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

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

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This Newsletter is also available on our Internet website:
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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®.

This issue includes recommendations from the working groups of the Thirty-eighth Annual Meeting of Representatives of National Pharmacovigilance Centres that was held in 2015, in Delhi, India.

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Amlodipine besilate

Risk of fulminant hepatitis, agranulocytosis and rhabdomyolysis

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have advised that the package inserts for amlodipine and amlodipine combinations containing: azilsartan; aliskiren fumarate; irbesartan; telmisartan; candesartan; valsartan; and atorvastatin calcium hydrate should list: fulminant hepatitis; agranulocytosis (except for preparations with candesartan and valsartan); and rhabdomyolysis as clinically significant adverse reactions.

Amlodipine is indicated for hypertension and angina pectoris. Amlodipine in combination with atorvastatin is used in patients with hypercholesterolemia or familial hypercholesterolemia in addition to hypertension or angina pectoris. The remaining combination products listed above are indicated for hypertension only.

Two cases of fulminant hepatitis, one case of agranulocytosis, and three cases of rhabdomyolysis have been reported in patients taking amlodipine in Japan during the last three years. A causal relationship could not be ruled out in some of these cases. In addition, there were a total of six cases of rhabdomyolysis reported in patients taking the amlodipine and atorvastatin combination. Following investigations and advice from experts, the MHLW/PMDA have decided that revision of the package insert is necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 12 January 2016 (www.pmda.go.jp/english/)

Antiretroviral medicines

Updated advice on body-fat changes and lactic acidosis

The United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has notified healthcare professionals that the product information for antiretrovirals will be updated to reflect current knowledge about lipodystrophy and lactic acidosis.

Class warnings about lipodystrophy (lipatrophy, lipoaccumulation, changes in weight and metabolism) were being routinely applied to all antiretroviral agents, and warnings of lactic acidosis were applied to nucleoside and nucleotide analogue medicines. These warnings may not accurately reflect current scientific understanding.

Following an EU-wide review, it was noted that lipoatrophy was related only to substances with a high risk of mitochondrial toxicity (zidovudine, stavudine, didanosine), and not seen in regimens with other nucleoside reverse transcriptase inhibitor products. In addition, evidence of disproportional body-fat redistribution in relation to antiretroviral treatment was not clear. Effects on blood lipids and glucose may occur with any HIV medicine and are not restricted to protease inhibitors, nucleoside and nucleotide analogues. The risk of lactic acidosis was considered to differ across nucleoside and nucleotide analogues, being most strongly associated with zidovudine, stavudine, and didanosine.

To be consistent with current HIV treatment guidelines and evidence, product information will be amended by:
- including advice that weight gain and metabolic changes (such as lipid and glucose increases) may occur during treatment with any HIV medicine. However, these changes are partly linked to underlying disease control and lifestyle in addition to antiretroviral treatment;
- retaining warnings for lipoatrophy and lipoaccumulation only for zidovudine, stavudine, and didanosine;
- removing warnings about lactic acidosis for nucleoside and nucleotide analogues, with the exception of products that contain zidovudine, stavudine, or didanosine.

Reference:
Drug Safety Update, MHRA, Volume 9, issue 5: 14 December 2015 (www.gov.uk/mhra)

Atovaquone

Cases of agranulocytosis and leukopenia

Japan. The MHLW and the PMDA have announced that the product labels for atovaquone (Samitrel®) and atovaquone/proguanil combination (Malarone®) have been revised to include warnings for agranulocytosis and leukopenia as adverse reactions.

Atovaquone as a single agent is indicated for the treatment and prevention of pneumocystis pneumonia. In combination with proguanil hydrochloride, it is used in the prophylaxis and treatment of malaria.

A total of 11 cases of agranulocytosis and leukopenia have been reported in patients taking atovaquone. The causal relationship to atovaquone could not be ruled out in five of these cases. Two cases were fatal (a causal relationship could not be established).

Following investigations and advice from experts, the MHLW/PMDA decided that revision of the package insert was necessary.
**Regulatory Matters**

“Agranulocytosis and leukopenia” have been added to the “Clinically significant adverse reaction” section of the product label for atovaquone and in the “pancytopenia” subsection in the atovaquone/proguanil preparation.

**Reference:**
Revision of Precautions, MHLW/PMDA, 12 January 2016 (www.pmda.go.jp/english/)

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**Azilsartan**

**Risk of rhabdomyolysis**

**Japan.** The MHLW and the PMDA have announced that the product information for azilsartan (Azilva®) and azilsartan/amlodipine preparation (Zacras®) have been revised to include rhabdomyolysis as an adverse effect.

Azilsartan is an angiotensin II receptor antagonist used in the treatment of hypertension. In Japan, a total of five cases in patients taking azilsartan as a single preparation associated with rhabdomyolysis have been reported (including four cases for which a causal relationship to the product could not be ruled out). One case of rhabdomyolysis associated with use of azilsartan/amlodipine combination has also been reported.

Following investigations and advice from experts, the MHLW/PMDA decided that changes to the package insert were necessary. “Rhabdomyolysis” will be added in the “Clinically significant adverse reaction” section.

**Reference:**
Revision of Precautions, MHLW/PMDA, 12 January 2016 (www.pmda.go.jp/english/)

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**Benzoyl peroxide and salicylic acid topical products**

**Risk of serious allergic reactions**

**Canada.** Health Canada has informed health-care professionals and consumers about the risk of serious hypersensitivity reactions, and changes to product information for over-the-counter (OTC) topical acne products containing either benzyl peroxide or salicylic acid.

Health Canada has conducted a health review and concluded that there is evidence to support a link between the use of OTC benzyl peroxide or salicylic acid topical acne products and serious hypersensitivity reactions including anaphylaxis. Health Canada received 10 and 16 cases of serious hypersensitivity reactions to OTC benzyl peroxide and salicylic acid products respectively of which five (benzyl peroxide) and four (salicylic acid) were anaphylaxis.

As a result Health Canada will update the directions of use and warning sections of the Health Canada Acne Therapy Monograph for topical OTC acne products containing these components.

An information update will be published and will provide the following consumer advice in the event of an anaphylactic reaction:

- if you develop severe itching and hives, with swelling on the face, eyes, lips, mouth or throat; difficulty breathing, throat tightness or hoarseness; and/or fainting, please see emergency medical services.

**Reference:**
Summary Safety Review, Health Canada, 10 December 2015 (www.hc-sc.gc.ca)

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**Bisphosphonates**

**Risk of osteonecrosis of the external auditory canal**

**The United Kingdom.** The MHRA has announced that the product information for bisphosphonates will be updated to advise health-care professionals and patients of the possibility of osteonecrosis of the external auditory canal with bisphosphonate use.

Bisphosphonates (alendronic acid, ibandronic acid, pamidronate disodium, risendronate sodium, sodium clodronate, zoledronic acid) are used to treat osteoporosis and Paget’s disease, and are part of some cancer regimens (particularly metastatic bone cancer and multiple myeloma). Individual bisphosphonates have different indications.

Benign idiopathic osteonecrosis of the external auditory canal is a rare condition that can occur in the absence of antiresorptive therapy (therapy to increase bone strength) and is sometimes associated with local trauma.

At the time of the announcement, there were 29 reports of osteonecrosis of the external auditory canal in association with bisphosphonates (oral and intravenous forms) for use in both cancer related and osteoporosis indications, that have been identified globally and 11 cases reported in the literature. Most cases were associated with long term bisphosphonate therapy (≥2 years) and included possible risk factors, for example steroid use. Evidence from cases reported and from the literature supports a causal association between
### Deferasirox

#### Risk of pancreatitis in paediatric patients

**Singapore.** The Health Sciences Authority (HSA) has announced that the package insert for deferasirox (Exjade®) will be strengthened to include warnings on the risk of acute pancreatitis.

Deferasirox is an oral iron chelator used for treatment of chronic iron overload due to: frequent blood transfusions (patients aged ≥6 years, or 2 years if other treatments are contraindicated), beta thalassaemia (patients aged ≥10 years), and non transfusion dependant thalassaemia syndromes.

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### Fluoroquinolones oral antibiotics

#### Risk of retinal detachment

**Canada.** Health Canada recommends that product labels for oral fluoroquinolones should be revised to highlight the urgency of seeking advice from health-care professionals if patients experience vision problems during or following use of fluoroquinolones.

Retinal detachment is a painless separation of the retina from the layer of
support tissue and blood vessels at the back of the eye that provide the retina with oxygen and nourishment. Retinal detachment is a medical emergency and symptoms include sudden appearance of debris in the field of vision, the perception of flashes of light in the affected eye, sensation of a shadow or curtain over the portion of the visual field, and sudden or complete loss of vision.

Oral fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin, and ofloxacin) are used to treat bacterial infections, in particular respiratory and urogenital system infections. The recommendations follow a review of evidence. At the time of the review 22 reports of retinal detachment linked to oral fluoroquinolones were reported internationally, and three reports were received in Canada. A causal relationship between the Canadian reports could not be established. In the literature two of four observational studies found a modest link between retinal detachments and use of fluoroquinolones. Health Canada concluded that a link cannot be ruled out at present.

Reference:
Summary Safety Review, Health Canada, 8 January 2016 (www.hc-sc.gc.ca)

Fomepizole

Risk of anaphylaxis

Japan. The MHLW and the PMDA have announced that the revision of the package insert for fomepizole should include anaphylaxis as an adverse reaction.

Fomepizole is used as an antidote for ethylene glycol and methanol poisoning. A case of anaphylaxis has been reported outside Japan. In Japan, there have been a number of reported adverse reactions including fatal cases, but no cases associated with anaphylaxis. Based on available evidence and advice of experts, the MHLW/PMDA have decided that it was necessary to revise the package insert.

"Anaphylaxis” will be added to the “Clinically significant adverse reaction” subsection in the “adverse reaction” section in the package insert.

