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WHO Vision for Medicines Safety

***No country left behind:
worldwide pharmacovigilance
for safer medicines, safer patients***

*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
national pharmacovigilance centres
and other sources such as
specialized bulletins and journals,
as well as partners in WHO.*

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

Safety and Vigilance: Medicines,

EMP-HIS,
World Health Organization,
1211 Geneva 27, Switzerland,
E-mail address: pvsupport@who.int

*This Newsletter is also available at:
<http://www.who.int/medicines>*

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®.

A brief report from the Thirteenth Meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) is included as a feature.

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Alpha lipoic acid

Potential risk of low blood sugar (hypoglycaemic episodes)

Canada. Health Canada will consider updating the labelling standard for alpha lipoic acid to include advice on management of hypoglycaemic episodes. This follows conclusions from a safety review of case reports and publications in the scientific literature that indicate a risk of developing insulin autoimmune syndrome (IAS) with use of alpha lipoic acid (medicinal ingredient in natural health products).

Alpha lipoic acid is used as an antioxidant to help promote the breakdown of glucose, and as a preservative in some natural health products.

At the time of the review, there were no reports of hypoglycaemic episodes reported with the use of alpha lipoic acid that originated from Canada. However, there were several published international case reports of hypoglycaemic episodes in individuals with IAS which may have been triggered by the use of oral products containing alpha lipoic acid. The cases of hypoglycaemia resolved once the alpha lipoic acid was stopped.

There is scientific evidence of a genetic predisposition for IAS and risk of developing hypoglycaemic episodes with the use of oral alpha lipoic acid. Most cases reported originated from Asia (where these genetic variations are more common), and recently cases originating in Europe have been reported.

Reference:

Summary Safety Review, Health Canada, 30 June 2016 (www.hc-sc.gc.ca)

Apixaban

Risk of hepatic function disorder

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package insert for apixaban (Eliquis®) has been updated to include the risk of hepatic function disorder as a clinically significant adverse reaction.

Apixaban is used to reduce the risk of ischemic stroke and systemic embolism in people with non-valvular atrial fibrillation. It is also used for treatment and prophylaxis of relapse of venous thromboembolism (deep vein thrombosis and pulmonary embolism).

A total of 16 cases of hepatic function disorder with the use of apixaban have been reported in Japan. Of these, a causal relationship could not be excluded in five cases.

Following an investigation of available evidence and advice from experts, the MHLW/PMDA concluded that revision of the package insert was necessary.

Reference:

Revision of Precautions, MHLW/PMDA, 5 July 2016 (www.pmda.go.jp/english/)

Benzoyl peroxide

Risk of wide-spread swelling

Japan. The MHLW and the PMDA have announced that the package inserts for benzoyl peroxide preparations (Bepio® and Duac combination gel®) have been updated to include the risk of wide-spread swelling as a precaution.

Benzoyl peroxide is indicated for acne vulgaris. It is available as a single agent or in combination with clindamycin (Duac combination gel®).

A total of seven cases of cutaneous symptoms with the use of benzoyl peroxide have been reported in Japan. Of these, a causal relationship could not be excluded in six cases.

Following an investigation of available evidence and advice from experts, the MHLW/PMDA concluded that revision of the package insert was necessary.

Reports on the cases of erythema and swelling spreading to the entire face and neck will be added as a precaution to the package insert.

Reference:

Revision of Precautions, MHLW/PMDA, 5 July 2016 (www.pmda.go.jp/english/)

Bisphosphonates

Risk of osteonecrosis of external auditory canal

Japan. The MHLW and the PMDA have announced that the package inserts for bisphosphonates (etidronate, pamidronate, alendronate, risedronate, zoledronic acid, minodronic acid and ibandronate) have been updated to include the risk of osteonecrosis of external auditory canal as an important precaution and a clinically significant adverse reaction.

Bisphosphonates are indicated for osteoporosis, Paget's disease of bone, or used for prevention of heterotopic ossification in the early or advanced stages.

Osteonecrosis of external auditory canal was added to the Summary of Product Characteristics for bisphosphonates in Europe. In addition, cases have been reported in people treated with bisphosphonates in Japan and in other countries.

Following an investigation of available evidence and advice from experts, the MHLW/PMDA

concluded that revision of the package insert was necessary.

(See WHO Pharmaceuticals Newsletter No.1, 2016: *Risk of osteonecrosis of the external auditory canal in the United Kingdom*)

Reference:

Revision of Precautions, MHLW/PMDA, 31 May 2016 (www.pmda.go.jp/english/)

Bromhexine-containing cough and cold medicines

Risk of allergy and skin reactions

Australia. The Therapeutic Goods Administration (TGA) has advised that product information for all bromhexine-products (including generics) should contain information on the small risk of severe allergic reactions and severe skin reactions. The current package insert for the brand, Bisolvon®, already includes a warning regarding anaphylactic reactions and skin reactions.

A number of over-the-counter cough and cold medicines contain bromhexine as a mucolytic.

As of 19 February 2016, 34 cases of hypersensitivity reactions, 10 cases of anaphylactic/anaphylactoid reactions, and five cases of severe cutaneous adverse reactions (SCARs) had been reported to the TGA.

A definite link to bromhexine in 29 of these cases could not be made because: they involved products with multiple active ingredients or excipients such as benzoates which can also cause hypersensitivity; or there were other confounding factors.

The TGA reviewed this issue following a review by Europe's Pharmacovigilance Risk Assessment Committee (PRAC) that confirmed the risk of

severe allergic reactions and SCARs associated with bromhexine- and ambroxol-containing medicines. Subsequently, product information for these products was updated with warnings of these potential adverse events.

The TGA has found that similar warnings to those being implemented in Europe are appropriate for bromhexine-containing medicines marketed in Australia.

(See WHO Pharmaceuticals Newsletter No.2, 2015: *Risk of allergy and skin reactions with the use of ambroxol and bromhexine expectorants in the EU*)

Reference:

Medicines Safety Update, TGA, Vol. 7, No. 3, June 2016 (www.tga.gov.au)

Canagliflozin and dapagliflozin

Strengthened warnings for acute kidney injury

USA. The US Food and Drug Administration (FDA) has revised the product information for canagliflozin (Invokana® and Invokamet®) and dapagliflozin (Farxiga® and Xigduo XR®) to strengthen the existing warning about the risk of acute kidney injury and to include recommendations to minimize this risk.

Canagliflozin and dapagliflozin are prescription medicines used with diet and exercise to help lower blood sugar in adults with type 2 diabetes.

From March 2013, (when canagliflozin was approved), to October 2015, the FDA received 101 reports of acute kidney injury, some of which required hospitalization and dialysis, with canagliflozin or dapagliflozin use.

The FDA has recommended that health-care professionals should consider factors that may predispose individuals to

acute kidney injury prior to starting them on canagliflozin or dapagliflozin. Kidney function should be assessed prior to starting canagliflozin or dapagliflozin and monitored periodically thereafter. If acute kidney injury occurs, the drug should be discontinued promptly and kidney impairment should be treated.

(See WHO Pharmaceuticals Newsletter No.6, 2015: *Risk of acute kidney injury with SGLT2 inhibitors in Canada*)

Reference:

Drug Safety Communication, US FDA, 14 June 2016 (www.fda.gov)

Carmustine (intracerebral implant)

Possible risk of air accumulation at the implant site

Japan. The MHLW and the PMDA have announced that the package insert for carmustine intracerebral implant (Gliadel®) has been updated to include the possible risk of air accumulation at the implant site as an important precaution.

Carmustine intracerebral implant is used for the treatment of malignant glioma.

A total of 17 cases of air accumulation at the implant site with the use of carmustine intracerebral implant have been reported in Japan, although a causal relationship with the product was not established in all cases.

Following an investigation of available evidence and advice from experts, the MHLW/PMDA concluded that revision of the package insert was necessary.

Reference:

Revision of Precautions, MHLW/PMDA, 5 July 2016 (www.pmda.go.jp/english/)

Diclofenac

Risk of gastrointestinal stenosis and obstruction

Japan. The MHLW and the PMDA have announced that the package inserts for diclofenac preparations (Voltaren® and Rectos®) have been updated to include the risk of gastrointestinal stenosis and obstruction as clinically significant adverse reactions.

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) and used for relief of pain and anti-inflammation.

A total of five cases of gastrointestinal stenosis or obstruction associated with the use of diclofenac have been reported in Japan. Of these, a causal relationship could not be excluded in four cases (one case was for a condition not included in the approved dosage and administration). In addition, the company core datasheet (CCDS) has been updated.

Following an investigation of available evidence and advice from experts, the MHLW/PMDA concluded that revision of the package insert was necessary.

Reference:

Revision of Precautions, MHLW/PMDA, 5 July 2016 (www.pmda.go.jp/english/)

Febuxostat

Possible risk of Drug Reaction/Rash with Eosinophilia and Systemic Symptoms (DRESS)

Canada. Health Canada has announced that the prescribing information for febuxostat (Uloric®) has been updated to include the risk of Drug Reaction/Rash with Eosinophilia and Systemic Symptoms (DRESS).

Febuxostat is used to lower blood uric acid levels in people with gout.

Health Canada conducted a safety review of available evidence and concluded that there is a possible link between DRESS and use of febuxostat.

At the time of this review, Health Canada had received one report of DRESS originating from Canada in a patient taking febuxostat and ten cases from the manufacturer. The World Health Organization (WHO) Global Individual Case Safety Reports (ICSR) database, Vigibase®) had received 13 international cases. Three additional cases of DRESS in association with febuxostat therapy were reported in the scientific literature, two of which were also reported by the manufacturer.

