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The aim of the Newsletter is to disseminate information on the safety and efficacy of pharmaceutical products, based on communications received from our network of "drug information officers" and other sources such as specialized bulletins and journals, as well as partners in WHO.

The information is produced in the form of résumés in English, full texts of which may be obtained on request from:

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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®.

As the Feature article, we have included a brief report from two recent WHO-led pharmacovigilance training events.

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Agomelatine

Risk of hepatic injury

Australia. The Therapeutic Goods Administration (TGA) has informed health professionals that the Product Information (PI) for agomelatine (Valdoxan®) has been updated to include further information about the risk of hepatic injury.

Agomelatine is a melatonin receptor (MT_1 and MT_2) agonist and 5-hydroxytryptamine (serotonin) receptor 2C antagonist. It is indicated for treatment of major depression in adults, including prevention of relapse.

The updated PI advises caution should be taken before initiation of treatment with agomelatine, and there should be close surveillance of liver function during continuation of treatment. This is important if agomelatine is used in combination with other medicines associated with risk of hepatic injury or where risk factors for hepatic injury, such as overweight/obesity, non-alcoholic fatty liver disease, diabetes and substantial alcohol consumption, are present.

In addition, liver function tests are recommended for all patients before initiation of treatment and/or after a dose increase. Tests should be repeated at week three, six, 12, 24 post initiation of treatment, after a dose increase and thereafter when clinically indicated.

Treatment should not be initiated if serum transaminase levels are greater than three times the upper limit of the normal range. If pre-treatment transaminase levels are greater than the upper limit of the normal range (but less than three times the upper limit), agomelatine should be used with caution.

Reference:
Medicines Safety Update, TGA, Vol. 6, No. 2, April 2015 (*www.tga.gov.au*)

(See WHO Pharmaceuticals Newsletters No.1, 2015 for risk of serious hepatic adverse reactions with agomelatine in Ireland, No.6, 2014 for risk of liver toxicity in Europe and No.6, 2012 for risk of dose-related hepatotoxicity and liver failure in the UK)

Amiodarone and hepatitis C treatments containing sofosbuvir

Serious slowing of the heart rate with co-administration

Egypt, EU and **USA.** The regulatory authorities have warned of serious symptomatic bradycardia when antiarrhythmic drug amiodarone is used with hepatitis C treatments containing sofosbuvir in combination with other drugs (e.g. ledipasvir, daclatasvir or simeprevir).

Sofosbuvir containing medicines (Harvoni® and Sovaldi®) are indicated for treatment of chronic hepatitis C virus, which can last a lifetime and lead to serious liver problems, including cirrhosis or liver cancer.

The US Food and Drug Administration (FDA) review of post-market reports of adverse events found that patients can develop serious and life-threatening symptomatic bradycardia when a sofosbuvir containing hepatitis C drug in combination with another direct-acting antiviral is taken together with amiodarone. The reports included the death of one patient due to cardiac arrest and three patients requiring placement of a pacemaker to regulate their heart rhythms. The other patients recovered after discontinuing either the hepatitis C drugs or amiodarone, or both. The cause of these events could not be determined. The FDA will continue to monitor sofosbuvir containing hepatitis C drugs for risks of serious symptomatic bradycardia and further investigate the reason why the use of amiodarone with these hepatitis C drugs led to the heart-related events.

The FDA recommends heart monitoring in an inpatient hospital setting for the first 48 hours. Subsequently, monitoring in a doctor's office or self-monitoring of the heart rate should be done every day through at least the first 2 weeks of treatment. Patients discontinuing amiodarone just prior to starting sofosbuvir containing hepatitis C drugs in combination with another direct-acting antiviral, should also undergo similar cardiac monitoring as outlined above.

The FDA is adding information about serious slowing of the heart rate, known as symptomatic bradycardia, to the labels of sofosbuvir containing hepatitis C drugs.

The Egyptian Pharmaceutical Vigilance Center (EPVC) has advised health-care professionals;

- A fixed dose combination with ledipasvir/sofosbuvir should not be co-administered with amiodarone.
- Sofosbuvir combined with another hepatitis C drug, such as investigational drug daclatasvir or simeprevir, should not be co-administered with amiodarone.
- Patients should be advised to seek medical attention immediately if they have signs and symptoms of symptomatic bradycardia including:

  - near-fainting or fainting (syncope)
  - dizziness or light headedness
  - malaise
  - weakness
  - excessive tiredness
  - shortness of breath
  - chest pains
  - confusion or memory problems
- For patients taking amiodarone who have no other alternative treatment options and who will be co-administered either a fixed dose combination with ledipasvir/sofosbuvir or sofosbuvir in combination with another direct acting antiviral:
  - counsel patients about the risk of serious symptomatic bradycardia
  - cardiac monitoring in an in-patient setting for the first 48 hours of co-administration is recommended, after which outpatient or self-monitoring of the heart rate would occur on a daily basis through at least the first 2 weeks of treatment
- Patients who are taking either a fixed dose combination with ledipasvir/sofosbuvir or sofosbuvir in combination with another direct acting antiviral, who need to start amiodarone therapy due to no other alternative treatment options, should undergo similar cardiac monitoring as outlined above.
- Due to the long half-life of amiodarone, patients discontinuing amiodarone just prior to starting a fixed dose combination with ledipasvir/sofosbuvir or sofosbuvir in combination with another direct-acting antiviral, should also undergo similar cardiac monitoring as outlined above.
- Encourage patients to read the patient information leaflet they receive with their prescription hepatitis C drugs and amiodarone as there may be new information.

Information in EU for health-care professionals include:

- Severe bradycardia and heart block have been reported in patients taking amiodarone and combination of sofosbuvir with ledipasvir, or amiodarone and a combination of sofosbuvir and daclatasvir. Of 8 cases reviewed up to April 2015, one case resulted in fatal cardiac arrest and two required pacemaker intervention.
- Onset of bradycardia was within 24 hours of initiating hepatitis C treatment in 6 cases and within 2 to 12 days in the other 2 cases. Rechallenge in the context of continued amiodarone treatment resulted in recurrence of symptomatic bradycardia in 2 cases. Recurrence was also seen on rechallenge with the antivirals 8 days after stopping amiodarone, but not 8 weeks after stopping.
- Amiodarone should only be initiated in patients treated with combination of sofosbuvir with ledipasvir, or sofosbuvir plus daclatasvir, if other antiarrhythmics are contra-indicated or not tolerated.
- If concomitant use with amiodarone is unavoidable, patients should be closely monitored, particularly during the first weeks of treatment. Those at high risk of bradyarrhythmia should be monitored in an appropriate clinical setting for 48 hours after starting concomitant treatment.
- Due to its long half-life, patients who have discontinued amiodarone within the past few months should also be monitored when starting hepatitis C treatment with combination of sofosbuvir with ledipasvir, or sofosbuvir plus daclatasvir.
- Patients receiving these hepatitis C medicines with amiodarone, with or without other medicines that lower heart rate, should be warned of the symptoms of bradycardia and heart block and should be advised to seek urgent medical advice if they experience them.
- The product information for these hepatitis C medicines will be updated appropriately. A letter will also be sent to health-care professionals involved in hepatitis C treatment explaining these risks and the measures to manage them.
- Because the number of patients taking amiodarone who have been exposed to combination of sofosbuvir with ledipasvir, or sofosbuvir plus daclatasvir is unknown, it is not possible to estimate the incidence of occurrence of these events. The mechanism behind the findings has not been established.

The regulatory authorities recommend that health-care professionals should not prescribe sofosbuvir containing hepatitis C drugs combined with another direct-acting antiviral drug with amiodarone. However, in cases where alternative treatment options are unavailable, patients should be closely monitored. As amiodarone persists for a long time in the body, monitoring is also needed if patients start such hepatitis C treatments within a few months of stopping amiodarone.

References:

Newsletter, Egyptian Pharmaceutical Vigilance Center (EPVC), Volume 6, Issue 5, May 2015

Press release, EMA, 24 April 2014 (*www.ema.europa.eu*)

Drug Safety Communication, US FDA, 24 March 2015 (*www.fda.gov*)

Amphetamines and methylphenidate

Risk of suicidal thoughts and behaviours

Canada. A safety review was initiated to evaluate information regarding the potential risk of suicidal related thoughts and behaviours with the use of amphetamine products or methylphenidate.

Amphetamine products (amphetamine, dextroamphetamine and lisdexamfetamine) and methylphenidate are used for the treatment of attention-deficit hyperactivity disorder (ADHD) in adults and children 6 years of age and older.

Cases of suicide related events have been reported with the use of amphetamine products or methylphenidate internationally. ADHD can be associated with other mental health conditions that may increase the risk of suicidal related thoughts and behaviours. Whilst most reports originating from Canada reported suicidal thoughts, a small number of suicide attempts and suicides were also reported. In general, the review of Canadian cases suggests that the use of amphetamine products or methylphenidate may contribute to suicidal related thoughts or actions in some patients with ADHD, either alone or in association with other mental conditions. At present, there is little information in the scientific literature to support this association.

A communication notifying the risk of suicide related thoughts and behaviours associated with amphetamine products and methylphenidate has been issued. Prescribing information for all amphetamine products and methylphenidate will be updated to include: reports of rare cases of suicidality in patients taking amphetamine products or methylphenidate. Although evidence is limited patients should be monitored for signs of suicidality.

Risks of suicide related thoughts and behaviours associated with the use of amphetamine products or methylphenidate will be continued to be monitored and evaluated.

Reference:
Summary Safety Review, Health Canada, 30 March 2015 (*www.hc-sc.gc.ca*)

Asunaprevir and daclatasvir hydrochloride

Risk of erythema multiforme

Japan. The Ministry of Health Labour and Welfare (MHLW) and the Pharmaceutical and Medical Devices Agency (PMDA) have announced the revision of the package insert for asunaprevir (Sunvepra®) and daclatasvir hydrochloride (Daklinza®) to include risk of erythema multiforme, following reports of cases occurring in Japan.

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

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

Erythema multiforme: Erythema multiforme may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

Reference:
Revision of Precautions, MHLW/PMDA, 23 April 2015 (*www.pmda.go.jp/english/*)

Azilsartan

Risk of "hepatic function disorder"

Japan. The MHLW and the PMDA have announced the revision of the package insert for azilsartan (Azilva®) to include risk of hepatic function disorder.

Azilsartan is indicated for hypertension.

The MHLW/PMDA stated that cases of hepatic function disorder have been reported in patients treated with azilsartan 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 package insert."

Hepatic function disorder: Hepatic function disorder associated with elevated AST (GOT), ALT (GPT), and γ-GTP levels may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

Reference:
Revision of Precautions,

MHLW/PMDA, 23 April 2015 (*www.pmda.go.jp/english/*)

BioCSL Fluvax®

Not for children under 5 years

Australia. The TGA has warned that health professionals should be reminded that bioCSL Fluvax® is registered for use in children from the age of 5 years and older, and must not be used in children under 5 years of age due to an increased risk of fever and febrile convulsions. The TGA also advises health professionals to avoid using Fluvax® as a generic term for influenza vaccine to minimise the potential for confusion.

The information is reinforced in the black box warning in the PI as follows:
WARNING: This season's vaccine is indicated for use only in persons aged 5 years and over. It must not be used in children under 5 years. It should only be used in children aged 5 to under 9 years based on careful consideration of potential risks and benefits in the individual.

Reference:
Medicines Safety Update, TGA, Vol. 6, No. 2, April 2015 (*www.tga.gov.au*)

Cefotaxime sodium

Risk of acute generalised exanthematous pustulosis

Japan. The MHLW and the PMDA have announced the revision of the package insert for cefotaxime sodium (Claforan® and Cefotax®) to include risk of acute generalised exanthematous pustulosis.

Cefotaxime sodium is an antibacterial agent used for treatment of infections such as: sepsis, infective endocarditis, secondary infections secondary to trauma, thermal burn, surgical wound, acute bronchitis, pneumonia, and lung abscess.

The MHLW/PMDA stated that cases of acute generalised exanthematous pustulosis have been reported in patients treated with cefotaxime sodium in other countries, and the company core datasheet (CCDS) has been updated.

Based on expert advice and available evidence, the MHLW/PMDA have recommended that: "acute generalised exanthematous pustulosis" should be added to the "Clinically significant adverse reactions" subsection of the "Adverse reactions" section in package insert.

Reference:
Revision of Precautions, MHLW/PMDA, 23 April 2015 (*www.pmda.go.jp/english/*)

Clopidogrel sulphate containing medicines

Risk of acute generalised exanthematous pustulosis

Japan. The MHLW and the PMDA have announced the revision of the package insert for clopidogrel sulphate (Plavix®) and clopidogrel sulphate/aspirin combination (Complavin Combination®) to include risk of acute generalised exanthematous pustulosis.

Clopidogrel sulphate containing medicines are indicated for suppression of recurrence after ischaemic cerebrovascular disorder and inhibition of thrombogenesis/embolization in peripheral arterial disease.

The MHLW/PMDA stated that cases of acute generalised exanthematous pustulosis have been reported in patients treated with clopidogrel sulphate in Japan and other countries, and the CCDS has been updated.

Based on expert advice and available evidence, the MHLW/PMDA have recommended that "acute generalised exanthematous pustulosis" should be added to the "Clinically significant adverse reactions" subsection of the "Adverse reactions" section in package insert.

Reference:
Revision of Precautions, MHLW/PMDA, 23 April 2015 (*www.pmda.go.jp/english/*)

Codeine-containing medicines

Not to be used in children below 12 years for cough and cold

EU. The EMA announced that the consensus of the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) are introducing new measures to minimise the risk of serious adverse effects (e.g. breathing problems), with codeine-containing medicines, when used for cough and cold in children. As a result of these new measures:

- Use of codeine for cough and cold is now contraindicated in children below 12 years.
- Use of codeine for cough and cold is not recommended in children and adolescents between 12 and 18 years who have breathing problems.

