) contained 13 international cases of agranulocytosis suspected of being associated with the use of febuxostat.

Two cases of febuxostat associated neutropenia were published in the scientific literature. Although neutropenia can occur without agranulocytosis, it is an important component of agranulocytosis. In both cases, while the patients may have been exposed to other medications that could have contributed to this reaction, the use of febuxostat was considered the probable cause of the neutropenia.

**Reference:**

### Ibuprofen in high dose (≥2400mg/day)

**Small increase in cardiovascular risk**

**UK.** The MHRA and other EU medicines regulators have reviewed the safety of high-dose ibuprofen, following the publication of a meta-analysis of clinical trial data and have concluded that there is an increase in risk of cardiovascular events in people taking high dose ibuprofen (≥2400 mg). Meta-analysis data showed that people taking ≥2400 mg of ibuprofen per day are at a higher risk of arterial thrombotic events (heart attack, stroke) than people taking placebo. The review confirmed that this higher risk is similar to that seen with COX-2 inhibitors and diclofenac.

The European review also considered the latest data on the possible interaction between ibuprofen and low-dose aspirin. The latest experimental data confirm previous findings that ibuprofen competitively inhibits the effect of low-dose aspirin on platelet aggregation in vivo, ex vivo and in vitro. It is uncertain if these data can be extrapolated to the clinical situation, and clinical data do not support a clinically meaningful interaction. However, the possibility that long-term, daily use of ibuprofen might reduce the
cardioprotective effects of low-dose aspirin cannot be excluded.

Occasional ibuprofen use is unlikely to have a clinically meaningful effect on the benefits of low-dose aspirin.

No increased risk of arterial thrombotic events is seen with ibuprofen at doses up to 1200 mg per day (the highest OTC dose available) compared with not taking ibuprofen. There are limited data on the risk with ibuprofen at doses up to 1200 mg per day (the highest dose available over the counter) compared with not taking ibuprofen.

The MHRA has warned health-care professionals when prescribing or dispensing ibuprofen:

- To consider that these recommendations also apply to dexibuprofen (a high dose of dexibuprofen is 1200 mg or more per day, which is equivalent to 2400 mg of ibuprofen).
- To consider that no increase in cardiovascular risk is seen with ibuprofen at doses up to 1200 mg per day (the highest dose available over the counter) compared with not taking ibuprofen.

Reference:
Drug Safety Update, MHRA, Volume 8, issue 11: 2, June 2015 (www.gov.uk/mhra)
(See page 8 for the action taken by Ireland on the same risk)

Influenza vaccine

Mild hypersensitivity reactions

New Zealand. The Medsafe announced that the Centre for Adverse Reactions Monitoring (CARM) has received an increased proportion of reports of hypersensitivity and local reactions with the seasonal influenza vaccination as compared with previous years (see Table). A similar situation has also been reported in Australia.

Hypersensitivity and local reactions reported to the CARM include dyspnoea (shortness of breath), pruritus (itching), paraesthesias (tingling or burning of the skin) and injection site inflammation, redness and pain. In the majority of reports the events were considered to be mild. None of the cases reported have required hospitalisation or been life threatening.

The Medsafe has reminded health-care professionals and consumers that immunization remains the best defence against the influenza virus and the overall benefit harm balance of the influenza vaccination remains positive.

Medsafe is continuing to monitor reports of adverse events to the seasonal influenza vaccination.

Table: Percentage of reports with hypersensitivity events associated with seasonal trivalent influenza vaccines since 2011

<table>
<thead>
<tr>
<th>Year</th>
<th>Hyper-sensitivity Reactions</th>
<th>Hyper-sensitivity Reports</th>
<th>% of Hyper-sensitivity/Total Reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>79</td>
<td>53</td>
<td>23.4</td>
</tr>
<tr>
<td>2012</td>
<td>79</td>
<td>58</td>
<td>29.4</td>
</tr>
<tr>
<td>2013</td>
<td>146</td>
<td>101</td>
<td>34.6</td>
</tr>
<tr>
<td>2014</td>
<td>110</td>
<td>75</td>
<td>29.4</td>
</tr>
<tr>
<td>2015</td>
<td>76</td>
<td>53</td>
<td>36.8</td>
</tr>
</tbody>
</table>

* to 20th May

Products Affected:
The influenza vaccination is used for prophylaxis against specific strains of the influenza virus in adults and children older than six months of age (with the exception of Fluvax® ®, which should not be used in children under five years of age).

<table>
<thead>
<tr>
<th>Product name</th>
<th>Sponsor</th>
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<tbody>
<tr>
<td>Fluvax® ®</td>
<td>GlaxoSmithKline (NZ)</td>
</tr>
<tr>
<td>Fluarix® ®</td>
<td>bioCSL (NZ)</td>
</tr>
<tr>
<td>Influvax® ®</td>
<td>BPG Products</td>
</tr>
<tr>
<td>Vaxigrip® ®</td>
<td>Sanofi-Aventis</td>
</tr>
</tbody>
</table>

Reference:
Safety Information, Medsafe, 22 June 2015 (www.medsafe.govt.nz)

Latanoprost eye drop

Increased reporting of eye irritation since reformulation

UK. The MHRA has recommended that health-care professionals advise patients to inform a health professional if they experience severe eye irritation with the use of latanoprost eye drops.
Treatment should be reviewed if patients mention severe eye irritation.

Latanoprost (Xalatan®) is an eye-drop licensed for the reduction of intraocular pressure in adults and children with ocular hypertension and open angle glaucoma.

In 2013, the pH of latanoprost eye drop was reduced from 6.7 to 6.0 to allow for long-term storage at room temperature. Following this reformulation there has been an increase in the number of reports of eye irritation from across the EU. The MHRA received no Yellow Card reports of eye irritation in people using latanoprost eye drop in the year before the reformulation, compared with 22 reports in the year after reformulation.

Reference:
Drug Safety Update, MHRA, Volume 8, issue 12: 2, July 2015 (www.gov.uk/mhra)

Melatonin

Possible risk of hallucinations

New Zealand. Medsafe has issued an early warning communicating the potential risk of hallucinations associated with melatonin (Circadin®).

This reaction has not been reviewed in detail, however, the overall benefit-risk balance of melatonin remains positive.

Melatonin prolonged-release tablets are indicated for the short term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over. The recommended dose is 2 mg once daily and may be continued for up to 13 weeks.