Health Canada has also published an article to raise awareness and encourage reporting by patients and health-care professionals.

Reference:

Summary Safety Review, Health Canada, 13 June 2016 (www.hc-sc.gc.ca)

Fingolimod

Potential lack of efficacy for Primary Progressive Multiple Sclerosis (PPMS)

Japan. The MHLW and the PMDA have announced that the package inserts for fingolimod preparations (Imusera® and Gilenya®) have been updated to include a cautionary note for the potential lack of efficacy when used for primary progressive multiple sclerosis (PPMS).

Fingolimod is used to prevent relapse and to delay the accumulation of physical disability in multiple sclerosis (MS). MS can be categorised as: Relapsing-remitting MS (RRMS); PPMS; and Secondary Progressive MS (SPMS).

After evaluating the manufacturing authorization

application for fingolimod, the PMDA has concluded that fingolimod is anticipated to be efficacious for SPMS with relapse.

Results from a clinical trial (D2306 Study) that was completed in July 2015 indicated that fingolimod did not demonstrate efficacy for PPMS.

For the time being, the PMDA does not think it is necessary to exclude PPMS from the indications of fingolimod based on lack of efficacy in one clinical trial which was conducted outside Japan. However, it is considered appropriate to be included in the section of precaution for indication.

Reference:

Revision of Precautions, MHLW/PMDA, 5 July 2016 (www.pmda.go.jp/english/)

Hydroxyzine

Potential risk of abnormal heart rhythm

Canada. Health Canada has updated dosing information for hydroxyzine (Atarax® and generics) to include advice on duration of dosing and new maximum daily doses (100 mg in adults and children over 40 kg), due to the potential risk of abnormal heart rhythm.

Hydroxyzine is a first-generation antihistamine used for anxiety; pruritus; pre-surgical medication; nausea and vomiting.

Health Canada conducted a safety review and concluded that there is evidence that hydroxyzine may contribute, along with other risk factors, to changes in the electrical activity of the heart and adversely affect heart rhythm.

At the time of Health Canada's review, there were 35 Canadian and 26 international cases of QT interval prolongation or torsades de

pointes (QTP/TdP) associated with the use of hydroxyzine reported. In the majority of these cases, the patients had additional risk factors, for example; concomitant medication (known to be associated with QTP/TdP and/or interact with hydroxyzine); electrolyte imbalances; family history; and exposure to daily doses of hydroxyzine over 100 mg.

Of these reports, only three cases (all international) provided enough information for a more detailed medical review. Hydroxyzine was found to have had a "possible" or "probable" contribution to QTP/TdP. However all cases had at least one other risk factor that could have contributed to development of QTP/TdP.

In addition, a review of the literature identified a slight QT interval prolongation after a single 100 mg dose of hydroxyzine in a recent clinical study, and with even higher doses in older clinical studies.

Health Canada is working with the manufacturers of hydroxyzine to update the product information to reflect the risk of changes in heart rhythm, especially in patients with predisposed risk factors.

(See WHO Pharmaceuticals Newsletters No.5, 2015: *Risk of prolonged QT interval and ventricular tachycardia in Japan* and No.3, 2015: *Risks of effects on heart rhythm in Europe and Risk of QT interval prolongation and Torsade de Pointes in the United Kingdom*)

Reference:

Summary Safety Review, Health Canada, 6 June 2016 (www.hc-sc.gc.ca)

Idelalisib

Risk minimization to prevent serious infections

EU. The EMA's PRAC has updated recommendation

about the initiation of idelalisib (Zydelig®) in patients with previously untreated chronic lymphocytic leukaemia (CLL) whose cancer cells have certain genetic mutations (17p deletion or TP53 mutation).

Idelalisib is used for the treatment of CLL in patients who have received previous treatment as well as in previously untreated patients who have certain genetic mutations in their cancer cells (17p deletion or TP53 mutation). It is used in combination with rituximab.

The EMA's PRAC has completed a review of idelalisib confirming that the benefits outweigh risks for the treatment of CLL and follicular lymphoma.

At the beginning of the review the PRAC had advised, as a precaution, not to start idelalisib in patients with previously untreated CLL whose cancer cells have certain genetic mutations (17p deletion or TP53 mutation). The PRAC now advises that idelalisib can again be initiated in these patients provided they cannot take any alternative treatment and that the measures agreed to prevent infection are followed.

The review confirmed that there is a risk of serious infections with idelalisib, including *Pneumocystis jirovecii* pneumonia; the PRAC has proposed updated recommendations to manage this risk.

(See WHO Pharmaceuticals Newsletters No.3, 2016: *Risk of serious infection and deaths in the United Kingdom* and No.2, 2016: *risk of a particular type of lung infection (pneumocystis jirovecii pneumonia) in the EU*)

Reference:

Press release, EMA, 8 and 22 July 2016 (www.ema.europa.eu)

Interferon beta-1a

Potential risk of kidney damage (nephrotic syndrome)

Canada. Health Canada has requested that the prescribing information for interferon beta-1a (Avonex®) is updated to include the potential risk of nephrotic syndrome.

Interferon beta-1a is used to reduce damage to the central nervous system, and slow down the worsening of multiple sclerosis (MS).

Health Canada carried out a safety review to investigate the potential risk of nephrotic syndrome with the use of interferon beta-1a.

At the time of the review, there was only one Canadian case of nephrotic syndrome reported in a patient with MS using interferon beta-1a.

A search in the WHO Global ICSR database, VigiBase® found 10 cases of nephrotic syndrome reported in MS patients treated with interferon beta products.

In the scientific and medical literature, there were seven cases of nephrotic syndrome found with the use of interferon beta products.

In addition, the manufacturer shared a report from the Global Safety Database which contained nine cases of nephrotic syndrome with interferon beta-1a. Upon review of these cases, they were considered to be possibly related to the use of interferon beta-1a.

Health Canada's safety review concluded that there is a potential risk of nephrotic syndrome with the use of interferon beta-1a for the following reasons:

- nephrotic syndrome has been linked to other interferon beta drugs;
- nephrotic syndrome has been reported with

- interferon beta-1a treatment;
- interferon beta-1a causes changes in the body which might bring about nephrotic syndrome as a side-effect.

Reference:

Summary Safety Review,
Health Canada, 30 June 2016
(www.hc-sc.gc.ca)

Lercanidipine

Cloudy peritoneal effluent in patients on peritoneal dialysis

Australia. The TGA has updated the product information for lercanidipine (Zanidip® and generics) to include information and precautions about cloudy peritoneal effluent (CPE) in patients on peritoneal dialysis as an adverse effect.

Lercanidipine is indicated for the treatment of hypertension.

Investigations by the TGA, including the review of medical literature, have found an association between calcium channel blockers and the development of CPE secondary to elevated triglyceride concentrations (in the effluent) in patients on peritoneal dialysis. This association is strongest for lercanidipine and manidipine.

As of 19 February 2016, there have been four cases of CPE associated with lercanidipine reported to the TGA. A further 23 cases were found in international medical literature. In addition three cases were identified for other calcium channel blockers: nifedipine (1), verapamil (1) and diltiazem (1). Of the total 27 cases of CPE with lercanidipine, 15 occurred within three days of commencing the medicine.

The TGA advises health-care professionals to consider a reversible medication-induced differential diagnosis for the development of cloudy

peritoneal effluent in patients on peritoneal dialysis who are taking lercanidipine and who have no other signs or symptoms of infective peritonitis.

Reference:

Medicines Safety Update, TGA,
Vol. 7, No. 3, June 2016
(www.tga.gov.au)

Levetiracetam

Risk of acute renal failure

Japan. The MHLW and the PMDA have announced that the package insert for levetiracetam (E Keppra®) has been updated to include the risk of acute renal failure as a clinically significant adverse reaction.

Levetiracetam is used to treat partial onset seizures in patients with epilepsy (including secondary generalized seizures). It is also used concomitantly with other antiepileptic drugs for tonic-clonic seizures in patients who fail to show a satisfactory response to other antiepileptic drugs.

A total of seven cases of acute renal failure have been reported with the use of levetiracetam in Japan. Of these, a causal relationship could not be excluded in two cases. The company core datasheet (CCDS) has also been updated following reported cases in Japan and in the other countries.

Following an investigation of available evidence and advice from experts, the MHLW/PMDA concluded that revision of the package insert was necessary.

Reference:

Revision of Precautions,
MHLW/PMDA, 31 May 2016
(www.pmda.go.jp/english/)

Natalizumab

Potential risk of haemolytic anaemia

Canada. Health Canada has announced that the prescribing information for natalizumab (Tysabri®) has been revised to reflect the risk of anaemia following conclusions from a safety review.

Health Canada has concluded that evidence of an increase in the risk of haemolytic anaemia in individuals with multiple sclerosis (MS) and with use of natalizumab is limited.

Natalizumab is used to treat patients with the relapsing-remitting form of MS.

The safety review considered Canadian and international post-market cases of anaemia that were reported in MS patients treated with natalizumab. Most case reports lacked detailed information, including information to determine if the cases of anaemia were of the haemolytic type.

The published articles consisted of reviews of possible haemolytic anaemia and anaemia cases.

Overall, the evidence was not sufficient to support a direct link between the use of natalizumab and the risk of haemolytic anaemia. However, the possible role of natalizumab in post-market cases of anaemia could not be ruled out.

Health Canada requested that the manufacturer update the prescribing information to better reflect the risk of anaemia.