The measures, recommended by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) will be directly implemented by

the Member States where the medicines are authorised, according to an agreed timetable.

Codeine is an opioid medicine that is converted into morphine in the body. High levels of morphine can lead to serious adverse effects, such as breathing difficulties. Codeine is converted into morphine in children below 12 years in a more unpredictable manner, making this population at special risk of such adverse effects. Children with existing breathing difficulties are more susceptible to respiratory effects of codeine. Codeine is widely used for pain relief and for the treatment of cough and cold symptoms. In the EU, codeine-containing medicines have been approved via national procedures, and are available either on prescription or over the counter in the different Member States. Codeine is marketed as a single-ingredient medicine or in combination with other active substances.

The PRAC also noted that cough and cold are generally self-limiting conditions and the evidence that codeine is effective at treating cough in children is limited.

In addition to the new measures for children, codeine must also not be used in people of any age who are known to convert codeine into morphine at a faster rate than normal ('ultra-rapid metabolisers') nor in breastfeeding mothers, as codeine can harm the baby because it passes into breast milk.

Information for health-care professionals:

- Codeine for cough and cold is now contraindicated in children below 12 years, and not recommended in children between 12 and 18 years with compromised respiratory function.
- Codeine is also contraindicated in women during breastfeeding and patients known to be CYP2D6 ultra-rapid metabolisers.

Reference:
Press release, EMA, 24 April 2014 (*www.ema.europa.eu*)

(See WHO Pharmaceuticals Newsletters No.5, 2013 for restrictions on use of codeine for pain relief in children in Europe and in the UK, No.4, 2013 for restricted use as analgesic in children and adolescents under 18 in the UK and No.5, 2012 for use in certain children after tonsillectomy and/or adenoidectomy - risk of rare, but life-threatening adverse events or death in the USA)

Cyclophosphamide hydrate

Risk of rhabdomyolysis

Japan. The MHLW and the PMDA have announced the revision of the package insert for cyclophosphamide hydrate (Endoxan®) to include risk of rhabdomyolysis.

Cyclophosphamide hydrate has various indications, including multiple myeloma, malignant lymphoma, lung cancer, breast cancer, acute leukaemia, and bone tumour etc.

The MHLW/PMDA stated that cases of adverse events suggestive of rhabdomyolysis have been reported in patients treated with cyclophosphamide hydrate injections in Japan.

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

Rhabdomyolysis:
Rhabdomyolysis characterized by myalgia, feelings of weakness, increased creatine kinase (creatine phosphokinase), increased blood myoglobin, and increased urine myoglobin may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

Reference:
Revision of Precautions, MHLW/PMDA, 24 March 2015 (*www.pmda.go.jp/english/*)

Duloxetine hydrochloride

Risk of neuroleptic malignant syndrome

Japan. The MHLW and the PMDA have announced the revision of the package insert for duloxetine hydrochloride (Cymbalta®) to include risk of neuroleptic malignant syndrome.

Duloxetine hydrochloride is indicated for depression/depressed state and diabetic peripheral neuropathic pain.

The MHLW/PMDA stated that cases of neuroleptic malignant syndrome have been reported in patients treated with duloxetine hydrochloride in Japan.

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

Neuroleptic malignant syndrome:
Neuroleptic malignant syndrome may occur. If any abnormalities such as fever,

akinetic mutism, strong muscle rigidity, swallowing difficult, tachycardia, blood pressure fluctuation, diaphoresis, increased white blood cell count, increased serum creatine kinase (creatine phosphokinase), etc. are observed, administration of this drug should be discontinued. Then whole-body control such as body cooling and rehydration should be conducted, and appropriate measures should be taken. In addition, decreased kidney function with myoglobinuria may lead to acute renal failure, and caution should therefore be exercised.

Reference:
Revision of Precautions, MHLW/PMDA, 23 April 2015 (*www.pmda.go.jp/english/*)

Epoetin beta

Increased risk of retinopathy in preterm infants cannot be excluded

UK. The Medicines and Health-care Products Regulatory Agency (MHRA) has warned of a possible increase in risk of retinopathy with epoetin beta in premature infants, particularly those with an underlying risk: born before 31 weeks of gestation, and those weighing less than 1.25 kg. The summary of product characteristics will be amended to include possible risk of retinopathy.

Epoetin beta (NeoRecormon®) is indicated for the prevention of anaemia of prematurity in infants with a birth weight of 0.75 to 1.5 kg and a gestational age of less than 34 weeks. Epoetin beta is identical to erythropoietin, a hormone that stimulates the production of red blood cells.

The MHRA has warned that when using epoetin beta for preventing anaemia of prematurity:

- consider the benefits and risks, including the possible risk of retinopathy
- monitor the infant for features of retinopathy
- advise parents or carers that their baby's eyes will be carefully monitored for any ill effects

This recommendation follows an European review that evaluated current evidence of retinopathy associated with epoetin beta treatment of anaemia of prematurity. Two systematic reviews investigating effectiveness also considered adverse effects, including retinopathy of prematurity.

Collectively the reviews suggest that epoetin beta may increase the underlying risk of retinopathy in premature infants.

The European review of available data concluded that more data are needed to draw a firm conclusion about erythropoietin and the risk of retinopathy of prematurity. However, the available data show that an increase in the underlying risk of retinopathy in premature infants with early epoetin use cannot be excluded.

Reference:
Drug Safety Update, MHRA, Volume 8, issue 10: 3, May 2015 (*www.gov.uk/mhra*)

Ferumoxytol

Risk of fatal allergic reactions

USA. The FDA has strengthened an existing warning of serious, potentially fatal allergic reactions with the anaemia drug ferumoxytol (Feraheme®). Prescribing instructions were changed to include a Boxed Warning and a contradiction with a strong recommendation against use of ferumoxytol in patients who have had an allergic reaction to any intravenous (IV) iron replacement product.

At the time of ferumoxytol's approval in 2009, this risk was described in the Warnings and Precautions section of the drug label. Since then, serious reactions, including deaths, have occurred. The FDA is continuing to monitor and evaluate the risk of serious allergic reactions with all IV iron products.

Ferumoxytol is in a class of medicines called IV iron replacement products. It is used to treat iron-deficiency anaemia—a condition in which there is a lower than normal number of oxygen-carrying red blood cells because of too little iron. Ferumoxytol is specifically approved for use only in adult patients with iron deficiency anaemia due to chronic kidney disease.

Based on the FDA evaluation, the following recommendations for health-care professionals were made:

- Only administer IV iron products to patients who require IV iron therapy.
- Do not administer ferumoxytol to patients with a history of allergic reaction to ferumoxytol or other IV iron products.
- Only administer diluted ferumoxytol as an IV infusion over a minimum of 15 minutes. Ferumoxytol should not be given as an undiluted IV injection.
- Closely monitor patients for signs and symptoms of serious allergic reactions, including monitoring blood pressure and pulse during ferumoxytol administration and for at least 30 minutes following each infusion.
- Carefully consider the potential risks and benefits of ferumoxytol administration in elderly patients with multiple or serious medical conditions,

as these patients may experience more severe reactions.
- Carefully consider the potential risks and benefits of ferumoxytol administration in patients with a history of multiple drug allergies. Patients with multiple drug allergies may also be at higher risk.

Reference:
Drug Safety Communication, US FDA, 31 March 2015 (*www.fda.gov*)

(See WHO Pharmaceuticals Newsletters No.5, 2014 for risk of serious hypersensitivity reactions in the UK and No.4, 2014 for hypersensitivity reaction in Canada)

Hydroxyzine-containing medicines

Risks of effects on heart rhythm

EU. The EMA has introduced new measures to minimise the risk of effects on heart rhythm with medicines containing the antihistamine hydroxyzine. The measures include restricting use of hydroxyzine in patients at high risk of problems with heart rhythm and using the medicine at the lowest effective dose for as short a time as possible.

Hydroxyzine medicines are available in most EU countries. Their approved uses (indications) vary between countries and may include treatment of anxiety disorders, relief of pruritus (itching), premedication before surgery, and treatment of sleep disorders. Hydroxyzine has the potential to block hERG channels and other types of cardiac channels, resulting in a potential risk of QT interval prolongation and cardiac arrhythmia events.

The EMA PRAC evaluated evidence of abnormal heart rhythms associated with hydroxyzine and have concluded that the risk did not differ between indications and that such events are most likely to occur in patients who have risk factors.

The new measures will be directly implemented by the Member States where the medicines are authorised. In particular, the product information of hydroxyzine-containing medicines will be updated with new dosing recommendations and warnings on use in patients who have risk factors for heart rhythm disturbances or who are taking certain medicines.

The EMA informed health-care professionals with the following:
- The maximum dose in adults should be a total of 100 mg daily; in the elderly, if use cannot be avoided the maximum daily dose should be 50 mg. The maximum daily dose in children up to 40 kg in weight should be 2 mg/kg/day; children over 40 kg should be given the adult dose.
- Use of hydroxyzine is contraindicated in patients with known acquired or congenital QT interval prolongation, or with a known risk factor for QT interval prolongation such as cardiovascular disease, significant electrolyte imbalance (hypokalaemia, hypomagnesaemia), family history of sudden cardiac death, significant bradycardia, or concomitant use of drugs known to prolong the QT interval and/or induce torsades de pointes.
- Use is not recommended in elderly patients, due to reduced elimination of hydroxyzine in these patients and greater vulnerability to anticholinergic effects and other adverse reactions. The medicine should be used with caution in patients with bradycardia, or who are taking hypokalaemia-inducing medicines. Care is also required when hydroxyzine is co-administered with drugs known to be potent inhibitors of alcohol dehydrogenase or CYP3A4/5.

Reference:
Press release, EMA, 27 March 2014 (*www.ema.europa.eu*)

Methylphenidate

Risk of priapism

Canada. Health Canada announced that the prescribing information for all brand name (Biphentin®, Concerta®, Ritalin®) and generic methylphenidate products will be updated to include the risk of priapism.

Methylphenidate products are used for the treatment of ADHD in adults and children 6 years of age and over.

Priapism (prolonged and painful erection) is a rare but serious adverse reaction that requires immediate medical attention to prevent possible long-term effects on the penis.

A safety review was initiated following the recommendation by the US FDA stating that all methylphenidate product labels and patient Medication Guides should be updated to include information about the risk of priapism.

Health Canada's actions were based on one report of priapism associated with the use of methylphenidate received at the time of review, together with a small number of cases of priapism in association with methylphenidate products reported internationally and in the literature. In nearly half of these cases, methylphenidate

products were found to be the probable cause of priapism.

Priapism has been reported during treatment with methylphenidate products after increasing the dose or stopping the product even for a short period of time.

The prescribing information for all brand name and generic methylphenidate products will be updated to include the very rare risk of priapism. Health Canada has issued a communication to inform health-care professionals and patients about the possibility of priapism associated with the use of methylphenidate products.

Reference:
Summary Safety Review, Health Canada, 21 April 2015 (*www.hc-sc.gc.ca*)

(See WHO Pharmaceuticals Newsletters No.5, 2014 for risk of priapism in Australia and No.1, 2014 for risk of long-lasting erections in the US)

Non-steroidal anti-inflammatory drugs and diclofenac

Cardiovascular risks

Australia. The TGA has informed health professionals of changes in PI and labels for non-steroidal anti-inflammatory drugs such as diclofenac, naproxen, ibuprofen, celecoxib, etoricoxib, indomethacin, meloxicam and piroxicam, to include cardiovascular risks. Diclofenac, naproxen and ibuprofen are available as OTC oral dosage forms (in lower doses). Diclofenac ibuprofen and piroxicam are also available as an OTC topical gel.

The changes follow a review of approximately 200 publications, information from companies, reports collected by TGA and expert advice obtained from the Advisory Committee on the Safety of Medicines. In addition, a full safety review of diclofenac was considered. The reviews found that OTC NSAIDs were safe if used according to the recommended doses for short durations, as instructed on the label. However, inappropriate use or overuse of these medicines could pose a significant risk of cardiovascular events and, in the case of diclofenac, hepatotoxicity.

Product labelling for OTC diclofenac, naproxen and ibuprofen did not carry strong enough warnings regarding these risks for all patients, or adequate advice for people with cardiovascular disease or risk factors.

TGA has advised health professionals to:

- avoid using prescription NSAIDs in patients who have previously had myocardial infarction, angina, cardiac failure, hypovolemia, significant peripheral vascular disease or pre-existing significant renal/hepatic dysfunction.
- use these medicines with caution in patients with identifiable risks factors for cardiovascular disease, undertaking individual assessment of each patient to ensure the benefits outweigh the risks.
- consider advising patients of the increased cardiovascular risks of using NSAIDs, including OTC products, and educating them regarding the signs and symptoms of serious cardiovascular events. Instruct them to seek medical attention immediately if they experience any.
- be aware that, in rare cases, diclofenac has been associated with a risk of hepatotoxicity and should be used at the lowest effective dose for only short periods of time.

Reference:
Medicines Safety Update, TGA, Vol. 6, No. 2, April 2015 (*www.tga.gov.au*)

(See WHO Pharmaceuticals Newsletters No.2, 2015, No.5, 2014, No.5, 2013, No.4, 2013 and No.6, 2012 for related information)

Oral ibuprofen

Risk of serious heart and stroke adverse events at high doses

Canada. Health Canada announced an update of prescribing information for ibuprofen-containing products, to include an increased risk of serious heart and stroke adverse events when taken at a daily dose of 2400 mg or more.

This follows a safety review of evidence by Health Canada to evaluate the possible link between heart and stroke related adverse events and the use of ibuprofen especially at high doses compared to other NSAIDs, including COX-2 selective inhibitors like celecoxib (Celebrex®).

Evidence of an association between oral ibuprofen at a daily dose of 2400 mg or more and an increased risk of heart attack and stroke related adverse events was found.

This was not found for OTC use at the maximum daily doses of 1200 mg or less. These findings were comparable to those associated with COX-2 inhibitors. The risk increases when ibuprofen is taken for a long duration and among patients having a history of, or risk factors for heart disease, stroke, or uncontrolled blood pressure.