The CARM has received three reports of hallucinations associated with melatonin use. Hallucinations generally occurred the same night melatonin was taken. In two of the three reports, no other medicines were reported and in all three reports, symptoms improved once the medicine was stopped. Hallucinations are not currently listed in the New Zealand data sheet for melatonin.

Reference:
Safety Information, Medsafe, 20 July 2015 (www.medsafe.govt.nz/)

Sodium glucose co-transporter 2 (SGLT2) inhibitors
(canagliflozin, dapagliflozin, empagliflozin)

Risk of diabetic ketoacidosis

UK. The MHRA has announced investigations into the risk of diabetic ketoacidosis (DKA) associated with sodium glucose co-transporter 2 (SGLT2) inhibitors.

SGLT2 inhibitors are licensed for use in adults with type 2 diabetes to improve glycaemic control.

Serious and life-threatening cases of DKA have been reported in patients taking SGLT2 inhibitors (canagliflozin, dapagliflozin or empagliflozin).

In several cases, blood glucose levels were only moderately elevated (e.g. <14 mmol/L or 250 mg/dL), which is atypical for DKA. This atypical presentation could delay diagnosis and treatment. Half of the cases occurred during the first 2 months of treatment. Some cases occurred shortly after stopping the SGLT2 inhibitor. One third of the cases involved off-label use in patients with type 1 diabetes.

It is recommended that patients are informed of the signs and symptoms of DKA (e.g. nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness) and are tested for raised ketones if presented with these signs and symptoms.

The underlying mechanism for SGLT2 inhibitor-associated DKA has not been established. The MHRA will communicate further advice as appropriate once the investigation is complete.

Reference:
Drug Safety Update, MHRA, Volume 8, issue 11: 1, June 2015 (www.gov.uk/mhra)

Zoledronic acid infusion

Risk of acute phase response and renal effects

New Zealand. The Medsafe has reminded health-care professionals that patients may experience an acute phase response or adverse effects on renal function following administration of zoledronic acid infusion.

Zoledronic acid (Aclasta® and Zometa®) is a bisphosphonate administered to patients by intravenous infusion.

The CARM has received 153 reports of musculoskeletal adverse reactions starting within one month after a zoledronic acid infusion. The CARM also received 26 reports of ocular adverse reactions and 33 reports of urinary adverse reactions within one month following an infusion.

Acute phase reactions may present with the following symptoms: chills, fever, influenza-like symptoms, night sweats, rigors and shivering,
diffuse musculoskeletal pain, gastrointestinal effects, and eye inflammation. Acute phase responses can occur at any time up to approximately two weeks following an infusion. The majority of patients will experience symptoms within the first three days after an infusion. These reactions are usually self-limiting and resolve completely within 24 to 48 hours. However, in some patients symptoms may persist for longer periods.

Renal reactions can also occur shortly after infusion. Adequate hydration can help to reduce the risk of renal deterioration after a zoledronic acid infusion. Renal deterioration, progression to renal failure and dialysis has been reported in patients following the initial dose of zoledronic acid.

If patients show signs of renal function decline after infusion, the benefits and risks of harm of continued treatment should be evaluated.

Reference:
Prescriber update, Medsafe, Vol. 36 No.2, June 2015
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 10 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 29). For information on the UMC Measures of Disproportionate Reporting please refer to WHO Pharmaceuticals Newsletter Issue No. 1, 2012.

UMC, a WHO Collaborating Centre, is an independent foundation and a centre for international service and scientific research within the field of pharmacovigilance. UMC’s vision is to improve worldwide patient safety and welfare by reducing the risk of medicines. For more information, visit www.who-umc.org. To leave a comment regarding the signals in this Newsletter, please contact: the Uppsala Monitoring Centre, Box 1051, SE-751 40 Uppsala, Sweden. E-mail: signals@who-umc.org.

### Atomoxetine and Dystonia in paediatric patients

**Dr Ian Boyd, Australia**

#### Summary

Atomoxetine is a relatively potent inhibitor of the presynaptic noradrenaline transporter, a moderate inhibitor of 5HT uptake, and a weak inhibitor of dopamine uptake with minimal affinity for the other noradrenergic receptors. It is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) as defined by DSM-IV criteria in children 6 years of age and older, adolescents and adults. After the elimination of suspected duplicates there are currently (1 September 2014) 31 individual case safety reports (ICSRs) in the WHO Global ICSR database, VigiBase® of dystonia in association with atomoxetine for children and adolescents up to 17 years of age. The reports are from Australia, Canada, Germany, Italy, Japan, New Zealand, South Africa, Spain, Switzerland and the United States. Atomoxetine was the only drug suspected in 21 of the 31 cases. The outcome of the dystonia was indicated in 17 reports. The patients were reported as recovered or recovering in 16 cases and not recovered in the remaining case. In the cases where recovery was reported, the drug was withdrawn in 13 cases, continued in one case and the fate of the drug was unknown in the remaining two cases.

Case reports in VigiBase® suggest that there is a possible signal for the association of atomoxetine and dystonia. The fact there was a positive dechallenge in 13 of the 16 reports where recovery was documented is suggestive of a drug-induced effect. However, the possible association of atomoxetine with dystonia appears restricted to the adolescent and paediatric population. A possible mechanism may be based on inhibition of dopamine uptake.

#### Introduction

Atomoxetine is a relatively potent inhibitor of the presynaptic noradrenaline transporter, a moderate inhibitor of 5HT uptake, and a weak inhibitor of dopamine uptake with minimal affinity for the other noradrenergic receptors. Atomoxetine has moderate affinity for 5HT2 and GABAA receptors but poor affinity for most other receptors. It is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) as defined by DSM-IV criteria in children 6 years of age and older, adolescents and adults. The most frequent adverse reactions reported during clinical trials of atomoxetine in children and adolescents include gastrointestinal reactions, increased blood pressure and heart rate, decreased appetite, decreased weight and skin reactions. Common neuropsychiatric reactions reported included dizziness, mood swings, somnolence, insomnia, irritability and depression.\(^1\)

Dystonia denotes abnormal movements that are slow or so sustained that they may appear as abnormal postures. These abnormal movements of groups of muscles or body segments include grimacing, torticollis, blepharospasm and limb torsions. Generally, they are absent during sleep and exacerbated by emotional stress or voluntary activity. Dystonia occurs as an occasional
complication of treatment with neuroleptic and dopaminergic drugs and many others. Drug-induced dystonia may be early (onset within one week of commencement of treatment) or late (onset after several weeks, months or years of treatment). Late persistent dystonia is usually termed tardive dyskinesia.²

Dystonia is a preferred term in WHO-ART with a number of included terms including trismus and various spasms (facial, infantile, cervical, oropharyngeal, tongue).