Reference:

Summary Safety Review,
Health Canada, 6 June 2016
(www.hc-sc.gc.ca)

Nintedanib

Risk of thrombocytopenia

Japan. The MHLW and the PMDA have announced that the package insert for nintedanib (Ofev®) has been updated to include the risk of thrombocytopenia as a clinically significant adverse reaction.

Nintedanib is indicated for idiopathic pulmonary fibrosis.

A total of five cases of thrombocytopenia with the use of nintedanib have been reported in Japan. Of these, a causal relationship could not be excluded in three cases, including one fatal case.

Following an investigation of available evidence and advice from experts, the MHLW/PMDA concluded that revision of the package insert was necessary.

Reference:

Revision of Precautions, MHLW/PMDA, 5 July 2016 (www.pmda.go.jp/english/)

Ombitasvir, paritaprevir and ritonavir combination

Risk of acute renal failure

Japan. The MHLW and the PMDA have announced that the package insert for the preparation of ombitasvir, paritaprevir and ritonavir combination (Viekirax®) has been updated to include the risk of acute renal failure as a clinically important precaution.

The preparation of ombitasvir, paritaprevir and ritonavir combination is indicated for improvement of viraemia in Serological Group 1 (Genotype 1) chronic hepatitis C or compensated cirrhosis C.

A total of 14 cases of acute renal failure with the use of this preparation have been reported in Japan. Of these, a causal relationship could not

be excluded in nine cases, including one fatal case.

Following an investigation of available evidence and advice from experts, the MHLW/PMDA concluded that revision of the package insert was necessary.

Reference:

Revision of Precautions, MHLW/PMDA, 5 July 2016 (www.pmda.go.jp/english/)

Oxytocin

Risk of anaphylaxis

Japan. The MHLW and the PMDA have announced that the package inserts for oxytocin have been updated to include the risk of anaphylaxis as a clinically significant adverse reaction.

Oxytocin is used for the induction and enhancement of uterine contractions and the treatment of uterine bleeding.

A total of five cases of anaphylaxis with the use of oxytocin have been reported in Japan. Of these, a causal relationship could not be excluded in three cases (one case was for a condition which was contraindicated in the package insert).

Following an investigation of available evidence and advice from experts, the MHLW/PMDA concluded that revision of the package insert was necessary.

The anaphylaxis will be added as a clinically significant adverse reaction.

Reference:

Revision of Precautions, MHLW/PMDA, 5 July 2016 (www.pmda.go.jp/english/)

Rivaroxaban, dabigatran and apixaban

Possible risk of hair loss (alopecia)

New Zealand. The Medicines and Medical Devices Safety Authority (Medsafe) has highlighted a possible risk of hair loss with the use of novel oral anticoagulants (rivaroxaban, dabigatran and apixaban) and has placed this safety concern on the medicines monitoring scheme, to obtain further information on these possible adverse reactions.

Novel oral anticoagulants are used in a variety of conditions including:

- Prevention of stroke and systemic embolism.
- Prevention of venous thromboembolism (VTE).
- Treatment of deep vein thrombosis (DVT) and/or pulmonary embolism (PE).
- Prevention of recurrent DVT and/or PE.

In July 2015, the Centre for Adverse Reactions Monitoring (CARM) received a report of hair loss with the use of rivaroxaban. The patient experienced significant and continuously worsening hair loss which was noticed four days after starting rivaroxaban. The patient had no previous history of hair loss. Review of data from the WHO Global ICSR database, VigiBase® also suggests that there may be a connection between novel oral anticoagulants and hair loss.

The overall benefit-risk balance of rivaroxaban, dabigatran and apixaban remains positive.

Reference:

Safety Information, Medsafe, 30 May 2016 (www.medsafe.govt.nz/)

Sodium-glucose cotransporter-2 (SGLT2) inhibitors

Risk of serious diabetic ketoacidosis (DKA)

Singapore. The Health Sciences Authority (HSA) has reminded health-care professionals of recommendations to minimize the risk of diabetic ketoacidosis (DKA) with use of sodium-glucose cotransporter-2 (SGLT2) inhibitors (canagliflozin, dapagliflozin).

SGLT2 inhibitors are indicated as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes mellitus (T2DM), as monotherapy or as an add-on combination therapy with other glucose-lowering agents including insulin.

The HSA has conducted a review of findings from scientific publications as well as information from local and overseas cases of DKA associated with SGLT2 inhibitors.

As of 1 February 2016, the HSA has received five local cases of DKA and one case of ketonaemia associated with SGLT2 inhibitors use, all of which had resulted in the patients being hospitalized. The time-to-onset of DKA from the initiation of treatment with SGLT2 inhibitors ranged from 11 to 169 days while that of ketonaemia was unknown. Risk factors such as infection, reduction in insulin dose, late-onset type 1 diabetes mellitus and long standing T2DM, were also observed in these local cases, which could have precipitated the development of DKA.

In consideration of the expert opinions from endocrinologists and the HSA's Pharmacovigilance Advisory Committee (PVAC), HSA has concluded that while the

benefit-risk profile of SGLT2 inhibitors remains favourable for their approved indications, the possibility of SGLT2 inhibitors leading to an increased risk of DKA cannot be excluded, particularly in the presence of predisposing factors.

The HSA is working with the product licence holders to strengthen the local package inserts of the SGLT2 inhibitor products, to warn of the risk of developing DKA during treatment with these medications. The HSA has also required the product licence holders to submit Periodic Benefit-Risk Evaluation Reports.

(See WHO Pharmaceuticals Newsletters No.2, 2016: *Risk of diabetic ketoacidosis in the EU*, No.1, 2016: *Risk of acid in blood and serious urinary tract infections in the USA*, No.6, 2015: *Interim update on risk of serious ketoacidosis in Singapore and Risk of diabetic ketoacidosis in Australia*, No.5, 2015: *Risk of ketoacidosis and sepsis in Japan* and No.4, 2015: *Risk of diabetic ketoacidosis in the United Kingdom*)

Reference:

Product Safety Alerts, HSA, 19 May 2016 (<http://www.hsa.gov.sg/>)

Sofosbuvir

Risks of hypertension and cerebrovascular disorder

Japan. The MHLW and the PMDA have announced that the package inserts for the sofosbuvir (Sovaldi®), sofosbuvir and ledipasvir combination (Harvoni®) and ribavirin (Rebetol® and Copegas®), have been updated to include the risk of hypertension and risk of cerebrovascular disorder as a clinically significant adverse reaction.

Sofosbuvir is used for improvement of viraemia in patients with chronic hepatitis

C virus infection or compensated cirrhosis C.

One case of hypertension with the concomitant use of sofosbuvir and ribavirin and a total of seven cases with the combination product of sofosbuvir and ledipasvir have been reported in Japan. Of these, a causal relationship with the combination product of sofosbuvir and ledipasvir could not be excluded in five cases.

In addition, a total of 25 cases of cerebrovascular disorder with the concomitant use of sofosbuvir and ribavirin and 30 cases with the combination product of sofosbuvir and ledipasvir have been reported in Japan. Of these, a causal relationship could not be excluded in eight cases and 11 cases, respectively.

Following an investigation of available evidence and advice from experts, the MHLW/PMDA concluded that revision of the package insert was necessary.

Reference:

Revision of Precautions, MHLW/PMDA, 5 July 2016 (www.pmda.go.jp/english/)

Vemurafenib

Risk of potentiation of radiation toxicity

Singapore. The HSA has announced that warnings for the risk of potentiating radiation toxicity will be strengthened in the package insert for vemurafenib (Zelboraf®).

Vemurafenib is a low molecular weight inhibitor of the BRAF serine-threonine kinase registered for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.

The risk of potentiating radiation toxicity, by radiation recall and radiation sensitization, has been known to be associated with the use

of certain chemotherapeutic agents in combination with radiation therapy. Serious cases of radiation recall and radiation sensitization in patients who were treated with radiation before, during, or after treatment with vemurafenib were reported in other countries, and regulatory actions were taken in the United Kingdom and Canada.

The HSA has not received any reports of radiation-related injuries associated with vemurafenib in Singapore.

The HSA advises health-care professionals to take into consideration the above safety information when prescribing vemurafenib concomitantly or sequentially with radiation treatment.

(See WHO Pharmaceuticals Newsletter No.6, 2015: Risk of potentiation of radiation toxicity in the United Kingdom)

Reference:

Product Safety Alerts, HSA,
19 May 2016
(<http://www.hsa.gov.sg/>)

Warfarin

Reports of calciphylaxis

The United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has stated that the product information for warfarin will be updated to include risk of calciphylaxis.

Calciphylaxis is a very rare but serious condition that is most commonly observed in patients with known risk factors such as end-stage renal disease.

Cases of calciphylaxis have been reported in patients taking warfarin, including those with normal renal function.

An EU-wide review of relevant evidence recently concluded that there is a possibility that on rare occasions warfarin use might lead to calciphylaxis. The patient information leaflet

will also be updated to warn patients of the risk of calciphylaxis, with advice to consult their doctor if they develop a painful skin rash.

Reference:

Drug Safety Update, MHRA,
Volume 9, issue 12:1, July
2016 (www.gov.uk/mhra)

Aspirin-containing over-the-counter antacid products

Serious bleeding risk

USA. The US FDA has warned consumers about the risk of serious bleeding when using over-the-counter (OTC) aspirin-containing antacid products to treat heartburn, sour stomach, acid indigestion, or upset stomach.

In 2009, a warning about the risk of serious bleeding was added to the labels of all OTC aspirin-containing antacid products. However, a search of the FDA Adverse Event Reporting System (FAERS) database identified eight cases of serious bleeding events associated with these products after the warning was added. All of these patients were hospitalized.