Reference:
Revisions of Precautions, MHLW/PMDA, 24 November 2015 (www.pmda.go.jp/english/)

Fingolimod

Recommendations to minimise progressive multifocal leukoencephalopathy (PML) and skin cancer

EU: The European Medicines Agency (EMA) has announced that product information for fingolimod (Gilenya®) will be updated with information about risk of progressive multifocal leukoencephalopathy (PML) and basal cell carcinoma.

Fingolimod is used to treat multiple sclerosis and works by reducing activity of the immune system, in particular T-cells which are involved in fighting infection.

PML is a rare brain infection caused by John Cunningham virus. Basal cell carcinoma is a slow-growing skin cancer. There have been 17 previous cases of PML reported in patients taking fingolimod with prior exposure to other immunosuppressive therapy (natalizumab). Recently there have been three cases of PML reported in patients that were treated with fingolimod and had not received previous treatment with natalizumab.

There have been 151 international cases of basal cell carcinoma reported with exposure to fingolimod (February 2015).

The EMA recommends that patients should be evaluated before and during treatment with fingolimod to allow early identification of signs and symptoms that could be linked to PML or basal cell carcinoma and they should be treated accordingly. Before starting treatment with fingolimod, a baseline MRI scan should be available (usually within three months) as a reference. If PML is suspected, a MRI should be performed immediately and treatment with fingolimod should be suspended until PML has been excluded. With regard to the risk of basal cell carcinoma, a medical evaluation of the skin is recommended before starting treatment, after at least one year and then at least yearly during treatment. Fingolimod must not be used in patients with basal cell carcinoma, or any other type of cancer.

(See WHO Pharmaceuticals Newsletter No.5, 2015: Risk of progressive multifocal leukoencephalopathy in USA and Japan.)

Reference:
Press release, EMA, 18 December 2015 (http://www.ema.europa.eu/)

Interferon beta-1a

Risk of thrombotic microangiopathy

Canada. Health Canada has requested manufacturers to update prescribing information for interferon beta-1a (Rebif®) to include the risk of thrombotic microangiopathy, following a safety review.

Rebif®, another brand of Type 1a interferon already includes prescribing information on thrombotic microangiopathy.
Avonex® interferon beta-1a is used to slow the progression of multiple sclerosis by reducing damage to the central nervous system.

Thrombotic microangiopathy involves the formation of clots in the small blood vessels which block blood flow and cause life-threatening damage to organs and body systems.

A report of cases of thrombotic microangiopathy identified in the Avonex Global Safety Database from the manufacturers triggered the safety review, which considered information from scientific and medical literature, Canadian and international adverse reaction reports.

The review concluded that there might be a possible link between the Avonex® preparation and thrombotic microangiopathy. Health Canada will continue to monitor adverse effects, and will take appropriate and timely action if and when any new health risks are identified.

Reference:

**Itraconazole**

**Reports of interstitial pneumonia**

**Japan.** The MHLW and the PMDA have recommended that the product label for itraconazole capsules, oral solution and injections are revised to include interstitial pneumonia as an adverse reaction.

Itraconazole is used for treatment and prophylaxis of fungal infections. Different formulations target different forms of fungal infections, for example: the capsules are used for dermatophytosis type infections; the oral solution is used for prophylaxis in certain patients at risk of neutropenia (hematopoietic stem cell transplant patients); the injection is used to treat febrile neutropenia.

A total of two cases associated with interstitial pneumonia have been reported in patients using itraconazole in Japan. In one of these cases a causal relationship could not be ruled out, however itraconazole was indicated for a condition outside the licensed recommendations. None of the cases were fatal. Following investigations and advice from experts, the MHLW/PMDA have decided that revision of the package insert was necessary.

The MHLW/PMDA recommend that "Interstitial pneumonia" should be added in the "Clinically significant adverse reaction" section.

Reference:
Revisions of Precautions, MHLW/PMDA, 12 January 2016 (www.pmda.go.jp/english/)

**Itraconazole**

**Risk of tumour haemorrhage, carotid artery exposure and haemorrhage.**

**Japan.** The MHLW and the PMDA have announced the addition of cautionary advice in the package insert for lenvatinib (Lenvima®) capsules. The advice warns health-care professionals of the possible association with tumour haemorrhage, carotid artery exposure and haemorrhage.

Lenvatinib is used to treat radically unresectable thyroid cancer. In Japan, a total of 14 cases associated with carotid artery exposure, carotid artery haemorrhage and tumour haemorrhage have been reported (including five cases for which a causal relationship to the product could not be ruled out). Of the 14 cases, six fatal cases have been reported (no established causal relationship with).

Based on available evidence and advice from experts the MHLW/PMDA have decided that it is necessary to revise the package insert for lenvatinib as follows:

- "Patients with tumour invasion in the carotid arteries, veins, etc." should be added in the "Careful Administration" section.

- Precautions regarding "carotid artery exposure, carotid artery haemorrhage, and tumour haemorrhage associated with tumour shrinkage or necrosis" should be added in the "Important Precautions" section and the "Haemorrhage" subsection in the "Clinically significant adverse reaction" section.

Reference:
Revisions of Precautions, MHLW/PMDA, 24 November 2015 (www.pmda.go.jp/english/)

**Levonorgestrel intrauterine contraceptive device (IUCD)**

**Risk of uterine perforation**

**Australia.** The Therapeutic Goods Administration (TGA) has announced that the product information for the intrauterine contraceptive device (IUCD) containing 52mg of levonorgestrel (Mirena®) will be revised to include increased uterine perforation risk for lactating women during the first 36 weeks postpartum.

A recent European study (n=61 446 levonorgestrel or copper IUCD users) resulted in 61 cases of perforations with levonorgestrel IUCD users. The risk is increased for lactating women and during the first 36 weeks postpartum.
The updated product information will also advise that there is an increased risk for women with a fixed, retroverted uterus.

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

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**Mycophenolate mofetil**

**New pregnancy-prevention advice for women and men**

The United Kingdom. The MHRA has updated new pregnancy-prevention advice for women and men prescribed mycophenolate mofetil. Mycophenolate mofetil (CellCept®), a prodrug of mycophenolic acid is an immunosuppressive agent used in combination with cyclosporin and corticosteroids for the prevention of acute transplant rejection in patients who have received kidney, heart, or liver transplants.

Mycophenolate mofetil is a known teratogen associated with a high rate of serious birth defects and increased risk of spontaneous abortion. Previously only ear malformations had been recognised, but prospectively gathered data have now identified a range of disorders such as congenital heart disease, facial malformations, eye abnormalities, finger malformation and others.

The MHRA advises that before starting mycophenolate mofetil treatment, women of childbearing potential should have a negative pregnancy test result to exclude unintended exposure of the embryo to mycophenolate. Two serum or pregnancy tests are recommended. Results of all pregnancy tests should be discussed with patients. Further advice includes: use of highly effective contraceptives (two forms) in female patients, female partners of male patients, and use of condoms in male patients during and for 90 days after treatment.

Dear doctor letters have been sent out to health-care professionals informing them of this advice.

**Reference:**
Drug Safety Update, MHRA, Vol.9, No.5, 14 December 2015 (www.gov.uk/mhra)

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**Nintedanib ethanesulfonate**

**Precaution in patients with moderate to severe hepatic function disorder**

Japan. The MHLW and the PMDA have recommended that the product labels for nintedanib ethanesulfonate (Ofev®) should include a precautionary warning for patients with moderate to severe hepatic function disorder (Child-Pugh B and C).

Nintedanib ethanesulfonate is indicated for treatment of idiopathic pulmonary fibrosis. This recommendation follows results of a clinical pharmacokinetic study, conducted among patients with hepatic function disorder. The study was on-going at the time nintedanib was approved and showed that blood concentrations of nintedanib ethanesulfonate increased in patients with hepatic function disorder.

Following investigations and advice from experts, the MHLW/PMDA have decided that revision of the package insert was necessary.

It is advised that "Patients with moderate to severe hepatic function disorder (Child-Pugh B and C)" should be newly added in the "Important Precautions" section.

**Reference:**
Revision of Precautions, MHLW/PMDA, 12 January 2016 (www.pmda.go.jp/english/)

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**Nivolumab**

**Reports of type-1 diabetes mellitus**

Japan. The MHLW and the PMDA have announced that the product label for nivolumab (Opdivo®) has been revised to include type-1 diabetes mellitus as an adverse reaction.

Nivolumab is used to treat radically unresectable malignant melanoma.

There have been five cases of type 1 diabetes mellitus associated with the use of nivolumab reported in Japan. In four of these cases a causal relationship between the product could not be ruled out.

"Type 1 diabetes mellitus” will be added to the Clinically significant adverse reaction section of the product label.

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

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**Ombitasvir hydrate/paritaprevir hydrate/ritonavir**

**Risk of hepatic failure**

Japan. The MHLW and the PMDA have announced that the product information for ombitasvir hydrate/paritaprevir hydrate/ritonavir preparation (Viekirax®) will be revised to include patients with hepatic dysfunction (Child-Pugh Class B) as a contradiction.

This preparation is used to improve symptoms of viraemia in patients with serogroup 1 (genotype 1) chronic hepatitis...
C or compensated cirrhosis type C.

There have been cases of hepatic failure with the Viekirax® preparation reported in other countries, and in Japan there have been three reports of fatal adverse reactions (not associated with hepatic failure). Following investigation of the available evidence and based on consideration of advice from experts, the MHLW/PMDA have decided that it was necessary to revise the package insert.

In addition to the contra-indication, hepatic failure will be listed as an adverse effect in the “Clinically significant adverse reaction” section, and will be added to the relevant section in the “Important precautions” section.

Reference:
Revision of Precautions, MHLW/PMDA, 26 November 2015 (www.pmda.go.jp/english/)

Peginterferon alfa-2a

Reports of facial palsy

Australia. The TGA advises health professionals that the product information for peginterferon alfa-2a has been updated to state that facial palsy has been reported.