**Reports in VigiBase®**

As of 1 September 2014, after the elimination of suspected duplicates, there are a total of 40 individual case safety reports (ICSRs) of dystonia in association with atomoxetine in the WHO Global ICSR database, VigiBase®. Out of these reports there are 31 cases of dystonia in children and adolescents up to 17 years of age (Table 1). Of the remaining reports one is a 51 year old and one a 24 year old and the rest are have reported age unknown. The reports from children and adolescents were submitted from the United States (20 reports), Australia (2), South Africa (2), Canada, Germany, Italy, Japan, New Zealand, Spain and Switzerland (1 each). The patients ranged in age from 5 to 17 years with a median of 9 years. There were 23 males and 8 females.

Atomoxetine was the only drug suspected in 21 of the 31 cases. There were other drugs also suspected in the remaining 10 cases and they included drugs for treatment of psychotic disorders in seven cases, drugs for treatment of depression (3 cases), epilepsy (3 cases) and ADHD (3 cases).

In seven of these 10 cases, at least one of these drugs (olanzapine, ziprasidone, risperidone, chlorpromazine) is a likely cause. Antipsychotic drugs are a well-known cause of dystonia and the four drugs listed above all refer to dystonia as a possible adverse effect in their product information.³ Concomitant drugs were reported in 20 of the 31 cases and showed a similar trend to that observed with the co-suspected drugs with considerable use of antipsychotic, anticonvulsant, and antidepressant drugs along with the use of other treatments for ADHD.

Time to onset was reported in only two of the reports and ranged from the same day the drug was administered to 24 days. The outcome of the dystonia was indicated in 17 reports. The patients were reported as recovered or recovering in 16 cases and not recovered in the remaining case. In the cases where recovery was reported, the drug was withdrawn in 13 cases, continued in one case and the fate of the drug was unknown in the remaining two cases. In the case where the patient had not recovered, the drug was continued.

The indication for use was stated in 23 reports and indicated ADHD or a related disease in all 23 cases. Dosage ranged from 10 mg to 160 mg (median: 25 mg) in the 16 cases which reported this information.

Other reactions were reported in 26 of the 31 reports. Other neuropsychiatric reactions were reported in 23 of those reports and six reports described gastrointestinal reactions. Changes in drug levels, changes in therapeutic response or medicine ineffective were reported in eight cases.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/Sex</th>
<th>Other suspected (S) or concomitant (C) drugs</th>
<th>Reactions (WHO-ART preferred terms)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10/M</td>
<td>Buspirone, citalopram, diphenhydramine, methylphenidate, risperidone, valproic acid (all C)</td>
<td>Dystonia, drug interaction, drug level decreased, EEG abnormal, muscle contractions involuntary, saliva increased, somnolence, mental status changes*</td>
<td>Unknown</td>
</tr>
<tr>
<td>2</td>
<td>16/F</td>
<td>Olanzapine (S)</td>
<td>Dystonia, coma, tongue disorder</td>
<td>Unknown</td>
</tr>
<tr>
<td>3</td>
<td>10/M</td>
<td>Fluoxetine, quetiapine (both C)</td>
<td>Dystonia, agitation, anxiety, asthenia, nausea, paraesthesia, SGOT increased, somnolence, drug level changed*, pain in extremity*</td>
<td>Recovered</td>
</tr>
<tr>
<td>4</td>
<td>7/M</td>
<td>None</td>
<td>Dystonia, abdominal pain, azotaemia, dyskinesia, eye abnormality, fever, hypercalcaemia, leukocytosis, opisthotonos, pharyngitis, phosphatase alkaline increased, therapeutic response decreased, varicella, vomiting, eye injury*, eye penetration*, treatment noncompliance*</td>
<td>Unknown</td>
</tr>
<tr>
<td>5</td>
<td>9/F</td>
<td>Olanzapine (S)</td>
<td>Dexamfetamine sulfate/amphetamine sulfate/dexamfetamine saccharate/amphetamine aspartate (C)</td>
<td>Dystonia, therapeutic response increased</td>
</tr>
<tr>
<td>No.</td>
<td>Gender</td>
<td>Drug</td>
<td>Case Description</td>
<td></td>
</tr>
<tr>
<td>-----</td>
<td>--------</td>
<td>------</td>
<td>------------------</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>16/F</td>
<td>Dexamfetamine sulfate/amfetamine sulfate/dexamfetamine saccharate/amfetamine aspartate (C)</td>
<td>Dystonia, hallucination, medication error, muscle contractions involuntary</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>15/F</td>
<td>Dexamfetamine sulfate/amfetamine sulfate/dexamfetamine saccharate/amfetamine aspartate (C)</td>
<td>Dystonia, diplopia, hallucination, medication error, muscle contractions involuntary, mydriasis, self-medication*</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>16/F</td>
<td>Levosalbutamol (C)</td>
<td>Dystonia, blepharospasm, dizziness, drug interaction, hypokinesia, speech disorder, tremor</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>8/F</td>
<td>Risperidone (C)</td>
<td>Dystonia</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>12/F</td>
<td>None</td>
<td>Dystonia, blepharospasm, dyskinesia, pruritus, therapeutic response decreased</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>9/M</td>
<td>Bupropion, oxcarbazepine, quetiapine, risperidone, valproic acid (all S)</td>
<td>Dystonia</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>9/M</td>
<td>Methylphenidate, ziprasidone (both S) Valproic acid (C)</td>
<td>Dystonia, anorexia, choreathetosis, convulsions grand mal, saliva increased, jaw disorder*</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>10/M</td>
<td>Oxybutynin (S)</td>
<td>Dystonia, drug interaction, dyspnoea, extrapyramidal disorder, face oedema, mental deficiency, muscle contractions involuntary, musculoskeletal disorder, neuralgia, pain, skeletal pain, speech disorder, tachycardia, tenderness NOS, totality</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>17/M</td>
<td>Guaiifenesin/dextromethorphan hydrobromide (C)</td>
<td>Dystonia, tachycardia, therapeutic response increased, amphetamines positive*</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>13/M</td>
<td>None</td>
<td>Dystonia</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>8/M</td>
<td>None</td>
<td>Dystonia, medicine ineffective, muscle contractions involuntary</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>10/M</td>
<td>Risperidone, sertraline (both C)</td>
<td>Dystonia, dysphagia, accident NOS</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>8/M</td>
<td>Loratadine (C)</td>
<td>Dystonia, abdominal pain, dizziness, insomnia, muscle contractions involuntary, nausea, somnolence</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>5/M</td>
<td>Risperidone (C)</td>
<td>Dystonia, muscle contractions involuntary</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>11/M</td>
<td>Lamotrigine (C)</td>
<td>Dystonia</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>6/M</td>
<td>None</td>
<td>Dystonia, extrapyramidal disorder, muscle contractions involuntary, jaw disorder*</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>15/M</td>
<td>None</td>
<td>Dystonia, paraesthesia</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>15/F</td>
<td>Fluoxetine (S) Bupropion, fluoxetine (both C)</td>
<td>Dystonia, agitation, amnesia, anxiety, coma, convulsions grand mal, headache, hypertension, oculogyric crisis, tachycardia, urinary incontinence, tongue biting*</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>9/M</td>
<td>Methylphenidate (S)</td>
<td>Dystonia, extrapyramidal disorder</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>5/M</td>
<td>Risperidone (S) Valproic acid (C)</td>
<td>Dystonia</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>9/M</td>
<td>Acetylsalicylic acid, risperidone, valproic acid (S)</td>
<td>Dystonia, dyskinesia</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>8/M</td>
<td>Pericazaine (C)</td>
<td>Dystonia</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>9/M</td>
<td>Fluticasone, paracetamol, salbutamol, salmeterol (C)</td>
<td>Dystonia, anxiety</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>13/M</td>
<td>Risperidone (C)</td>
<td>Dystonia, diarrhoea bloody, extrapyramidal disorder, fatigue, gastritis, hepatic enzymes increased, oedema generalised, urine abnormal, vomiting, weight decrease</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>5/M</td>
<td>Olanzapine, aripiprazole, carbamazepine, chlorpromazine, clonidine, dexamfetamine, iloperidone, lisdexamfetamine, lithium, methylphenidate, quetiapine, valproic acid, ziprasidone (S)</td>
<td>Dystonia, aggressive reaction, anxiety, choreathetosis, crying abnormal, coordination abnormal, depression, dyskinesia, emotional lability, fatigue, hyperkinesia, infection bacterial, insomnia, medicine ineffective, nervousness, sleep disorder, speech disorder, suicide ideation, teeth-grinding, decreased eye contact*, homicidal ideation*, oppositional defiant disorder*</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>5/M</td>
<td>Risperidone (S)</td>
<td>Dystonia, convulsions</td>
<td></td>
</tr>
</tbody>
</table>