As a result, the FDA will continue to evaluate this safety concern and plan to convene an advisory committee of external experts to provide input regarding whether additional actions are needed.

Reference:

Drug Safety Communication, US FDA, 6 June 2016 (www.fda.gov)

Canagliflozin

Signal of increased risk of lower extremity amputations in high cardiovascular risk patients

The United Kingdom. The MHRA has stated that a signal of increased lower limb amputation (primarily of the toe) in people taking canagliflozin in high risk cardiovascular patients is currently under investigation.

Canagliflozin is indicated in adults with type 2 diabetes mellitus to improve glycaemic control when diet and exercise

alone do not provide adequate glycaemic control.

The signal was detected during a clinical trial of high risk cardiovascular patients (CANVAS, an on-going long-term cardiovascular outcomes trial). In this trial the incidence of lower limb amputation (primarily of the toe) is higher in the canagliflozin groups (100 mg: 7 per 1000; 300 mg: 3 per 1000 patient years) compared with the placebo (3 per 1000). The mean and median follow-up time is approximately four and a half years.

Twelve other completed phase III and IV trials, with a mean follow up time of 0.9 years, have shown no increase in amputation incidence with canagliflozin.

The MHRA has outlined interim advice and recommended that health-care professionals follow the advice while this signal is being investigated by the EMA. The results of the review will be communicated when available.

(See WHO Pharmaceuticals Newsletter No.3, 2016: *Risk of leg and foot amputations: under investigation in the USA*)

Reference:

Drug Safety Update, MHRA, Volume 9, issue 11:1, June 2016 (www.gov.uk/mhra)

Citalopram

Suspected drug interaction with cocaine

The United Kingdom. The MHRA issued a notification reminding health-care professionals of the potential increase in the risk of bleeding when citalopram is taken by patients who are also taking cocaine.

Citalopram is a selective serotonin reuptake inhibitor (SSRI) indicated for the treatment of major depressive

disorder, panic disorder, and obsessive compulsive disorder.

The MHRA received a Coroner's report of a man who died of a subarachnoid haemorrhage. The report raised concerns about a suspected drug interaction between citalopram and cocaine.

The case was discussed by the UK Commission on Human Medicine's Pharmacovigilance Expert Advisory Group. One plausible mechanism for an interaction between cocaine and citalopram is that the combined hypertensive effect of cocaine and the risk of bleeding with citalopram can lead to subarachnoid haemorrhage.

The MHRA advised that health-care professionals must have, or take an adequate history, which considers recent use of other medicines—including non-prescription medicines, herbal medicines, illegal drugs, and medicines purchased online. In particular, when prescribing SSRIs, health-care professionals are reminded to enquire about cocaine use when considering drug-drug interactions and the need to avoid concurrent use of multiple serotonergic drugs.

Reference:

Drug Safety Update, MHRA, Volume 9, issue 12:2, July 2016 (www.gov.uk/mhra)

Denosumab

Hearing loss and deafness: insufficient evidence

Canada. Health Canada has carried out a safety review of the risk of hearing loss and deafness with the use of denosumab (Prolia® or Xgeva®), and has concluded that the information currently available is not sufficient to confirm this link at this time.

Denosumab is a unique immune system protein (monoclonal antibody) and is

used to slow bone loss and increase bone strength. It is indicated for treatment of osteoporosis and prevention of bone fractures in certain conditions such as giant cell tumours.

At the time of the review, Health Canada had received 16 Canadian reports, of hearing loss associated with denosumab use, from the manufacturer. Due to limited information from these cases no conclusions could be made regarding what role, if any, the drug may have played.

Worldwide, 89 reports of hearing loss had been reported in patients using denosumab at the time of this review. However, it is important to consider the background rate of hearing loss in the general public and additional risk factors for hearing loss (age, having other diseases and concomitant medicines) when evaluating risks.

Health Canada has asked the manufacturer of denosumab to actively monitor the risk of hearing loss and deafness in patients worldwide and to report these to Health Canada.

Reference:

Summary Safety Review,
Health Canada, 6 June 2016
(www.hc-sc.gc.ca)

Doxylamine and pyridoxine combination

No change of benefit/risk profile for use in pregnancy

Canada. Health Canada has reviewed the safety of doxylamine and pyridoxine combination for use in pregnancy, and has concluded that the evidence continues to support that the preparation is safe and effective to use during pregnancy.

A fixed dose-combination product of doxylamine (an antihistamine) and pyridoxine (a form of vitamin B6)

(Diclectin®) is used to treat nausea and vomiting in pregnancy (i.e. morning sickness).

The Canada Vigilance database was searched for all reports that listed doxylamine/pyridoxine combination. Seventy five cases of adverse effects (since 1975) were identified. Of these, 29 cases were further investigated. Seven cases were assessed as 'possibly associated' with this drug use while the remaining 22 were classified as unlikely to be associated with use of this preparation or causality assessment was un-assessable.

The safety review considered the scientific and medical literature published up to 20 May, 2015. Five separate meta-analyses, which combined numerous individual studies, concluded that doxylamine/pyridoxine was not associated with increased risk of birth defects. While some individual studies reported possible links between doxylamine/pyridoxine use by pregnant women and the occurrence of various birth defects, the majority of the studies did not find a link.

The number of cases reported is considered to be within the expected incidence (natural occurrence) of major birth defects (3-5%) in newborn babies.

No pattern of malformation types or group of malformations was identified in these case reports. The summary of these findings do not indicate a change in the current benefit/risk profile of the product.

Health Canada has found that the benefits of using this combination (as authorized) outweigh its risks.

Reference:

Summary Safety Review,
Health Canada, 19 July 2016
(www.hc-sc.gc.ca)

Etonogestrel implants (Nexplanon®)

Reports of device relocating to vasculature system and lung

The United Kingdom. The MHRA has issued advice on the use of etonogestrel (Nexplanon®) implants to minimize risk of implants reaching the lung via the pulmonary artery.

Nexplanon® is a long-acting contraceptive implant containing the active ingredient etonogestrel. Nexplanon® is usually effective for three years.

For maximum effectiveness Nexplanon® needs to be correctly implanted by someone who is trained to fit it. The number of reports of Nexplanon® implants in the vasculature received by the licence-holder is estimated to be approximately 1.3 per million implants sold worldwide.

The MHRA has advised that: if an implant cannot be palpated at its insertion site in the arm, it should be located as soon as possible and removed at the earliest opportunity. It is also advised that chest imaging is performed, should this occur. Correct subdermal insertion reduces the risk of these events.

Evidence from literature shows that implants found in the vasculature can become endothelialized into the pulmonary artery. If they are located early enough it is possible to remove them by an endovascular procedure. Women should therefore be shown how to locate the implant immediately following insertion and advised to check the position of the implant frequently for the first few months.

Reference:

Drug Safety Update, MHRA, Volume 9, issue 11:2, June 2016 (www.gov.uk/mhra)

Loperamide**Serious heart problems with high doses**

USA. The US FDA has warned that taking higher than recommended doses of loperamide (Imodium®), can cause serious heart problems that can lead to death.

The risk of these serious heart problems, including abnormal heart rhythms, may also be increased when high doses of loperamide are taken with several kinds of medicines that interact with loperamide.

Loperamide is approved to help control symptoms of diarrhoea, including travellers' diarrhoea. Loperamide can be obtained over the counter (OTC) and the maximum approved daily dose for adults is 8 mg per day for OTC use and 16 mg per day for prescription use.

The majority of reported serious heart problems occurred in individuals who were intentionally misusing and abusing high doses of loperamide in attempts to self-treat opioid withdrawal symptoms or to achieve a feeling of euphoria. The FDA continues to evaluate this safety issue and will determine if additional FDA actions are needed.

The FDA has advised that health-care professionals should be aware that use of higher than recommended doses of loperamide can result in serious cardiac adverse events. Loperamide should be considered as a possible cause of unexplained cardiac events including; QT interval prolongation, torsades de pointes or other ventricular arrhythmias, syncope, and cardiac arrest.

Reference:

Drug Safety Communication, US FDA, 7 June 2016 (www.fda.gov)

Marcaïn Spinal 0.5% Heavy®**Reports of failed or incomplete spinal anaesthesia**

Australia. The TGA has investigated a recent cluster of reports of failed or incomplete spinal anaesthesia with use of Marcaïn Spinal 0.5% Heavy® (bupivacaine hydrochloride anhydrous). The TGA has found these reports did not indicate a quality or efficacy issue with the product.

Bupivacaine is an amide-type local anaesthetic.

In August 2015, the TGA received notification from one hospital that there had been five occasions where hyperbaric Marcaïn® failed to achieve adequate spinal anaesthesia, despite administration by experienced clinicians.

Three batches of Marcaïn Spinal 0.5% Heavy® were implicated in the reports (batch numbers F0122-1, F0127-1 and F0139-1).

The TGA undertook surveillance of this adverse event for three months after the initial notification of the most recent cluster of reports.

As of 3 November 2015, the TGA received 30 reports of failed or incomplete spinal anaesthesia, each of which can be related to an individual patient. Of these, nine describe a complete absence of spinal blockade, while the remaining 21 reports described incomplete spinal blockade.

AstraZeneca has provided information regarding an internal investigation of this issue, including that testing

does not demonstrate a quality issue.

Based on investigations, the TGA has found that there is no evidence of a quality or efficacy issue with Marcaïn Spinal 0.5% Heavy® at this time.