Peginterferon alfa-2a is a recombinant interferon alfa-2a protein conjugated with a single branched polyethylene glycol chain. It is marketed in Australia as Pegasys® and in combination with ribavirin as Pegasys-RBV®. Peginterferon alfa-2a is indicated for use, under specific circumstances, in treatment of chronic hepatitis C and chronic hepatitis B.

Up until 19 August 2015, the TGA had received five reports of VIIth nerve paralysis associated with peginterferon alfa-2a, including three cases in which it was the sole suspected medicine. Based on this safety concern, and using information provided internationally, the TGA has worked with the sponsor to update the product information. Facial palsy has been listed in the adverse effect observed in post-marketing setting.

At this stage there have been no reports of facial palsy for Pegasys-RBV® or the other six pegylated and non-pegylated interferon products available in Australia.

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

Piperacillin sodium

Risk of acute generalised exanthematous pustulosis

Japan. The MHLW and the PMDA have announced that the product information for piperacillin sodium products has been revised to include acute generalised exanthematous pustulosis as an adverse effect.

Piperacillin sodium is an antibiotic used to treat infections susceptible to strains of microorganisms such as Staphylococcus, Streptococcus, and Klebsiella genus. It is indicated for infections of the lung, intra-abdominal infections, complicated urinary tract infection and others.

There have been cases of acute generalised exanthematous pustulosis in patients treated with piperacillin and tazobactam/piperacillin hydrate preparations in Japan (none in the last 3 years).

Based on available evidence and advice from experts the MHLW/PMDA have decided that it was necessary to revise the package inserts for piperacillin sodium products.

Reference:
Revision of Precautions, MHLW/PMDA, 12 January 2016 (www.pmda.go.jp/english/)

Posaconazole

Dosing errors while switching formulations

USA. The US Food and Drug Administration (FDA) has approved of label changes in prescribing and patient information to alert health-care professionals and patients that two oral formulations of posaconazole (Noxafil®) cannot be directly substituted for each other and require a dosage adjustment when switching formulations. This measure was taken to prevent medication errors.

Posaconazole is an antifungal used to prevent invasive fungal infections caused by Aspergillus and Candida in patients with a weakened immune system, and to treat fungal infections caused by Candida in the mouth and throat. It is available in two oral formulations: an oral suspension and a delayed release tablet.

At the time of the alert, the FDA had received 11 reports of wrong formulations being prescribed/dispensed to patients, two of which had serious outcomes. Lack of knowledge for the need to adjust the dosage with different oral formulation resulted in these errors.

The FDA recommends:
Prescribers should specify the dosage form, strength, and frequency on all prescriptions they write for posaconazole. Pharmacists should request clarification from prescribers when the dosage form, strength, or frequency is not specified. Patients should talk to a health-care professional before they switch from one oral formulation to the other.
### Regulatory Matters

**Reference:**

**Repaglinide and clopidogrel**

**Risk of hypoglycaemia by drug-drug interaction**

**Singapore.** The HSA is strengthening local package inserts for repaglinide (Novonorm®) and clopidogrel (Plavix®) to include warnings and precautions with regard to the potential risk of hypoglycaemia in patients taking concomitant repaglinide and clopidogrel.

Repaglinide is an oral antidiabetic agent used for the treatment of adults with type-2 diabetes mellitus as monotherapy or in combination with metformin.

Clopidogrel is an antiplatelet used for the prevention of atherothrombotic events in adults with a recent myocardial infarct, stroke, established peripheral arterial disease or acute coronary syndrome, as well as in combination with aspirin for the prevention of atherothrombotic and thrombembolic events in selected adult patients with atrial fibrillation.

In a study using nine healthy subjects, co-administration of repaglinide and clopidogrel was shown to result in an increase in repaglinide systemic exposure compared with placebo. The elimination half-life of repaglinide was also observed to be prolonged. The study authors recommended that concomitant use of repaglinide and clopidogrel is best avoided. They also postulated that clopidogrel is likely to cause drug-drug interactions with other CYP2C8 substrates, such as montelukast, paclitaxel and pioglitazone, which warrant further clinical studies.

The HSA is working with the pharmaceutical companies to strengthen the local package inserts of both products to include warnings and precautions with regard to the potential risk of hypoglycaemia arising from their drug-drug interactions.

**Reference:**

**Sodium glucose co-transporter 2 (SGLT2) inhibitors**

**Risk of acid in blood and serious urinary tract infections**

**USA.** The US FDA has updated the product labels (Warnings and Precautions) of sodium-glucose cotransporter-2 (SGLT2) inhibitors to include warnings about risk of too much acid in the blood and serious urinary tract infections. Prescribing and monitoring recommendations were also added.

SGLT2 inhibitors (canagliflozin, dapagliflozin, and empagliflozin) are indicated for use with diet and exercise to lower blood sugar in adults with type-2 diabetes.

High levels of blood acid are a result of ketoacidosis. Symptoms of ketoacidosis include nausea, vomiting, abdominal pain, tiredness, and trouble breathing.

The changes to these product labels follow a review of the FDA Adverse Event Reporting System (FAERS), which identified 73 cases of ketoacidosis in patients with type-1 and -2 diabetes treated with SGLT2 inhibitors (March 2013-May 2015), and 19 cases (March 2013-October 2014) of life-threatening blood infections (urosepsis) and Kidney infections (pyelonephritis). The FDA has requested that manufacturers conduct a postmarket study to investigate these safety issues further.

The US FDA recommends that patients should stop taking their SGLT2 inhibitor and seek medical attention immediately if they have any symptoms of ketoacidosis.

Health-care professionals should assess for ketoacidosis and urinary tract infections in patients taking SGLT2 inhibitors who present with suggestive symptoms (nausea, vomiting, abdominal pain, tiredness, and trouble breathing).

**Reference:**
Safety Alerts for Human Medical Products, US FDA, 4 December 2015 ([www.fda.gov](http://www.fda.gov))

**Thalidomide**

**Reduced starting dose in patients >75 years of age**

**The United Kingdom.** The MHRA has recommended that the starting dose of thalidomide in patients aged over 75 years should be reduced to 100 mg/day. The recommended starting dose of thalidomide remains 200 mg once a day for patients aged 75 years or younger.

Thalidomide combined with melphalan and prednisolone is indicated as first-line treatment of patients with untreated multiple myeloma who are aged 65 years or older or who are ineligible for high-dose chemotherapy.

This recommendation follows results of two clinical trials which showed that the frequency of serious or fatal adverse reactions was higher in patients older than 75 years who received thalidomide 100 mg once daily than in younger patients who received thalidomide 200 mg once daily (56.5% vs 46.5% for serious

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reactions and 10.3% vs 5.3% for fatal reactions, respectively. There were no clinically relevant differences in frequency of specific adverse effects or primary causes of death between both age groups.

Reference:
Drug Safety Update, MHRA, Volume 9, issue 5: 14 December 2015 (www.gov.uk/mhra)

Varenicline and alcohol

Risk of psychiatric symptoms by drug-alcohol interaction

Australia. The TGA has announced the revision of the product information for varenicline (Champix®) to reinforce the risk of psychiatric symptoms and include the potential interaction with alcohol.

Varenicline is used to reduce nicotine cravings and withdrawal symptoms in adults attempting to stop smoking.

Psychiatric symptoms can involve: changes in behaviour, thinking or mood, depression, anxiety, agitation, aggression, mood swings, self-harm, thoughts of self-harm, hallucinations and delusions.

The TGA advises health-care professionals to discuss the benefits and risks of treatment with varenicline, including potential psychiatric symptoms before initiation.

Psychiatric symptoms are now in bold at the beginning of the Precautions section (under 'Psychiatric symptoms'). The "Precautions, Interactions With Other Medicines and Adverse Effects" sections of the product information have also been updated to advise patients that consuming alcohol may increase the risk of psychiatric symptoms.

The updated product information also includes information from clinical trials and observational studies, which found similar incidence rates of suicidal thoughts and/or behaviour, and other psychiatric symptoms, in patients treated with varenicline compared to those treated with placebo or alternative treatments.

The TGA will continue to monitor this issue.

Reference:
Safety Information Alerts, TGA, 2 December 2015 (www.tga.gov.au)

Correction: We regret the typographic error in WHO Pharmaceuticals Newsletter No. 6, 2015, pg 9, Line 40. The sentence should read “Roxithromycin is an antimicrobial used for treatment...”
Allopurinol

**Interaction with 6-mercaptopurine and azathioprine**

**Australia.** The TGA has issued a reminder to health professionals that concomitant use of allopurinol with 6-mercaptopurine or azathioprine should be avoided, due to increased risk of potentially fatal bone marrow toxicities and blood dyscrasias.

Allopurinol is an anti-uricaemic agent used to treat gout, uric acid nephrolithiasis and hyperuricaemia, including the prevention of tumour-lysis syndrome. Azathioprine is used as an immunosuppressant and 6-mercaptopurine as a cytotoxic agent.

Allopurinol reduces metabolism of 6-mercaptopurine and azathioprine, increasing the risk of bone marrow toxicities and blood dyscrasias, such as leukopenia, thrombocytopenia and pancytopenia.

If co-administration of allopurinol with 6-mercaptopurine or azathioprine is necessary, the dose of 6-mercaptopurine or azathioprine should be reduced to one quarter of the normal dose and the patient’s complete blood count should be closely monitored in accordance with the product information.

The TGA recommends that, health professionals should check if patients are being treated with allopurinol when prescribing azathioprine or 6-mercaptopurine, and they should educate patients about this medicine interaction.

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

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Bevacizumab

**Risk of irreversible vocal cord damage**

**Canada.** Health Canada has informed health professionals of findings from a safety review that assessed the potential risk of irreversible vocal cord damage with use of bevacizumab (Avastin®).