NOS = Not otherwise specified
*MedDRA terms
**Signal**

**Literature and Labelling**

The product literature does not refer to dystonia although it does mention that very common, common or uncommonly reported neurological reactions included headache, dizziness, somnolence including sedation, insomnia, syncope and tremor. Post-marketing adverse neurological events reported very rarely include seizures, paraesthesia in children and adolescents, hypoesthesia and tics. No reports of dystonia in association atomoxetine could be found in the literature.

**Discussion**

Case reports in VigiBase® suggest that there is a possible signal for the association of atomoxetine and dystonia in children and adolescents. Atomoxetine was the only drug suspected in 21 of the 31 cases. In the remaining 10 cases, other suspected drugs would appear to be a more likely cause in seven reports but atomoxetine would appear an equally likely cause in the other three cases.

Time to onset was reported in only two of the reports and ranged from the same day the drug was administered to 24 days. The outcome of the dystonia was indicated in 17 reports. The patients were reported as recovered or recovering in 16 cases and not recovered in the remaining case. In the cases where recovery was reported, the drug was withdrawn in 13 cases, continued in one case and the fate of the drug was unknown in the remaining two cases. In the case where the patient had not recovered, the drug was continued. The fact there was a positive dechallenge in 13 of the 16 reports where recovery was documented is suggestive of a drug-induced effect.

The possible association of atomoxetine with dystonia appears restricted to the adolescent and paediatric population. There is a total of 33 reports of dystonia in association with atomoxetine in the total population where the age is known. Thirty-one of these reports were reported in the adolescent and paediatric age groups which represents 93.9% of all the reports. While it may be considered that atomoxetine is used preferentially in the younger age groups, overall reporting in VigiBase® indicates that of the 16,592 reports submitted, the age group from 2 to 17 years represents 72.3% of the total reports in which the age is known.

The pathophysiological mechanisms underlying acute extrapyramidal symptoms such as dystonia are usually attributed to the effects of dopamine receptor blockade in the basal ganglia. As atomoxetine is a weak inhibitor of dopamine uptake, it is possible that this may be the basis of a possible mechanism. It is also possible that children and adolescents may be at greater risk as it is known that younger age is a risk factor for the development of dystonia in patients receiving antipsychotic treatment.

**Conclusion**

In summary, there are 31 reports associating dystonia with the use of atomoxetine from children and adolescents. Atomoxetine was the only drug suspected in 21 of the 31 cases. The fact there was a positive dechallenge in 13 of the 16 reports where recovery was documented is suggestive of a drug-induced effect. However, the possible association of atomoxetine with dystonia appears restricted to the adolescent and paediatric population. A possible mechanism may be based on inhibition of dopamine uptake.

**References**

Response from Eli Lilly & Company

Thank you for the opportunity to provide our comments on the thorough assessment conducted by Dr Boyd. Eli Lilly & Company (Lilly) routinely queries reported adverse events in databases (Lilly’s internal safety database and FDA Adverse Event Reporting System) for early signs of potential adverse drug reactions in patients treated with Lilly drugs. Lilly recognizes the importance of early signal detection and also acknowledges that database queries are only one method that can be employed. Additionally, Lilly’s reviews of the spontaneously reported adverse events involve medical assessment of the narratives where information provided and not captured in the standard fields often helps to refine the assessment.

Consistent with the Uppsala Monitoring Centre, Lilly recognizes that signals are uncertain and preliminary in nature (Uppsala Monitoring Centre, Signals selected by UMC and the clinical review panel: How the process works). This is because, for any given adverse event report considered in generating a signal, there is no certainty that the adverse event was caused by the suspected drug. Rather, the adverse event could have resulted from the underlying condition being treated, a comorbid condition, a concomitant medication, or may simply be the result of chance.