Reference:

Medicines Safety Update, TGA, Vol. 7, No. 3, June 2016 (www.tga.gov.au)

Metformin**Precaution during administration of contrast media**

Egypt. The Egyptian Pharmaceutical Vigilance Center (EPVC) has reminded health-care professionals of precautionary measures needed during the administration of contrast media, in patients taking metformin.

Metformin is an oral medicine used to control blood sugar levels in type 2 diabetes.

The EPVC has advised that metformin should be temporarily stopped in patients who undergo an X-ray or CT scan using contrast dye, because such interventions with iodinated materials may result in acute alteration of renal function.

This Precaution is already mentioned in Egyptian labels of metformin-containing products.

The EPVC has stated that metformin must be withheld after the administration of the contrast agent for 48 hours to avoid this complication. If renal function is normal at 48 hours, metformin can be restarted.

Reference:

Newsletter, EPVC, Volume 7, Issue 6, June 2016

Miconazole (topical use including oral gel)

Potential for serious drug-drug interactions with warfarin

The United Kingdom. The MHRA is considering the use of further measures to minimize the risk of potentially serious interactions between miconazole and warfarin, to prevent bleeding.

Miconazole (Daktarin® and Daktacort®) is an antifungal indicated for prevention and treatment of various infections of the mouth, throat, skin, nails, or genitals.

Warfarin is an oral anticoagulant that has been widely used for prophylaxis of thromboembolic events.

Up until 13 April 2016, the MHRA has received 146 reports of possible drug interactions between miconazole and warfarin. Most reports concerned the oral gel form of miconazole.

The potential for drug interactions between miconazole and warfarin is well established. The mechanism is understood to be inhibition by miconazole of one of the main cytochrome P450 isozymes involved in warfarin metabolism (CYP2C9), resulting in reduced warfarin clearance and an enhanced anticoagulant effect.

The MHRA is currently reviewing available data for this interaction. This review follows a coroner's report of a death, which may have been partly due to the co-administration of miconazole oral gel and warfarin. Further advice will be communicated as appropriate when the review is complete.

Reference:

Drug Safety Update, MHRA, Volume 9, issue 11:3, June 2016 (www.gov.uk/mhra)

Zecuity® (sumatriptan) migraine patch

Risk of burns and scars

USA. The US FDA has stated that the FDA is investigating the risk of serious burns and potential permanent scarring with the use of sumatriptan iontophoretic transdermal system (Zecuity®) patch for migraine headaches.

The manufacturer has decided to temporarily suspend sales, marketing, and distribution to investigate the cause of burns and scars associated with the Zecuity® patch.

Sumatriptan is used to treat acute migraine headaches in adults. The patch delivery system is designed to deliver a dose of medicine by way of a single-use, battery-powered patch that is wrapped around the upper arm or thigh. It should remain in place for no longer than four hours.

Since marketing of the Zecuity® patch began in September 2015, a large number of patients have reported that they experienced burns or scars on the skin where the patch was worn. The reports included descriptions of severe redness, pain, skin discoloration, blistering, and cracked skin. As a result, FDA is investigating these serious adverse events to determine whether future regulatory action is needed, and will update the public with new information when the FDA review is complete.

Health-care professionals should advise patients who complain of moderate to severe pain at the application site to remove the Zecuity® patch immediately. A different formulation of sumatriptan or alternative migraine medicine should be considered.

Reference:

Drug Safety Communication, US FDA, 2 and 13 June 2016 (www.fda.gov)

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 VigiBase®, the WHO international database of suspected adverse drug reactions. The database contains over 13 million reports of suspected adverse drug reactions, submitted by National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring. VigiBase® is, on behalf of the WHO, maintained by the Uppsala Monitoring Centre (UMC) and periodic analysis of VigiBase® data is performed in accordance with UMC's current routine signal detection process.

More information regarding the ICSRs, their limitations and proper use, is provided in the UMC Caveat document available at the end of Signal (page 22). For information on the UMC Measures of Disproportionate Reporting please refer to WHO Pharmaceuticals Newsletter Issue No. 1, 2012.

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

Thiamazole and rhabdomyolysis

Dr Ian Boyd, Australia

Summary

Thiamazole, also known as methimazole, inhibits the syntheses of thyroid hormones and thus is effective in treating hyperthyroidism. Thiamazole is indicated in patients with Graves' disease with hyperthyroidism or toxic multinodular goitre for whom surgery or radioactive iodine therapy is not an appropriate option and to ameliorate symptoms of hyperthyroidism in preparation for thyroidectomy or radioactive iodine therapy. After the elimination of a duplicate there are currently (1 September 2015) 19 individual case safety reports in VigiBase®, the WHO international database of suspected adverse drug reactions, of rhabdomyolysis in association with thiamazole. The reports are from Germany, Japan and Spain. The outcome of the rhabdomyolysis was stated in 14 reports and the patients were reported as recovered or recovering in 12 cases and not recovered in the remaining two cases. In the 12 cases where recovery was reported, it is likely that the drug was withdrawn in seven cases, the dose reduced in three cases, the drug withdrawn prior to the onset of the reaction in one case and the fate of the drug was unknown in the remaining case. In one case where recovery was documented, the reaction recurred on rechallenge.

Case reports in VigiBase® suggest that there is a possible signal for the association of thiamazole and rhabdomyolysis. Thiamazole was the only suspected drug in 13 of the 19 cases and although there were other drugs suspected in six of the 19 reports, thiamazole appears to be the most likely

explanation in two of the six reports as well as in the other 13 reports. Time to onset is consistent with a drug induced effect. Dechallenge is supportive of a drug association with probably 10 of the 12 patients recovered or recovering on withdrawal or dose reduction of thiamazole as well as a positive rechallenge in one case. In addition, there is a report in the literature describing rhabdomyolysis in association with thiamazole as well as a report of a closely related antithyroid drug, carbimazole, of three patients who developed rhabdomyolysis during treatment with that drug.

Introduction

Thiamazole, also known as methimazole, inhibits the syntheses of thyroid hormones and thus is effective in treating hyperthyroidism. In the United States, Thiamazole is indicated in patients with Graves' disease with hyperthyroidism or toxic multinodular goitre for whom surgery or radioactive iodine therapy is not an appropriate option and to ameliorate symptoms of hyperthyroidism in preparation for thyroidectomy or radioactive iodine therapy. More broadly, it is used for treatment of hyperthyroidism. Minor adverse reactions include gastrointestinal disorders, skin reactions and a variety of other reactions including myalgia. Serious adverse reactions include inhibition of myelopoieses (agranulocytosis, granulocytopenia, thrombocytopenia and aplastic anaemia), drug fever, a lupus-like syndrome, insulin autoimmune

syndrome, hepatitis, periarteritis, and hypoprothrombinaemia.¹

Rhabdomyolysis is characterized by the leakage of muscle-cell contents, including electrolytes, myoglobin, and other sarcoplasmic proteins (e.g., creatine kinase, aldolase, lactate dehydrogenase, alanine aminotransferase, and aspartate aminotransferase) into the circulation. Massive necrosis, which is manifested as limb weakness, myalgia, swelling, and commonly, gross pigmenturia without haematuria, is the common denominator of both traumatic and nontraumatic rhabdomyolysis. Acute kidney injury is a potential complication of severe rhabdomyolysis. There are a number of possible causes including trauma, exertion, muscle hypoxia, genetic defects, infections, body temperature changes, metabolic and electrolyte disorders and drugs and toxins. Drugs include lipid lowering agents such as statins and fibrates, alcohol, heroin and cocaine.²

Reports in VigiBase®

As of 1 September 2015 there are 20 individual case safety reports of rhabdomyolysis in association with thiamazole in VigiBase®, the WHO international database of suspected adverse drug reactions (Table 1). After the elimination of one suspected duplicate, the reports were submitted from Japan (16 reports), Germany (2) and Spain (1). The patients ranged in age from 9 to 77 years with a median of 39 years. There were 10 males and 9 females.

Thiamazole was the only drug suspected in 13 of the 19 cases. In the six cases with co-suspected drugs, four cases reported propylthiouracil, rosuvastatin, ketotifen, and an unknown drug respectively as the other suspected drug and one case reported alprazolam, bisoprolol, candesartan, furosemide, lansoprazole, propylthiouracil, spironolactone and warfarin. The remaining case suspected an interaction between thiamazole and simvastatin. Concomitant drugs were reported in 12 of the 19 cases. Apart from drugs indicated for the treatment of atrial fibrillation in three cases, other drugs for the treatment of a thyroid-related condition in two cases and drugs for the treatment of cardiovascular conditions in a few cases, the concomitant drugs were used to treat a variety of conditions. Thiamazole was reported to have been administered orally, as expected, in 17 of the 18 cases which provided this information. In the remaining case, the drug was administered intravenously. The indication for use was stated in 16 reports and included Basedow's disease in 10 reports, hyperthyroidism in three reports, thyrotoxicosis in two reports and toxic diffuse goitre in the remaining report. Dosage was reported in 15 cases and varied from 2.5 mg daily to 80 mg daily with many cases showing variation

in dosage as the dose was titrated to achieve the most appropriate maintenance dosage.

Time to onset was reported in 13 of the reports and ranged from two days to six months with a median of about two months.

The outcome of the rhabdomyolysis was stated in 14 reports and the patients were reported as recovered or recovering in 12 cases and not recovered in the remaining two cases. In the 12 cases where recovery was reported, it is likely that the drug was withdrawn in seven cases, the dose reduced in three cases, the drug withdrawn prior to the onset of the reaction in one case and the fate of the drug was unknown in the remaining case. In some reports the dates were unclear but the interpretation above is considered to be the most likely. In one case where recovery was documented, the reaction recurred on rechallenge.