Bevacizumab by itself is used to treat patients with a specific type of aggressive brain cancer who have not improved enough with other treatments. In combination with other anti-cancer drugs, it is used to treat a specific type of lung cancer or large bowel cancer metastases.

Health Canada initiated a review into this potential adverse effect following a case of vocal cord necrosis after exposure to bevacizumab and another anti-cancer drug. Internationally, from the years 2000 to 2014, there were 14 reports of adverse effects related to the vocal cord, of which three were for vocal cord necrosis. In international clinical studies (n=26,420 patients) there were 11 reports of possible vocal cord necrosis. In the scientific and medical literature there were 16 cases of damage to the vocal cords, three of which were confirmed cases of irreversible damage.

Health Canada concluded that there is not enough evidence to link bevacizumab treatment with an increased risk of vocal cord necrosis. Health Canada will continue to monitor for information about this safety issue.

**Reference:**

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Codeine

**Risk of serious breathing problems in children and adolescents**

**Canada** Health Canada maintains its recommendation that codeine prescription products should not be recommended in children less than 12 years of age following a new review assessing the risk of breathing problems in children and adolescents treated with codeine prescription products for cough.

Codeine containing products (alone or in combination with acetaminophen or aspirin in some cough and cold medication) are approved for use in adults and children ≥12 years to treat pain and reduce cough. Caution is advised regarding the use of codeine in patients with breathing conditions, including children.

Codeine is converted to morphine in the liver. Due to genetic variations of liver enzymes some people can convert codeine to morphine faster and more completely than others, which can result in high levels of morphine in the blood leading to breathing difficulties and death.

Health Canada conducted a new safety review to further assess the risk of serious breathing problems in children and adolescents treated with codeine prescription products for cough following emergence of new evidence. At the time of the current review, no cases of these drug-adverse events in children and adolescents were reported. Since the initial review in 2013, one international case was published in the literature, which resulted in the death of a six-year old patient, however a causal link could not be concluded.
No modifications were recommended to the Canadian prescribing information.

Reference:

**Finasteride**

**Risk of suicidal thoughts and behaviour**

Canada. A Health Canada review of data considers that the evidence of suicidal thoughts and behaviour associated with use of finasteride (Proscar® and Propecia®) is limited.

Finasteride is used to treat and control benign prostatic hyperplasia (non-cancerous enlargement of the prostate gland). In addition, at a lower dose, it is used to treat male pattern hair loss.

At the time of the review, 11 reports of suicide related adverse effects were reported to Health Canada, and 170 to the WHO global database of Individual Case Safety Reports (ICSRs). Six of the cases reported to Health Canada described factors that appeared to be related to finasteride, however the remaining reports and reports in the WHO global database data were not robust to form a conclusion.

Reports in the medical literature describe a potential link between finasteride and suicidality, however studies were few, used small number of patients, had limitations and were inconclusive.

Currently, the prescribing information for finasteride lists depression as an adverse effect. Health Canada will publish a Health Product InfoWatch article to inform Canadians of the safety review, and will continue to monitor safety information involving finasteride.

Reference:

**Melatonin**

**Neurological adverse effects in children and adolescents, conflicting evidence**

Canada. Health Canada concludes that the information available on neurological adverse effects associated with use of melatonin (N-acetyl-5-methoxytryptamine) in children is conflicting. Parents and caregivers are encouraged to consult a health-care professional before giving melatonin to children and adolescents.

Melatonin is a naturally occurring hormone used to help adults, adolescents and children with sleep problems as an OTC natural health product in Canada.

International reports of neurological defects such as anxiety, panic reaction, visual hallucinations and seizures in children and adolescents (newborn to 18 years) led Health Canada to conduct a review of scientific and medical literature in this age group.

Eighteen reports from Canada Vigilance Program and 163 reports (8 from Canada) in the WHO global database of suspected adverse reaction associated with the use of melatonin in the paediatric population were identified. The most common adverse effects reported in the WHO global database were: general fatigue, aggression, abnormal dreams, and headache. Serious cases could not be linked to melatonin as information in reports were not complete.

The benefits of treating sleep disorders with short term use of melatonin (< 4 months) in those with disorders of brain function that affect emotion, learning and memory (attention deficit hyperactivity disorder and autism spectrum disorders) are limited. The impact on psychological development and long term risk on growth in the paediatric population is still uncertain.

Health Canada will continue to evaluate this safety issue and will proactively monitor for safety information related to the use of melatonin in the general paediatric population.

Reference:

**Pazopanib**

**Risk of pericardial effusion: lack of information**

Canada. Health Canada has concluded that there is not enough information to support a link between the risk of pericardial effusion and use of pazopanib (Votrient®), following a safety review of evidence.

Pazopanib is used to treat metastatic cancer of the kidney and advanced soft tissue cancers (cancer occurs in soft tissues such as fat, muscle, tendon and nerves).

Pericardial effusion is a serious condition, involving the accumulation of fluid around the heart which can cause heart problems and/or lead to death.

At the time of the review no cases of pericardial effusion linked with pazopanib were reported in Canada. Health Canada’s review of reported cases in the literature and from manufacturers were limited by factors such as the progression of the cancer, and concluded that there is not enough information to support a link between the risk of pericardial effusion and use of pazopanib.

Reference:
**Safety of Medicines**

Effusion and use of pazopanib. Health Canada will continue to monitor adverse effect information on pazopanib.

*(See WHO Pharmaceuticals Newsletter No. 6, 2013: Signal - Pazopanib and pericardial effusion)*

**Reference:**

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**Proton pump inhibitors**

**Lack of evidence for increased risk of cardiovascular risk**

**Australia.** The TGA has concluded that available evidence does not adequately demonstrate an increased risk of cardiovascular risk in patients taking proton pump inhibitors (PPIs).

PPIs include esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole and are a class of drugs that reduce production of gastric acid.

Two studies were investigated:

The first study used national Danish data (n=56,406), and found a 29% increase in cardiovascular death or rehospitalisation for stroke or myocardial infarction in patients taking a PPI. The second used two sources of electronic health records, and found an increase in odds ratio for myocardial infarction in patients taking PPIs (odds ratios 1.16 [95% CI 1.09-1.24]) compared to H₂ antagonists (1.19 [95% CI 1.09-1.24]). However, authors concluded that these findings can be explained by differences in baseline comorbid conditions (e.g. smoking status, lipid levels) that were missed or not sufficiently measured and lack of consideration of important confounding factors in study design. Because of these limitations, these two studies did not demonstrate an increased cardiovascular risk for PPIs that was independent of the patient population in which they were being used.

**Reference:**

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**Rosiglitazone**

**Removal of risk evaluation and mitigation strategy (REMS)**

**USA.** The US FDA has announced that they are eliminating the Risk Evaluation and Mitigation Strategy (REMS) for rosiglitazone-containing type-2 diabetes medicines.

Type-2 diabetes is a disease that can lead to serious complications such as kidney failure, blindness, and premature death. Rosiglitazone can be used along with diet and exercise to control blood sugar in adults with the disease.

In 2013, the FDA removed the prescribing suspension and dispensing restrictions for rosiglitazone medicines that were introduced in 2010, after determining that data for rosiglitazone containing medicines do not show an increased risk of heart attack. Due to previous suggestions of an elevated risk of heart attack an REMS was required. This restricted the use of rosiglitazone medicines to help ensure that their benefits outweighed the risks. The FDA also requested that the drug manufacturers provide educational training to health-care professionals about the current state of knowledge regarding the heart risks of rosiglitazone medicines. Manufacturers have since fulfilled these requirements.

The FDA continued to monitor these medicines and identified no new pertinent safety information. As a result, the FDA concludes that the REMS is no longer necessary to ensure that the benefits of rosiglitazone medicines outweigh their risks.

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

The signals in this Newsletter are based on information derived from Individual Case Safety Reports (ICSRs) available in the WHO Global ICSR database, VigiBase®. The database contains over 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 ICSR, their limitations and proper use, is provided in the UMC Caveat document available at the end of Signal (page 23). 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.

Vemurafenib and Atrial fibrillation: Signal strengthening
Dr Ruth Savage, New Zealand

Summary
Vemurafenib, a tyrosine kinase inhibitor, is a suspect medicine in 29 reports of atrial fibrillation in the WHO Global Individual Case Safety Report Database, VigiBase®, and the sole suspect in 27. Vemurafenib is indicated for metastatic or unresectable malignant melanoma with the BRAF V600E mutation. Atrial fibrillation can be triggered by a range of underlying pathologies and drugs and needs to be treated promptly when it is deemed likely to increase the risk of stroke. Thus, assessment of a causal relationship with a particular medicine is complex. Product information and literature sources indicate that atrial fibrillation occurred in patients taking vemurafenib in phase II and III clinical trials but no published evidence of causality has been identified. In the VigiBase® reports older patients were most often affected and a high proportion were taking medicines usually prescribed for comorbidities likely to increase the risk of atrial fibrillation. However, seven of the VigiBase® reports recorded improvement on dechallenge with little evidence of alternative explanations. In four of these reports time to onset was 19 days or less and the same was true in a fifth report when a potentially interacting medicine, carvedilol, was added to vemurafenib. One patient being treated for atrial fibrillation with amiodarone experienced a recurrence when vemurafenib was commenced. Vemurafenib is a CYP3A4 and P-glycoprotein substrate and a CYP3A4 inducer. Carvedilol is a P-glycoprotein inhibitor and amiodarone is a CYP3A4 inhibitor which may be explanations for these possible interactions. One other patient recovered on vemurafenib dose reduction. This report, together with the carvedilol/vemurafenib report, suggests a dose-response relationship. The reports do represent a signal and add another reason, as well as QT prolongation, for cardiovascular monitoring before and after treatment with vemurafenib is commenced. The reports also suggest that the risk might be greatest in the first month and, possibly, after an increased dose or the addition of potentially interacting medicines.