Treatment-emergent dystonias have been associated with reduced dopamine neurotransmission in the basal ganglia, as typically described with antipsychotic medications such as risperidone or quetiapine (Tarsy and Simon, 2006). In this respect, it is pertinent that atomoxetine and other attention deficit hyperactivity disorder (ADHD) medications are not infrequently given in conjunction with concomitant medications including antipsychotic medications to treat the commonly occurring comorbid conditions associated with ADHD. Furthermore, as Dr Boyd mentioned in his assessment, younger individuals may be at greater risk of developing dystonia when they receive antipsychotic treatment. Lilly agrees with Dr Boyd’s observation that in seven of the 31 cases co-suspect antipsychotic medications were a likely cause. Lilly also agrees with Dr Boyd’s comment that, upon review of the data in Table 1, concomitant drugs were reported in 20 of the 31 cases and that these showed a similar trend to that observed with the co-suspected drugs with considerable use of antipsychotic, anticonvulsant, and antidepressant drugs. This observation seems to indicate that, although not considered suspect per se, many cases involved concomitant medications that have been associated with dystonic or other similar movement effects and hence, may also possibly be confounded.

Based on in vivo preclinical data, atomoxetine enhances dopamine release in the prefrontal cortex, but not in the basal ganglia (i.e. striatum; Bymaster et al. 2002). Therefore, the mechanism by which atomoxetine could stimulate an induced dystonia via the dopaminergic pathway is unclear.

In the current report, no rechallenge information was included, so Lilly presumes that none of the case reports involved a rechallenge situation. Positive dechallenge was, however, described in 13 of the 16 reports where recovery was documented. The significance of this information is not entirely clear as it was not mentioned if atomoxetine alone was stopped or if any concomitant medications (neuroleptics, antidepressants, stimulants, or other drugs) were stopped at the same time as atomoxetine or if the dystonia events may have been treated with pharmacological intervention. All of these factors would confound the assessment.

Although Lilly regularly conducts ongoing surveillance, including automated signal detection for all its medications, Lilly has not previously identified a signal for dystonia with atomoxetine from any of our available data sources, including clinical trials. As noted in Dr Boyd’s evaluation, no reports of dystonia in association with atomoxetine could be found in the literature. Nevertheless, Lilly takes the information provided by the Uppsala Monitoring Centre seriously, and therefore, based on the possible signal reported by Dr Boyd, plans to conduct a comprehensive review of dystonia events in atomoxetine-treated patients.

References


**Summary**

Tumour Lysis Syndrome (TLS) in relation to treatment of malignant melanoma with vemurafenib has been identified and filtered as a potential signal from the WHO Global Individual Case Safety Report (ICSR) database, VigiBase®. TLS is a rare, potentially fatal syndrome caused by a sudden massive lysis of tumour tissue with severe electrolyte disturbances and threat of kidney failure as a result. TLS has classically been observed in association with chemotherapeutic agents in the treatment of hematologic and lymphatic malignancies. With the arrival of new targeted drugs in oncology and their growing and important role, during the last decades TLS has increasingly begun to be reported in association with the treatment of solid tumours, including malignant melanoma. In this setting the possibility of TLS could initially be overlooked with the risk of detrimental effects for the patient. Analysis of current available information suggests that vemurafenib may cause TLS and that informing oncologists about this rare event would be of value to increase patient safety.

**Introduction**

Four cases of Tumour Lysis Syndrome (TLS) in association with vemurafenib treatment have been identified and filtered as a potential signal from the WHO Global Individual Case Safety Report (ICSR) database, VigiBase®.

Vemurafenib is a B-Raf enzyme inhibitor indicated for the treatment of malignant melanoma. It was first approved in 2011 in the US, and has since been approved in other countries including Canada, and in the EU. Vemurafenib causes programmed cell death and works in about 60% of melanoma patients whose cancer has either a V600E BRAF mutation or the more rare BRAF V600K mutation. Melanoma cells without these mutations are not inhibited by vemurafenib; instead the drug paradoxically stimulates normal BRAF and may promote tumour growth in such cases.

TLS is a rare and potentially fatal syndrome where a sudden, rapid and massive lysis of tumour tissue occurs, resulting in severe disturbances in electrolytes and renal failure. TLS has predominantly been observed in association with various treatments for hematologic malignancies but has also been described with the treatment of solid tumours; e.g. a handful of cases having been reported in scientific literature in patients under treatment for malignant melanoma.

While the VigiBase® cases herein are few and contain a relative scarcity of data and TLS is considered by some merely as a consequence or a sign of effective treatment regardless of type, the TLS finding is discussed here as a signal of a new adverse drug reaction for vemurafenib.

**Reports in VigiBase®**

A search in VigiBase® in August 2014 retrieved four reports on TLS associated with vemurafenib treatment. The cases originated from Germany and the US, and presented with varying degree of information.

Case 1: A 24-year-old male study patient was treated for malignant melanoma with vemurafenib at a dose of 960 mg twice daily. Dates of treatment and onset of symptoms, medical history or concurrent illness, and concomitant or past medication were not recorded. The patient was admitted to hospital with severe worsening of general condition, abdominal complaints, flank pain, nausea, vomiting and proteinuria and was diagnosed with TLS. The therapy, outcome and any causality assessment by the reporter was not provided. The marketing authorisation holder (MAH) assessed the TLS as related to vemurafenib.

Case 2: A 58-year-old female patient was treated for malignant melanoma with vemurafenib in a dose of 960 mg twice daily. Concomitant medications were enoxaparin, metoclopramide, betamethasone, orlistat, levothyroxine, omeprazole, and paracetamol. The diagnosis of TLS was reported after five days of vemurafenib treatment. The patient recovered within three weeks. No further relevant information was provided but the narrative mentions a previous TLS report on a 40-year-old female for which the investigator assessed vemurafenib to be related to the event. Among the concomitant medications noted in this case was the corticosteroid betamethasone. Corticosteroids are among the agents classically associated with TLS. Treatment time and time to onset was not reported in relation to the concomitant drug betamethasone, and it was not clear whether the drug was administered before or as treatment after the event.

Case 3: A patient of unknown gender and age was treated for malignant melanoma with vemurafenib with an unknown dose. The patient’s medical history, concomitant medication, concurrent conditions and past drugs were not reported. After an unspecified amount of time the patient died due to TLS; in the opinion of the reporter this was...
related to the treatment with vemurafenib. The patient was enrolled in a healthcare providers’ programme for malignant melanoma. The narrative indicated that this case actually described two different patients experiencing the event as described above.