Ibuprofen is an NSAID used to treat pain, reduce fever, and relieve inflammation. Most ibuprofen-containing products are sold as OTC preparations for use by adults and children.

These products contain 400 mg or less of ibuprofen, and the maximum recommended daily dose of ibuprofen for these products is 1200 mg. Products containing 600 mg of ibuprofen are available by prescription only for use by adults and children above 12 years to relieve the symptoms of arthritis (osteoarthritis and rheumatoid arthritis). The maximum recommended daily dose of ibuprofen for these prescription products is 2400 mg.

The overall benefits of ibuprofen continue to outweigh the risks when used as recommended. Oral ibuprofen at a daily dose of 2400 mg should be avoided in patients, with ischemic heart disease, cerebrovascular disease, congestive heart failure or with risk factors for cardiovascular disease.

Reference:
Summary Safety Review, Health Canada, 23 April 2015 (*www.hc-sc.gc.ca*)

Panitumumab

Risk of oculomucocutaneous syndrome (Stevens–Johnson syndrome)

Japan. The MHLW and the PMDA have announced the revision of the package insert for panitumumab (Vectibix®) to include information on oculomucocutaneous syndrome.

Panitumumab is indicated for KRAS wild-type, incurable, unresectable, advanced/recurrent colorectal cancer.

The MHLW/PMDA stated that cases of adverse events suggestive of oculomucocutaneous syndrome (Stevens–Johnson syndrome) have been reported in patients treated with panitumumab in Japan and in other countries, and the MHLW/PMDA also stated the CCDS for panitumumab has been revised to include information on oculomucocutaneous syndrome.

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

Oculomucocutaneous syndrome (Stevens–Johnson syndrome):
Oculomucocutaneous may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

Reference:
Revision of Precautions, MHLW/PMDA, 24 March 2015 (*www.pmda.go.jp/english/*)

(See WHO Pharmaceuticals Newsletter No.5, 2012 for risk of necrotising fasciitis in the UK)

Panitumumab and cetuximab

Necessity of assess the RAS (KRAS and NRAS) gene mutation status and select the suitable patients

Japan. The MHLW and the PMDA have announced the revisions of the package inserts for panitumumab (Vectibix®) and cetuximab (Erbitux®) to include the need to assess RAS gene mutation status.

Panitumumab is indicated for KRAS wild-type, incurable, unresectable, advanced/recurrent colorectal cancer. Cetuximab is used for the treatment of EGFR-positive, incurable, unresectable, advanced/recurrent colorectal cancer and head and neck cancer.

The MHLW/PMDA stated that the efficacy of treatment in patients with or without the RAS (KRAS and NRAS) gene mutation was retrospectively analysed in a total of 4 phase III studies of panitumumab and cetuximab involving patients with colorectal cancer. The results revealed a trend that suggested no add-on effect could be expected with coadministration of panitumumab or cetuximab as compared with the control group amongst the patient population with the RAS gene mutation.

Based on expert advice and available evidence, the MHLW/PMDA have recommended the addition of the following information to the Precautions for "Indications" section in package insert:
Prior to initiation of treatment, assess the RAS (KRAS and NRAS) gene mutation status and select the suitable patients.

Reference:
Revision of Precautions, MHLW/PMDA, 8 April 2015 (*www.pmda.go.jp/english/*)

(See WHO Pharmaceuticals Newsletters No.5, 2013 for importance of establishing wildtype RAS (KRAS and NRAS) status before treatment of metastatic colorectal cancer with panitumumab in the UK and No.2, 2014 Importance of establishing wild type RAS (KRAS and NRAS) status before treatment of metastatic colorectal cancer with cetuximab in the UK)

Pazopanib hydrochloride

Risk of retinal detachment

Japan. The MHLW and the PMDA have announced the revision of the package insert for pazopanib hydrochloride (Votrient®) to include risk of retinal detachment.

Pazopanib hydrochloride is indicated for soft tissue sarcoma and radically unresectable or metastatic renal cell carcinoma.

The MHLW/PMDA stated that cases of adverse events suggestive of retinal detachment have been reported in patients treated with pazopanib hydrochloride in Japan and other countries, and the MHLW/PMDA also stated that the CCDS for pazopanib hydrochloride has been revised to include information on retinal detachment.

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

Retinal detachment:
Retinal detachment may occur. Patients should be carefully monitored. If any abnormalities such as muscae volitantes, photopsia, visual field defect and reduced visual acuity are observed, ophthalmologic examination should be performed and appropriate measures such as discontinuation of administration should be taken.

Reference:
Revision of Precautions, MHLW/PMDA, 24 March 2015 (*www.pmda.go.jp/english/*)

Pomalidomide

Risks of cardiac failure, interstitial lung disease and hepatotoxicity

UK. The MHRA has informed health-care professionals of new monitoring instructions to detect signs/symptoms of cardiac failure, interstitial lung disease (ILD) and hepatotoxicity with use of pomalidomide.

Pomalidomide in combination with dexamethasone is licensed to treat adults with relapsed and refractory multiple myeloma who have received at least two treatments, including lenalidomide and bortezomib, and whose disease has worsened since the last treatment.

A review by the MHRA and other EU medicine regulators concluded that pomalidomide can cause ILD, cardiac failure and hepatotoxicity. This conclusion was based on data from clinical trials, reports from clinical practice and published case reports.

The risk of serious hepatic events appears to be highest in the first 6 months of treatment, therefore regular liver function monitoring is recommended during this period.

In most cases, cardiovascular effects occurred in patients with cardiac disease or cardiac risk factors and within 6 months of starting pomalidomide. The review also concluded that pomalidomide can cause atrial fibrillation, which may precipitate cardiac failure.

Pomalidomide can cause ILD and related events such as pneumonitis. The review concluded that this side effect is common. Onset of respiratory symptoms is usually within 6 months of starting treatment. However, there have been cases where ILD occurred approximately 18 months after starting pomalidomide. ILD usually resolves with steroid treatment and stopping pomalidomide.

The MHRA has advised that when using pomalidomide:

- in patients with cardiac disease or cardiac risk factors, use with caution and if used, monitor for signs or symptoms of cardiac failure
- carefully assess patients with any acute onset or unexplained worsening of respiratory symptoms to confirm or exclude ILD; stop pomalidomide treatment during assessment
- if ILD is confirmed, treat appropriately and only resume pomalidomide treatment after thoroughly evaluating the benefits and risks
- regularly monitor liver function for the first 6 months of pomalidomide treatment and as clinically indicated thereafter

Reference:
Drug Safety Update, MHRA, Volume 8, issue 10: 2, May 2015 (*www.gov.uk/mhra*)

Rebamipide (Ophthalmic solution)

Risk of lacrimal duct obstruction and dacryocystitis

Japan. The MHLW and the PMDA have announced the revision of the package insert for rebamipide ophthalmic solution (Mucosta Ophthalmic Suspension UD®) to include risk of lacrimal duct obstruction and dacryocystitis.

Rebamipide ophthalmic solution is indicated for dry eyes.

The MHLW/PMDA stated that cases of adverse events suggestive of lacrimal duct

obstruction or dacryocystitis have been reported in patients treated with rebamipide ophthalmic solution in Japan.

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

Lacrimal duct obstruction and dacryocystitis:
Lacrimal duct obstruction and/or dacryocystitis may occur. Patients should be carefully monitored through ophthalmologic examination etc. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken. White matters may be observed in lacrimal passage of patients with lacrimal duct obstruction and/or dacryocystitis.

Reference:
Revision of Precautions, MHLW/PMDA, 24 March 2015 (*www.pmda.go.jp/english/*)

Sevoflurane

Severe low heart rate in children with Down syndrome

Canada. Health Canada announced that the Canadian prescribing information for sevoflurane (Sevorane AF®) has been updated to highlight the occurrence of cases of bradycardia in paediatric patients with Down syndrome. Manufacturers of generic versions of this drug are in the process of updating their product information.

Sevoflurane is used as a general anaesthetic during surgery to make a patient unconscious and unable to feel pain.

Health Canada initiated a safety review to evaluate the possible link between a severe lowering of the heart rate (a medical condition known as severe bradycardia) and the use of the general anaesthetic sevoflurane in children with Down syndrome. This issue was identified by Health Canada during routine review of safety information provided by the manufacturer.

At the time of the review, Health Canada had not received any reports of sevoflurane-associated bradycardia in children with Down syndrome. International reports of severe bradycardia in children with Down syndrome suspected to be associated with sevoflurane use were provided by the company that first marketed sevoflurane.

A review of the scientific and medical literature identified a number of relevant research articles. Although reports are limted in numbers and quality the literature highlighted the possibility of sevoflurane-induced bradycardia in children with Down syndrome.

Health Canada advised that the risk of bradycardia (slowing of the heart rate) with sevoflurane should be considered for all children. The existing prescribing information for sevoflurane mentions the risk of bradycardia in healthy children and in children with neuromuscular problems. This will be updated to mention the occurrence of cases of bradycardia in children with Down syndrome.

Reference:
Summary Safety Review, Health Canada, 13 May 2015 (*www.hc-sc.gc.ca*)

Sitagliptin phosphate hydrate

Risk of thrombocytopenia

Japan. The MHLW and the PMDA have announced the revision of the package insert for sitagliptin phosphate hydrate (Glactiv® and Januvia®) to include risk of thrombocytopenia.

Sitagliptin phosphate hydrate is indicated for type 2 diabetes mellitus.

The MHLW/PMDA stated that cases of adverse events of thrombocytopenia have been reported in patients treated with sitagliptin phosphate hydrate in Japan.

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

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

Reference:
Revision of Precautions, MHLW/PMDA, 24 March 2015 (*www.pmda.go.jp/english/*)

Triamcinolone acetonide

Risk of tendon rupture

Japan. The MHLW and the PMDA have announced the revision of the package insert for triamcinolone acetonide injection (Kenacort-A®) to include risk of tendon rupture.

Triamcinolone acetonide is used for various treatments including chronic adrenocortical insufficiency, rheumatoid arthritis, lupus erythematosus, nephrosis and nephrotic syndrome, congestive cardiac failure, cirrhosis, encephalomyelitis, malignant lymphoma, acute/chronic otitis media, and allergic rhinitis.

The MHLW/PMDA stated that cases of adverse events suggestive of tendon rupture have been reported in patients treated with triamcinolone acetonide in Japan.

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

Tendon rupture:
Tendon rupture may occur when this drug is injected into the tendon repeatedly. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be taken.

Reference:

Revision of Precautions, MHLW/PMDA, 24 March 2015 (*www.pmda.go.jp/english/*)

Capecitabine and folic acid

Risk of enhancement of toxicity of capecitabine

Egypt. The EPVC has publicised a report concerning the risk of enhanced capecitabine toxicity when taken with folic acid.

Capecitabine (Xeloda®) is a fluoropyrimidine carbamate and a pro-drug of 5'-deoxy-5-fluorouridine (5' DFUR). It is administered orally and is converted to 5-fluorouracil. It has antineoplastic activity and is used for colon, colorectal and gastric cancer, either as a single agent (monotherapy) or in combination therapy.

Centrum® is a multivitamin and mineral supplement. It is used to provide extra vitamins and minerals that are not taken in through the diet. Multivitamins and minerals are also used to treat vitamin or mineral deficiencies caused by illness, pregnancy, poor nutrition, digestive disorders, certain medications, and many other conditions. One of its components is folic acid.

According to the capecitabine Summary of Product Characteristics (SmPC), under section "4.5 Interaction with other medicinal products and other forms of interaction": folinic acid has no major effect on the pharmacokinetics of capecitabine and its metabolites. However, folinic acid has an effect on the pharmacodynamics of capecitabine. The toxicity of capecitabine may be enhanced by folinic acid. This may also be relevant with folic acid supplementation for folate deficiency due to the similarity between folinic acid and folic acid.

THE EPVC has recommended for health-care professionals that:

- The co-administration of capecitabine with folate therapy may potentiate the pharmacologic effects of 5-fluorouracil (5-FU).
- A lower dosage of 5-FU or the pro-drug may be required.
- Patients should be monitored closely for potential toxicities of 5-FU such as neutropenia, thrombocytopenia, stomatitis, gastrointestinal haemorrhage, severe diarrhoea, vomiting, cutaneous reactions, and neuropathy.
- Patients should be instructed to avoid taking folic acid supplementation or multivitamin preparations containing folic acid without first speaking with their physician.
- Caution should be taken when receiving tablets containing multivitamins with chemotherapy.

Reference:
Newsletter, Egyptian Pharmaceutical Vigilance Center (EPVC), Volume 6, Issue 5, May 2015

Ceftolozane and tazobactam

Dose confusion and medication errors

USA. The FDA has issued a warning to health-care professionals regarding the risk of dosing errors with the antibacterial drug Zerbaxa® (ceftolozane and tazobactam) due to confusion about the drug strength displayed on the vial and carton labelling.

The Combination of ceftolozane and tazobactam is used to treat complicated infections in the urinary tract, or in combination with the antibacterial drug metronidazole to treat complicated infections in the abdomen. Antibacterial drugs work by killing or stopping the growth of bacteria that can cause illness.

The FDA evaluated seven reported cases of medication errors that occurred during preparation of the dose in the pharmacy due to confusion with the display of the strength of individual ingredients on the product vial labels and carton labelling. Listing the individual drug strengths led to confusion because it was different from labelling for other drugs in the beta-lactam/beta-lactamase class that express strength as the sum of the two active ingredients. In some cases, this led to administration of 50% more drug than was prescribed. No adverse events were reported among these seven cases.

Reference:
Drug Safety Communication, US FDA, 20 May 2015 (*www.fda.gov*)

Ceftriaxone and calcium containing diluents

Drug-drug interaction

Egypt. The EPVC has reminded health-care professionals of a well-known interaction that occurs between (ceftriaxone sodium) for injection and calcium-containing IV solutions.