Introduction
Vemurafenib is a tyrosine kinase inhibitor. It inhibits some mutated forms of BRAF serine-threonine kinase, including BRAF V600E. It is indicated in the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA approved test. The recommended dose is 960 mg twice daily and patients should be treated with vemurafenib until disease progression or unacceptable toxicity occurs.¹

Atrial fibrillation is caused by a variety of clinical conditions. These can be divided into structural heart disease such as myocardial infarction, cardiomyopathy, cardiac valve disorders, hypertensive heart disease; right atrial stretch caused by pulmonary disorders; high adrenergic states such as thyrotoxicosis, major surgery and alcohol withdrawal; anomalous conduction pathways and sinus node dysfunction; acute alcohol intoxication and drugs such as anti-arrhythmics, other cardiovascular medicines, medicines that alter sympathetic or vagal drive, cardiotoxic cytostatic medicines, diuretics causing hypokalaemia and others with unidentified mechanisms. Because of the underlying clinical
conditions that may cause atrial fibrillation its prevalence increases with age. Atrial fibrillation is the commonest supraventricular tachycardia and predisposes patients to systemic embolism and therefore stroke.\(^2\)\(^3\)

Assessment of a causal relationship between a drug and atrial fibrillation is complicated by the need to consider all the possible alternative or contributory causes of atrial fibrillation for a particular patient, its frequently paroxysmal nature and the need for prompt treatment to avoid systemic embolism without sufficient time to assess the outcome when the suspected drug is withdrawn, especially if it has, like vemurafenib, a long elimination half-life.\(^1\)

There is a small amount of information about vemurafenib and atrial fibrillation in the literature but comparative rates with placebo or published case reports have not been identified. The case reports in the WHO Global Individual Case Safety Report (ICSR) Database, VigiBase®, were therefore examined for evidence of causality and the characteristics of the patients affected.

### Reports in VigiBase®

Vemurafenib is a suspect medicine in 30 reports of atrial fibrillation. The reports were submitted from eight countries. The drug/ADR combination was identified using the vigiRank method.\(^4\) One report was excluded from the assessment as it originated from a double-blind placebo-controlled study and both the placebo and vemurafenib were listed as suspect.

In the 29 reports assessed 15 females and 14 males developed atrial fibrillation with an age range, recorded for 17 patients, of 39 to 87 years, median 71 years. Indication for vemurafenib use was recorded in 20 reports. Eighteen patients were being treated for malignant melanoma. Eleven of these were reported to have metastatic disease. For two patients the indication was thyroid cancer. One patient had pre-existing atrial fibrillation and hypertension and one had recently diagnosed mitral insufficiency. Eight patients were taking medicines indicative of hypertension, angina, arrhythmia or cardiac failure (diuretics, digoxin, ACE inhibitors, angiotensin II receptor blockers, beta-blockers, calcium channel blockers). Three of these patients and one other patient were taking a statin. One was taking warfarin and a beta-adrenergic blocking agent suggesting that they might have pre-existing atrial fibrillation.

Vemurafenib was the sole suspect medicine in 27 reports. Only one patient of 19 for whom daily doses were recorded exceeded the recommended daily dose. Time from starting vemurafenib to onset of atrial fibrillation ranged from 12 days to seven months (15 reports). The time to onset was 12 to 19 days for six patients and between three and seven months for seven patients. Time to onset for the two other patients was 60 days (but 18 days from addition of a potentially interacting medicine) and 37 days. There were no consistently reported concomitant medicines that may have contributed. One patient was taking amiodarone for atrial fibrillation. A pharmacokinetic interaction with vemurafenib is theoretically possible.

Adverse reaction terms that were co-reported with atrial fibrillation that may have been the trigger for atrial fibrillation, rather than a direct effect of vemurafenib on cardiac conduction, were pleural effusion (2 reports), pericardial effusion (1), pneumothorax (1), electrolyte abnormalities (2), myocardial infarction (1) and cardiomegaly (1). Other co-reported adverse reaction terms were hypotension and cardiac failure, known consequences of atrial fibrillation although one of these patients also had multi-organ failure. Four patients developed arthralgia and three fever, these are recognised vemurafenib adverse reactions.

Table 1 shows reports that recorded recovery on dechallenge or a stop date and recovery. The first three provide best evidence of causality as there were no clear alternative explanations for the atrial fibrillation. In case 1, after developing atrial fibrillation, the patient was treated with antithrombotic but not anti-arrhythmic agents so that the treatment is not an explanation for recovery. Case 3 suggests a dose-response relationship. Case 4 and 5 both contain evidence of a drug interaction. Carvedilol is a substrate and inhibitor of the efflux transporter P-glycoprotein and there is in vitro evidence that vemurafenib has the same characteristics.\(^1\) It is possible, in case 4, that carvedilol increased the bioavailability of vemurafenib and this is supported by the observation that the patient also developed fever with no evidence of infection, a documented adverse reaction to vemurafenib. Case 5 is of interest as the patient had pre-existing atrial fibrillation treated with amiodarone. Both vemurafenib and amiodarone are substrates for CYP3A4. Amiodarone is an inhibitor and there is evidence that vemurafenib is an inducer.\(^1\) Theoretically therefore, atrial fibrillation may have recurred because amiodarone clearance was increased thus reducing its therapeutic effect and vemurafenib clearance reduced thus increasing its postulated pro-arrhythmic effect.

Two other reports also recorded that the patient recovered on dechallenge but these were not included in the Table. The narratives were complex, one patient recovered from atrial flutter but atrial fibrillation recurred the following day and the outcome was not recorded. In the other report there are contradictory statements about recovery and mitral insufficiency had been diagnosed the same year.
Table 1. VigiBase® reports of vemurafenib and atrial fibrillation with recovery on dechallenge

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/ Sex</th>
<th>Medical history</th>
<th>Other concomitant medicines</th>
<th>Indication</th>
<th>Daily dose</th>
<th>Reactions (WHO-ART preferred terms)</th>
<th>Time to onset</th>
<th>Dechallenge/ Rechallenge</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>74/F</td>
<td>-</td>
<td>-</td>
<td>Metastatic melanoma</td>
<td>1920 mg</td>
<td>Fibrillation atrial, hyperpyrexia, synovitis, vomiting, asthenia</td>
<td>19 days</td>
<td>Dechallenged/ Rechallenged</td>
<td>Recovering/ Unknown for rechallenge</td>
<td>Treated with antithrombotic agent</td>
</tr>
<tr>
<td>2</td>
<td>78/F</td>
<td>-</td>
<td>Enoxaparin, simvastatin, omeprazole</td>
<td>Metastatic melanoma</td>
<td>960 mg</td>
<td>Fibrillation atrial</td>
<td>15 days</td>
<td>Dechallenged/ Rechallenged</td>
<td>Recovered/Unknown for rechallenge</td>
<td>&quot;Ambulatory treatment&quot; given, the atrial fibrillation did not recur. Indication for enoxaparin was &quot;prophylaxis&quot;</td>
</tr>
<tr>
<td>3</td>
<td>82/F</td>
<td>Unspecified underlying conditions</td>
<td>Unspecified medication</td>
<td>Malignant melanoma</td>
<td>1920 mg</td>
<td>Fibrillation atrial</td>
<td>12 days</td>
<td>Dose reduction</td>
<td>Recovered on unknown date</td>
<td>Treated with metoprolol</td>
</tr>
<tr>
<td>4</td>
<td>72/M</td>
<td>Hypertension</td>
<td>Carvedilol</td>
<td>Malignant melanoma of skin</td>
<td>1920 mg</td>
<td>Fibrillation atrial, fever</td>
<td>2 months</td>
<td>Dechallenged/ Rechallenged</td>
<td>Recovered from atrial fibrillation on unknown date after vemurafenib and carvedilol stopped* and from fever nine days after Unknown for rechallenge</td>
<td>Possible interaction with carvedilol via P-glycoprotein. Vemurafenib restarted after 15 days.** Treated with metoprolol and warfarin. ECG 7 days after vemurafenib re-started showed sinus rhythm</td>
</tr>
<tr>
<td>5</td>
<td>62/F</td>
<td>Hypertension, atrial fibrillation, hypernatraemia, cholecystolithiasis, Dupuytren’s contracture, anemia, rosacea</td>
<td>Amiodarone, nebivolol, lisnopril, hydrochlorothiazide, metoprolol, prasugrel, perphenazine</td>
<td>Malignant melanoma</td>
<td>1920 mg</td>
<td>Fibrillation atrial, hypertension</td>
<td>16 days</td>
<td>Dechallenged/ Reintroduction at lower dose</td>
<td>Recovered/Unknown for reintroduction</td>
<td>Cardioversion Vemurafenib half-life of 59 hours may explain persistency for 4 days. Amiodarone inhibition of vemurafenib CYP3A4 metabolism possible.</td>
</tr>
<tr>
<td>6</td>
<td>72/F</td>
<td>Mitral insufficiency</td>
<td>-</td>
<td>Skin melanoma, metastatic or unresectable</td>
<td>960 mg</td>
<td>Fibrillation atrial, paroxysmal</td>
<td>4.5 months</td>
<td>Dechallenged</td>
<td>Recovered</td>
<td>Treated with rivaroxaban, metoprolol. ECHO- LVEF 55%, moderate tricuspid and mild aortic insufficiency</td>
</tr>
<tr>
<td>7</td>
<td>64/M</td>
<td>-</td>
<td>-</td>
<td>Malignant melanoma stage 4</td>
<td>1440 mg</td>
<td>Fibrillation atrial</td>
<td>7 months</td>
<td>Dechallenged</td>
<td>Recovered</td>
<td>Treated with amiodarone</td>
</tr>
</tbody>
</table>

Of the patients not discussed above, three others recovered, one while vemurafenib was continued. For the other two, action with vemurafenib was not recorded or was discontinued 45 days before onset of atrial fibrillation. Two patients did not recover and the action with vemurafenib was not recorded. Four patients died. Outcome was not recorded in the remaining reports.