Case 4: A male patient was reported to have experienced TLS while receiving treatment with vemurafenib. No further relevant information was provided.

As is noted from the case descriptions above, the four cases of TLS reported in relation to treatment with vemurafenib do not themselves contain enough background information to allow for a high quality causality assessment.

In VigiBase® a total of 1,157 reports of TLS for all drugs in the database were present as of 12 August, 2014. The cases were predominately from the US, a majority of them concerned men, middle-aged and older, and almost all of them had been reported after 1 January, 2001.

Between 1 January and 12 August, 2014, one hundred ten TLS cases were reported to VigiBase®. Half (55) of these cases concerned treatments for hematologic malignancies, 30 patients were treated for solid malignancies and 25 were treated for an unknown indication. Most commonly reported solid malignancy treatment indications were breast cancer (n=5) and colorectal cancer (n=6). Among TLS cases in solid malignancies and cases of unknown indication two thirds were treated with modern biologic/targeted therapy while one third were reportedly treated with classic chemotherapy agents or steroids only.

The signal for vemurafenib may be seen as a part of a larger pattern increasing reporting of TLS in cancer treatments in general, in line with increased effectiveness of modern targeted anti-cancer drugs.

**Literature and Labelling**

According to the approved EU SPC the most common side effects of vemurafenib treatment are arthralgia, fatigue, skin reactions, light sensitivity reactions, nausea, alopecia and pruritus. TLS, or signs and symptoms associated with TLS such as acute renal failure, other renal side effects, hyperuricaemia, hypocalcaemia, hyperphosphataemia, and hyperkalaemia are not labelled side effects of vemurafenib according to the EU SPC.

TLS is a feared acute and potentially fatal side effect of treatment of primarily hematologic or lymphatic malignancies caused by abrupt, massive tumour cell death. It is a complication of the treatment of bulky, highly proliferative, chemoresponsive disease. Signs and symptoms associated with TLS are hyperuricaemia, hypocalcaemia, hyperphosphataemia, hyperkalaemia with subsequent risk of acute kidney failure, cardiac arrhythmia and seizures with a case classification definition suggested by Cairo and Bishop in 2004. The incidence of TLS in different diagnoses is not known in any detail due to the variability of patients in cohorts investigated and a lack of standard diagnostic criteria used in studies. The vast majority of data on TLS incidence refer to hematologic malignancies with an incidence range between 0 and 23% and a fatality rate ranging between 0 and 2.5%. The high end incidence in some publications may appear to include cases of TLS diagnosed based on laboratory data without significant clinical manifestation. In solid tumours data is scarce with an incidence of TLS of 0.02% reported for colorectal cancer.

TLS has been described in association with different treatment modalities including chemotherapy, radiation and steroids and when none of these modalities is present even as occurring spontaneously. Among solid tumours TLS has been seen as expected in both highly chemosensitive tumours (e.g. small cell carcinomas and germ cell tumours) and also in tumours less sensitive to treatment such as malignant melanoma.

In TLS case histories reported in literature, in association with malignant melanoma, the TLS has occurred spontaneously or within hours to days of treatment described as corticosteroids, classic chemotherapy, monoclonal antibodies, interleukin, interferon and combinations of these.

The detailed mechanism by which TLS is induced in malignant melanoma and other malignancies is largely unknown although any drug causing death of cancer cells by any mechanism may lead to TLS in certain circumstances. In lymphatic tumours, corticosteroids may induce the production of endonucleases in the malignant cells of melanoma, which leads to DNA fragmentation and eventually cell lysis.

Treatment of TLS includes supportive care including preservation of renal function, prevention of cardiac arrhythmias and seizures. Preventive measures for high risk patients with lymphomas and leukaemias include prophylactic allopurinol or rasburicase.

**Discussion and Conclusion**

The four VigiBase® cases of TLS reported in relation to treatment with the new biologic drug vemurafenib do not contain sufficient background information to allow for a high quality causality assessment. In the literature a handful of cases of TLS in relation to malignant melanoma have ever been published, none of which concern treatment...
7. Review.


54. The reporting pattern in VigiBase® of TLS as an adverse drug reaction for any drug during recent years would suggest an overall increase in the incidence of TLS in association to targeted cancer therapy and in solid tumour indications. In line with this some authors have noted that TLS would be expected to increase also in non-hematologic malignancies with more effective treatment, i.e. targeted therapy, including vemurafenib. A causal relationship between vemurafenib and TLS is in light of this and with the reported cases not unlikely, as any effective cancer therapy can lead to TLS. As mentioned previously, while being a signal of a serious side effect, the association could equally be seen as a sign of an effective treatment. Physicians treating solid tumours should be made aware of the apparent increased risk of TLS with vemurafenib or other targeted therapies to be able to determine on a case-by-case basis the need for immediate treatment should TLS appear and also for appropriate prophylaxis.

References


Response from Roche

In November 2014 the WHO collaborating centre for international drug monitoring in Uppsala invited Roche to comment on a potential signal of TLS in melanoma patients treated with vemurafenib. They cited 4 cases of TLS associated with vemurafenib treatment in their global ICSR database, VigiBase®. The report concluded that the information was insufficient for causality analysis, but raised concerns over the lack of clinician awareness of TLS and potential causality with vemurafenib.

TLS is an uncommon but potentially fatal syndrome caused by massive tumour cell lysis. This leads to severe electrolyte abnormalities and is often accompanied by acute renal failure. TLS most often occurs after cytotoxic therapy for certain types of lymphoma and leukaemia. TLS also occurs in other tumour types that possess high proliferative rate, large tumour burden, or high sensitivity to cytotoxic therapy. In addition, TLS has been described to occur spontaneously and with other treatment modalities such as radiation and corticosteroids. TLS in solid tumours is felt to be a rare phenomenon, and in 2010 an expert panel did not recommend routine TLS prophylaxis for solid tumours as the estimated risk was below 1 percent.

Vemurafenib inhibits mutant BRAFV600 and is approved for the treatment of metastatic melanoma (mM) harbouring this mutation. To date, there has been no described mechanistic association between the RAF/MEK/ERK pathway and TLS. TLS has also not been described with dabrafenib, another BRAF inhibitor. Currently the vemurafenib reference safety information does not include TLS as an adverse drug reaction.
Preclinical studies do not support an association with TLS.