Ceftriaxone injection (cephalosporin antibiotic) is used to treat certain infections caused by bacteria such as gonorrhoea, pelvic inflammatory disease, meningitis and infection of the lungs, ears, skin, urinary tract, bones, blood, joints and abdomen.

A small number of cases with fatal outcomes have been reported. Cases of crystalline material observed in the lungs and kidneys at autopsy have been reported in neonates

receiving ceftriaxone and calcium-containing fluids. In some of these cases, the same intravenous infusion line was used for both ceftriaxone and calcium-containing fluids and a precipitate was observed in the intravenous infusion line.

There is a theoretical possibility for an interaction between ceftriaxone and IV calcium-containing solutions in patients other than neonates (i.e. adults), although this has not been reported.

Prescribing information advises that ceftriaxone and IV calcium-containing solutions should not be mixed or co-administered to any patient irrespective of age, even via different infusion lines at different sites. In addition they should not be administered within 48 hours of each other.

The EPVC recommendations to health-care professionals include:

- Diluents containing calcium, such as Ringer's solution or Hartmann's solution should not be used to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for IV administration because a precipitate can form.
- Precipitation of ceftriaxone-calcium can also occur when ceftriaxone is mixed with calcium-containing solutions in the same IV administration line. Ceftriaxone must not be administered simultaneously with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site.
- However, in patients other than neonates, ceftriaxone and calcium-containing solutions may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid. In vitro studies using adult and neonatal plasma from umbilical cord blood demonstrated that neonates have an increased risk of precipitation of ceftriaxone-calcium.

Reference:
Newsletter, Egyptian Pharmaceutical Vigilance Center (EPVC), Volume 6, Issue 5, May 2015

Clozapine with another antipsychotic drugs

Risk of eosinophilia, hypo-chromia, leucocytosis and erythro-cytosis

Egypt. The EPVC has received nine reports of eosinophilia, hypo-chromia, leuco-cytosis and erythro-cytosis in patients with long term exposure to clozapine in combination with another antipsychotic. The patients varied in age and gender. Patients also presented with chronic inflammation and sore throat and recovered after administration of an anti–inflammatory drug.

Clozapine is an antipsychotic drug with a broad range of antipsychotic activity. Clozapine has a low affinity for D2 receptor is not associated with extrapyramidal adverse effects. However, due to a risk of agranulocytosis, the therapeutic indication is restricted to schizophrenic patients resistant or intolerant to other antipsychotics.

The EPVC has recommended that:

- Clozapine should be limited to schizophrenic patients who are non-responsive or intolerant to antipsychotic medication with psychosis in Parkinson's disease when other treatment strategies have failed.
- WBC and differential blood counts must be performed within 10 days prior to initiating clozapine treatment, weekly after initiation for the first 18 weeks and then at least at four week intervals thereafter. Only patients with normal WBC counts and Absolute Neutrophil Count (ANC) (WBC $\geq 3500/mm^3$ and $ANC \geq 2000 mm^3$) should receive the drug.
- It is mandatory, at any time during clozapine treatment to discontinue treatment if WBC<3000 ($3x10^9$) and ANC<1500 ($1.5x10^9$). If this occurs blood levels should be monitored daily until haematological abnormality is resolved, and patient should be monitored for infection, without re-exposure.
- In general, clozapine should not be used in combination with other antipsychotics.
- Treatment must be discontinued immediately in the event of neutropenia or agranulocytosis.

Reference:
Newsletter, Egyptian Pharmaceutical Vigilance Center (EPVC), Volume 6, Issue 5, May 2015

Dimethyl fumarate

Fatal PML in an MS patient with severe, prolonged lymphopenia

UK. The MHRA has instructed that full blood counts should be taken prior to prescribing dimethyl fumarate, and every 6 to 12 months after initiation. If progressive multifocal leukoencephalopathy (PML) is suspected, treatment should be stopped immediately.

Dimethyl fumarate is licensed to treat relapsing remitting multiple sclerosis in adults. Clinical trials have shown

dimethyl fumarate can cause severe lymphopenia, with a decrease of lymphocyte counts by approximately 30% from baseline values. Medicines containing dimethyl fumarate and other fumaric acid esters are not licensed in the UK for use in psoriasis. However, the MHRA is aware that these medicines are sometimes imported as 'specials'. If considering such use, prescribers should be aware of the risks of severe, prolonged lymphopenia and serious opportunistic infections.

The MHRA has the following advice for health-care professionals:

- Before prescribing dimethyl fumarate:
  - ensure that the full blood count (including lymphocytes) has been checked - note that dimethyl fumarate has not been studied in patients with pre-existing lymphopenia or in combination with other immunosuppressive medicines.
  - explain the risk of lymphopenia and potential risk of PML to patients and carers.
- During dimethyl fumarate treatment:
  - monitor patients - check full blood counts, including lymphocytes, every 6 to 12 months or more frequently if clinically indicated.
  - monitor patients with lymphopenia closely for features of PML (e.g. signs and symptoms of neurological dysfunction) and other opportunistic infections.
  - stop dimethyl fumarate treatment immediately and investigate appropriately if you suspect PML.
  - consider that PML can present with similar features to multiple sclerosis because PML is also a demyelinating disease.

The licence-holder is working with the European Medicines Agency to evaluate the evidence for the risk of PML and to consider changes to the prescribing information.

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

(See WHO Pharmaceuticals Newsletter No.1, 2015 for Case of progressive multifocal leukoencephalopathy with the use of dimethyl fumarate reported in the US)

Flurbiprofen-containing topical pain medications

Illnesses and deaths in pets exposed to prescription topical pain medication

USA. The FDA has alerted pet owners, veterinarians, health-care providers and pharmacists that pets are at risk of illness and death when exposed to topical pain medications containing the NSAID flurbiprofen.

The FDA received reports of cats in two households that became ill or died after their owners used topical medications containing flurbiprofen on themselves to treat muscle, joint, or other pain. The pet owners had applied the cream or lotion to their own neck or feet, and not directly to the pet. It is not known exactly how the cats were exposed to the medication. The products contained the NSAID flurbiprofen and the muscle relaxer cyclobenzaprine, as well as other varying active ingredients, including baclofen, gabapentin, lidocaine, or prilocaine.

The FDA recommends that people who use topical medications containing flurbiprofen should use with care when applying them in a household with pets, as even very small amounts could be dangerous to these animals. Health-care providers who prescribe topical pain medications containing flurbiprofen, and pharmacists who fill these prescriptions, should advise patients with pets to take care to prevent exposure of the pet to the medication.

Reference:
Drug Safety Communication, US FDA, 17 April 2015 (*www.fda.gov*)

Goldenseal (*Hydrastis canadensis*)

Potential herb-drug interaction

Canada. Health Canada has initiated a safety review to evaluate available information regarding the potential risk of herb-drug interactions associated with the herbal ingredient goldenseal. This review was prompted by an article published by the New Zealand Medicines and Medical Devices Safety Authority (MedSafe). This article mentioned goldenseal, among other herbal ingredients and food products, as having a potential risk for interaction with certain medications (through certain cytochrome P450 enzymes).

Goldenseal-containing oral health products are traditionally used in herbal medicine for aiding or alleviating a variety of digestive problems such as indigestion or heartburn, infectious and inflammatory conditions of the digestive

tract such as inflammation of the lining of the stomach (gastritis), or to increase appetite in Canada. Health Canada has licensed several hundred natural health products (NHPs) that have goldenseal listed as a medicinal ingredient.

The current available evidence suggests that use of oral goldenseal may contribute to herb-drug interactions, but the data is limited and no domestic or international cases of goldenseal-drug interactions are known to Health Canada.

Some published studies have shown that goldenseal can slow down the activity of certain enzymes referred to as "cytochrome P450 enzymes" mainly in the liver. These enzymes are responsible for processing and eliminating many substances that are orally ingested, including medications (e.g. certain antidepressant drugs). In some cases, these enzymes convert medications from their inactive form to an activate form in the body.

By slowing the activity of these enzymes, certain medications could remain in the body for longer than normal, potentially reaching toxic levels. Health Canada has identified that many other factors can also affect the potential for any herb-drug interaction, including genetics, age and health status as well as the type, dose, timing and composition of health products being used together.

At this time, Health Canada continues to monitor adverse reaction information for oral goldenseal-containing health products, as it does for all health products, to identify and assess potential harms.

Health Canada published an article in the April 2015 issue of the Health Product InfoWatch to raise awareness and to encourage the reporting of related adverse reactions with goldenseal.

Reference:
Summary Safety Review, Health Canada, 30 April 2015 (*www.hc-sc.gc.ca*)

Guaifenesin

Reports of tinnitus

NZ. The Medsafe has informed health-care professionals of recent reports of tinnitus associated with the use of guaifenesin, received at the Centre of Adverse Reactions Monitoring (CARM). It was reported that the patient was taking guaifenesin 600 mg for an upper respiratory tract infection and experienced profound tinnitus followed by deafness in the right ear with facial and outer ear numbness. In a second report, a patient who was using guaifenesin for a different indication experienced hearing loss in the right ear after the guaifenesin dose was increased to 600 mg twice daily. There are no reports of tinnitus, deafness or numbness with use of guaifenesin in the literature.

Guaifenesin can be an OTC expectorant used for the symptomatic relief of productive (chesty) coughs. Expectorants help to loosen phlegm and thin the mucus in the lungs. Guaifenesin is available as a single-ingredient product or with other active ingredients for the treatment of cough and cold symptoms. Tinnitus can be described as ringing in the ears. Tinnitus is not listed as an adverse event in the guaifenesin (Mucinex®) data sheet or in the product packaging.

The overall benefit-risk balance of guaifenesin remains positive.

Reference:
Safety Information, Medsafe, 7 April 2015 (*www.medsafe.govt.nz/*)

Hydroxyzine

Risk of QT interval prolongation and Torsade de Pointes

UK. The MHRA has issued a warning not to prescribe hydroxyzine to people with a prolonged QT interval or risk factors for QT interval prolongation, and has decreased the maximum adult daily dose of hydroxyzine to 100 mg.

Hydroxyzine is an antihistamine used to treat anxiety in adults, and pruritus in adults and children.

The MHRA has informed health-care professionals, when using hydroxyzine:

- not to prescribe hydroxyzine to people with a prolonged QT interval or who have risk factors for QT interval prolongation.
- to avoid use in the elderly - they are more susceptible than younger patients to the side effects of hydroxyzine.
- to consider the risks of QT interval prolongation and Torsade de Pointes before prescribing to patients taking medicines that lower heart rate or potassium levels.
- to be aware that the maximum daily dose is now:
  - 100 mg for adults
  - 50 mg for the elderly (if use cannot be avoided)
  - 2 mg per kg body weight for children up to 40 kg in weight
- to prescribe the lowest effective dose for as short a time as possible.

A European review of the safety and efficacy of hydroxyzine was conducted following concerns of heart

rhythm abnormalities associated with this medicine. The review concluded that hydroxyzine is associated with a small risk of QT interval prolongation and Torsade de Pointes. Such events are most likely to occur in patients who already have risk factors for QT prolongation, such as:

- concomitant use of medicines that prolong the QT interval
- cardiovascular disease
- family history of sudden cardiac death
- significant electrolyte imbalance (low potassium or magnesium levels)
- significant bradycardia.

Reference:
Drug Safety Update, MHRA, Volume 8, issue 9: 1, April 2015 (*www.gov.uk/mhra*)

(See WHO Pharmaceuticals Newsletter No.3, 2014 for review started on the side effects of hydroxyzine-containing medicines on the heart in Europe)

Olanzapine pamoate

Deaths associated with the injectable schizophrenia drug

USA. The FDA has announced the outcome of an investigation into two deaths following injection of long acting olanzapine pamoate (Zyprexa Relprevv®).

A study to determine the cause of elevated levels of the injectable schizophrenia drug olanzapine pamoate in two patients who died was conducted. The study results were inconclusive. The possibility that the deaths were caused by rapid, but delayed, entry of the drug into the bloodstream following intramuscular injection could not be excluded. However the drug level increase could have occurred after death.. On the basis of all of the information reviewed, the FDA is not recommending any changes to the current prescribing or use of olanzapine pamoate injection at this time. Patients should not stop receiving treatment without first talking to their health-care professionals.

Olanzapine pamoate may be used for the treatment of schizophrenia symptoms, which include hearing voices, seeing things that are not there, and being suspicious or withdrawn.

The FDA informed that Health-care professionals should continue to follow the Zyprexa Relprevv® Patient Care Program Risk Evaluation and Mitigation Strategy (REMS) requirements and current label recommendations. Notable requirements of the REMS include:

- For a patient to receive treatment, the prescriber, health-care facility, patient, and pharmacy must all be enrolled in the Zyprexa Relprevv® Patient Care Program.
- olanzapine pamoate injections must be administered at a REMS-certified health-care facility with ready access to emergency response services.
- Patients must be continuously monitored at the REMS-certified health-care facility for at least 3 hours following an intramuscular injection.
- Patients receiving olanzapine pamoate must be accompanied to their destination from the health-care facility.

Reference:
Drug Safety Communication, US FDA, 23 March 2015 (*www.fda.gov*)

(See WHO Pharmaceuticals Newsletter No.4, 2013 for investigating two deaths following injection of olanzapine pamoate in the US)

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 34). 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.

Prucalopride and Suicidal ideation

Mr Alessio Gasparotto and Dr Rebecca E Chandler, Uppsala Monitoring Centre

Summary

Suicidal ideation has been identified in association with the gastrointestinal prokinetic agent, prucalopride, as a potential signal from the WHO Global Individual Case Safety Report database, VigiBase®. Prucalopride is the third 5-HT_4 receptor agonist licensed as a prokinetic agent but its highly selective nature represents an advantage over the previously licensed products cisapride and tegaserod which have both been withdrawn due to adverse cardiac effects. While the total number of case reports for suicidal ideation and prucalopride is small, there is evidence of psychiatric events, specifically anxiety, confusional state, and depression, from clinical trial data as well as a notable number of reports of suicidal ideation for tegaserod. Of potential concern is the inconsistency in the labelling for CNS events between the EU and Canada, the two regions in which prucalopride has been approved. The potential for psychiatric adverse events should be acknowledged in the EU as has been done in Canada. Furthermore, with the identification of these case reports of suicidal ideation, a possible recommendation would be for increased surveillance for such events related to suicide. Additionally, the potential for a relationship between adverse events with prucalopride and certain 5-HT_4 polymorphisms should be explored.