Of the four reports recording death as the outcome, two patients appeared to have disease progression and were seriously unwell and one had a pneumothorax and multi-organ failure. There was no evidence that atrial fibrillation was the direct cause of death in these reports. One patient had hypotension, which may have been a result of atrial fibrillation, and increased hepatic transaminases. In this case, atrial fibrillation may have contributed to death although the patient was taking morphine which could indicate advanced malignancy.

Related reports in VigiBase®

At the time of assessment there were 47 reports of prolonged QT interval, a recognised adverse reaction to vemurafenib. There were also 15 reports of arrhythmia. One recorded recovery on dechallenge. This was a report of sick sinus syndrome with progressive regression of signs after vemurafenib was stopped. Sick sinus syndrome can lead to atrial fibrillation.

Literature and Labelling

The FDA label indicates that atrial fibrillation was an adverse event observed in < 10% of patients in phase II and III clinical trials. A veterans affairs summary of vemurafenib randomised clinical trials indicates that nine patients developed atrial fibrillation. Neither source discusses causality or observed rates with vemurafenib compared with placebo. There is no mention of atrial fibrillation in the EMA Summary of Product Characteristics.

In a review of cardiac adverse effects of tyrosine kinase inhibitors (TKIs) the authors state that the type of cardiovascular side effect differs between TKIs based on which cellular signalling pathways they inhibit. They divided the agents into two clinical groups:

(i) the VSP (VEGF signalling pathway) inhibitors and
(ii) the non-VSP inhibitor agents (which include vemurafenib).
They went on to state that VSP inhibitors are typically associated with hypertension, cardiomyopathy and arterial ischemia. Non-VSP inhibitors are more commonly associated with QT prolongation, arrhythmia, fluid retention and rarely cardiomyopathy. However, only vemurafenib was linked with atrial fibrillation in a table of reported cardiac adverse effects associated with TK inhibitors. The incidence was reported as 5% but without a reference or discussion.

Discussion and Conclusion

In a 2004 review of drug-induced atrial fibrillation the authors found that the evidence for causality for the wide range of suspect medicines came from published case reports rather than clinical studies. The clinical management of patients with serious disease requiring medicines that are reported to be pro-arrhythmic is particularly difficult if atrial fibrillation develops. It is important that the best evidence is available to aid decisions about drug discontinuation. For this reason, given scant data in the literature regarding vemurafenib and atrial fibrillation, the VigiBase® reports were assessed.

Table 1 shows the seven reports providing the best evidence of causality. Of note is the possibility of a dose response in case 3. Although not strong evidence because metoprolol was commenced, the observation is supported by the onset of atrial fibrillation after carvedilol, a P-glycoprotein inhibitor, was added to vemurafenib in case 4. It is interesting to note that four of the reports in Table 1 are in the group of six with a time to onset of 12 to 19 days. Also, in case 4, although the time to onset of atrial fibrillation was two months after vemurafenib was started, it was 18 days after carvedilol was added. One other report with time to onset 13 days did not contain any other possible explanations for the development of atrial fibrillation but it is not included in Table 1 as there was no dechallenge information. These reports with a short time to onset and evidence of causality suggest the possibility that atrial fibrillation is more likely to be due to vemurafenib if it occurs within the first month after vemurafenib is commenced or exposure to it is increased.

The patient aged 39 years was an outlier and the remainder of the 17 patients with age recorded were 62 to 87 years. There is an increasing prevalence of atrial fibrillation with age. The question is whether older age and the co-morbidities many of the patients experienced were the sole cause of the atrial fibrillation or whether vemurafenib contributed. The FDA product information states that phase III study data showed that elderly patients (≥ 65 years old) may be more likely to experience adverse events, including cardiac disorders.1

It is interesting to note that vemurafenib, if causal, appeared to overcome the anti-arrhythmic effect of beta-adrenergic-blocking agents in some patients. However, in most of these reports the evidence for causality was weak or absent. Of greater importance is the co-prescription of amiodarone or carvedilol because of the possible pharmacokinetic interactions increasing exposure to vemurafenib. Furthermore both vemurafenib and amiodarone can prolong the QT interval and product information recommends against prescribing QT prolonging medicines with vemurafenib.1 As a substrate for CYP3A4 and P-glycoprotein vemurafenib is particularly vulnerable to drug interactions.

Even in the reports with best evidence of causality shown in Table 1 the majority of patients were treated for atrial fibrillation on stopping verapamil and this is a limitation when assessing causality. However, the consistent time to onset within three weeks in most of the reports that contained the best evidence of causality in other respects, the evidence of a dose response and the evidence for interactions with biological plausibility all support there being a signal for vemurafenib and atrial fibrillation. However, it is not a strong signal and further investigation would be useful. The advice to undertake cardiovascular monitoring before and after treatment with vemurafenib2 is important to detect both prolonged QT interval and atrial fibrillation. The VigiBase® reports with best evidence of causality suggest that the greatest risk is within a month of starting vemurafenib and, possibly, after a dose increase or after prescription of a potentially interacting medicine.

References


Response from Roche

The WHO Collaborating Centre in Uppsala invited Roche to comment on a signal of atrial fibrillation (AF) in patients treated with vemurafenib based on 29 cases in the VigilBase®.

AF is the most common pathologic supraventricular tachycardia affecting more than 3 million people in the US and many more worldwide. Risk factors for AF include older age, male sex, hypertension, and underlying cardiac disease. The incidence increases with age up to 4% of the adult population >60 years will experience arrhythmia (Stricker, van der Hooft, & Al, 2004).

The incidence of drug induced atrial fibrillation (DIAF) is unknown but is likely very low, and no risk factors have been characterized. Cancer itself creates an arrhythmogenic environment and is difficult to determine whether AF reflects the disease or is an adverse effect of the treatment. The onset of DIAF is variable depending on the inducing drug. The correlation is easy to demonstrate in healthy individuals when AF appears after drug administration with close temporal relationship between drug pharmacokinetics and initiation/termination of AF (Tamargo, Caballero, & Delpon, 2012). Possible mechanisms of DIAF are adrenergic or vagal stimulation, direct cardiotoxicity, coronary vasoconstriction/ischemia, and electrolyte disturbances (Stricker, van der Hooft, & Al, 2004).

Vemurafenib inhibits mutant BRAFV600 approved for the treatment of metastatic melanoma (mM) harbouring this mutation. There has been no described association between the RAF/MEK/ERK pathway and AF. The current vemurafenib label does not include AF as an ADR, however prolongation of QT interval, which could potentially cause ventricular tachyarrhythmias is a known ADR of vemurafenib. Vemurafenib (a CYP 3A4 substrate/inducer and P-gp substrate) (Roche, 2015) may also potentially interact with concomitant medications in patients with cardiac conditions and exacerbate pre-existing cardiac pathology putting patient at risk for AF.

An analysis of the Truven Healthcare MarketScan® Commercial Claims and Encounters database estimates the overall prevalence of AF following a diagnosis of mM at 12.5%. The overall incidence rate in mM was estimated as 30.9 (CI 28.77-33.24) per 1000 patient years and significantly higher in patients > 60 years.

In comparison, the incidence of AF among vemurafenib patients in the Phase III clinical study was 3.5% (12 out of 337) with a median age of 70.5 years (range 58-78). All 12 patients had confounding/risk factors for AF such as medical history of AF or unspecified arrhythmia (n=4), mitral valve prolapse (n=1) and concurrent medical conditions of hypertension (n=1), myocardial infarction (n=1) and pericardial effusion (n=2). In the dacarbazine arm, the incidence was 0.34% (1 out of 294, aged 82). Latency for the 12 cases ranged from 9-952 days (median 63). In ten of the 12 cases, vemurafenib was maintained and the event resolved in 7 cases, persisted in one case even when vemurafenib was eventually discontinued, and unknown outcome in the remaining cases. In two of the 12 cases, vemurafenib was interrupted and dose reduced with resolution of events.

In the Phase IV safety study (MO25515), 54 out of the 3222 (1.7%) patients reported AF. Median age was 68.5 years (range 36-84) with 49 patients (90%) >60 years. Median latency was 78 days (range 2-659). The majority of patients (83%) had risk/contributing factors such as hypertension, thyroid disease, structural heart disease, myocardial infarction, systemic infection/sepsis, and pericardial effusion.

As of May 19, 2015, there are 68 cases of AF reported with vemurafenib use in the Roche safety database. Twenty-seven cases (40%) were from company sponsored interventional clinical trials (15 of the 27 from the MO25515 phase IV study) and 41 cases were from other sources. Age was reported in 63 of the 68 cases with a median of 71 years (range 39-85), and 55 patients (87%) > 60 years. Thirty-three were male (49%), 34 (51%) were female, and one unreported gender. Seven patients (10%) have a medical history of AF. Latency was provided in 52 of the 68 cases with a median of 84 days (range 1-952).

Based on Roche’s medical review of the 68 AF cases, causal association cannot be excluded in 5 cases based on latency, absence of reported risk factors, and positive dechallenge (Table 1). The remaining cases had inadequate case information, or had strong alternative etiology for AF, had longer than expected latency relative to vemurafenib’s pharmacokinetic profile (>200 days), or had negative dechallenge/rechallenge.

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The incidence rate of AF for vemurafenib based on the 27 cases from clinical trials is estimated at 7.05 cases per 1000 patient years*. The 54 cases in the MO25515 Phase IV study yield an incidence rate of 17.5 per 1000 patient years. Both rates are significantly lower when compared to the background incidence for the mM population in a commercial claims and reimbursement database (30.9 per 1000 patient years). In addition, the cases had wide latency ranging from 1 to 965 days, with majority of the cases (88%) having pre-existing risk factors or a negative dechallenge. Our review of the literature also did not provide any evidence on plausible mechanism of action of vemurafenib/BRAF inhibitors causing cardiac arrhythmias.