The literature describes TLS as rare in mM, and there is no epidemiological assessment of the true incidence of TLS in mM. Our literature search via PubMed current as of 3 December 2014 revealed a total of 11 case reports of TLS in mM patients since 1994. All 11 cases described patients with bulky or widely metastatic disease with liver involvement. TLS was attributed to chemotherapy in 5 cases, biological therapy in 1 case, corticosteroids alone in 2 cases, radiation alone in 1 case, and occurred spontaneously in 1 case. Acute renal failure occurred in 10 patients.

As of August 2014, the estimated number of patients exposed to vemurafenib was 28,809 and calculated patient-years of 17,729. The Roche Global Safety Database (RGSD) contained 6 cases of TLS, and included all 4 cases described in the WHO report. We further analysed these 6 cases by applying the case definition of TLS established by Cairo and Bishop. The Cairo and Bishop classification of laboratory TLS stipulates that 2 or more of the following lab changes occur within 3 days before and 7 days after starting therapy. These lab changes are: hyperuricaemia, hyperkalaemia, hyperphosphatemia, and hypocalcaemia. Clinical TLS occurs when these lab changes are accompanied by increased creatinine level, seizures, cardiac dysrhythmia, or death.

All 6 cases of TLS in the RGSD were medically confirmed; 5 patients were treated with vemurafenib for mM and 1 patient for hairy cell leukaemia. These 6 cases reflect a crude reporting rate of 3.4 per 10,000 patient-years. Excluding the hairy cell leukaemia case the 5 cases involving mM reflect a crude reporting rate of 2.8 per 10,000 patient-years. Of the 6 cases, 1 case had acute renal failure and 1 case had a fatal outcome, both involving mM patients. It was uncertain if the fatal outcome was associated with TLS. A quality assessment was not possible for 4 cases that failed to contain sufficient information to apply the TLS case definition. These 4 cases also failed to provide the timing of vemurafenib initiation relative to the onset of TLS and did not provide sufficient clinical information to support the diagnosis of TLS. Therefore the case definition was applied to the remaining 2 cases.

The first case involved an adult female patient who was treated with vemurafenib for mM. TLS was diagnosed 31 days after vemurafenib initiation when the patient developed fevers and chills. The only laboratory results available were white blood cell counts, neutrophil counts, and LDH, which were all normal. Vemurafenib was stopped on the same day but was resumed on an unspecified date and TLS was reported as resolved on day 36. This case failed to meet case definition for TLS and was notable for the unusually long latency between therapy initiation and TLS onset.

We identified 6 cases of TLS in our safety database, but 4 cases lacked sufficient information for further analysis. Of the remaining 2 cases, 1 case failed to meet case definition for TLS primarily due to long latency. In the lone case that did meet the case definition for TLS, it was confounded by concomitant corticosteroids. Our overall assessment showed temporal association and a plausible mechanism of action. This signal, however, lacked statistical correlation, was not specific, and was not supported by experimental evidence or an analogous drug reaction. We found no convincing evidence in our analysis to support a causal relationship between vemurafenib and TLS at this time. Roche recognizes this signal involving TLS and vemurafenib in mM and will continue to monitor the events of TLS through routine pharmacovigilance activities.

References
**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®.**

2011
Summary of Recommendations from the Twelfth Meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP)
15-16 April 2015, Geneva

The WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) has been constituted to provide advice on Pharmacovigilance (PV) policy and issues related to the safety and effectiveness of medicinal products. A summary of recommendations from the 12th meeting of ACSoMP is included below.

Specific recommendations:

- WHO should establish a strategic sub-group of the Committee to help align the ACSoMP Terms of Reference with the requirements of the reorganised Safety & Vigilance (SAV) Team in WHO and to guide the work of all five WHO Collaborating Centres that support the work of WHO Safety & Vigilance Team.

- WHO/SAV should work with its Collaborating Centres to develop a pharmacovigilance (PV) strategy with a road map and an annual work plan for the programme; and manage and sustain resources for the activities.

- WHO and its Collaborating Centres should work with countries to strengthen PV systems, and to decrease the lag times between the general occurrence of a medicine-related adverse event and recording the event in VigiBase (the WHO global database of Individual Case Safety Reports (ICSRs)).

- The WHO/SAV and its Collaborating Centres should meet regularly, and co-ordinate and plan training programmes collectively to ensure they complement each other.

- The algorithm developed by the Uppsala Monitoring Centre (UMC) to detect substandard/spurious/falsely-labelled/falsified/counterfeit (SSFFC) medical products in large ICSR databases should be tested in regions such as the East African Community (EAC). A sub-committee should be established to work with WHO/SAV team and the EAC to take this forward and link with ongoing counter-SSFFC initiatives.

- WHO/SAV should develop a follow-on document to the WHO handbooks on Cohort Event Monitoring (CEM), to define and describe the criteria and various scenarios in which CEM could be used, together with examples of research questions in public health programmes that may be addressed by CEM. A working group from ACSoMP should review the value added with CEM, analyse the cost-benefit of CEM, and options for managing and analysing data from CEM.

- UMC should develop guidelines for national pharmacovigilance centres on how best to manage their PV data. Clear guidance should also be provided on the roles and responsibilities of various stakeholders involved in different aspects of data management.

- SAV to establish a sub-committee within ACSoMP to work with WHO/SAV and Neglected Tropical Disease (NTD) teams for integrating PV within neglected tropical disease prevention and treatment programmes.

- In 2012, WHO made a recommendation for the implementation of seasonal malaria chemoprevention (SMC) in areas of Sahel sub-regions where highly seasonal malaria transmission occurs. This consists of a combination of amodiaquine and sulfadoxine-pyrimethamine (AQ + SP) which will be administered to children aged between 3 and 59 months at monthly intervals, beginning at the start of the transmission season, to a maximum of four doses during the malaria transmission season, provided both drugs retain sufficient antimalarial activity. The policy also recommends that PV should be strengthened where it exists, and where there is no PV, it should be instituted. ACSoMP recommends that all adverse events (both serious and non-serious events) should be collected in countries where SMC will be launched; WHO (SAV and TDR, the special programme for Research and Training in Tropical Diseases) should work with partners to ensure this. ACSoMP also recommends that an independent regional committee should be established by WHO TDR and its consortium of partners engaged in the SMC initiative, to review the safety

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1 WHO Collaborating centres: WHO Collaborating Centre for International Drug Monitoring, The Uppsala Monitoring Centre, Uppsala, Sweden; WHO Collaborating Centre for Drug Statistics and Methodology, Oslo, Norway; WHO Collaborating Centre for Advocacy & Training in Pharmacovigilance, Accra, Ghana; WHO Collaborating Centre for Pharmacovigilance, Rabat, Morocco; Pharmacovigilance in Education and Patient Reporting, ’s-Hertogenbosch, the Netherlands.
data from the SMC initiative and to report to ACSoMP at its next meeting in 2016, or through other ad hoc meetings if needed. PV support for SMC should build on existing systems; in the absence of a PV system in a country, SMC should be leveraged to introduce PV within the country.