Introduction

Prucalopride was licensed for use by the European Medicines Agency in July 2009 and in Canada in December 2011 with an indication for use in the symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief.[1,2]

Serotonin or 5-hydroxytryptamine (5-HT) acts as a neurotransmitter and paracrine agent that mediates a wide variety of functions, including cognitive and emotional processes, regulation of sleep and food intake, as well as cardiovascular and gastrointestinal mechanisms. To date 14 different 5-HT receptors, classified into seven subclasses, have been identified.[3]

Prucalopride is a dihydro-benzofurancarboxamide derivative which is highly selective and has high affinity for serotoninergic 5-HT_4 receptors. 5-HT_4 receptors are located both in the central nervous system (CNS) and in the peripheral tissues, specifically the gastrointestinal tract. Activation of 5-HT_4 in the gastrointestinal tract promotes gastrointestinal motility and mucosal secretion. Experimental models both in vitro and in vivo have demonstrated that prucalopride facilitates gastrointestinal motility by promoting longitudinal smooth muscle contractility while suppressing the resistance to propulsion due to circular smooth muscle contraction.[4]

The highly selective nature of prucalopride for the 5-HT_4 receptor represents an advantage over previous prokinetic non-selective 5-HT_4 agonists, such as cisapride and tegaserod. Both of these agents have appreciable affinity for other receptors, channels or transporters [e.g. cisapride: human ether-a-go-go-related gene (hERG)/K^+ channel and tegaserod: 5-HT_{1D} and 5-HT_{2B}

receptors] which resulted in adverse event profiles (QT prolongation and cardiovascular ischemic events, respectively) which limited their clinical success.[5-7]

The European Summary of Product Characteristics (SmPC) for prucalopride notes the most commonly occurring events to be headache, nausea, diarrhoea, abdominal pain. Other commonly occurring events were dizziness, fatigue, pollakiuria, vomiting, dyspepsia, rectal haemorrhage, flatulence, and abnormal bowel sounds. Uncommon events included palpitations, anorexia, and tremors.[8] The labelling for Health Canada in contrast notes the following events from the Psychiatric disorders SOC: anxiety, confusional state, and depression.[9]

Suicidal ideation is defined as thoughts about self-harm, with deliberate consideration or planning of possible techniques of causing one's own death.[10] Suicidal ideation is more common than suicide attempts or completed suicide.[11] A 1995 study found that 3.3 percent of patients in an urban primary care outpatient clinic reported suicidal ideation.[12] Risk factors for suicidal behaviours include female gender, younger age, fewer years of education, unmarried status and the presence of a mental disorder, with psychiatric comorbidity significantly increasing risk.[13] In addition, some prescription drugs, such as selective serotonin re-uptake inhibitors, can have suicidal ideation as a side effect.

Reports in VigiBase®

There were a total of four case reports in the WHO Global Individual Case Safety Report (ICSR) database, VigiBase® as of December 2014 which reported suicidal ideation in association with prucalopride.

The four case reports were submitted from three countries: Germany, the United Kingdom, and Italy. All case reports were received from health-care professionals. One of the reports was determined to be a duplicate. Two of the reports described events occurring in females, ages 44 and 61; one report described events occurring in a male whose age was not reported. Time to onset was reported in all cases and ranged from "hours after the first dose" to 16 days after initiation of prucalopride. Prucalopride was withdrawn and the outcome was reported as recovered in all of the cases.

One of the reported cases was the subject of a published case report.[14] It describes a 61 year old female who was in reportedly good health and not taking any other medications. She was initiated on prucalopride 2 mg per day for the treatment of chronic constipation. Within a few hours after oral administration, she experienced suicidal ideation, visual hallucinations, disorientation, and a loss of balance and memory. The drug was withdrawn and symptoms resolved within 24 hours. She had never previously experienced similar symptoms.

There were an additional 27 case reports of suicide ideation with another 5-HT_4 agonist, tegaserod. There were a total of 24 cases from the USA, two from Canada, and one from Mexico. Several of the 27 cases report depression and are complicated by the use of multiple concomitant medications. However, five of these reports document a positive dechallenge.

Table 1. Characteristics of reports for prucalopride and suicidal ideation in VigiBase®

Case	Age/ Sex	Medical history	Suspected (S) or concomitant drugs (C)	Time to onset	Indication	Dechallenge/ Rechallenge	ADR terms (WHO-ART)	Outcome
1	-/M	Not provided	Prucalopride (S) Beta blocking agents (C)	3-4 days	Chronic constipation	Withdrawn	Suicidal ideation, off-label use	Recovered
2	44/F	Not provided	Prucalopride (S) Paracetamol, mebeverine, tramadol, fluocinonide, levothyroxine, omeprazole, propantheline, pregabalin, morphine, hyoscine (all C)	16 days	Constipation	Positive dechallenge	Suicidal ideation, thoughts of self harm, depression	Recovered
3	61/F	None	Prucalopride (S) Brotizolam (C)	Hours after first dose	Chronic constipation	Positive dechallenge	Suicidal ideation, balance difficulty, prostration, hallucination visual, amnesia, disorientation	Recovered with sequelae

Literature and Labelling

Three 5-HT_4 receptor agonists have been variously approved for use as prokinetic agents. The first approved agent was cisapride which has subsequently been removed from both the US and EU markets secondary to cardiovascular events, specifically QT-prolongation.

A second agent, tegaserod, was initially licensed in the US for the treatment of irritable bowel syndrome, but an observed increased risk in myocardial infarctions and strokes led to its withdrawal five years after approval. Tegaserod was never approved for use in the EU. In the refusal assessment report from the EMA's Committee for Human Medicinal Products (CHMP), it is noted that findings in mice safety pharmacology studies suggest certain CNS related effects, such as increased activity, abnormal gait, and hypothermia at doses 10 to 100-fold higher than therapeutically relevant. Furthermore, it is reported that 2.1% of all tegaserod subjects reported adverse events in the Psychiatric disorders SOC (compared to 1.6% in placebo subjects). There were a total of six deaths in subjects taking tegaserod during clinical development, two of which were reported as suicide (12,032 total subjects in the safety database received tegaserod); no deaths were felt by the investigator to be related to study drug. CNS/psychiatric events were considered to be an outstanding safety issue.[15]

Prucalopride is the third 5-HT_4 receptor agonist. It has not been approved for licensure in the US; however, it was approved for use in chronic constipation in the EU in 2009 and in Canada in 2011. In the Committee for Medicinal Products for Human Use approval assessment report, it is noted that in single dose toxicity studies performed on mice that there were CNS effects seen "at very high doses" However, there was no discussion in the report regarding events from the Psychiatric disorders SOC. There were two deaths in the double-blind placebo controlled trials and four deaths in open-label studies. The report notes only that none of the deaths were considered related to treatment by the investigator. Neither suicidal ideation nor other CNS events are included in the risk management plan for prucalopride.[1] In contrast, the Summary Basis of Decision for Health Canada notes that prucalopride: "…may act on receptors in the brain having the following 5-hydroxytryptamine (5-HT) receptors: 5-HT_1; 5-HT_2; and 5-HT_3; that could be involved in anxiety and depression. It is unclear whether 5-HT_4 may be related to depression and anxiety. However, anxiety has been reported in many clinical studies and some cases were reported as serious events. The open-label studies recorded anxiety in 1.9% of the patients treated with the 2 mg dose, and similar results were found with 4 mg dose. In these studies, depression was elicited at a higher incidence than anxiety (3.5% versus 1.9%) with the 2 mg dose."[2]

The 5-HT_4 receptor (5-HT_4-R) is located both in the CNS and in the peripheral tissues. In the human brain, 5-HT_4-Rs have been localized in the basal ganglia, the hippocampal formation and the cortical mantle.[3] It could be hypothesized that prucalopride, acting upon the 5-HT_4 receptors in the basal ganglia could lead to a syndrome of dysphoria and suicidal ideation, as substantia nigra hyperactivity has been implicated in schizophrenia.[11] Also, available evidence for another serotonin receptor agonist, metoclopromide, suggest that different polymorphisms in 5-HT_4 receptor HTR4 genes are associated with adverse events and clinical effectiveness. There is the potential that only patients with certain genetic variations in the 5-HT_4 receptor are susceptible to neuropsychiatric side effects.[16]

Discussion and Conclusion

The signal for a possible association between prucalopride and suicidal ideation is based upon only three cases. It is notable that in none of the cases are there any past histories of depression or concomitant medication use implying a history of psychiatric disorders. Furthermore, the time to onset is relatively short for two of the cases, within hours to days. All cases had documentation of resolution of symptoms after drug withdrawal.

The highly selective nature of prucalopride has been the focal point of the development of this agent given the limitations of its predecessors. To this end, multiple preclinical investigations into the cardiac effects have been completed and showed a lack of interaction with the hERG potassium channel and 5-HT_{1D} and 5-HT_{2B} receptors. Both approval reports from the EU and Canada thoroughly described this data. However, there is an inconsistency in the presentation of data regarding potential psychiatric effects between the EU and the Canadian reports. As a result, there is no labelling for such events in the EU SmPC (or inclusion of these events into the Risk Management Plan) but the inclusion of the events of anxiety, confusional state, and depression in the Canadian label.

It is clear that prucalopride represents therapeutic alternative with an improved safety profile and that the signal for an association with suicidal ideation is weak at the current time. However, the potential for psychiatric adverse events should be acknowledged in the EU as has been done in Canada. Furthermore, with the identification of these case reports of suicidal ideation, a possible recommendation would be for increased

surveillance for such events related to suicide. Additionally, the potential for a relationship between adverse events with prucalopride and certain 5-HT_4 polymorphisms should be explored.

References

1. Approval assessment report for Resolor (prucalopride). URL: http://www.ema.europa.eu/docs/en_GB/docu-ment_library/EPAR_-_Public_assessment_report/human/001012/WC500053997.pdf. Accessed: 4 February 2015.
2. Summary Basis of Decision for Resotran (prucalopride). URL: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd_smd_2012_resotran_141157-eng.php#a334. Accessed: 10 February 2015.
3. Hoyer D, Clarke DE, Fozard JR, Hartig PR, Martin GR, Mylecharane EJ et al. International Union of Pharmacology classification of receptors for 5-hydroxy-tryptamine (serotonin). Pharmacol Rev. 1994;46:157-203.
4. Wong BS, Manabe N, Camilleri C. Role of prucalopride, a serotonin (5-HT4) receptor agonist, for the treatment of chronic constipation. Clin Exp Gastroentrol. 2019;3:49-56.
5. Mohammad S, Zhou Z, Gong Q, January CT. Blockage of the HERG human cardiac K+ channel by the gastrointestinal prokinetic agent cisapride. Am J Physiol Hear Circ Physiol. 1997;273(5):H2534-8.
6. Wysowski DK, Corken A, Gallo-Torres H, Talarico L, Rodriguez EM. Postmarketing reports of QT prolongation and ventricular arrhythmia in association with cisapride and FDA regulatory actions. Am J Gastroentrol. 2001;96(6):1698-703.
7. De Maeyer JH, Lefebvre RA, Schuurkes JA. 5-HT4 receptor agonists: similar but not the same. Neurogastroenterol Motil. 2008;20(2):99-112.
8. Electronic Medicines Compendium UK. Resolor (prucalopride). URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001012/WC500053998.pdf. Accessed: 4 February 2015.
9. Product Information for Resotran (prucalopride). URL: http://webprod5.hc-sc.gc.ca/dpd-bdpp/info. do?code=86259&lang=eng. Accessed: 4 February 2015.
10. American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Washington, DC. ISBN 978-0-89042-555-8.
11. Marzuk PM. Suicidal behavior and HIV illnesses. Int Rev Psychiatry. 1991;3:365-71.
12. Zimmerman M, Lish JD, Lush DT, Faber NJ, Plescia G, Kuzma MA. Suicidal ideation among urban medical outpatients. J Gen Intern Med. 1995;10:573-6.
13. Nock MK, Borges G, Bromet EJ, Alonso J, Angermeyer M, BeautraisA et al. Cross-national prevalence and risk factors for suicidal ideation, plans and attempts. Brit J Psychiatr. Feb 2008;192(2):98-105.
14. Carovale C, Pellegrino P, Perrone V, Antoniazzi S, Pozzi M, Nisic A et al. Neurological and psychiatric adverse events with prucalopride: case report and possible mechanisms. J Clin Pharm Ther. 2013;83:524-5.
15. Refusal assessment report for Zelnorm (tegaserod). URL: http://www.ema.europa.eu/docs/en_GB/docu-ment_library/EPAR_-_Public_assessment_report/human/000621/WC500058849.pdf. Accessed: 04 February 2015.
16. Parkman HP, Mishra A, Jacobs M et al. Clinical response and side effects of methoclopromide: associations with clinical, demographic, and pharmacogenetic parameters. J Clin Gastroenterol. 2012;46:494-503.

Response from Shire

Suicide-related events include passive and active thinking, planning, and finally taking action to commit suicide. Passive death thoughts are common in the general population. In a cross-national (17 countries) sample, Nock et al estimated the lifetime prevalence of suicidal ideation at 9.2% (1).

For prucalopride there was no signal for suicide-related events in the developmental clinical trials of this product for chronic constipation.

The Shire global safety database contains the same postmarketing reports tabulated by the authors and, except for one duplicate, no other report of suicide-related events.