Roche acknowledges the signal for atrial fibrillation raised by the WHO. Although there are 5 cases of AF where causal association cannot be excluded, our overall assessment showed that there is no convincing evidence supporting a causal association between vemurafenib and AF based on low statistical strength, negative dechallenge in majority of cases, wide latency, and lack of plausible mechanism. This signal is monitored through routine pharmacovigilance.

*estimated cumulative patient exposure = 3828 patient years

References


Table 1. Cases of interest in Roche Safety Database

<table>
<thead>
<tr>
<th>MCN/Origin</th>
<th>Age/Gender</th>
<th>Total daily dose</th>
<th>Latency (days)</th>
<th>Vemurafenib outcome</th>
<th>Event outcome</th>
<th>Relatedness</th>
<th>Dechallenge</th>
<th>Rechallenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>1065081 CT</td>
<td>74 F</td>
<td>1920 mg</td>
<td>28</td>
<td>Interrupted / dose reduced</td>
<td>Resolved</td>
<td>Related</td>
<td>Positive</td>
<td>Not reported</td>
</tr>
<tr>
<td>1071170 Spont</td>
<td>82 F</td>
<td>1920 mg</td>
<td>12</td>
<td>Dose reduced</td>
<td>Resolving</td>
<td>Unknown</td>
<td>Positive</td>
<td>Not applicable</td>
</tr>
<tr>
<td>1293946 Spont</td>
<td>62 F</td>
<td>1920 mg</td>
<td>15</td>
<td>Interrupted/ dose reduced</td>
<td>Resolved</td>
<td>Related</td>
<td>Positive</td>
<td>Not reported</td>
</tr>
<tr>
<td>1327287 CT</td>
<td>53 M</td>
<td>1920 mg</td>
<td>13</td>
<td>Interrupted/ dose reduced</td>
<td>Resolved</td>
<td>Related</td>
<td>Positive</td>
<td>Not reported</td>
</tr>
<tr>
<td>1418386 Spont</td>
<td>78 F</td>
<td>960 mg</td>
<td>14</td>
<td>D/C</td>
<td>Resolving</td>
<td>Related</td>
<td>Positive</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

CT: Clinical Trial, Spont: Spontaneous, D/C: Discontinued
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.

Confidential data
According to WHO policy and UMC Guidelines, ICSRs sent from the WHO PIDM member countries to VigiBase® are anonymized, but they are still to be considered sensitive due to the nature of the data.

When receiving and using adverse reaction data ("Data"), the user agrees and acknowledges that it will be the controller of any such Data. Accordingly, the user shall adhere to all applicable legislation such as, but not limited to, EU and national legislation regarding protection of personal data (e.g. the Data Protection Directive 95/46/EC and Regulation (EC) No 45/2001, as applicable). As the controller of the Data, the user shall be liable for any and all processing of the Data and shall indemnify and hold the UMC harmless against any claim from a data subject or any other person or entity due to a breach of any legislation or other regulation regarding the processing of the Data.

Non-permitted use of VigiBase® Data includes, but is not limited to:
- patient identification or patient targeting
- identification, profiling or targeting of general practitioners or practice

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.

UMC may, in its sole discretion, provide further instructions to the user, responsible person and/or organization in addition to those specified in this statement and the user, responsible person and/or organization undertakes to comply with all such instructions.

Omission of this statement may exclude the responsible person or organization from receiving further information from VigiBase®.
Recommendations from the 38th Annual Meeting of Representatives of the National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring

The annual meeting of National Pharmacovigilance Centres (NPCs) participating in the WHO Programme for International Drug Monitoring provides a platform for representatives from around the world to meet and discuss pharmacovigilance (PV) issues. Representatives of Member States have the opportunity to interact with WHO and WHO Collaborating Centres (WHO CCs) face to face, exchange information on country needs, and propose how WHO and WHO CCs can support them. One of the most important outcomes from this meeting is the formation of recommendations which shape the direction of future PV activities. Recommendations are made by delegates through group work. The thirty-eighth annual meeting of representatives of National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring was held from 4 to 6 November 2015, at New Delhi, India. The meeting included eight working groups that discussed various issues in PV. The topics for the working groups had been suggested by National PV Centres. The summary of discussions and the recommendations are described below.

Selection of topics for working groups at the WHO annual meeting of National Pharmacovigilance Centres

The format of the WHO National Pharmacovigilance Centres meeting is structured into three components: plenaries, group exercises (working groups) and update sessions. The topics of these meetings are proposed by Member States at the end of the annual meeting for National Pharmacovigilance Centres. WHO then distributes a questionnaire with the proposed topics to all Member States participating in the programme during the first quarter of every year. By completing the questionnaire topics can be prioritised to fit country’s requirements ensuring the forthcoming meeting agenda has a good mix of subjects that are of interest and relevance in both advanced and resource limited settings.

Generation of Recommendations

The annual meetings of National Pharmacovigilance Centres usually have eight working groups, run in parallel on two days. Delegates are provided with a list of objectives and expected outcomes prior to the working groups. During these sessions a moderated discussion is conducted and attendees formulate and agree on a list of recommendations that are specifically targeted at WHO, WHO CCs and / or the National Pharmacovigilance Centres. A rapporteur is delegated from amongst the workshop participants and recommendations are then presented to the whole delegation in a plenary session. Following this, recommendations are finalized and confirmed.
Practicalities of establishing and running a pregnancy register to follow outcomes of drug exposure

Moderators: A Kant and N Iessa

The session started with an overview of outcomes discussed in the previous year’s working group on pregnancy registers. Participants agreed that information from spontaneous reporting is not enough to monitor safety of medication during pregnancy. Amongst the representatives, two countries (Malaysia and Armenia) had a check box to indicate pregnancy in their adverse drug reaction (ADR) reporting forms. Two NPCs with pregnancy registries were identified; Lareb (the Netherlands), and South Africa. During discussions representatives from these two centres explained how pregnancy registers were initiated, and challenges and opportunities that were encountered. Challenges included: lack of financial support, late presentation of pregnant patient (i.e. first appointment is time of birth with no prior clinical visits throughout the pregnancy), and loss of patients to follow-up. South Africa shared how they sought and obtained political will and funding to set up their pregnancy register: at first the records covered a population in a small area, later this extended to cover a district and now there is a plan to expand coverage of pregnancies for the whole population.

Recommendations from the working group on practicalities of establishing and running a pregnancy register to follow outcomes of drug exposure

For WHO CCs and WHO:

- Lareb (the WHO Collaborating Centre for Pharmacovigilance in Education and Patient Reporting) to provide technical support, with WHO as lead, in the development of tools (which would include specific guidelines, communication and training materials) that would be used by other countries. The developed tools should take into account the differences between countries.
- WHO to support model National Pharmacovigilance Centres in the process of developing tools.

For National Pharmacovigilance Centres:

- To support the integration of ‘pregnancy PV activities’ into their public health programmes.
- Countries that would like to develop registries should start on a small scale and expand gradually.

Reporting and learning systems for medication errors, the role of national centres, WHO Collaborating Centres and WHO

Moderators: S Pal and S Olsson

The workshop started with a presentation that outlined: the extended scope of PV, frequency of preventable adverse drug reactions (ADRs); current projects investigating the detection of Medication Errors (ME); the WHO publication "Reporting and learning systems for medication errors: The role of pharmacovigilance centres". Discussions centred around: the need to modify definitions used for relevant terms (e.g. adverse event, preventable ADR); the need to modify reporting forms to allow for collection of ME reports; validating the P-method for detecting preventable ADRs; communication to potential reporters, the need to encourage the submission of information on MEs; and collaboration with other organizations or groups within countries to strengthen the work for prevention of medication errors. Participants proposed that forms for collecting Individual Case Safety Reports (ICSRs) could be improved to optimize detection of MEs. Items such as: patient weight, relevant medical history, suspected and concomitant medications, and room for narratives could be present on the ICSR form.
## Feature

**Recommendations from working group on reporting and learning systems for medication errors, the role of national centres, WHO Collaborating Centres and WHO**

**For National Pharmacovigilance Centres:**
- To increase capacity and competence of the National PV Centres to identify and analyze Medication Errors (ME).
  - Identify obstacles to reporting ME and learning
  - Document procedures
  - Investigate if funds from public health programmes may be used to support MEs Reporting and Learning Systems
  - Invest in research on ME, to find out the burden of MEs in public health programmes.
- To optimize the Individual Case Safety Reporting Forms to capture MEs.
- To focus on reporting and publishing.
- To adapt definitions of adverse drug reaction and medication errors for the local legal situation (e.g. in the EU, medication errors are included in the definition of ADR).
- To improve individual record-keeping in medical facilities.
- To pursue regional collaboration between centres for competence-sharing and training on ME analysis.
- To make ADR/ME reporting one of the criteria in the private health care sector for accreditation.
- To conduct a study with volunteer countries to validate the 'P method' for detecting preventable ADRs.

**For WHO and WHO CCs:**
- To propose a Council for International Organizations of Medical Sciences (CIOMS) working group, to clarify discrepancies in definitions between patient safety and PV networks.