Most of the reports (13) described only rhabdomyolysis as a reaction. In the six other reports other reactions were reported but only white cell disorders and hypothyroidism, which probably relates to the underlying condition, were reported twice. There was only one report in which adverse renal function was reported but this was only abnormal renal function rather than acute renal injury. Rhabdomyolysis is characterised by high levels of creatine kinase (CK). Twelve reports provided laboratory values for CK and these ranged from a maximum value of 927 IU/L to a maximum value of 66,580 IU/L (median: 4406 IU/L).

Literature and Labelling

The product literature does not refer to rhabdomyolysis although it does mention myalgia as a possible adverse reaction. In the literature, there is one report describing rhabdomyolysis in association with thiamazole, interpreted as Case 18 in Table 1.³ This was reported as the first reported case of such an association. There is a literature report of another antithyroid drug, carbimazole (which is converted to thiamazole in the body) as a possible cause of rhabdomyolysis, in which Seow et al reported three patients who developed rhabdomyolysis during treatment with carbimazole.⁴ In the product literature for carbimazole, it is noted that isolated cases of myopathy have been reported.⁵

Discussion

Case reports in VigiBase® suggest that there is a signal for the association of thiamazole and rhabdomyolysis. Thiamazole was the only drug suspected in 13 of the 19 cases. There were other drugs suspected in the remaining six cases.

Table 1. Case overview of reports in VigiBase® of rhabdomyolysis in association with thiamazole

Case	Age/Sex	Other suspected (S) interacting (I) or concomitant (C) drugs	Reactions (WHO-ART preferred terms)	Outcome
1	9/M	Carbocisteine, clostridium butyricum/enterococcus faecalis/bacillus mesentericus, unknown drug* (all C)	Rhabdomyolysis	Recovering
2	13/F	None	Rhabdomyolysis, hypothyroidism	Unknown
3**	27/F	Propylthiouracil (S)	Rhabdomyolysis	Unknown
4**	27/F	Propylthiouracil (S)	Rhabdomyolysis	Unknown
5	57/M	Bisoprolol, febuxostat, warfarin (all C)	Rhabdomyolysis	Recovered
6	33/M	Alprazolam, bisoprolol, candesartan, furosemide, lansoprazole, propylthiouracil, spironolactone, warfarin (all S)	Rhabdomyolysis	Recovering
7	66/M	Rosuvastatin (S) Bisoprolol, dabigatran, tamsulosin (all C)	Rhabdomyolysis	Recovering
8	58/M	Pilsicainide, propranolol (both C)	Rhabdomyolysis	Recovered
9	38/F	Arotinolol, cetirizine (both C)	Rhabdomyolysis	Recovered
10	72/F	None	Rhabdomyolysis	Not recovered
11	39/M	Propranolol, propylthiouracil (both C)	Rhabdomyolysis	Recovering
12	35/M	None	Rhabdomyolysis, neutropenia	Unknown
13	46/F	Propylthiouracil (C)	Rhabdomyolysis	Recovered
14	77/F	None	Rhabdomyolysis	Unknown
15	53/M	Unknown drug*(S) Bisoprolol, dabigatran (both C)	Rhabdomyolysis, hypothyroidism	Recovering
16	35/M	Insulin human (C)	Rhabdomyolysis, arthralgia, fever, granulocytopenia	Unknown
17	14/F	Ketotifen (S)	Rhabdomyolysis	Recovering
18	34/F	Oral contraceptive NOS (C)	Rhabdomyolysis	Recovered
19	62/M	Dobutamine, heparin, norepinephrine, piperacillin sodium/tazobactam sodium (all C)	Rhabdomyolysis, myopathy, renal function abnormal	Recovered
20	69/F	Simvastatin (I) Enalapril, phenprocoumon, piretanide, propranolol (all C)	Rhabdomyolysis, creatine phosphokinase increased, paresis, term under assessment for WHO-ART*	Not recovered

NOS = Not otherwise specified

*Drug name/term shown as reported

**Cases 3 and 4 are suspected duplicates

In Case 7, rosuvastatin is a co-suspected drug. Statins are a well-known cause of rhabdomyolysis and could be a more likely cause. Onset occurred nine days after initiation of rosuvastatin and recovery occurred after rosuvastatin withdrawal. This seems more indicative of causality than the use of thiamazole for which the reaction occurred six months after use - however, recovery also occurred after dose reduction of thiamazole. As discussed below, there is a possibility of an interaction between methimazole and rosuvastatin but rosuvastatin is less likely to be involved in CYP interactions than simvastatin.⁶ In Case 20, an interaction between simvastatin and thiamazole was suspected by the reporter. Thiamazole has been demonstrated to be an inhibitor of cytochrome P450 (CYP) 3A4 and a published case report demonstrated an interaction between thiamazole and erythromycin, well known to be metabolised by CYP 3A4.^{7,8} Inhibition of this enzyme can result in an accumulation of

erythromycin and the occurrence of toxic effects. It is possible in Case 20 that thiamazole may have inhibited the metabolism of simvastatin and resulted in an accumulation of the drug which may have made the patient more susceptible to rhabdomyolysis. Precise dates are unavailable in this report but for rhabdomyolysis to be in association with thiamazole, it had to occur within six days of starting thiamazole. On the other hand, simvastatin had been taken for 4 months and either simvastatin alone or an interaction with thiamazole seems a more likely cause. In Case 3/4, propylthiouracil was also suspected and although there are no dates available on which to ascertain the likelihood of causality, myopathy is listed as an adverse reaction in the product information for propylthiouracil and it may be a more likely cause.⁹ In Case 15, an unknown drug was co-suspected. However, although the nature of this drug is unknown, it was continued while thiamazole was withdrawn and the patient

recovered so thiamazole appears a more likely cause. In Case 17, ketotifen was also suspected and although there are no dates available on which to ascertain the likelihood of causality, there is no reference to any muscle effects in the product information for ketotifen, and there is no reason to suspect it as a more likely cause.¹⁰ In Case 6, there were other suspected drugs including propylthiouracil, alprazolam, bisoprolol, candesartan, furosemide, lansoprazole, spironolactone and warfarin. In this case, thiamazole was replaced with propylthiouracil five weeks before onset of rhabdomyolysis and thiamazole appears an unlikely cause with propylthiouracil a much more likely cause. The role of the other seven drugs is unclear but none of them appear to be a likely cause.

Time to onset was reported in 13 of the reports and ranged from two days to six months with a median of about two months. This would appear to be consistent with a thiamazole related event.

The outcome of the rhabdomyolysis was stated in 14 reports and the patients were reported as recovered or recovering in 12 cases and not recovered in the remaining two cases. In the 12 cases where recovery was reported, it appears likely that the drug was withdrawn in seven cases, the dose reduced in three cases, the drug withdrawn prior to the onset of the reaction in one case and the fate of the drug was unknown in the remaining case. In one case where recovery was documented, the reaction recurred on rechallenge. The observation of recovery on withdrawal or dose reduction in 10 cases as well as the observation of recurrence on rechallenge are strongly suggestive of a drug-induced effect.

In the literature, there is one report describing rhabdomyolysis in association with thiamazole.³ In addition, there is a literature report of another antithyroid drug, carbimazole (which is converted to thiamazole in the body) of three patients who developed rhabdomyolysis during treatment with carbimazole.⁴ It is also known that hypothyroidism can cause myopathy and rhabdomyolysis.^{11,12,13} This gives rise to the possibility that thiamazole-induced hypothyroidism may have been a cause. Only two of the reports, however, mention hypothyroidism as a reaction so this appears to be an unlikely cause.

It is interesting that 16 of the 19 patients were Japanese. There is, however, no evidence in the literature that metabolism of thiamazole is different in Japanese patients and it is possible that the high proportion of Japanese patients may be related to usage.

Conclusion

In summary, there are 19 reports reporting rhabdomyolysis with the use of thiamazole and this appears to be a signal. Although there were other drugs suspected in six of the 19 reports, thiamazole appears to be the most likely explanation in two of the six reports as well as in the other 13 reports in which it was the only suspected drug. Time to onset is consistent with a drug induced effect. Dechallenge is very supportive of a drug association with probably 10 of the 12 patients who were reported as recovered or recovering on withdrawal of, or dose reduction of thiamazole. There is also a report of a positive rechallenge. Rhabdomyolysis is not mentioned in the product information for thiamazole although it does mention myalgia as a possible adverse reaction. In the product literature for carbimazole (which is converted to thiamazole in the body), it is noted that isolated cases of myopathy have been reported. In the literature, there is one report describing rhabdomyolysis in association with thiamazole. In addition, there is a literature report of three patients who developed rhabdomyolysis during treatment with carbimazole.

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CAVEAT DOCUMENT

Accompanying statement to data released from VigiBase®, the WHO international database of suspected adverse drug reactions

Uppsala Monitoring Centre (UMC) in its role as the World Health Organization (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 (PIDM). The information is stored in VigiBase®, the WHO international database of suspected adverse drug reactions (ADRs). 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.

If in doubt or in need of help for interpretation of country specific data, UMC recommends to contact the concerned NC before using the data.

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, ADR reports 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). Transfer of sensitive data to a third party is generally prohibited subject to limited exceptions explicitly stated in applicable legislation.

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

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

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

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

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.