In review of the three postmarketing cases in the database, the first case involved a male of unknown age and was derived from sparse documentation which included no information on medical history or concurrent disorders. The second case involved a 44-year old female who was concomitantly treated with tramadol, a medication with a known association with suicidal events and depression (2,3).

The third and most recent case was presented as a published case report where suicidal thoughts were reported amongst a plethora of other events including balance difficulty, prostration, visual hallucinations, amnesia and disorientation. Interestingly, the publication failed to mention this patient's concomitant treatment with brotizolam, a benzodiazepine. The constellation of events described is considered to be clinically compatible with a paradoxical benzodiazepine reaction given that such reactions may typically include hallucinations, inconsolable crying, agitation, restlessness, disorientation, aggressive behaviour and/other psychological phenomena (4). Additionally, benzodiazepine use has been identified in at least one published study as among a number of variables associated with suicide in older adults (5).

In summary, suicide-related events did not constitute a signal during clinical development of prucalopride. In the postmarketing review, 2 of the 3 case reports of suicidal ideation were confounded by potentially relevant concomitant medication exposures, and the third case report was poorly documented. Based on the information available at this time, Shire does not believe there is sufficient evidence to support a causal association of suicidal ideation with the use of prucalopride.

For Shire,
Anders Lindholm MD, PhD
Therapeutic Area Head, Pharmacovigilance & Risk Management, Shire

References

1. Nock MK; Borges, G; Bromet EJ, et al. Cross-National Prevalence and Risk Factors for Suicidal Ideation, Plans, and Attempts. Br J Psychiatry 2008;192:98-105.
2. "FDA Warns of Suicide Risk for Tramadol." http://www.medscape.com/viewarticle/722488 (accessed 23-Mar-15)
3. "Ultram (tramadol hydrochloride), Ultracet (tramadol hydrochloride/acetaminophen): Label Change." http:// www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm213264.htm (accessed 23-Mar-15)
4. Young Hee Shin, Myung Hee Kim, Jung Jin Lee, Soo Joo Choi, Mi Sook Gwak, Ae Ryoung Lee, et al. The effect of midazolam dose and age on the paradoxical midazolam reaction in Korean pediatric patients. Korean J Anesthesiol 2013 July 65(1): 9-13
5. Voaklander DC, Rowe BH, Dryden DM, Pahal J, Saar P, Kelly KD. Medical illness, medication use and suicide in seniors: a population-based case-control study. J Epidemiol Community Health. 2008 Feb;62(2):138-46.

Vemurafenib and Thrombocytopenia

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Summary

Vemurafenib is a protein kinase inhibitor with activity against mutated B-RAF protein; it is used in the treatment of metastatic or unresectable malignant melanoma that carries the BRAF V600E mutation. B-RAF protein acts in the RAS-RAF-MEK-ERK intracellular signalling pathway that leads to cell growth and proliferation: by targeting mutated B-RAF, vemurafenib inhibits the growth of melanoma cells containing the mutated B-RAF gene. At the time of assessment (March 2015), The WHO Global Individual Case Safety Report (ICSR) database, VigiBase® contains 28 ICSRs in which vemurafenib is associated with thrombocytopenia (after exclusion of two duplicates). One case provides information that suggests a 'certain' causal relationship between vemurafenib and thrombocytopenia, four cases suggest a 'probable' causal relationship and a further 14 cases can be assessed to have a 'possible' causal relationship to vemurafenib. Six cases include co-reported ADR terms that indicate a more widespread myelosuppression, rather than an isolated thrombocytopenia. The RAS-RAF-MEK-ERK intracellular signalling pathway is involved in the production and differentiation of haematopoietic progenitor cells. It is possible that thrombocytopenia associated with vemurafenib may be part of a spectrum of drug induced myelosuppression, possibly brought about through an effect on the RAS-RAF-MEK-ERK intracellular signalling pathway in haematopoietic progenitor cells.

Introduction

Vemurafenib is a serine-threonine protein kinase inhibitor that inhibits the kinase activity of mutated B-RAF protein. The RAS-RAF-MEK-ERK mitogen activated protein kinase (MAPK) cascade is an important cytoplasmic signalling pathway involved in the regulation of normal somatic cell proliferation. Mutations in the genes encoding components of this pathway have been associated with a number of human cancers.[1] An activating mutation in the BRAF gene, which encodes the serine-threonine protein kinase B-RAF, has been found to be present in 40-60 percent of melanomas, most commonly the BRAF V600E mutation.[2] Vemurafenib is indicated for the treatment of metastatic or unresectable melanomas that carry the BRAF V600E mutation. The recommended dose is 960 mg twice daily and it is currently available in 240 mg tablets.[3] Vemurafenib has also been used off-label for other types of malignancy carrying the BRAF V600E mutation.

Thrombocytopenia is defined as a platelet count of less than 150 x 10^9/L (150 000 per µL). A grading system for thrombocytopenia has been developed by the United States National Cancer Institute in which platelet counts between 75 x 10^9/L and 150 x 10^9/L are classified as Grade 1, while platelet counts below 25 x 10^9/L are classified as Grade 4.[4] Patients with platelet counts above 20 x 10^9/L are usually asymptomatic, but the risk of spontaneous mucocutaneous bleeding (gingival bleed, epistaxis, menorrhagia, petechiae and ecchymoses) and life-threatening, spontaneous intracranial hemorrhage or gastrointestinal bleeding increases rapidly with platelet counts below 10 x 10^9/L.

Thrombocytopenia in the context of metastatic malignancy may result from a number of causes including metastatic infiltration of the bone marrow, sepsis, disseminated intravascular coagulation (DIC), radiation and drugs. Drug-induced thrombocytopenia (DIT) is associated with many drugs and results from either decreased platelet production or increased platelet consumption. Decreased platelet production as a consequence of generalized myelosuppression is a relatively common adverse effect of many chemotherapeutic drugs, while selective suppression of megakaryocyte production leading to isolated thrombocytopenia has been associated with thiazide diuretics, alcohol and tolbutamide. Increased platelet destruction is further categorized as either immune or non-immune: drug-induced immunologic thrombocytopenia (DITP) is associated with a large number of drugs (most notably heparin) and several immunologic mechanisms have been identified. Non-immune platelet destruction such as TTP-HUS (thrombotic thrombocytopenic purpura – haemolytic uraemic syndrome) occurs less commonly, in association with a small number of anti-neoplastic agents.[5]

Reports in VigiBase®

At the time of assessment (March 2015), there were 30 individual case safety reports (ICSRs) of thrombocytopenia in association with vemurafenib in the WHO Global ICSR database, VigiBase®. Two duplicates were identified bringing the number of assessed case reports to 28. The reports came from

10 countries: United States (9), France (8), Germany (4) and Austria, Colombia, Italy, Netherlands, Norway, Turkey and United Kingdom

(1 each). Twenty-three of the ICSRs were serious and three reports were fatal.

The cases concerned 9 males and 19 females. Age was reported for 24 cases and ranged from 37 to 70 years (median age 56.5 years).

The indication for treatment was reported as malignant melanoma in 21 cases, colorectal cancer in one case and hairy cell leukaemia in one case; in the remaining five cases, the indication for treatment was reported either as unknown (three cases) or was not stated (two cases). Vemurafenib was the only suspected drug in 21 of the 28 cases: in 14 of these cases, vemurafenib was the only reported drug while the other seven cases reported concomitant medicines. In the remaining seven cases, other medicines for which thrombocytopenia is a known potential adverse effect were also suspected, including oxaliplatin, fluorouracil, cladribine, fotemustine, rituximab, aflibercept, levetiracetam, valproic acid, carvedilol, spironolactone, piperacillin/tazobactam and a combination medicine containing chlorpheniramine. Two of these ICSRs also reported co-suspected medicines that are not known to be associated with thrombocytopenia, including clobazam, folinic acid and caffeine/paracetemol/papaver somniferum latex. The total daily dose of vemurafenib was reported in half of the cases and ranged from 240 mg to 1920 mg (median dose 1920 mg).

The time-to-onset was reported for 12 cases and ranged from 3 to 225 days, with a median time-to-onset of 20 days. Vemurafenib was withdrawn following the onset of thrombocytopenia in 12 cases: dechallenge was positive in eight of these cases, negative in one case and the outcome of dechallenge was not stated in the remaining three cases. In one case the dechallenge action was reported as dose reduced but the dechallenge outcome was not reported. In six cases the dechallenge action was reported as 'dose not changed': thrombocytopenia resolved in two of these cases, no effect was observed in two cases and the effect was unknown in two cases. The dechallenge action was reported as unknown in four cases, was not reported in three cases and was not applicable in two cases (due to the death of the patient). In three of the cases with a positive dechallenge, vemurafenib was subsequently reintroduced at a lower dose: one case reported recurrence of thrombocytopenia (positive rechallenge) while the remaining two cases reported no recurrence. The outcome for thrombocytopenia was reported in 19 of the cases as follows: recovered (7), recovering (4), not recovered (6) and died (2). For the remaining nine cases, the outcome was reported as unknown.

Literature and Labelling

Thrombocytopenia is not listed as a possible ADR for vemurafenib in any of the sources that were checked, including the EMA[6], UK Summary of Product Characteristics[7] and the US FDA Product Label.[3] Neutropenia is the only haematological ADR listed in the product information.

Discussion

In this series of 28 ICSRs in which vemurafenib is associated with thrombocytopenia, one case met the criteria for a 'certain' causal relationship between the suspected drug and the reported ADR according to the WHO-UMC System for Case Causality Assessment.[8] Four cases had sufficient evidence to suggest a 'probable' association and a further 14 cases could be considered 'possible'. These 19 cases are summarised in Table 1. Bony infiltration associated with metastatic malignant melanoma (the indication for 21 of the 23 cases in which this information was provided) should be considered a risk factor for thrombocytopenia in each of these cases.

Case 22 provides the strongest evidence in this series for a causal relationship between vemurafenib and thrombocytopenia in that it has a plausible time relationship to drug exposure, no alternative explanation for the ADR, a positive dechallenge and a positive rechallenge. The case concerns a 65 year old female with a history of end-stage renal disease, arterial hypertension and a previous DVT. Thrombocytopenia and anaemia developed 19 days after initiation of treatment with vemurafenib for melanoma, and pancytopenia with febrile neutropenia developed on day 22 of therapy. Platelets were transfused. Vemurafenib was stopped for six days, during which time the platelet count improved; vemurafenib was then reintroduced at half the original dose but three days later the platelet count had again dropped, consistent with a positive rechallenge. Vemurafenib was stopped definitively and the platelet count returned to normal. Clinical investigations ruled out alternative explanations for the thrombocytopenia.

Cases 2, 3, 5 and 13 could be considered to have a 'probable' causal relationship. The time-to-onset (TTO) for three of these cases ranged from 15-29 days; TTO was not stated for the fourth case but other information provided in the report indicates that the reaction occurred between 6 and 10 weeks after starting vemurafenib. In each of these four cases vemurafenib was withdrawn and the thrombocytopenia resolved; in Case 2, the drug was subsequently restarted at a lower dose with no recurrence of the ADR. No other drugs were suspected in any of the four cases (in three cases vemurafenib was the only reported drug).

The remaining 14 cases shown in Table 1 could be considered to have a 'possible' causal relationship to vemurafenib. The time-to-onset for these 14 cases, where reported, ranged from 3 to 169 days. Two of the cases reported co-suspected medicines known to be associated with thrombocytopenia: piperacillin/ tazobactam (Case 17) and carvedilol, spironolactone (Case 20). The latter case also reported the combination analgesic caffeine/paracetemol/papaver somniferum latex as suspected, but it is not known to be associated with thrombocytopenia. Levetiracteam, which is known to be associated with thrombocytopenia, was listed as a concomitant medicine in Case 11. Among these 14 cases, three cases reported evidence of a positive dechallenge (Cases 7, 12 and 23), one of which subsequently restarted vemurafenib with no recurrence of thrombocytopenia (Case 23). Concurrent infections including pneumonia and urinary sepsis may have accounted for the thrombocytopenia in each of these cases, and Case 23 was also confounded by other medicines.

The remaining six cases (not shown in Table 1) lacked sufficient evidence to suggest a causal relationship between vemurafenib and thrombocytopenia. In Case 8, the patient received radiation therapy to the lumbar vertebrae one day prior to starting treatment with vemurafenib and the thrombocytopenia improved while treatment with vemurafenib continued; in Cases 9 and 16, the thrombocytopenia appears to have preceded treatment with vemurafenib, and in Cases 25, 29 and 30, the temporal relationship to other medicines provides a more plausible alternative explanation for the thrombocytopenia. Causality could not be assessed for the remaining three cases (Cases1, 4 and 10) due to a lack of information in the reports.

Vemurafenib acts on mutated B-RAF protein to inhibit the RAS-RAF-MEK-ERK intracellular signalling pathway in melanoma cells to prevent cell growth and proliferation. This same pathway is also present in haematopoietic progenitor cells and plays a role in haematopoietic cell differentiation,[9,10] suggesting a possible mechanism by which vemurafenib might cause thrombocytopenia. Platelets (thrombocytes) are formed from megakaryocytes, which derive from the multipotential hematopoietic stem cell (HSC). The HSC gives rise to progressively committed progenitor cells, including the common myeloid progenitor (CMP) and the megakaryocyte-erythroid progenitor (MEP). MEPs in turn give rise to both megakaryocytic and erythroid cell lineages. Multiple transcription factors are involved in the differentiation of these MEPs to megakaryocytes, the most important of which is thrombopoietin (TPO). Binding of TPO to the TPO receptor on the MEP cell surface membrane activates the intracellular signaling protein Jak2, which in turn activates several intracellular signaling cascades, including the RAS-RAF-MEK-ERK cascade.[11]

Six of the cases shown in Table 1 include co-reported ADR terms that indicate a more widespread myelosuppression, rather than an isolated thrombocytopenia (Cases, 5, 11, 13, 18, 22 and 26). These co-reported terms are highlighted in bold in Table 1. Granulocytopenia has previously been signalled for vemurafenib (SIGNAL, issue 3, 2013) and neutropenia has since been added to the US, UK and EMA product information sheets, adding support to the notion that vemurafenib may affect the RAS-RAF-MEK-ERK cascade in haematopoietic cells. It is possible that all of these cases in which vemurafenib is associated with depression of various blood cell lineages may represent a spectrum of drug induced myelosuppression, possibly brought about through an effect on the RAS-RAF-MEK-ERK intracellular signalling pathway in haematopoietic progenitor cells.