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### Data mining/signal detection at national centres: when, how, why

*Moderators: YK Gupta and Laura Sottosanti*

The signal process in Italy was shared. During the discussions it was agreed that there is no specific number of reports needed for data mining. There needs to be a balance between quality, quantity and critical mass of information for signal detection. In addition, statistical evidence may not be needed if clinical evidence is overwhelming and it is important to confirm statistical reports with clinical analysis and obtain expert opinions. It was suggested that Standard Operating Procedures (SOPs) for signal detection should be country specific and should be different for vaccines and medicines. It is critical to identify experts who are trained and knowledgeable, with different medical backgrounds. Predefined criteria should be set and different data sources such as literature, VigiBase® and national databases should be used. Communication of signals was discussed, for example when to communicate and to whom. All stakeholders should be informed and communication methods include ‘Dear health-care professional’ letters and websites. Countries with less established PV systems, in particular Low-and Middle-Income Countries (LMICs) might lack the capacity for using and analyzing data mining software. In some Member States there may be a relatively small number of reports; hence databases are small, making it difficult to detect signals statistically. In this case, software and sophisticated data-mining methods may not be useful. However, data can be pulled from other countries. In addition LMICs may lack expertise and knowledge. In terms of software, the WHO CCs can provide support through online-webinars and face to face meetings. Countries should not be deprived of this support due to lack of funds. In high income countries, statistical software is often developed internally or purchased.
Recommendations from working group on data mining/signal detection at national centres: when, how, why

For WHO and WHO CCs:
- To help with capacity building in NPCs for data-mining and signal detection.
- To facilitate training through e-training and e-fora.
- To develop standardized tools for data-mining and signal generation (incorporating VigiLyze™).
- To help develop a template/generic SOP for signal detection to be adopted by interested countries.
- To help build data-mining and signal detection into public health programmes at the point of inception, and to advise on/provide software to assist this process.
- To continue to develop and increase awareness of software, in particular VigiLyze™, for data-mining and signal detection and make these freely available to the countries (downloadable on the internet) to help compare national data with that of other countries.
- To support NPCs with a strategy for raising funds for this area of work.

How can PV centres work with any relevant associations that can provide data and/or insights, including patient organizations and public health programmes

Moderators: V M Šarinić and A Mengistu

This session started by discussing collaborations with public health programmes (PHP) and patient involvement in countries represented in the working group. Many stories were shared. In some countries, although effort was invested, outcomes were not as anticipated. These stories were used to draw up recommendations. Representatives from 14 different countries attended this working group.

Recommendations from working group on how can PV centres work with any relevant associations that can provide data and/or insights, including patient organizations and public health programmes

National PV Centres should consider the following in their collaborations with:

1. Public health programmes (PHPs)
   - Collaborations should be beneficial for both parties
   - Make best use of the available resources
     - PHP infrastructure to promote reporting
     - PV centre knowledge for designing reporting form for PHPs (which might need modification from the spontaneous reporting form) and signal detection
   - Schedule regular meetings where information is exchanged, so that all information can be used both by PHP and PV centres in their decision making
   - Define roles and responsibilities clearly
   - Keep scientific independence
   - Document agreements (memorandum of understanding)
   - Consider that different PHP programmes in one country may require a different approach.

2. Patient organizations
   - Collaboration should be beneficial for both parties
   - Listen to what patient organizations want
   - Clarify what can and cannot be done
   - Use patient organizations as ambassadors for National Pharmacovigilance Centres
   - Also involve other organizations, for example women’s associations or consumer organizations.
## Feature

**For contacting patient organizations**

- Raise the awareness about PV centres and what is being done in media directed to the public (this will encourage patient organizations to contact or invite National Pharmacovigilance Centres to collaborate)
- Choose either an umbrella organization or the biggest/most active organizations and approach these actively.

**WHO and WHO CCs are recommended to:**

- Create a platform where experiences (success stories but also initiatives that failed) can be shared. The stories should be practical, so that readers can try and adopt them in their own setting
- Modify existing platforms such as Vigimed and Uppsala Reports instead of creating new ones
- Include these subjects (PHPs, patient organizations) in training, using experienced organizations as trainers.

### Where is PV heading / the future of PV

*Moderators: B Medhi and M Lindquist*

This working group had 28 participants from 16 countries. The PV vision in ten years was discussed to include: a broader field of action for PV, integration of PV in all health-care aspects, and routine PV education. PV should be supported by legislation in all countries, with predictable, sufficient and sustainable funding. Prescribing should be rational and, preventable ADRs and medications errors should be minimised. PV needs to be cost-effective, responsive, and supported by the best of modern technology and media.

Methods and tools for this vision were discussed. These include, raising awareness, establishing universal reporting, decentralising, work-sharing, refined benefit-harm assessment, clinical guidance for management of ADRs, metrics for PV, creating smart and agile systems to prepare for emergencies and integrating PV into Public Health Programmes.

### Recommendations from working group on where is PV heading / the future of PV

**For all:**

- Develop and promote education and training for health-care professionals and pharmacovigilance staff
  - Support and streamline existing curriculum initiatives (including WHO-ISO and Lareb curricula) to meet the needs of basic medical and PV education
- Explore innovative methods for raising public awareness of pharmacovigilance.
  - Facilitate the collection of best practice examples for sharing among member countries (including the dissemination of "Take&Tell")
- Implement the WHO pharmacovigilance indicators in member countries using a standard protocol
  - Assess impact of pharmacovigilance activities
- Explore new sources and new methods for collection of patient safety data
- Explore the benefits of engaging professionals from other disciplines such as psychologists, health economists, social scientists, implementation scientists, communications experts, eco-pharmacologists, and others

**For WHO CC UMC:**

- Find a technical solution for reporting adverse drug reactions in situations without internet access
- Develop Vigimed as a user-friendly collaboration portal and encourage its use
- Familiarise all member countries with the use of database tools such as VigiLyze™, VigiGrade, etc.

*The working group recognises and commends the Sierra Leone Pharmacovigilance Centre for its courage and persistence they displayed in the Ebola epidemic in their country; the working group proposes that such vivid examples of the robust effectiveness of PV should be collected and used at the highest levels for the purposes of advocacy and fund-raising.*
The need for quantitative benefit-risk assessment in PV

Moderators: R Savage and E van Puijenbroek

This working group consisted of 40 participants. The challenges and advantages of qualitative and quantitative approaches to risk benefit assessments were discussed. Qualitative is more subjective, whereas quantitative can be used to compare. However this approach can be complex and requires expertise. Many of the representatives attending this working group had experience using qualitative assessments (Namibia, Republic of Korea, Thailand, Turkey, Chile, Vietnam, India, Belgium) but none had quantitative experience. The opportunities and challenges for qualitative risk benefit assessments were identified. For qualitative assessments, an example of an opportunity is access to global data. Challenges include variation between populations, lack of efficacy data and potential bias (due to subjective nature). Challenges of quantitative assessment included lack of expertise and manpower. Data and skills needed to perform risk benefit analysis were listed.

Recommendations from working group on the need for quantitative benefit-risk assessment in PV

For WHO and WHO CCs
- Provide training (capacity building)
- Provide technical guidance
- Include benefit-risk information in newsletters

For National Pharmacovigilance Centres
- Regulators such as FDA and EMA should share how they reach benefit-risk conclusions

Revisiting the WHO Minimum PV Requirements

Moderators: A Dodoo and H B Ndagije

Twenty participants from seven countries attended this working group. Current minimum requirements are available on the WHO website: http://www.who.int/medicines/areas/quality_safety/safety_efficacy/saf_pub/en/.

The PV landscape has changed since the WHO minimum requirements for NPC were proposed in 2009. They need to be made clearer, simple and measurable. They should not give the impression that they are the only requirements. Additional requirements should be added to the existing ones. New requirements should have accompanying guidelines and explanatory notes.

Recommendations from working group on revisiting the WHO Minimum PV Requirements

For WHO:
- WHO should develop the new set of minimum requirements for PV and detailed guidelines to accompany the minimum PV requirements, and submit these to the 2016 National Centres meeting for approval
Proposed Minimum Requirements for National Pharmacovigilance Centres

- A National Pharmacovigilance Centre collaborating with the WHO Programme for International Drug Monitoring and implementing at least a spontaneous reporting system
- National spontaneous reporting system with form(s) for capturing and reporting adverse events to medical products including medicines, vaccines, medical devices etc.
- A national database or system for collating, managing and sharing PV data
- A functional national advisory body for pharmacovigilance
- A communication plan for stakeholders in pharmacovigilance (to include over-the-counter, internet-purchases and non-medicinal drugs)
- Legislation on pharmacovigilance
- Formal link to National Regulatory Authority
- Established procedures for measuring impact of the national pharmacovigilance system
- Designated full-time staff to fulfil the minimum requirements of national PV centre
- Dedicated financial and technical resources to fulfil the minimum requirements of national PV centre

How to capture adverse events due to over-the-counter (OTC), internet purchased (IP) and non-medicinal drugs (NMD)

Moderators: B Harvey and M Dheda

The working group consisted of 40 participants. Discussions included information sources, experiences of NPCs in capturing ADRs due to over-the-counter (OTC), internet-purchased (IP) and non-medicinal products (NMDs). Most countries do not have a specific system to capture ADRs from OTC, IP and NMDs. The Republic of Korea has a specific system for reporting and analysing reports (many OTC medications are available in convenience stores). Such reports can be used for consumer education (e.g. liver toxicity). Generally consumers do not link ADRs to these products and many believe natural ingredients are safe. Access to the internet has increased and it is difficult to regulate internet sales of medicines. Regulations are less stringent for OTCs and herbal medicines. There may be many drug-drug interactions and patients may use products with similar ingredients. Sources of information that can be used to capture ADRs include: patients, face-to-face meetings, help lines, health-care professionals, PV networks (some countries may detect ADRs faster, related to specific products than others), social media and collaborations with other stakeholders. Vigimed needs to be made more user-friendly to improve communications between countries. The public can be educated and awareness built through: social media, patient-targeted portals, websites of regulators, awareness campaigns (television and radio, print media). Health-care professionals should be trained to ask patients if they are taking OTC and IP medications and NMDs. This will give the opportunity to educate the patient. Challenges include: lack of funding, lack of cooperation from consumers, inability to trace source of supply. Opportunities include: presence of existing systems, sources such as herbal pharmacopoeia.

Recommendations from working group on how to capture adverse events due to over-the-counter (OTC), internet purchased (IP) and non-medicinal drugs (NMD)

- Set up a website of agents/groups that are accredited for online sale of medicines.
- Develop a tool that can help NPCs to detect adverse events online e.g. stories shared on social media
- Make Vigimed more user-friendly