- The ACSoMP will remain prepared to advise, if needed, on the deployment of therapeutics, vaccines and health system strengthening initiatives in relation to the WHO response to Ebola Virus Disease (EVD). WHO/SAV should keep the Committee informed on current developments and WHO initiatives related to EVD-response.

- The African Medicines Regulatory Harmonization (AMRH) Initiative was established in 2009 following the efforts of WHO, the New Partnership for Africa’s Development (NEPAD), World Bank and others. AMRH aims to improve the access to safe and effective medicines in Africa through regulatory harmonization in the continent. Pharmacovigilance has been included as a component within the AMRH initiative. WHO has reviewed and discussed the PV proposal with ACSoMP. ACSoMP will guide WHO/SAV in drafting a document to highlight the importance of including pharmacovigilance in the AMRH initiative, clarifying the vision and priorities for PV within the initiative, incorporating lessons learnt from other harmonization models, and building on good science, existing systems and networks.

- WHO/SAV routinely receives requests from WHO Member States from individuals working in pharmacovigilance in low- and middle- income countries for learning opportunities in PV through exchange visits with well-resourced regulatory agencies such as the US FDA, MHRA, EMA etc. SAV will follow up with a strategy to manage such requests and facilitate learning opportunities through various mechanisms including bilateral cooperative agreements with selected regulatory agencies.

**General Recommendations**

- Early involvement of WHO/SAV in WHO public health programmes is recommended, commencing already at the planning stage of the programme, together with relevant resources for SAV, to better plan and support PV requirements and applications within these programmes.

- Risk management plans should be an inherent part of all public health programmes.

- Public health programmes can learn from each other, hence it is recommended that public health programmes share what they are doing in PV, for example, through a conference day on PV, facilitated by the SAV team, to discuss common PV needs and shared solutions.
Implementing Patient Reporting of Adverse Reactions in Ghana
Mrs Delese Mimi Darko and Mr George Sabblah (Food and Drugs Authority, Ghana)

Background
The contribution of patients towards ensuring the safety of marketed drugs and vaccines cannot be underestimated. First of all patients can communicate their own adverse experiences with medicines better than health-care professionals. And secondly, patients are more motivated and better placed to observe the signs and symptoms of their adverse events more comprehensively than health-care professionals. Patients will therefore record with precision, any adverse experiences with their medicines and other health products.

Patients’ Contribution to Spontaneous Reporting
Since Ghana joined the WHO Programme for International Drug Monitoring in November 2001, adverse drug reaction reports from patients have been received mainly through their health-care professionals. Direct reporting by patients has been discussed in the past, but has not been fully implemented; the National Pharmacovigilance Centre (NPvC) has received only two reports directly from patients since 2005. The NPvC at the Food and Drugs Authority (FDA) in Ghana has made good progress with its plans to introduce patient reporting. It is expected that the FDA will fully launch patient reporting by the fourth quarter of 2015. It is hoped that implementing this programme will improve the adverse reaction reporting rate and contribute to the generation of signals and early detection of safety problems with drugs, vaccines and other health products being marketed in Ghana.

The NPvC receives on an average 12 adverse drug reaction reports per 1,000,000 inhabitants per year for a population of approximately 27,000,000. This figure is less than the Uppsala Monitoring Centre (UMC) experience, that a fully functional pharmacovigilance system receives 200-250 reports per million inhabitants per year. Due to a high level of underreporting it is possible that safety problems with medicines used in Ghana will go undetected. In view of this the NPvC is being supported by the United Kingdom’s Department for International Development (DFID), to introduce patient/consumer reporting in an attempt to boost adverse reaction reporting, and also increase the chances of early detection of safety problems.

Benefits of Patient Reporting
There are also several other benefits of patient reporting:
1) Patient reports are direct, detailed and unambiguous because these reports describe exactly how the patient feels.
2) Reports from patients will usually provide information on concomitant medicines, including herbal medicines and over-the-counter medicines. This is an important aspect given the high level of self-medication in the country.
3) Spontaneous reporting by patients has important benefits beyond pharmacovigilance because the patient plays an active role in his or her treatment regimen instead of being a largely passive recipient of treatment.
4) In the process of actively reporting any adverse reactions to their medicines, the patient learns how to manage his/her medicines and to communicate more effectively with, and better provide critical information to their health professionals.

The Strategy in Ghana
The NPvC is working with the Pharmaceutical Society of Ghana through the Community Pharmacy Practice Association (CPPA) to promote Patient Reporting by designating participating Community Pharmacies as “Patient Safety Centres”.

Community Pharmacies have been chosen to introduce this concept because of easy accessibility to patients within the community and also on account of the services they offer, which are quicker and meet the primary
health-care needs of the population. Since most patients visit Community Pharmacies as compared to hospitals and clinics, it is expected that greater number of safety issues with health products will be reported to these pharmacies.

Community Pharmacies that apply to participate will then be responsible for teaching patients how to complete the BlueForm® (the Patient Reporting Form), making the forms available to patients who visit their facilities and collating the forms for onward submission to the NPvC.

The patient reporting concept will also be promoted through the print and electronic media using posters, billboards, advertisement in newspapers, television and radio, text messaging, social media and other internet platforms.

**Motivation for Professionals and Benefits for Health-care**

In addition to the overall goal of promoting patient safety, the NPvC believes these activities will also motivate pharmacies to participate in the programme. Pharmacies that perform exceptionally well will be awarded with varying levels of certificates (Bronze, Silver and Gold) and ultimately, a plaque.

It will also improve confidence of patients in services provided by pharmacies, contribute to rational use of drugs and improve pharmaceutical care provided by community pharmacies in Ghana.