Uppsala Monitoring Centre (UMC) Box 1051, SE-751 40 Uppsala, Sweden
Tel: +46-18-65 60 60, E-mail: info@who-umc.org www.who-umc.org

Report from the Thirteenth Meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) 21-22 June 2016, Geneva

The WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) has been constituted to provide advice on Pharmacovigilance (PV) policy and issues related to the safety and effectiveness of medicinal products. A brief summary of discussions and recommendations from the 13th meeting of ACSoMP is provided below.

List of Abbreviations

ACSoMP: Advisory Committee on Safety of Medicinal Products	LMIC: Low- and Middle-income Countries
AE: Adverse Event	MDR-TB: Multi-Drug-Resistant Tuberculosis
AMRH: African Medicines Regulatory Harmonization	MMV: Medicines for Malaria Venture
AVAREF: African Vaccines Regulatory Forum	NRA: National Regulatory Agency
BDQ: Bedaquiline	NPC: National Pharmacovigilance Centre
BMGF: Bill and Melinda Gates Foundation	NTD: Neglected Tropical Diseases
CC: Collaborating Centre	PIDM: Programme for International Drug Monitoring (WHO)
CEM: Cohort Event Monitoring	PRAC: Pharmacovigilance Risk Assessment Committee (EMA)
CIOMS: Council for International Organizations of Medical Sciences	PSUR: Periodic Safety Update Report
DCGI: Drugs Controller General of India	PV: Pharmacovigilance
DSMC: Data Safety Monitoring Committee	PvPI: Pharmacovigilance Programme of India
EMA: European Medicines Agency	SAE: Serious Adverse Event
EU: European Union	SAV: Safety and Vigilance (WHO)
GACVS: Global Advisory Committee on Vaccine Safety	SMC: Seasonal Malaria Chemoprevention
GFATM: The Global Fund to Fight AIDS, Tuberculosis and Malaria	STH: Soil-Transmitted Helminthiasis
GMP: Global Malaria Programme	TB: Tuberculosis
ICH: International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use	TdP: Torsades de Pointes
ICSR: Individual Case Safety Report	UK: United Kingdom
ISO: International Organization for Standardization	UMC: Uppsala Monitoring Centre
ISoP: International Society of Pharmacovigilance	US FDA: United States Food and Drug Administration
KPI: Key Performance Indicator	WHO: World Health Organization
	XDR-TB: Extensively Drug-Resistant Tuberculosis

Pharmacovigilance (PV) Priorities for World Health Organization (WHO):

- Increasing access to essential, quality, safe and affordable medical products is a leadership priority for WHO. The ongoing WHO-reform process is to ensure that the organization is more effective, efficient, responsive, objective, transparent and accountable to its partners and stakeholders. The scope of the Safety and Vigilance (SAV) team within WHO includes: advocacy for safety and vigilance activities, establishing and consolidating partnerships for implementing and advancing the safety and safe use of medical products, strengthening infrastructure, active surveillance and training in pharmacovigilance (PV), and supporting the use of effective tools and systems for monitoring medical products of significant public health importance.
- The 2016-2017 priorities for SAV/Medicines Safety are to focus on a few countries, to build capacity and support them through the full cycle of PV activities, from collecting PV data and information, to making regulatory decisions and therapeutic choices based on the collected information. The strategy would be to assess and to improve the quantitative and qualitative aspects of PV activities and outcomes in these countries. The long-term objective is to build comprehensive, sustainable, results-driven PV systems that improve our knowledge, power our decisions and promote the safe use of medicines.
- In moving forward, WHO should consider if the current programme needs to be more 'global' and include the safety and vigilance of all health-care products including medical devices, and diagnostic tests, how the lessons learnt from the WHO Programme for International Drug Monitoring (PIDM) could be developed further, and how PV systems could be enhanced to cover emerging priorities such as monoclonal antibodies, biosimilars and products of human origin.

WHO Collaborating Centres (CCs) that support the WHO PIDM¹

- The Uppsala Monitoring Centre (UMC), a WHO CC for International Drug Monitoring will continue to develop user-friendly information materials on PV and step up its support to countries in signal detection, through the refinement of UMC's training curriculum and updates of data management tools such as VigiLyze and VigiFlow. The Centre will implement automated feedback to national PV centres (NPCs) submitting Individual Case Safety Reports (ICSR).
- In improving PV in sub-Saharan Africa, the WHO CC in Accra, Ghana, will collaborate with partners for comprehensive health and epidemiological surveillance systems and platforms for long-term and sustainable drug and vaccine safety monitoring in these settings. The Centre will provide training and support PV research and other activities in countries, including cohort event monitoring (CEM) and targeted spontaneous reporting of specified products and relevant data management systems.
- The WHO CC in Rabat, Morocco, plans to provide courses on medication errors and promote the P-method² and use of root cause analysis, to detect and understand the reasons why preventable adverse events (AEs) continue to occur. The Centre will continue its work on integrating vigilance systems and harmonizing Arabic terminologies in PV.
- The WHO CC in the Netherlands will continue to exploit its research and experience in patient reporting, for additional insights into the value of patient reports, to support NPCs in setting up and running patient adverse drug reaction reporting systems. The Centre will support WHO in integrating PV in the medical curriculum. Its experience in establishing registers on the use of medicines in pregnancy as well as a toolkit will be useful to WHO in providing technical and country support in this area of work.
- The broader scope of PV requires a regulatory framework, to include planning, assessing and taking action in addition to collecting and investigating evidence of harm. The proposal to establish a new collaborating centre for PV in India should be considered in light of these requirements.
- The use of mobile phone and smart phone technology in AEs data collection and transmission is progressing rapidly, but given the limited internet access in some settings, applications that do not need immediate internet connectivity should be considered and promoted. Both WHO and its CCs should make this a priority and provide guidance and ensure that the necessary tools are available to those in resource-limited settings.

WHO-Bill and Melinda Gates Foundation (BMGF) partnership for PV

- According to the report of the BMGF-appointed Safety Surveillance Working Group, new drugs, vaccines and diagnostics are now being developed specifically for low- and middle-income countries (LMIC) and it is a challenge for PV activities to keep pace with this new trend. In consequence, LMIC can no longer rely on post-market safety surveillance from developed economies. LMIC would thus need to be supported with a prioritized, well-coordinated and agile PV system. The Foundation supports focusing surveillance initially on specific risks and on products with a high risk profile, for a targeted period of time, through a single system for both vaccines and medicines, with tailoring only when required, using existing standards and platforms (Council of International Organization of Medical Sciences, CIOMS; ICH, WHO and others) and ongoing initiatives (e.g. African Medicines Regulatory Harmonization, AMRH; African Vaccines Regulatory Forum, AVAREF). PV capacity varies between countries and a stepwise approach appropriate to each country is needed. Overall there is strong encouragement and support for this approach.
- BMGF notes that there are many different stakeholders conducting a mixture of PV activities which are not coordinated and have resulted in duplication of efforts. WHO is in a key position to coordinate these activities. The divide between pre and post market safety data is merging, with some newer products reaching the market earlier in the phase of development. Risk management planning will be very important for these products and the role of WHO-appointed committees such as ACSoMP and the Global

¹ WHO Collaborating centres: WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre, Uppsala, Sweden; WHO Collaborating Centre for Advocacy & Training in Pharmacovigilance, Accra, Ghana; WHO Collaborating Centre for Strengthening Pharmacovigilance Practices, Centre Anti Poison et de Pharmacovigilance du Maroc, Rabat, Morocco; WHO Collaborating Centre for Pharmacovigilance in Education and Patient Reporting, the Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, the Netherlands.

² A method that relies on preventability criteria to systematically detect medication errors in Individual Case Safety Reports that are sent to Pharmacovigilance Centres.

Advisory Committee on Vaccines Safety (GACVS) will be important in both risk management planning and in reviewing the global safety data from such products.

Medicines in Pregnancy:

- Sodium valproate, although very effective in epilepsy, has teratogenic properties and a serious risk of neurodevelopmental disorders. A number of regulatory steps to communicate and minimize risks have been pursued by the European Union (EU) regulatory authorities. However, there is still insufficient knowledge on the safety of this and other drugs during pregnancy, more needs to be done to improve understanding as well as risk minimization practices.
- A diagnostic decision-making tool using about 200 original cases of thalidomide-associated limb deformities and 200 negative controls (cases of known hereditary problem) has been developed to sift out the more robust cases. The tool has around 95% positive predictive value and 80% negative predictive value (i.e. it could miss 20% of people eligible for compensation). This tool is the result of a technical consultation convened in WHO upon the request of the United Kingdom (UK) Thalidomide Association. Full details of this work are available in a complete report and can be requested from WHO.
- ACSoMP suggested that the principles, ideas and logic used to form this tool should be used to develop a generic tool for similar situations with other medications taken in pregnancy. The Committee could also be requested to review information on specific risks with medicines in pregnancy and to advise on how best to signpost new information. Agencies such as the European Medicines Agency (EMA) could be approached to organize a scientific workshop on drugs in pregnancy, to help WHO develop a general guidance document on the subject.

WHO guidance on Minimum PV Requirements

- NPCs have requested revisions to the WHO Minimum PV Requirements (Core Components) document. The existing version was designed for a specific purpose: to help the Global Fund (GFATM) support and monitor the implementation of PV within countries that received financial aid from GFATM. The revised document needs to be more comprehensive, designed to present the requirements more clearly and concisely, with a detailed description of the requirements that considers special needs of smaller countries, and provides broad guidance on the implementation of the requirements together with references to any existing guidelines. The Minimum PV Requirements document needs to align with the WHO PV indicators and the WHO National Regulatory Agency (NRA) assessment tool, and the step wise approach adopted in these documents.