Table 1: Cases of interest in VigiBase® of Vemurafenib and thrombocytopenia

Case	Age/ Sex	Other suspected (S) or concominant (C) drugs	Other reported ADRs (WHO-ART Preferred Term)* *(Reported terms in italic- included where more informative)*	Time to onset (days)	Dechallenge/ Rechallenge	Outcome at time of reporting
2	58/F	Zolendronic acid (C)	Bilirubinaemia, rash	20	Withdrawn, reaction abated Subsequently reintroduced at a lower dose with no recurrence	Recovered
3	66/M	-	Oedema, generalised oedema, neoplasm, musculoskeletal pain, pulmonary oedema, duodenal ulcer, GI haemorrhage	-	Withdrawn, reaction abated	Recovered
5	51/M	-	**Leukopenia, pancytopenia**, paralysis facial	29	Withdrawn, reaction abated	Recovered

6	53/F	-	-	< 7	Withdrawn	Unknown
7	58/M	-	- (Pneumonia)**	46	Withdrawn, reaction abated	Recovering
11	53/M	Levetiracetam, omeprazole (both C)	**Anaemia, leukopenia**	43	-	Died
12	-/F	-	Bronchitis, *black eye*	4	Withdrawn, reaction abated	Recovering
13	68/F	-	Haemorrhage, **leukopenia**	15	Withdrawn, reaction abated	Recovering
14	68/F	-	-	7	Unknown	Not recovered
15	61/M	Gabapentin (C)	Disseminated intravascular coagulation, haematoma, *venipuncture site haemorrhage*, urinary tract infection, *soft tissue haemorrhage*, haematuria, fibrinolysis increased, C-reactive protein increased, leukocytosis, *skin haemorrhage*, haematoma, anaemia, *metabolic disorder*	3	Withdrawn	Not recovered
17	70/F	Piperacillin/tazobactam (S) Allopurinol, amlodipine, clonidine, colchicine, daptomycin, darbepoetin alfa, diphenhydramine, enoxaparin, famotidine, insulin glargine, ipratropium, lisinopril, megestrol, methylprednisolone, omeprazole, prednisolone, salbutamol, simvastatin, sodium bicarbonate, sulfamethoxazole/trimethoprim, tigecycline, timolol, tobramycin (all C)	Palmar-plantar erythrodysaesthesia, bronchitis, infection bacterial, AST increased, acidosis, pulmonary congestion, hyperglycaemia, pancreatitis, pleural effusion, gastric dilatation, infection staphylococcal, fibrillation atrial, cerebral disorder, renal failure chronic, hyperuricaemia, bilirubinaemia, tachycardia ventricular, ECG abnormal specific, candidiasis, alkaline phosphatase increased, medical device complication, respiratory insufficiency, urinary tract infection, failure to thrive, atelectasis, bilirubinaemia, cardiac arrest, neuropathy peripheral, ALT increased, dermatitis exfoliative	-	Not applicable	Unknown
18	52/F	-	Dehydration, *disease progression*, **white blood count decreased**, infection	-	Not applicable	Died
20	44/M	Carvedilol, spironolactone, saffeine/paracetemol/papaver somniferum latex (all S)	-	163	Dose not changed, no effect	Not recovered
22	65/F	Atenolol, sodium polystyrene sulfonate, furosemide, losartan, sevelamer, calcifediol, prasozin, paracetamol, esloratadine (all C)	**Anaemia, pancytopenia, febrile neutropenia**	19	Withdrawn, reaction abated Restarted 6 days later with recurrence of thrombocytopenia	Recovered
23	56/F	Folic acid, cyanocobalamin (both C)	Fever, urinary tract infection, arthropathy, arthrosis, rash, *mass*, rash erythematous, hypokalaemia, haemorrhage nos, alopecia, pruritis, hepatic enzymes increased, arthralgia, arthritis, *joint swelling*	-	Drug withdrawn, reaction abated Drug restarted with no recurrence of thrombocytopenia	Unknown
24	64/F	-	-	169	-	Not recovered
26	38/F	Fotemustine, polyvalent immunoglobulins (both C)	**Neutropenia**	79	Dose not changed, no effect	Not recovered
27	37/F	-	-	55	Dose not changed, outcome unknown	Unknown
28	38/F	-	Purpura, *bruising of leg*	> 122	Dose not changed, outcome unknown	Unknown

*Co-reported ADR terms highlighted in bold suggest a more widespread myelosuppression rather than isolated thrombocytopenia

**Case 7: Narrative states that patient was hospitalised for pneumonia when thrombocytopenia was diagnosed

Conclusion

The data provided in the case series strongly supports a signal for the association between vemurafenib and thrombocytopenia. The suggestion of a possible mechanism, although speculative, adds further support for the signal.

References

1. Davies H, , Bignell GR, Cox C, Stephens P, Edkins S, Clegg S et al. Mutations of the BRAF gene in human cancer. Nature 2002;417(6892):949-54.
2. Roberts PJ, Der CJ. Targeting the Raf-MEK-ERK mitogen-activated protein kinase cascade for the treatment of cancer. Oncogene 2007;26(22):3291-310.
3. US Food and Drug Administration. Zelboraf Label (Nov 2014) http://www.accessdata.fda.gov/drugsatfda_ docs/label/2014/202429s006lbl.pdf. Accessed: 3 March 2015.
4. National Cancer Institute, Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. 2010, U.S. Department of Health and Human Services
5. Visentin GP, Liu CY. Drug Induced Thrombocytopenia. Hematology/oncology clinics of North America 2007;21(4):685-96.
6. European Medicines Agency, Zelboraf : EPAR - Product Information http://www.ema.europa.eu/docs/en_GB/ document_library/EPAR_-_Product_Information/human/002409/WC500124317.pdf. Accessed: 3 March 2015.
7. Electronic Medicines Compendium UK. Zelboraf 240 mg film-coated tablets http://www.medicines.org.uk/emc/medicine/26056. Accessed 3 Mar 2015.
8. Uppsala Monitoring Centre. The use of the WHO-UMC system for standardised case causality assessment. [pdf] 2012 [cited 2015 3 March] http://www.who-umc.org/Graphics/26649.pdf.
9. Chung E, Kondo M. Role of Ras/Raf/MEK/ERK signaling in physiological hematopoiesis and leukemia development. Immunol Res. 2011;49(1-3):248-68.
10. Hsu CL, Kikuchi K and Kondo M. Activation of mitogen-activated protein kinase kinase (MEK)/ extracellular signal–regulated kinase (ERK) signaling pathway is involved in myeloid lineage commitment. Blood 2007;110(5):1420-8.
11. Geddis AE, Megakaryopoiesis. Seminars in hematology 2010;47(3):212-9.

Response from Roche

In March 2015 the WHO Monitoring centre in Uppsala invited Roche to comment on a signal of thrombocytopenia in patients treated with vemurafenib. WHO cited 28 cases of thrombocytopenia associated with vemurafenib treatment in the VigiBase®. The report concluded that the data provided in their case series strongly supports a signal for the association between vemurafenib and thrombocytopenia.

Drug induced thrombocytopenia has a reported frequency of approximately 19% to 25% in acutely ill patients. Clinical manifestation usually consists of moderate to severe thrombocytopenia (platelet count of less than 50×10^9/L) and spontaneous bleeding which could be potentially life threatening. (Visentin & Liu, 2007) Typically, the thrombocytopenia occurs 1 to 2 weeks after the introduction of a new drug or 2-3 days after a single dose when a drug has previously been taken intermittently. Demonstration of drug-dependent anti-platelet antibodies is important to confirm the etiology of drug-induced thrombocytopenia. Recovery from drug-induced thrombocytopenia usually begins within 1 to 2 days of stopping the drug and is typically completed within a week. Drug-dependent antibodies can persist for many years.

Several mechanisms have been described in the pathogenesis of drug-induced thrombocytopenia, with accelerated platelet destruction in the presence of the offending drug as the most common immune mechanism. Non immune platelet destruction associated with a small number of antineoplastic agents, such as bleomycin, can occur in thrombotic microangiopathy and its variant form, hemolytic uremic syndrome. (Goerge & Aster, 2009)

The literature describes case reports of thrombocytopenia in metastatic melanoma patients as part of massive bone marrow infiltration (Deepali, Daga, & et Al, 2007), secondary to chemotherapy or immunotherapy (e.g., ipilimumab, high dose IL2), and secondary to platelet consumption in disseminated intravascular coagulation (Lepelley-Dupont, Chevrant-Breton J, & et Al, 2009). We performed an analysis on the background incidence rate of secondary thrombocytopenia and all thrombocytopenia in patients with metastatic melanoma using the Truven Healthcare MarketScan® Commercial Claims and Encounters (Commercial) database. The incidence of thrombocytopenia following a diagnosis of metastatic melanoma was estimated as 5.93

(secondary thrombocytopenia) and 42.2 (all thrombocytopenia) per 1,000 patient years.

Vemurafenib inhibits mutant BRAFV600 and is approved for the treatment of adult patients with metastatic melanoma harboring this mutation. Currently the vemurafenib label does not include thrombocytopenia as an adverse drug reaction. Preclinical studies do not support a direct association with thrombocytopenia, however one case of bone marrow necrosis was noted in one of two moribund sacrificed dogs in the prematurely terminated 39-week dog study (Roche, 2015). In the Phase III trial, <1 % of 337 patients dosed with vemurafenib reported thrombocytopenia.

As of March 24, 2015, there are 45 cases of thrombocytopenia related adverse events (AEs) reported with vemurafenib use in the Roche safety database, thirty-two of which were assessed as serious. Median age was 59.5 years (31-80). Gender was provided for 43 cases of which 22 were males and 21 were females. Indication was provided for 33 cases of which 32 were malignant melanoma cases and one case was hairy cell leukemia. Latency was provided for 20 of the 45 cases.

Median latency was 24 days with a range of 3-225 days.

Thirteen of these 20 cases had a latency of ≤ 30 days.

Based on medical review, 6 out of the 45 cases were assessed to have a likely causal association to vemurafenib. The remaining cases were:

a. lacking vital information that makes meaningful assessment difficult (n=20),
b. have an unlikely causal association based on strong alternative etiology for the event of thrombocytopenia such as concomitant use of fotemustine, bone marrow infiltration by melanoma cells, or secondary to microangiopathy or DIC (n=13); and
c. assessed to have possible causal association based on the latency that was longer than expected for drug-induced thrombocytopenia or a negative dechallenge/ rechallenge (n=6).

Table 1 below provides the case details on the 6 cases that are assessed to have a likely causal association based on case presentation, temporal association, and dechallenge information. Of the 6 cases, two cases had associated depression of other blood cell lineage.

Table 1: Cases of interest in Roche Vemurafenib Safety Database

Case	Age Gender	Concom Medication	Indication	Initial total daily dose	Adverse Event Term	Other Reported Adverse Events	Highest CTCAE Severity Grade	AE Duration (days)	Latency (days)	Event outcome	Reporter Causality	Vem outcome	Dechall	Rechall
1	Unk Female		Unknown indication	1920mg	Platelet count decreased	Lower respiratory tract infection Periorbital contusion	3	Not reported	4	Resolving	Related	D/C	Positive	N/A
2	66 Male		Malignant melanoma	1920mg	Thrombocytopenia	Gastrointestinal haemorrhage Duodenal ulcer Pulmonary oedema Musculoskeletal pain Neoplasm Generalised oedema	2	7	15	Resolved	Related	D/C	Positive	N/A
3	Unk Male	Saquinavir Bisoprolol Aspirin Simvastatin Allopurinol Prednisolone	Malignant melanoma	1920mg	Platelet count abnormal	Rash Pruritus	4	N/A	11	Resolving	Related	D/C	Positive	N/A
4	51 Male		Malignant melanoma	480mg	Thrombocytopenia	Leukopenia Facial paresis	3	7	29	Resolved	Related	D/C	Positive	N/A
5*	65 Female	Furosemide Losartan Sevelamer Atenolol Prozosine	Malignant Melanoma	Not reported	Thrombocytopenia	Anemia Pancytopenia Febrile neutropenia	4	8; 17 (2nd episode)	22; 3 (2nd episode)	Resolving to grade 1; Resolved (2nd episode)	Related	Interrupted and dose reduced; D/C (2nd episode)	Positive**; Positive	Positive; N/A
6	58 Female	Zoledronic Acid	Unknown indication	1920mg	Thrombocytopenia	Rash Blood bilirubin increased	2	NR	20	Resolved	Not reported	Interrupted and dose reduced	Positive	Negative

Legend: *Case number 22 in the WHO report; vem = vemurafenib; D/C = discontinued; N/A = not applicable; dechalle=dechallenge; rechalle=rechallenge; ** confounded by platelet treatment

AER number 1351266 was identified in the WHO Report as case 22 and where causal relationship between vemurafenib and thrombocytopenia was described as "certain" in that report. Similarly, Roche assessed this case to be likely associated with vemurafenib treatment.

The 6 cases of thrombocytopenia yield a crude reporting rate of 0.67 cases per 1000 patient years based on an estimated cumulative patient exposure to vemurafenib of 17,729 patient years. Using a conservative approach, the crude reporting rate of 45 cases is 2.54 per 1,000 patient years. These rates are significantly lower than expected for the metastatic melanoma population based on the Marketscan analysis.