PV of medicines used in TB treatment

- Multi Drug-Resistant Tuberculosis (MDR-TB) or Extensively Drug-Resistant TB (XDR-TB) patients are being treated with new medicines (e.g. bedaquiline (BDQ), delamanid), novel regimens (e.g. MDR-TB shorter regimen) and repurposed drugs (e.g. clofazimine, linezolid). Three levels of monitoring are being used: Core package, which requires monitoring for and reporting of all serious adverse events (SAEs); Intermediate package, which includes SAEs as well as AEs of special interest; and Advanced package, which includes all AEs of clinical significance. The level of monitoring is selected in accordance with the PV capacity in the country, for example a country with limited capacity may adopt the core package.
- The Drugs Controller General of India (DCGI) has approved the use of BDQ to treat MDR-TB in six TB-treatment centres across India, the country with the highest TB burden (annual incidence 2.2 million). The first patient was enrolled in June 2016. Owing to the complexity of treatment (involving as many as 16 medicines), extensive training of medical staff is needed. A national workshop on BDQ was held in July 2015 and a subsequent workshop that focuses on PV, CEM and causality assessments will take place in August 2016. The Indian Council of Medical Research (ICMR) and Central TB Division have developed guidelines, ready-reckoners and reference manuals for patients, health workers, medical officers and specialists for prevention and management of anti-TB drugs. Two reporting forms have been developed for CEM: a treatment initiation form and a treatment review form for use at every follow-up visit or event.

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Paper forms will be filled on site, and then entered into the TB software, NIKSHAY. Parallel to this, routine spontaneous reporting forms will also be available. Any SAE will be reported within 24 hours through NIKSHAY (automatic Short Message Service (SMS) and email to the Data Safety Monitoring Committee (DSMC)). This data will then pass via the NIKSHAY-VigiFlow bridge to VigiFlow, the national data management system used by the PV programme in India (PvPI), ensuring seamless transfer of information between the TB programme and the PV Centre. Causality assessment will be carried out at the treatment sites and interpreted further by the expert safety committee, DSMC that includes a hepatologist, cardiologist, respiratory specialist and a general physician. The DSMC will also carry out periodic benefit harm assessment to inform the Revised National Tuberculosis Programme (RNTCP) and the DCGI on safety aspects of BDQ-containing regimen.

- Whilst it is necessary to monitor adverse effects, the effectiveness of new products such as BDQ is also very important and needs to be captured to assist in benefit-harm assessment and to provide balanced therapeutic recommendations. It is also important to have access to pre marketing safety and efficacy data. In the interest of patients and global learning, ACSoMP recommends sharing of pre marketing and post marketing safety and effectiveness data on BDQ by all concerned: EMA and US FDA who originally approved its use; countries that are rolling out BDQ; and Janssen Pharmaceuticals, the manufacturer.
- India would also request ACSoMP's review of data as these accumulate. Acknowledging the local solutions proposed by countries such as India and Indonesia, to share data between the TB programmes and the PV centres, ACSoMP recommended similar collaborations and software solutions for seamless data entry and data sharing between PV centres and other public health programmes.

Integrating PV in seasonal malaria chemoprevention (SMC) programmes.

- The SMC programme involves treatment at monthly intervals with amodiaquine and sulfadoxine-pyrimethamine for children aged between 3 and 59 months living in areas of high seasonal malaria transmission across the Sahel region. The treatment begins at the start of the malaria transmission season and continues for up to four months during the season. The treatment gives a high level of protection for four weeks, so it has to be taken at monthly intervals. PV is very important for the success of this programme and needs strengthening throughout the region. A 3-day workshop on PV in SMC was held in Rabat, Morocco in 2015. In a second meeting held in February 2016 which focused on lessons learnt, participants requested more PV training in countries implementing SMC, with contents tailored to the different cadres of care providers. WHO has now adapted the WHO-International Society of Pharmacovigilance (ISoP) PV curriculum to SMC-specific PV training modules and will use this in subsequent PV trainings in the countries implementing SMC.
- The Committee endorsed the training material and emphasized the importance of involving PV centres in the training, to include training well before SMC-launch, and tailored-training. The Committee also reiterated its previous recommendation that all AEs (both serious and non-serious events) should be collected in SMC.
- A SMC safety review committee has been established, to review PV data from SMC in countries and to provide advice on any risk management plans.

Antimalarial cardiotoxicity

- Several WHO-recommended quinoline antimalarials (chloroquine, quinine, mefloquine and piperaquine) are associated with prolongation of the QTc interval. A lengthened QT interval is a risk factor for ventricular tachyarrhythmias, like torsades de pointes (TdP), which can cause sudden cardiac death. TdP is a significantly underestimated problem. There are often many potential confounding factors, including many concomitant medications that could provoke QT prolongation. There is a possibility that these factors are not captured adequately in spontaneous reports of TdP. WHO is reviewing all available data on cardiotoxicity of antimalarials, and will provide these to an Expert Review Group, to understand the magnitude of the problem and propose how the risk could be managed. A recommendation was made that AEs detected in clinical studies are submitted to VigiBase®, the WHO Global database of ICSR.

WHO response plan to identified safety concerns of antimalarial medicines

- No medicine is without risk. Risk assessment considers the specific risks of the medicine, together with the seriousness of the condition being treated, the expected benefit of the drug, the population being targeted, the expected use of the medicine in actual practice, the setting of care, the potential for misuse, and the available alternatives. A number of tools can be used for risk minimization, including information notes and guidelines, updating product information, and manufacturing restrictions such as restricted pack size and withdrawal of a product from the market. The WHO Global Malaria Programme (GMP) has proposed a framework for risk management plans to identified risks and safety concerns with antimalarial medicines. The framework is intended for various stakeholders including pharmaceutical industry, private-public partnerships, for example, medicines for malaria venture (MMV) and will advance risk management plans that consider feasibility (on the ground practicalities), proportionality and burden when making decisions. The framework on the response plan will be elaborated to provide detailed guidance on avoiding risk (when possible) and early detection, empowering patients and health care providers. Planning and frequent communication will form essential elements of the plan.

Control of soil-transmitted helminthiasis (STH) (deworming activities)

- STH is endemic in 102 countries, and there are approximately 266 million preschool-age children, 600 million school-age children and 250 million women of child-bearing age at risk. They are at risk because they are in a period of intense need of micronutrients, and a high worm load is very demanding nutritionally. The WHO objective is to reduce morbidity due to STH to a level below which it would not be considered a public health problem. At-risk groups in endemic areas are given preventive chemotherapy consisting of large-scale administration of the anthelmintic drugs albendazole and mebendazole. From the veterinary field, there is evidence that helminths can develop resistance against benzimidazoles when drug pressure is intense. For this reason it is proposed to limit drug distribution to the above-mentioned at-risk groups and to maintain a background number of unexposed individuals in the population. In order to broaden drug treatment options against STH, it is now being proposed to use three different drug combinations: (1) albendazole and ivermectin (existing combination but new indication for STH); (2) pyrantel and oxantel; and (3) tribendimidine and moxidectin (innovative drugs). Retrospective data will be collected on the safety of these medicines, using literature reviews, other large-scale Neglected Tropical Diseases (NTD) campaigns, Vigibase® and EudraVigilance. New data will be collected from drug trials when existing safety and efficacy data are insufficient.
- ACSoMP will be fully informed of potential 'new' drugs/drug combinations for STH and the rationale for treatment expansion, and will be requested to provide input on sources of safety data and to provide guidance on appropriate steps for increasing drug expansion in NTD recommendations. The Committee will be updated on progress of collection of safety data.
- The Committee noted that communication before rolling out large scale deworming programmes is very important, particularly since many teachers and community workers are involved in the administration of medication. Integration of the NPC with the National NTD programme facilitates communication and reporting of adverse effects. Greater links with WHO CCs on the field would also be useful.
- Mass drug administration of the new medications will not be considered in the initial stages of use as safety data from clinical trials are insufficient. The safety profile should be gathered from use on a small scale before scaling up. If available, periodic safety update reports (PSURs) for the listed medications in the EU should be shared with the WHO NTDs. Safety reports/evidence should be reviewed by ACSoMP or a subgroup that is accessible to ACSoMP before presentation to the decision makers.

Updates on PV in EU

- The Pharmacovigilance Risk Assessment Committee (PRAC) is the committee at the EMA that is responsible for planning, assessing and monitoring safety issues for human medicines. In 2015, they reviewed over 650 draft risk management plans. Risk management plans are critical for early market entry of promising medicines with limited safety data.

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- Approximately half of new and follow-up signals that are presented to PRAC lead directly to a label change, highlighting how a PV system can lead to regulatory change.
- Large volumes of PSURs are submitted to the EMA through one portal within the EU. High level summaries of the reports are made public.
- In January 2016, PRAC adopted a strategy for measuring the impact of PV activities. The Key Performance Indicators (KPIs) used to measure the impact of PV are being analysed within the European system and can be presented to ACSoMP at a future meeting. During the development of the KPIs, the WHO PV Indicators were noted and additional regulatory indicators were added. WHO/SAV is encouraged to consider a subset of relevant KPIs in its work. A workshop on measuring the impact of PV activities will be held at the EMA office in London, 5-6 December 2016. The workshop will focus on the methodology of measuring impact in three areas: process, health related, and patient engagement.
- There is a legal requirement to develop a new version of the EudraVigilance that delivers better health protection through simplified reporting, better quality data and better searching, analysis and tracking functionalities. The new International Organization for Standardization (ISO)-ICSR data format will be used. All reports from EudraVigilance will go directly to UMC (rather than from 31 individual EU countries). This will start in late 2017.