Roche acknowledges the signal for thrombocytopenia raised by the WHO. This event including other cell lines and pancytopenia are closely monitored. Bone marrow toxicity remains a potential risk for vemurafenib and is included in the Risk Management Plan (RMP) for the drug. The assessment of this event, as part of bicytopenia or pancytopenia in the context of bone marrow suppression is currently being investigated by Roche.

References

1. Bluteau, D., Raslova, H., & et Al. (2014). Thrombocytopenia-associated mutations in the ANKRD26 regulatory region induce MAPK hyperactivation. The Journal of Clinical Investigations, 124(2), 580-91.
2. Clerico, M., et Al, & Turrisi G. (2006). Persistent thrombocytopenia during melanoma treatment with fotemustine. Melanoma Research, 16(6), 543-4.
3. Deepali, J., Daga, M., & et Al. (2007). Metastatic Malignant Mellanoma in Bone Marrow with Occult Primary Site - a Case Report with Review of Literature. Diagnostic Pathology, 2(38).
4. Goerge, J., & Aster, R. (2009). Drug-induced thrombocytopenia: pathogenesis, evaluation, and management. ASH education book, 1, 153-8.
5. Lepelley-Dupont, C., Chevrant-Breton J, & et Al. (2009). Melanoma-associated disseminated intravascular coagulation. Journal of the European Academoy of Dermatology and Venerology, 23(6), 720-1.
6. Roche, F. H.-L. (2015). Investigator's Brochure for vemurafenib.
7. Visentin, G., & Liu, C. (2007). Drug induced thrombocytopenia. Hematology Oncology clinics of Norht America, 21(4), 685-96.

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CAVEAT DOCUMENT

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

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

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

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

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

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

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

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

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

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

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

Omission of this statement may exclude the responsible person or organization from receiving further information from VigiBase®.

2011

Strengthening pharmacovigilance in countries: a brief report from two WHO events

Pharmacovigilance workshop, Indonesia, April 2015

Access to new drugs and vaccines in low and middle income countries has been made easier through various Public Health initiatives. Many of these treatments have the potential to save and improve the quality of many lives, however many counties in which these products are deployed do not have the capacity to effectively monitor their post market safety. This is of particular concern with medications that are being introduced through an accelerated approval process, well before all phases of clinical trials can be completed.

Pharmacovigilance (PV) and the management of adverse drug reactions are essential when introducing such fast-tracked, novel medications. The focus on PV presents an opportunity to strengthen and build PV systems in countries where such medications will be introduced but where there is little or no capacity for pharmacovigilance.

The national TB programme in Indonesia plans to introduce bedaquiline (BDQ) in August 2015. BDQ is a new medication for the treatment of MDR TB and has received accelerated marketing approval in some countries (1, 2).

The Badan POM (BPOM), the National Agency of Drug and Food Control (NADFC) in Indonesia, have recognized the need to improve PV capacity in the country, for the effective monitoring of safety of drugs such as BDQ and other medicines used in its Public Health Programmes. A collaboration between BPOM, WHO country office in Indonesia and WHO/EMP[a] led to the planning of a successful PV workshop in Bogor, Indonesia.

The workshop was supported through a grant from the Access and Delivery Partnership project that is funded by the Government of Japan, coordinated and led by United Nations Development Programme, with WHO/TDR[b] as one of the project partners involved in strengthening capacity for safety monitoring with technical support from WHO/EMP.

The workshop aimed to strengthen PV and networking between PV staff and public health programs, build PV capacity and introduce the principles of cohort event monitoring, an active pharmacovigilance method developed by the WHO Department of Essential Medicines and Health products (EMP) (3-6). The workshop was also an opportunity to review basic PV concepts and principles, with a view to strengthening key technical areas in PV in Indonesia.

There were approximately 40 participants and the workshop consisted of: academics (from the main universities in Indonesia), BPOM staff, health-care professionals from hospitals (clinicians and pharmacists), staff from provincial health offices (Jakarta, East and West Java), staff from the KNCV TB foundation, members of WHO Indonesia country office, and staff working under the ministry of health, dedicated to Public Health Disease Programmes such as national TB, HIV and Malaria Programmes, and the Directorate of Pharmaceutical Services. Representatives from the WHO collaborating centre for Advocacy and Training in Pharmacovigilance in Accra, Ghana, staff from WHO HQ (Geneva) and a PV specialist from the National Agency for Food and Drug Administration and Control (NAFDAC) in Nigeria presented and facilitated the workshop activities.

The three-day workshop was officially opened by Director of Distribution Control of Therapeutic products from the Ministry of Health, Dr Arustiyono. Dr Salma Burton from the WHO country office in Indonesia also spoke at the opening session, linking PV to access, priority medicines, and universal health coverage.

On Day 1, a presentation from BPOM described the national PV centre in the country, its organization, roles and responsibilities. Fundamental principles of PV were presented, and the importance of integrating PV in public health programmes was introduced. Presentations on VigiFlow and VigiLyze highlighted different levels of baseline knowledge of PV and experience amongst participants. PV is a centralized function in Indonesia and BPOM faces many challenges in implementation and resources, given the size and spread of the country

a Essential Medicines and Health Products, Medicines Safety Unit.
b The Special Programme for Research and Training in Tropical Diseases at the World Health Organization.

over several provinces and island states. BPOM is discussing the concept of centres of excellence in some of the teaching hospitals, to increase its outreach, competence and capacity to provide training in key aspects within PV.

Day 2 consisted of interactive sessions on CEM, and causality assessments. Participants were trained through working groups on assessments, and mock-up exercises of CEM methodology and its implementation. A more intensive training on causality assessments was requested as one of the future activities.

Presentations on communication, crises management, and benefit harm analysis were well received on Day 3. Participants shared examples of escalated miscommunications that have occurred in public health programmes, emphasizing the importance of good communication and training. Examples of cases where the regulators had faced difficult decisions about registering or continuing a product were shared.

From the participants' feedback it would appear that the workshop achieved its objectives, of improving basic knowledge and capacity for PV in the country. It also provided an opportunity to strengthen collaborations between the public health programmes and the national PV Centre in Indonesia.

As a follow up, BPOM will establish a PV and risk assessment / safety advisory committee in the country, with the relevant expertise and experience in benefit risk assessment and patient safety management.

References:

1. FDA News Release. In FDA U.S. Food and Drug Administration , Protecting and Promoting Your Health:[http://ww.fda.gov]. USA: U.S. Department of Health and Human Services; 2012 (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm333695.htm, accessed 19 June 2015)
2. European Medicines Agency recommends approval of a new medicine for multidrug-resistant tuberculosis. In: European Medicines Agency, Science Medicines Health [http://www.ema.europa.eu/ema/]. London: European Medicines Agency; 2013 (http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/12/news_detail_001999.jsp&mid=WC0b01ac058004d5c1, accessed 19 June 2015)
3. Pal SN, Duncombe C, Falzon D, Olsson S. WHO strategy for collecting safety data in public health programmes: complementing spontaneous reporting systems. Drug Saf, 2013, 36(2):75-81.doi: 10.1007/s40264-012-0014-6.
4. A practical handbook on the pharmacovigilance of antimalarial medicines. Geneva: World Health Organization.; 2008 (http://www.who.int/malaria/publications/atoz/malaria-pharmavigil.pdf, accessed 22 June 2015).
5. A practical handbook on the pharmacovigilance of antiretroviral medicines. Geneva: World Health Organization.; 2009 (http://apps.who.int/medicinedocs/documents/s16882e/s16882e.pdf, accessed 22 June 2015)
6. A practical handbook on the pharmacovigilance of medicines used in the treatment of tuberculosis. Geneva: World Health Organization; 2012 (http://www.who.int/medicines/publications/pharmacovigilance_tb/en/, accessed 22 June 2015)

Seasonal Malaria Chemoprevention and Pharmacovigilance, Morocco, May 2015

Severe malaria is a life-threatening disease that occurs mostly among children living in Africa, where it is estimated that a child dies every minute from malaria (1). Natural immunity to malaria is usually acquired in children living in malaria endemic areas by the age of seven-ten (2, 3). However younger children living in these areas have inadequate immunity and are at greater risk of developing severe malaria.

There are several approaches to malaria control such as vector control through the use of insecticide treated mosquito nets and indoor residual spraying with insecticides. Another measure is the use of medications as a preventive measure. This can be through daily or weekly doses of a medication, or alternatively, the medication can be given as a preventive treatment at regular intervals during transmission season. The latter is known as seasonal malaria chemoprevention SMC, (previously known as intermittent treatment), defined as the intermittent administration of full treatment courses of an antimalarial medicine during the malaria season to prevent malaria illness with the objective of maintaining therapeutic antimalarial drug concentrations in the blood throughout the period of greatest malarial risk (4).

In 2012, WHO made a recommendation for the implementation of SMC in areas of highly seasonal malaria transmission across the Sahel sub-regions (4). 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.

ACCESS-SMC is a UNITAID-funded project, led by the malaria Consortium in partnership with Catholic Relief Services, which is scaling up access to SMC across the malaria endemic sub-Saharan countries (5). The project will last three years in collaboration or with technical support from the London School of Hygiene and Tropical Medicine, Centre de Support de Santé International, Management Sciences for Health, Medicines for Malaria Venture, and Speak Up Africa. It will provide 30 million SMC treatments annually to 7.5 million children less than five years of age in Burkina Faso, Chad, the Gambia, Guinea, Mali, Niger and Nigeria (6).

PV in SMC will involve the participation of staff from the National PV Centre and the health facility and health-care workers/volunteers. Health-care workers/volunteers will be trained on various aspects of basic skills, such as how to administer medication, what advice to provide to parents, and to refer adverse events to health-care facilities. They will be responsible for providing the medications to the parents of the children. Health-care staff working in local health facilities will be trained on reporting adverse events (as one aspect of overall training). National PV centres will be responsible for analysing data on potential drug-related adverse events, and for signal detection.

The countries providing SMC vary in their PV capacity. Some have an established PV system, and others have no formal national centres for PV and are not part of the WHO Programme for International Drug Monitoring (PIDM). And then there are those with a rudimentary PV system that is not fully functional.

In order to build and / or strengthen PV systems in SMC countries, the WHO Collaborating Centre for PV in Rabat, Morocco hosted a workshop in May 2015. The workshop was conducted in collaboration with the London School of Hygiene and Tropical medicine WHO/EMP, WHO/TDR, the, University of Cheikh Anta Diop and Access-SMC. The aim of the workshop was to help Sub-Saharan African countries develop an appropriate PV plan in preparation for the implementation of SMC scheduled to commence between July and August 2015.

Participants included representatives of national PV centres and those responsible for PV in National Malaria Control Programmes in the following countries: Burkina Faso, Chad, the Gambia, Guinea, Mali, Niger and Nigeria. Countries presented their national PV systems and identified focal PV persons (if present). Countries that are not members of the WHO PIDM were given guidance on steps needed to join the WHO PIDM.
The programme for the workshop consisted of presentations on the SMC programme, previous experience of SMC in Senegal, the WHO Programme for International Drug Monitoring, use of VigiFlow as a data management system, causality assessment, signal detections and risk minimizations plans. The majority of countries have had experience using VigiFlow as a data management system. Concerns over the time taken for reports to reach VigiBase[c] were expressed. Working groups discussed PV training needs for community health workers, health facilities and national PV centres.

[c] **VigiBase®** is the name of the WHO Global ICSR database; it consists of reports of adverse reactions received from member countries since 1968. VigiBase® is updated with incoming ICSRs on a continuous basis. National centres are recommended to send reports at least quarterly; most national centres adhere to these guidelines, and several report more frequently.

The workshop discussed the adverse events to report, when to refer patients to health facilities; and which adverse events would require SMC to be discontinued, resources required to manage serious adverse reactions such as anaphylaxis.. It was recommended that all adverse events should be reported initially in order to build the safety profile of medications used in the younger age groups. Community workers should refer patients with adverse events to healthcare facilities. More information on the safety profile of the medications will help the proposed regional committee for safety monitoring to develop a risk management plan and a decision tree on how to manage adverse events and when to continue or stop SMC. .

Next steps, for WHO and Access-SMC partners will be: supporting non WHO PIDM members to join the programme; developing training material for actors involved in SMC deployment; and supporting countries to develop a PV plan which will strengthen systems for the sustainable monitoring of adverse events.

References:

1. Malaria. In: WHO/Mediacentre [http://www.who.int]. Geneva: World Health Organization, 2015 (http://www.who.int/mediacentre/factsheets/fs094/en/, accessed 19 June 2015)
2. Branch OH, Udhayakumar V, Hightower AW, Oloo AJ, Hawley WA, Nahlen BL, et al. A longitudinal investigation of IgG and IgM antibody responses to the merozoite surface protein-1 19-kiloDalton domain of Plasmodium falciparum in pregnant women and infants: associations with febrile illness, parasitemia, and anemia. Am J Trop Med Hyg. 1998; 58(2):211-9.
3. Warrell DA. "To search and Studdy out the secrett of Tropical Diseases by way of Experiment". Lancet. 2001; 358(9297):1983-8.
4. WHO Global Malaria Programme: WHO policy recommendation: Seasonal malaria chemoprevention (SMC) for Plasmodium falciparum malaria control in highly seasonal transmission areas of the Sahel sub-region in Africa. Geneva: World Health Organization; 2012 (http://www.who.int/malaria/publications/atoz/smc_policy_recommendation_en_032012.pdf, accessed 22 June 2015).
5. Tine RC, Ndour CT, Faye B, Cairns M, Sylla K, Ndiaye M, et al. Feasibility, safety and effectiveness of combining home based malaria management and seasonal malaria chemoprevention in children less than 10 years in Senegal: a cluster-randomised trial. Trans R Soc Trop Med Hyg. 2014; 108(1):13-21.
6. Access-SMC. In Malaria consortium, disease control, better health [http://www.malariaconsortium.org/]. United Kingdom: Malaria Consortium Headquarters; Malaria Consortium. (http://www.malariaconsortium.org/pages/access-smc.htm, accessed 19 June 2015)

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